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The Crystal and Molecular Structure of 7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (Oxazepam)

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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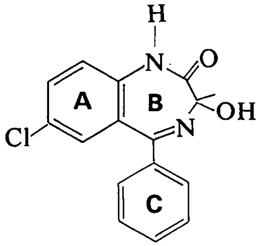
$C_{15}H_{11}ClN_2O_2$, triclinic, $P\bar{1}$ (No. 2), $a = 10.852$ (3), $b = 14.144$ (4), $c = 9.437$ (3) Å, $\alpha = 102.20$ (4), $\beta = 106.58$ (4), $\gamma = 98.65$ (4)°, $Z = 4$, $D_c = 1.39$ g cm^{-3}, μ(Cu $K\alpha$) = 24.6 cm^{-1}. The structure consists of infinite layers of molecules linked by a net of hydrogen bonds in the *ac* plane and stacked along *b* by van der Waals forces. The seven-membered ring is in a boat conformation and it has been proved that the small geometrical changes of the ring in different benzodiazepines are irrelevant to the biological activity.

Introduction

Benzodiazepines are a class of psychotherapeutic drugs discovered at the end of the 1950's and now widely used owing to their broad spectrum of biological activities. They are mainly used as tranquillizers but are also of interest for their muscle relaxant, anticonvulsant and sleep-induction effects.

In a previous paper (Gilli, Bertolasi, Sacerdoti & Borea, 1977) we have raised two main points on the relationship between molecular structure and biological activity of these drugs. The first was whether the small geometrical changes observed in the molecular frame of the benzodiazepines of known structure were relevant to the biological activity; the present work reports the crystal structure of oxazepam (I), a benzodiazepine of high biological activity, and tries to give a definite answer to this problem. The second point originated from the hypothesis of Camerman & Camerman (1974), of a common steric pattern of most anticonvulsant agents, such as benzodiazepines, hydantoins and barbiturates. This hypothesis will not be dealt with here, as it seems hardly confirmable on pure stereochemical bases but probably needs to be supported also by neurophysiological data, that is by evidence of the fact that the different anticonvulsants are acting on the same part of the central nervous system. Such evidence is lacking; in contrast, distinct differences between the actions of benzodiazepines and those of other anticonvulsants, particularly barbiturates, have been reported (Randall, Schallek, Sternbach & Ning, 1974).



(I)

Experimental

The crystals, kindly provided by the pharmacological firm Boeringer–Ingelheim, Florence (Italy), were recrystallized from ethanol. Intensities were collected from a crystal having dimensions 0·14 × 0·45 × 0·60 mm on an automatic Philips PW1100 diffractometer (Cu $K\alpha$ radiation and $\omega/2\theta$ scan). Of the 4811 reflections collected ($\theta \leq 55°$) only 2837 having $I_o \geq 2.5\sigma(I_o)$ were used in the refinement.

The crystal data are: $C_{15}H_{11}N_2ClO_2$, triclinic, $P\bar{1}$ (No. 2), $a = 10.852$ (3), $b = 14.144$ (4), $c = 9.437$ (3) Å, $\alpha = 102.20$ (4), $\beta = 106.58$ (4), $\gamma = 98.65$ (4)°, $Z = 4$, $D_c = 1.39$ g cm^{-3}, μ(Cu $K\alpha$) = 24.6 cm^{-1}. Scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The structure was solved by direct methods with the *MULTAN* system (Main, Woolfson, Lessinger, Germain & Declercq, 1974) and the following calculations were mainly carried out by the *SHELX* 76 system of programs (Sheldrick, 1976). All the H atoms were found from the difference Fourier map. However, only the H atoms implied in hydrogen bonds were actually refined; the others were attributed calculated positions (C—H bond distance of 1·08 Å). The structure was refined by the block-diagonal least-squares method using anisotropic temperature factors for all the non-hydrogen atoms. Final disagreement

