Acta Cryst. (1984). C**40**, 986–988

Structure of 2-[7-Chloro-2(3*H*)-oxo-5-phenyl-1*H*-1,4-benzodiazepin-1-yl]ethyl Hydrogen Succinate N^4-Oxide, $C_{21}H_{19}ClN_2O_6$

BY V. FERRETTI, V. BERTOLASI AND G. GILLI

Centro di Strutturistica Diffrattometrica, Università di Ferrara, Italy

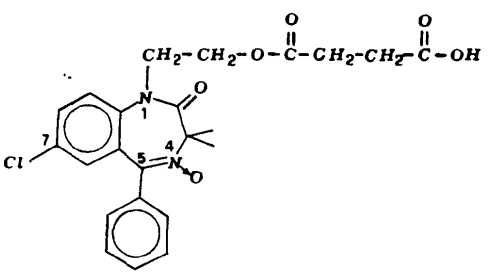
AND P. A. BOREA

Istituto di Farmacologia, Università di Ferrara, Italy

(*Received* 2 *August* 1983; *accepted* 21 *November* 1983)

Abstract. $M_r = 430{\cdot}84$, monoclinic, $P2_1/n$, $a = 17{\cdot}269$ (3), $b = 9{\cdot}823$ (3), $c = 11{\cdot}477$ (3) Å, $\beta = 98{\cdot}48$ (3)°, $U = 1925{\cdot}6$ (9) Å^3, $Z = 4$, $D_x = 1{\cdot}49$ Mg m^{-3}, $T = 298$ K, $\lambda = 1{\cdot}54178$ Å, $F(000) = 896$, μ(Cu $K\alpha$) = 2·019 mm^{-1}, $R = 0{\cdot}039$ for 2474 reflections with $I_o \geq 3\sigma(I_o)$. The compound displays very low binding affinity for the benzodiazepine receptor. Its structure is compared with those of other benzodiazepines having high affinity and it is found that small geometrical differences are unimportant in determining the biological activity of benzodiazepines when compared with the role played by the ring substituents.

Introduction. Benzodiazepines (BDZ's) are among the most widely used classes of drugs as a consequence of their spectrum of anxiolytic, sedative–hypnotic, anticonvulsant and muscle-relaxant properties. A few years ago high-affinity and stereospecific binding sites were discovered in the central nervous system (Squires & Braestrup, 1977) which are supposed to represent the substrate wherein BDZ's produce their biological action. Recently we have measured (Borea & Bonora, 1983) the receptor binding affinity of the title compound (I) and found that it is considerably lower than those of the other benzodiazepin-2-one derivatives, *e.g.* diazepam, nitrazepam or oxazepam. As the large majority of crystal structures of BDZ's are of highly active compounds we thought it worth while to undertake the crystal analysis of a BDZ displaying low *in vivo* and *in vitro* potency.

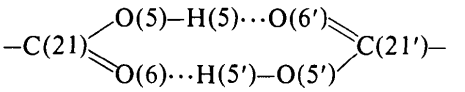


(I)

Experimental. Product recrystallized from ethanol. 3452 independent reflections collected on a Siemens AED diffractometer with Ni-filtered Cu $K\alpha$ radiation and $\omega/2\theta$ scans ($2° \leq \theta \leq 60°$; $-19 \leq h \leq 19$, $0 \leq k \leq 10$, $0 \leq l \leq 12$) from a crystal of dimensions 0·26 × 0·07 × 0·5 mm, 2474 reflections having $I_o \geq 3\sigma(I_o)$ used in the refinement. One reflection intensity monitored every 50 reflections showed no significant variation during data collection. Structure solved by direct methods and refined on F by blocked matrix least squares (two blocks) with anisotropic non-hydrogen and isotropic H atoms to $R = 0{\cdot}039$ and $R_w = \sum w^{1/2}|\Delta| / \sum w^{1/2}|F_o| = 0{\cdot}043$. All H atoms located from a difference map. $3{\cdot}13/w = 1/\sigma^2(|F_o|) + 0{\cdot}000378|F_o|^2$. $(\Delta/\sigma)_{max} = 0{\cdot}44$, $S = 1{\cdot}8$ in the last cycle. Final difference-map peaks in the range −0·12–0·12 e Å^{-3}. All calculations by *SHELX*76 (Sheldrick, 1976), scattering factors from *International Tables for X-ray Crystallography* (1974).

