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7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (Medazepam)

BY G. GILLI, V. BERTOLASI AND M. SACERDOTI

Centro di Strutturistica Diffrattometrica, Università di Ferrara, Italy

AND P. A. BOREA

Istituto di Farmacologia, Università di Ferrara, Italy

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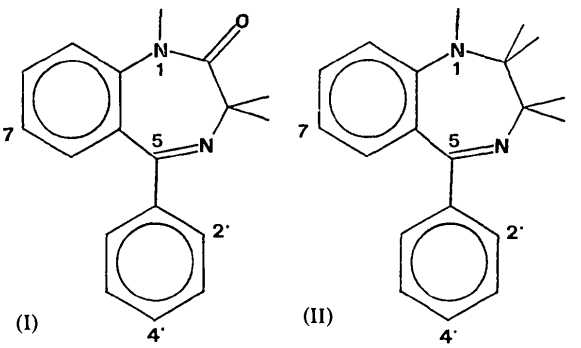
Abstract. $C_{16}H_{15}N_2Cl$, orthorhombic, $P2_12_12_1$ (No. 19), $a = 12{\cdot}857$ (3), $b = 28{\cdot}518$ (6), $c = 7{\cdot}683$ (3) Å, $Z = 8$, $D_c = 1{\cdot}28$ g cm^{-3}. The structure was solved by direct methods and refined to an R value of 0·053 from diffractometer data. The asymmetric unit consists of two molecules of opposite conformational chirality. The geometries of the two molecules have been compared by half-normal probability plots. The seven-membered ring is in a twisted-boat conformation and a comparison with the rings of the 1*H*-1,4-benzodiazepin-2-one derivatives of known molecular structure has been carried out.

Introduction. In a recent paper (Gilli, Bertolasi, Sacerdoti & Borea, 1978) we have determined the crystal structure of oxazepam (I*b*) and have shown that the 2*H*-1,4-benzodiazepin-2-one derivatives do not differ in configuration and are very similar in conformation as far as the benzodiazepine group is concerned. In fact the molecules of oxazepam, diazepam (Camerman & Camerman, 1972), lorazepam (Bandoli & Clemente, 1976), nitrazepam (Gilli, Bertolasi, Sacerdoti & Borea, 1977), dechlorodiazepam and 4′-fluorodiazepam (Sternbach, Sancilio & Blount, 1974) are practically superposable on the mean plane of the phenyl group. As the biological activities (mainly expressed as anticonvulsant, myorelaxant and taming activities) of the six compounds are very different, it was concluded that the contribution to activity of the molecular frame was constant and that the differences in activity should be ascribed to the physico-chemical parameters of the substituents.



I(*a*) Diazepam: 7-Cl, 1-Me
II(*a*) Medazepam: 7-Cl, 1-Me
I(*b*) Oxazepam: 7-Cl, 3-OH
I(*c*) Lorazepam: 7-Cl, 3-OH, 2′-Cl
I(*d*) Nitrazepam: 7-NO_2
I(*e*) Dechlorodiazepam: 1-Me
I(*f*) 4′-Fluorodiazepam: 7-Cl, 1-Me, 4′-F

However, the 2*H*-1,4-benzodiazepin-2-one frame is not unique in imparting biological activity to benzodiazepines. For instance medazepam (II*a*) is a 1*H*-1,4-benzodiazepine derivative but displays the same biological action as diazepam (I*a*) at a dosage only two or three times larger. The present paper reports the crystal structure of medazepam and is part of a study intended to establish which degree of variability is allowed in the geometry of the ring without deleting its biological activity.

The product was kindly provided by the pharmacological firm Prodotti Roche, Milan, and recrystallized from ethanol. Intensity data were collected from a crystal of 0·20 × 0·25 × 0·38 mm on a Siemens AED diffractometer with Ni-filtered Cu $K\alpha$ radiation and an $\omega/2\theta$ scan ($\theta \leq 55°$). Out of the 1998 reflections collected, 1908 having $I_o \geq 2{\cdot}5\sigma(I_o)$ were used in the refinement. The structure was solved by *MULTAN* (Main, Woolfson, Lessinger, Germain & Declercq, 1974) and refined by a blocked-matrix least-squares method (one block for each independent molecule in the asymmetric unit) with anisotropic temperature factors for all the non-hydrogen atoms using the *SHELX* 76 system of programs (Sheldrick, 1976). H atoms were assigned calculated positions. Scattering factors were taken from *International Tables for X-ray Crystallography* (1974) and allowance was made for the f' and f'' terms of the Cl atom. Final disagreement factors were $R\ (=\sum|\Delta|/\sum|F_o|) = 0{\cdot}053$ and $R_w\ [=(\sum w|\Delta|^2/\sum w|F_o|^2)^{1/2}] = 0{\cdot}067$. Weights were given according to the formula $1/w = \sigma^2_{F_o} + 0{\cdot}0061|F_o|^2$. The final coordinates for the two independent molecules are reported in Table 1.*

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33778 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Positional parameters* ($\times 10^4$) *of the non-hydrogen atoms, with e.s.d.'s in parentheses*