Table 1. *Positional* ($\times 10^4$) *parameters with e.s.d.'s in parentheses*

	Molecule *A*			Molecule *B*		
	x	*y*	*z*	*x*	*y*	*z*
Cl	9209 (1)	737 (1)	9001 (2)	5017 (1)	8699 (1)	3599 (1)
C(1)	9013 (4)	1931 (3)	9624 (4)	5595 (3)	7761 (3)	4340 (4)
C(2)	10093 (3)	2720 (3)	10087 (4)	4841 (3)	7225 (3)	4996 (4)
C(3)	9929 (3)	3658 (3)	10579 (4)	5346 (3)	6533 (3)	5668 (4)
C(4)	8699 (3)	3832 (2)	10616 (4)	6576 (3)	6346 (2)	5659 (4)
N(1)	8646 (3)	4822 (2)	11178 (4)	7046 (3)	5659 (2)	6431 (4)
C(5)	7619 (3)	3034 (2)	10159 (4)	7324 (3)	6878 (2)	4967 (4)
C(6)	7788 (3)	2073 (2)	9649 (4)	6810 (3)	7597 (3)	4314 (4)
C(7)	7656 (3)	5271 (2)	10645 (4)	7747 (3)	4997 (2)	5984 (4)
O(1)	7684 (3)	6134 (2)	11185 (3)	8162 (2)	4447 (2)	6743 (3)
C(8)	6516 (3)	4577 (2)	9298 (4)	7953 (3)	5013 (2)	4459 (4)
O(2)	5686 (2)	5109 (2)	8526 (3)	8328 (3)	4155 (2)	3853 (3)
N(2)	5796 (3)	3887 (2)	9900 (3)	8971 (3)	5902 (2)	4766 (3)
C(9)	6300 (3)	3170 (2)	10248 (4)	8656 (3)	6745 (2)	4973 (4)
C(10)	5506 (3)	2414 (2)	10709 (4)	9675 (3)	7646 (2)	5216 (4)
C(11)	4126 (3)	2218 (3)	10106 (5)	10528 (4)	7610 (3)	4353 (5)
C(12)	3371 (4)	1485 (3)	10469 (6)	11486 (4)	8449 (3)	4581 (5)
C(13)	3969 (4)	947 (3)	11431 (6)	11613 (4)	9313 (3)	5656 (6)
C(14)	5322 (4)	1148 (3)	12041 (5)	10788 (5)	9339 (3)	6525 (6)
C(15)	6094 (4)	1880 (3)	11688 (5)	9825 (4)	8520 (3)	6307 (5)
H(1)	9334 (41)	5195 (28)	11954 (46)	6715 (40)	5553 (28)	7112 (46)
H(2)	5488 (46)	5513 (32)	9202 (53)	9290 (57)	4225 (37)	4597 (64)

factors were R $(=\sum|\Delta|/\sum|F_o|)$ = 0·051 and R_w $[=(\sum w|\Delta|^2/\sum w|F_o|^2)^{1/2}]$ = 0·057. Weights were given according to the formula $1/w = \sigma^2(F_o) + 0{\cdot}0027|F_o|^2$. The final coordinates of the atoms are reported in Table 1.*

Discussion

The crystal packing is shown in Fig. 1. The molecules are linked by a net of hydrogen bonds lying approximately in a plane at $\frac{1}{2}$ along *b*, the *y* coordinates of the atoms implied in the hydrogen bonds ranging from 0·39 to 0·61. This net forms infinite layers of molecules one cell high along *b*, packed by van der Waals forces through the basal planes. The hydrogen bonds are different in the two independent molecules of the asymmetric unit.

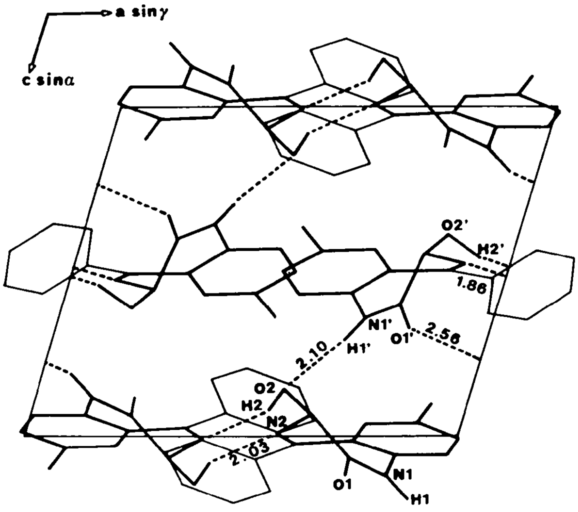


Fig. 1. The packing of the molecules in the crystal.