Discussion. Final positional and isotropic thermal (Hamilton, 1959) parameters are given in Table 1.* An *ORTEP* (Johnson, 1971) view of the molecule is shown in Fig. 1. Bond distances and angles are given in Tables 2 and 3.

The structure consists of dimers in which the two molecules are linked by a double hydrogen bond



through a centre of symmetry. The packing is mainly controlled by a network of short C—H···O contacts (see Table 4) which could be considered weak hydrogen bonds (Taylor & Kennard, 1982). The diazepine ring

* Lists of structure factors, anisotropic thermal parameters and selected torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39038 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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adopts an almost perfect boat conformation. The asymmetry parameter (Duax, Weeks & Rohrer, 1976) $\Delta C_s[C(8)] = \{[T_0^2 + \sum_{i=1}^{3}(T_i + T_i')^2]/4\}^{1/2}$ is close to zero [2·0 (6)°], indicating a quite small deviation from the ideal value. A different method for defining the ring conformation makes use of three mean planes: *A* through C(9),C(5),C(4),N(1) [$\sum(\Delta/\sigma)^2 = 34{\cdot}5$], *B* through C(9),N(2),C(7),N(1) [$\sum(\Delta/\sigma)^2 = 38{\cdot}8$] and *C* through C(7),C(8),N(2). The bow (*B*–*C*) and stern (*A*–*B*) angles assume values of 60·4 (2) and 41·7 (1)° respectively. Owing to the boat conformation of the seven-membered ring the molecule is chiral and both enantiomers are contained in the centrosymmetric

Table 1. *Positional* ($\times 10^4$, $\times 10^3$ *for* H) *and thermal* (Å^2 $\times 10^3$) *parameters with e.s.d.'s in parentheses*

	x	*y*	*z*	U_{eq}/U
Cl	9639·4 (3)	5249·4 (6)	12155·6 (5)	52·5 (3)
C(1)	9215 (1)	4240 (2)	10994 (2)	36 (1)
C(2)	8914 (1)	4843 (2)	9938 (2)	39 (1)
C(3)	8586 (1)	4033 (2)	9020 (2)	36 (1)
C(4)	8546 (1)	2626 (2)	9138 (2)	32 (1)
C(5)	8835 (1)	2020 (2)	10213 (2)	32 (1)
C(6)	9181 (1)	2844 (2)	11141 (2)	36 (1)
C(7)	8535 (1)	699 (2)	7779 (2)	36 (1)
C(8)	9264 (1)	252 (2)	8562 (2)	43 (1)
C(9)	8783 (1)	541 (2)	10430 (2)	36 (1)
C(10)	8486 (1)	63 (2)	11499 (2)	39 (1)
C(11)	7938 (1)	871 (2)	11955 (2)	48 (1)
C(12)	7670 (1)	540 (3)	12992 (2)	60 (2)
C(13)	7959 (2)	−601 (3)	13609 (3)	66 (2)
C(14)	8489 (1)	−1419 (3)	13165 (2)	59 (1)
C(15)	8748 (1)	−1114 (2)	12114 (2)	49 (1)
C(16)	7411 (1)	2223 (2)	7568 (2)	37 (1)
C(17)	6805 (1)	1971 (2)	8359 (2)	40 (1)
C(18)	6360 (1)	131 (2)	9412 (2)	36 (1)
C(19)	6331 (2)	−1392 (2)	9502 (2)	48 (1)
C(20)	5869 (2)	−1866 (2)	10456 (2)	50 (1)
C(21)	5483 (1)	−3221 (2)	10216 (2)	42 (1)
N(1)	8194 (1)	1843 (2)	8154 (1)	33 (1)
N(2)	9010 (1)	−300 (2)	9656 (2)	42 (1)
O(1)	8258 (1)	58 (1)	6915 (1)	48 (1)
O(2)	8992 (1)	−1612 (1)	9712 (2)	65 (1)
O(3)	6810 (1)	525 (1)	8619 (1)	40 (1)
O(4)	6013 (1)	913 (1)	9944 (1)	56 (1)
O(5)	5192 (1)	−3702 (2)	11130 (1)	55 (1)
O(6)	5424 (1)	−3804 (2)	9273 (1)	55 (1)
H(2)	894 (1)	582 (2)	990 (2)	43 (6)
H(3)	838 (1)	439 (2)	834 (2)	36 (5)
H(5)	493 (2)	−451 (4)	1092 (3)	102 (11)
H(6)	939 (1)	247 (2)	1190 (2)	54 (6)
H(81)	964 (1)	103 (2)	878 (2)	46 (6)
H(82)	951 (1)	−51 (2)	822 (2)	52 (6)
H(11)	772 (1)	167 (3)	1149 (2)	54 (6)
H(12)	729 (2)	115 (3)	1334 (2)	72 (8)
H(13)	778 (2)	−83 (3)	1429 (3)	75 (9)
H(14)	870 (1)	−222 (3)	1360 (2)	63 (7)
H(15)	912 (1)	−170 (2)	1176 (2)	56 (7)
H(161)	730 (1)	166 (2)	687 (2)	37 (5)
H(162)	740 (1)	316 (2)	738 (2)	38 (5)
H(171)	629 (1)	220 (2)	794 (2)	54 (7)
H(172)	691 (1)	246 (2)	910 (2)	45 (6)
H(191)	685 (2)	−169 (3)	957 (2)	59 (7)
H(192)	613 (2)	−175 (3)	878 (3)	75 (9)
H(201)	623 (2)	−192 (3)	1130 (3)	88 (9)
H(202)	544 (2)	−126 (3)	1051 (2)	71 (8)