	Molecule *A*			Molecule *B*		
	x	*y*	*z*	*x*	*y*	*z*
Cl	5136 (2)	7407 (1)	4892 (3)	7467 (1)	7561 (1)	9744 (3)
C(1)	4112 (4)	7012 (1)	4586 (6)	8400 (4)	7132 (1)	9428 (6)
C(2)	3164 (5)	7122 (1)	5172 (6)	9384 (5)	7186 (1)	10060 (6)
C(3)	2349 (4)	6806 (1)	4970 (5)	10103 (3)	6838 (1)	9899 (5)
C(4)	2509 (3)	6377 (1)	4171 (5)	9855 (3)	6412 (1)	9070 (5)
C(5)	3523 (3)	6271 (1)	3545 (5)	8845 (3)	6359 (1)	8363 (5)
C(6)	4307 (3)	6590 (1)	3775 (5)	8118 (3)	6719 (1)	8582 (5)
C(7)	1768 (3)	5584 (2)	4591 (6)	10379 (3)	5593 (1)	9536 (6)
C(8)	2861 (4)	5417 (1)	4811 (5)	9243 (3)	5477 (1)	9606 (6)
C(9)	3735 (3)	5823 (1)	2607 (5)	8563 (3)	5934 (1)	7365 (5)
C(10)	4325 (3)	5840 (1)	941 (5)	8056 (2)	5988 (1)	5630 (5)
C(11)	4880 (3)	5458 (1)	364 (6)	7585 (3)	5602 (1)	4844 (5)
C(12)	5414 (4)	5470 (2)	−1191 (6)	7099 (3)	5639 (1)	3232 (5)
C(13)	5388 (4)	5865 (2)	−2209 (6)	7069 (3)	6065 (1)	2410 (5)
C(14)	4838 (3)	6255 (2)	−1670 (6)	7536 (3)	6453 (1)	3150 (6)
C(15)	4308 (3)	6245 (1)	−82 (5)	8032 (3)	6414 (1)	4754 (5)
C(16)	635 (3)	6234 (2)	4089 (7)	11687 (3)	6187 (2)	9116 (6)
N(1)	1705 (2)	6061 (1)	3901 (5)	10594 (2)	6058 (1)	8840 (4)
N(2)	3433 (3)	5420 (1)	3142 (5)	8758 (3)	5521 (1)	7887 (4)

Table 2. *Interatomic distances* (Å) *with e.s.d.'s in parentheses*

	Molecule *A*	Molecule *B*
C(1)–Cl	1·750 (5)	1·732 (5)
C(1)–C(2)	1·336 (9)	1·364 (8)
C(1)–C(6)	1·376 (6)	1·391 (6)
C(2)–C(3)	1·389 (8)	1·362 (6)
C(3)–C(4)	1·385 (5)	1·407 (5)
C(4)–C(5)	1·422 (5)	1·416 (5)
C(4)–N(1)	1·388 (5)	1·398 (5)
C(5)–C(6)	1·370 (5)	1·401 (5)
C(5)–C(9)	1·492 (5)	1·479 (5)
C(7)–C(8)	1·493 (6)	1·498 (6)
C(7)–N(1)	1·461 (6)	1·456 (5)
C(8)–N(2)	1·478 (6)	1·466 (6)
C(9)–C(10)	1·488 (5)	1·492 (5)
C(9)–N(2)	1·281 (4)	1·268 (4)
C(10)–C(11)	1·375 (5)	1·395 (5)
C(10)–C(15)	1·396 (5)	1·389 (5)
C(11)–C(12)	1·378 (6)	1·390 (6)
C(12)–C(13)	1·371 (7)	1·371 (6)
C(13)–C(14)	1·383 (7)	1·381 (6)
C(14)–C(15)	1·398 (6)	1·392 (6)
C(16)–N(1)	1·468 (6)	1·469 (5)