A view of the two independent molecules is shown in Fig. 2. Their bond distances and angles are reported in Tables 2 and 3. The two sets of parameters have been compared by means of half-normal probability (HNP) plots (Abrahams & Keve, 1971). The HNP plots are nearly linear and the parameters of the regression line, for bond distances and angles respectively, are: intercept = −0·17 and −0·18, slope = 1·23 and 1·40, and correlation coefficient = 0·98 and 0·98. It can be concluded that the two molecules are configurationally indistinguishable and that the e.s.d.'s are underestimated by a factor of 1·4. The only differences between the two molecules are observed in the conformation of the phenyl ring *C*, the torsion angles C(5)–C(9)–C(10)–C(15) being respectively 29·9 and 42·4° for molecules *A* and *B*.

Bond distances and angles are in good agreement with those determined in nitrazepam (Gilli, Bertolasi, Sacerdoti & Borea, 1977). The diazepine ring is in the boat conformation and the displacements of its atoms from the least-squares plane through the phenyl ring *A*

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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 33579 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

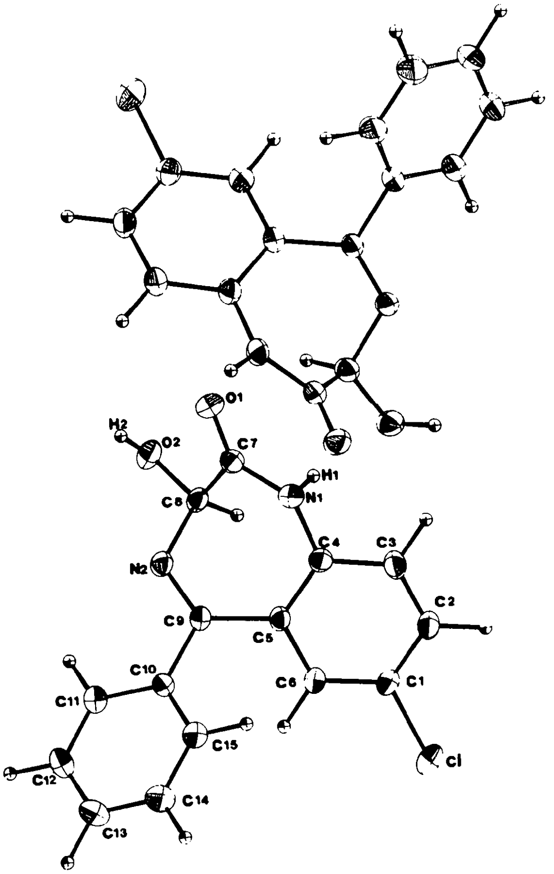

Fig. 2. A projection in the *ab* plane (*b* pointing upwards) of the two molecules of the asymmetric unit. Thermal ellipsoids of non-hydrogen atoms are drawn at 40% probability (Johnson, 1965).

Table 2. *Interatomic distances* (Å) *with standard deviations in parentheses*

	Molecule *A*	Molecule *B*
C(1)–Cl	1·733 (4)	1·741 (4)
C(1)–C(2)	1·385 (5)	1·387 (6)
C(1)–C(6)	1·380 (6)	1·379 (6)
C(2)–C(3)	1·366 (5)	1·375 (6)
C(3)–C(4)	1·402 (5)	1·402 (5)
C(4)–N(1)	1·404 (4)	1·403 (5)
C(4)–C(5)	1·393 (4)	1·407 (6)
N(1)–H(1)	0·88 (3)	0·85 (5)
N(1)–C(7)	1·358 (5)	1·365 (5)
C(5)–C(6)	1·401 (5)	1·401 (5)
C(5)–C(9)	1·496 (5)	1·484 (5)
C(7)–O(1)	1·211 (4)	1·216 (5)
C(7)–C(8)	1·523 (4)	1·522 (6)
C(8)–O(2)	1·403 (5)	1·398 (4)
C(8)–N(2)	1·465 (5)	1·460 (4)
O(2)–H(2)	0·86 (5)	1·06 (5)
C(9)–N(2)	1·279 (5)	1·280 (5)
C(9)–C(10)	1·487 (5)	1·486 (5)
C(10)–C(11)	1·401 (5)	1·396 (6)
C(10)–C(15)	1·390 (6)	1·386 (5)
C(11)–C(12)	1·386 (7)	1·388 (6)
C(12)–C(13)	1·389 (7)	1·373 (6)
C(13)–C(14)	1·375 (6)	1·375 (8)
C(14)–C(15)	1·389 (6)	1·374 (6)