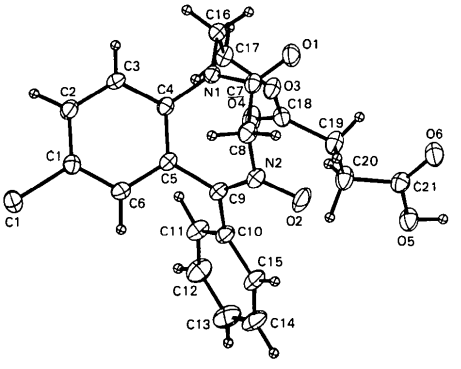

Fig. 1. An *ORTEP* (Johnson, 1971) view of the molecule showing the thermal ellipsoids at 40% probability.

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

Cl–C(1)	1·734 (2)	C(11)–C(12)	1·377 (4)
C(1)–C(2)	1·380 (3)	C(12)–C(13)	1·379 (4)
C(1)–C(6)	1·384 (3)	C(13)–C(14)	1·372 (4)
C(2)–C(3)	1·374 (3)	C(14)–C(15)	1·380 (4)
C(3)–C(4)	1·391 (3)	C(16)–C(17)	1·504 (3)
C(4)–C(5)	1·395 (2)	C(16)–N(1)	1·466 (2)
C(4)–N(1)	1·426 (2)	C(17)–O(3)	1·451 (2)
C(5)–C(6)	1·400 (3)	C(18)–C(19)	1·501 (3)
C(5)–C(9)	1·479 (3)	C(18)–O(3)	1·339 (3)
C(7)–C(8)	1·500 (3)	C(18)–O(4)	1·196 (3)
C(7)–N(1)	1·368 (2)	C(19)–C(20)	1·519 (4)
C(7)–O(1)	1·212 (2)	C(20)–C(21)	1·496 (3)
C(8)–N(2)	1·491 (3)	C(21)–O(5)	1·317 (3)
C(9)–C(10)	1·475 (3)	C(21)–O(6)	1·215 (3)
C(9)–N(2)	1·315 (3)	N(2)–O(2)	1·292 (2)
C(10)–C(11)	1·395 (3)	O(5)–H(5)	0·93 (4)
C(10)–C(15)	1·395 (3)	C–H	0·88 (2)–1·07 (3)