Table 3. *Interatomic angles* (°) *with e.s.d.'s in parentheses*

	Molecule *A*	Molecule *B*
C(2)–C(1)–Cl	119·3 (3)	120·8 (3)
C(6)–C(1)–Cl	119·0 (4)	118·9 (4)
C(6)–C(1)–C(2)	121·6 (4)	120·3 (4)
C(3)–C(2)–C(1)	119·8 (4)	121·0 (4)
C(4)–C(3)–C(2)	120·7 (5)	121·1 (4)
C(5)–C(4)–C(3)	118·3 (4)	118·3 (3)
N(1)–C(4)–C(3)	122·0 (4)	121·8 (3)
N(1)–C(4)–C(5)	119·7 (3)	119·7 (3)
C(6)–C(5)–C(4)	119·3 (3)	119·1 (3)
C(9)–C(5)–C(4)	120·8 (3)	120·9 (3)
C(9)–C(5)–C(6)	119·8 (3)	120·0 (3)
C(5)–C(6)–C(1)	120·3 (4)	120·2 (4)
N(1)–C(7)–C(8)	113·0 (3)	113·4 (3)
N(2)–C(8)–C(7)	111·6 (4)	111·3 (4)
C(10)–C(9)–C(5)	118·7 (3)	119·0 (3)
N(2)–C(9)–C(5)	123·9 (3)	123·2 (3)
N(2)–C(9)–C(10)	117·5 (3)	117·7 (3)
C(11)–C(10)–C(9)	121·0 (3)	119·6 (3)
C(15)–C(10)–C(9)	120·2 (3)	122·2 (3)
C(15)–C(10)–C(11)	118·8 (4)	118·1 (3)
C(12)–C(11)–C(10)	121·3 (4)	121·4 (4)
C(13)–C(12)–C(11)	120·1 (4)	119·4 (4)
C(14)–C(13)–C(12)	120·2 (4)	120·5 (4)
C(15)–C(14)–C(13)	119·6 (4)	120·0 (4)
C(14)–C(15)–C(10)	120·1 (4)	120·6 (4)
C(7)–N(1)–C(4)	120·6 (3)	118·9 (3)
C(16)–N(1)–C(4)	117·7 (4)	116·7 (3)
C(16)–N(1)–C(7)	109·2 (4)	110·9 (3)
C(9)–N(2)–C(8)	115·8 (3)	116·6 (3)

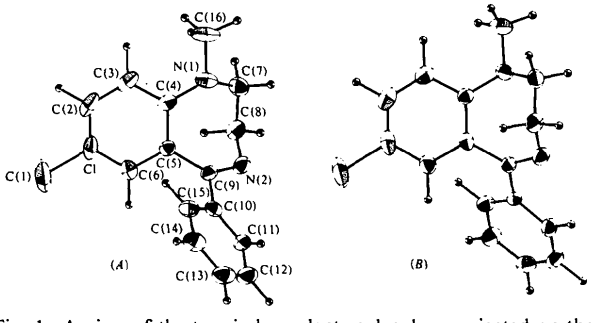


Fig. 1. A view of the two independent molecules, projected on the mean plane through the C(1)–C(6) phenyl ring (Johnson, 1965).

Discussion. The structure consists of couples of molecules packed with no contacts shorter than the sums of the van der Waals radii, except for the intermolecular hydrogen-bond distance of 2·43 Å occurring between N(2*A*) and C(7*B*).

Table 4. *Displacements* (Å) *from the least-squares plane through the* C(1)–C(6) *phenyl ring in medazepam and comparison with the corresponding values in nitrazepam and oxazepam*

	Molecule	N(1)	C(7)	C(8)	N(2)	C(9)	C(10)	C(16)	Reference
Medazepam	*A*	0·04	−1·01	−1·67	−0·69	0·06	1·04	0·42	(*a*)
	B	0·03	−1·04	−1·65	−0·63	0·10	1·13	0·40	(*a*)
Oxazepam	*A*	0·03	−0·63	−1·48	−0·58	0·07	0·88	–	(*b*)
	B	0·08	−0·56	−1·47	−0·60	0·04	0·88	–	(*b*)
Nitrazepam		0·05	−0·59	−1·41	−0·52	0·09	0·97	–	(*c*)

References: (*a*) Present work. (*b*) Gilli, Bertolasi, Sacerdoti & Borea (1978). (*c*) Gilli, Bertolasi, Sacerdoti & Borea (1977).

Owing to the boat conformation of the seven-membered ring, the molecule exists in enantiomorphous pairs (conformational chirality), which can switch by ring reversal from one chiral form to another. In space groups lacking rotational-inversion axes, the molecule must form crystals of opposed chirality by spontaneous resolution of the enantiomers, otherwise the asymmetric unit must be doubled to incorporate molecules of both chiralities (Rogers, 1975). In the present case molecules crystallize as 'racemates' and the enantiomorphous pair building up the asymmetric unit is shown in Fig. 1.

Bond distances and angles are reported in Tables 2 and 3. The two sets of values have been compared by half-normal probability plots (Abrahams & Keve, 1971). The plots are nearly linear and their regression parameters for bond lengths and angles are respectively: intercept, 0·06 and −0·36; slope, 1·89 and 2·16 and correlation coefficient, 0·99 and 0·98. That is, the e.s.d.'s reported in Tables 2 and 3 are underestimated by a factor of two and the two molecules are indistinguishable as far as bond distances and angles are concerned. They are however opposed in chirality and differ in the conformation of the 5-phenyl ring [torsion angles C(15)–C(10)–C(9)–C(5) of −26·1 and 13·6° in molecules *A* and *B* respectively].

Bond lengths correspond well to standard values, with the exception of the shrinkage observed in the C(1)–C(2) and C(2)–C(3) distances which is very likely to be caused by the high vibrational disorder of this part of the molecule.

A comparison of the geometry of the 1*H*-1,4-benzodiazepine group found in the present compound with that of the 2*H*-1,4-benzodiazepin-2-one group in oxazepam and nitrazepam is shown in Table 4. It can be seen that the seven-membered ring is in a boat conformation in the last two compounds, while it is in a twisted-boat conformation in medazepam. However, the two rings are very similar when projected on to the mean plane of the C(1)–C(6) phenyl ring.

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