Table 3. *Interatomic angles* (°) *with standard deviations in parentheses*

	Molecule *A*	Molecule *B*
C(2)–C(1)–Cl	119·0 (3)	119·0 (3)
C(6)–C(1)–Cl	119·3 (3)	119·2 (3)
C(6)–C(1)–C(2)	121·7 (3)	121·8 (4)
C(3)–C(2)–C(1)	118·6 (4)	118·5 (4)
C(4)–C(3)–C(2)	121·4 (3)	121·1 (4)
N(1)–C(4)–C(3)	116·7 (3)	117·5 (4)
C(5)–C(4)–C(3)	119·6 (3)	120·0 (3)
C(5)–C(4)–N(1)	123·6 (3)	122·3 (3)
H(1)–N(1)–C(4)	117 (3)	116 (3)
H(1)–N(1)–C(7)	116 (3)	116 (3)
C(7)–N(1)–C(4)	127·0 (3)	126·3 (4)
C(6)–C(5)–C(4)	118·9 (3)	118·2 (3)
C(9)–C(5)–C(4)	122·0 (3)	122·7 (3)
C(9)–C(5)–C(6)	119·1 (3)	119·0 (3)
C(5)–C(6)–C(1)	119·8 (3)	120·3 (4)
O(1)–C(7)–N(1)	123·3 (3)	122·6 (4)
C(8)–C(7)–N(1)	112·9 (3)	113·9 (3)
C(8)–C(7)–O(1)	123·8 (3)	123·5 (4)
O(2)–C(8)–C(7)	111·3 (3)	111·0 (3)
N(2)–C(8)–C(7)	107·7 (3)	106·4 (2)
N(2)–C(8)–O(2)	111·3 (3)	111·4 (3)
H(2)–O(2)–C(8)	108 (3)	105 (3)
C(9)–N(2)–C(8)	118·2 (3)	118·3 (3)
N(2)–C(9)–C(5)	123·6 (3)	123·9 (3)
C(10)–C(9)–C(5)	118·4 (3)	117·7 (3)
C(10)–C(9)–N(2)	118·0 (3)	118·4 (3)
C(11)–C(10)–C(9)	118·8 (3)	119·5 (3)
C(15)–C(10)–C(9)	121·8 (3)	121·7 (4)
C(15)–C(10)–C(11)	119·4 (4)	118·8 (3)
C(12)–C(11)–C(10)	119·6 (4)	119·7 (4)
C(13)–C(12)–C(11)	120·6 (4)	120·8 (5)
C(14)–C(13)–C(12)	119·8 (5)	119·3 (4)
C(15)–C(14)–C(13)	120·4 (4)	120·8 (4)
C(14)–C(15)–C(10)	120·3 (4)	120·6 (5)

Table 4. *Displacements* (Å) *from the least-squares plane through the* C(1)–C(6) *phenyl ring*

Molecule *A*				Molecule *B*			
C(1)	–0·001	Cl	0·002	C(1)	0·005	Cl	0·097
C(2)	0·001	N(1)	0·031	C(2)	–0·011	N(1)	0·081
C(3)	0·002	C(7)	–0·634	C(3)	0·007	C(7)	–0·556
C(4)	–0·004	O(1)	–0·561	C(4)	0·002	O(1)	–0·401
C(5)	0·004	N(2)	–0·577	C(5)	–0·007	N(2)	–0·602
C(6)	–0·002	C(8)	–1·483	C(6)	0·003	C(8)	–1·471
		O(2)	–2·412			O(2)	–2·367
		C(9)	0·067			C(9)	0·042
		C(10)	0·880			C(10)	0·879