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

Cl–C(1)–C(2)	119·4 (1)	C(10)–C(11)–C(12)	121·5 (2)
Cl–C(1)–C(6)	119·6 (1)	C(11)–C(12)–C(13)	119·6 (3)
C(2)–C(1)–C(6)	121·0 (2)	C(12)–C(13)–C(14)	119·7 (3)
C(1)–C(2)–C(3)	119·0 (2)	C(13)–C(14)–C(15)	121·2 (2)
C(2)–C(3)–C(4)	121·4 (2)	C(10)–C(15)–C(14)	119·9 (2)
C(3)–C(4)–C(5)	119·6 (2)	C(17)–C(16)–N(1)	111·0 (2)
C(3)–C(4)–N(1)	118·7 (2)	C(16)–C(17)–O(3)	107·5 (2)
C(5)–C(4)–N(1)	121·7 (2)	C(19)–C(18)–O(3)	111·3 (2)
C(4)–C(5)–C(6)	118·9 (2)	C(19)–C(18)–O(4)	125·6 (2)
C(4)–C(5)–C(9)	123·1 (2)	O(3)–C(18)–O(4)	123·1 (2)
C(6)–C(5)–C(9)	118·0 (2)	C(18)–C(19)–C(20)	112·4 (2)
C(1)–C(6)–C(5)	120·1 (2)	C(19)–C(20)–C(21)	114·0 (2)
C(8)–C(7)–N(1)	114·5 (2)	C(20)–C(21)–O(5)	112·6 (2)
C(8)–C(7)–O(1)	122·2 (2)	C(20)–C(21)–O(6)	124·1 (2)
N(1)–C(7)–O(1)	123·2 (2)	O(5)–C(21)–O(6)	123·3 (2)
C(7)–C(8)–N(2)	106·7 (2)	C(4)–N(1)–C(7)	122·6 (2)
C(5)–C(9)–C(10)	119·3 (2)	C(4)–N(1)–C(16)	118·8 (2)
C(5)–C(9)–N(2)	118·2 (2)	C(7)–N(1)–C(16)	118·4 (2)
C(10)–C(9)–N(2)	122·5 (2)	C(8)–N(2)–C(9)	119·6 (2)
C(9)–C(10)–C(11)	118·0 (2)	C(8)–N(2)–O(2)	114·7 (2)
C(9)–C(10)–C(15)	123·9 (2)	C(9)–N(2)–O(2)	125·5 (2)
C(11)–C(10)–C(15)	118·0 (2)	C(17)–O(3)–C(18)	115·9 (2)

Table 4. *Intermolecular hydrogen bonds and* C–H···O *short contacts* (Å)

E.s.d.'s are in the range 0·002–0·004 and 0·02–0·04 Å for C/O–O and C/O–H respectively.

	$d_{O/C\cdots O}$	$d_{O/C-H}$	$d_{H\cdots O}$	Symmetry*	Vector
O(5)–H(5)···O(6)	2·684	0·93	1·77	−1	1,−1,2
O(6)···H(5)–O(5)				−1	1,−1,2
O(1)···H(162)–C(16)	3·106	0·95	2·38	2	1,−1,1
C(16)–H(162)···O(1)				2	1,0,1
O(3)···H(3)–C(3)	3·343	0·88	2·48	2	1,−1,1
C(3)–H(3)···O(3)				2	1,0,1
O(4)···H(14)–C(14)	3·430	0·97	2·48	2	1,0,2
C(14)–H(14)···O(4)				2	1,−1,2
O(4)···H(202)–C(20)	3·348	0·96	2·51	−1	1,0,2
C(20)–H(202)···O(4)				−1	1,0,2
O(5)···H(6)–C(6)	3·505	0·96	2·55	2	1,−1,2
C(6)–H(6)···O(5)				2	1,0,2

* The symmetry operations are (1) *x*,*y*,*z* and (2) $\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}+z$.

space group. This is quite common in BDZ's which prefer to crystallize either in centrosymmetric space groups or in non-centrosymmetric ones with an asymmetric unit containing both enantiomers. The conformation of the side chain is such that it bends over the diazepine ring. There is an intramolecular contact between N(1) and O(3) of 2·837 (2) Å which is considerably shorter than the sum of the van der Waals radii (3·07 Å: Bondi, 1964). This seems to indicate a specific attraction between the two atoms able to affect the chain conformation.

Bond distances and angles have been compared with those of other benzodiazepin-2-one derivatives, *i.e.* diazepam (DIA: Camerman & Camerman, 1972), nitrazepam (NIT: Gilli, Bertolasi, Sacerdoti & Borea, 1977) and oxazepam (OX: Gilli, Bertolasi, Sacerdoti & Borea, 1978). None of them has the N→O group. Moreover DIA differs in having $-CH_3$ in position 1, NIT in having $-NO_2$ in position 7 and H in position 1 and OX in having H and $-OH$ in positions 1 and 3 respectively (see I). It is found that bond distances and angles of the benzodiazepinone moiety are strictly comparable in the four compounds with two definite exceptions. The first concerns the effect of *N*-oxide formation. It causes a widening of 1·6 (2)° of the C(8)–N(2)–C(9) angle and a narrowing of 5·8 (2)° of the C(5)–C(9)–N(2) angle, together with a lengthening of 0·030 (3) and 0·031 (3) Å of the C(8)–N(2) and C(9)–N(2) bond lengths respectively. These differences are obtained by comparing values in the present structure with the weighted averages for DIA, NIT and OX, that is C(8)–N(2) = 1·461 (2), C(9)–N(2) = 1·284 (2) Å, C(8)–N(2)–C(9) = 118·0 (2) and C(5)–C(9)–N(2) = 124·0 (4)°. The reasons for this have already been discussed in the structure of chlordiazepoxide (Bertolasi, Sacerdoti, Gilli & Borea, 1982). The other difference concerns alkylation at N(1), which causes a narrowing of the C(4)–N(1)–C(7) angle by 3·7 (2)° and a lengthening of the C(4)–N(1) distance by 0·020 (2) Å, while the C(7)–N(1) distance is practically unchanged.* A simple interpretation of the effect can be given in terms of the Bent rule (Bent, 1960, 1961) which states that the electron-donating properties of the alkyl group concentrate the *s* character in the C(alkyl)–N bond and cause an increase of the *p* character of the two other N–C bonds; accordingly, these last two lengths slightly increase while the angle encompassed decreases. In the present case the lengthening of the N(1)–C(7) bond is not actually observed as its length is practically determined by the mesomery of the amide moiety.

* This results from the following weighted averages:

	C(4)–N(1)	C(7)–N(1)	C(4)–N(1)–C(7)
DIA & present work	1·424 (2) Å	1·366 (2) Å	122·8 (3)°
NIT & OX	1·404 (3)	1·362 (3)	126·5 (3).

The strict similarity in bond distances and angles between the present compound and the three other benzodiazepinones is paralleled by their conformational features. In DIA, NIT and OX the stern and bow angles of the diazepine ring and the absolute value of the C(5)–C(9)–C(10)–C(11) torsion angle are found to lie in the ranges 31·3–37·9, 58·4–65·7 and 25·5–42·4° respectively (Gilli, Borea, Bertolasi & Sacerdoti, 1982). These values compare well with those presently found, that is 41·7 (1), 60·4 (2) and 30·3 (3)°. Nevertheless the present compound binds to the BDZ's receptor 184 times less than OX and 500 times less than DIA or NIT, which is a clear indication that small geometrical differences are unimportant in determining the biological activity in BDZ's. Elsewhere (Borea & Gilli, 1983; Borea & Bonora, 1983) we have explained the dramatic fall of binding ability in the present compound both by the decrease in lipophilicity caused by the hydrophilic groups in the side chain and by the fact that the presence of the *N*-oxide group hinders one of the main points of BDZ-receptor interaction which would be located at the N(2) atom.

The authors thank Mr G. Bertocchi for skilful technical assistance. Research supported by 'Progetto Finalizzato-Chimica Fine e Secondaria', CNR (Rome).

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