$\chi^2 = 0{\cdot}43$ (five degrees of freedom) $\chi^2 = 2{\cdot}62$ (five degrees of freedom)

are shown in Table 4. These displacements are nearly equal in the two molecules and very near to the corresponding values found in nitrazepam. This supports the idea of a remarkable conformational stability of the seven-membered ring, caused by ring annelation and the presence of the C=N double bond. In this connection it may be remarked that the ring reversal barrier has been determined as 17·7 kcal mol^{-1} in diazepam by NMR spectroscopy (Linscheid & Lehn, 1967).

Table 5. 5-*Phenyl-2H*-1,4-*benzodiazepin-2-one derivatives of known molecular structure*

	Substituents	Anticonvulsant activity*	References
Oxazepam	7-Cl, 3-OH	0·05	Present work
Diazepam	7-Cl, 1-CH_3	−0·15	Camerman & Camerman (1972)
Lorazepam	7-Cl, 3-OH, 2′-Cl	0·70	Bandoli & Clemente (1976)
Nitrazepam	7-NO_2	0·15	Gilli, Bertolasi, Sacerdoti & Borea (1977)
Dechlorodiazepam	1-CH_3	−2·90	Sternbach, Sancilio & Blount (1974)
4′-Fluorodiazepam	7-Cl, 1-CH_3, 4′-F	−2·90	Sternbach, Sancilio & Blount (1974)

* Expressed as log (1/*ED*) for the anti-metrazole test.

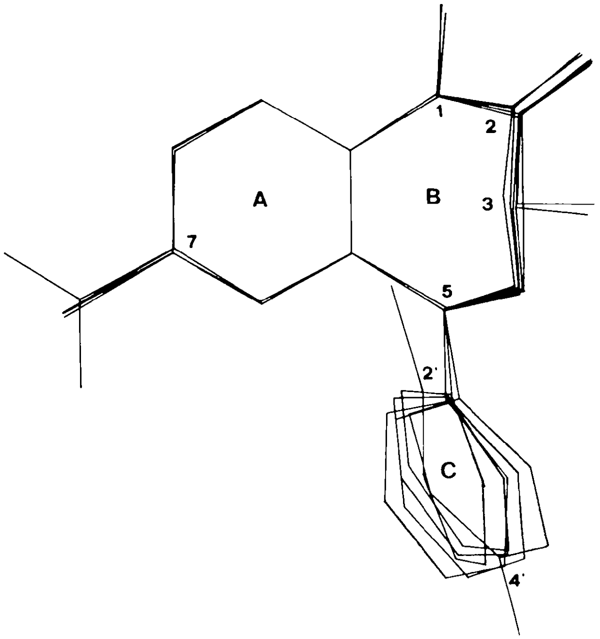

Fig. 3. Superposition of the structures of Table 5, projected on the plane of the phenyl ring *A*.

Table 5 lists the derivatives of 5-phenyl-2*H*-1,4-benzodiazepin-2-one of which the structures have been determined. A superposition of their structures, projected on the plane of the phenyl ring *A*, is shown in Fig. 3. Four of these compounds are highly active as anticonvulsant agents and two are practically inactive, as reported in Table 5. However, they do not differ in configuration (as can be proved by HNP plots on bond distances and angles) and Fig. 3 shows that they are very similar in conformation. Moreover these small conformational changes are not correlated in any way with their anticonvulsant activity.

In conclusion it can safely be said that no correlation between molecular geometry and activity can be established within this class of drugs. This matches the conclusion drawn by Sternbach, Sancilio & Blount (1974) on a smaller set of benzodiazepines. On the other hand our preliminary results in quantitative structure–activity relationships on 7-substituted benzodiazepines (Gilli, Borea, Bertolasi & Sacerdoti, 1977) show that the activities of these compounds can be explained in terms of linear free-energy-related parameters of the substituents (Purcell, Bass & Clayton, 1973). This supports the idea that the contribution to activity of the molecular frame is constant and indirectly confirms that the small geometrical changes observed are irrelevant to the biological response.

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