Crystal, Molecular, and Electronic Structure of an Antianxiety Agent: 7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-1,4-benzodiazepin-2-one

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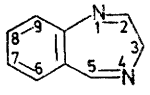
The crystal and molecular structure of the ethanol adduct of the title compound has been performed, from three-dimensional *X*-ray counter data by use of the symbolic addition procedure, and refined by least-squares methods to *R* 0.066 for 2 024 observed reflections. Crystals are monoclinic, space group $P2_1/n$, with cell dimensions: a = 13.446(15), b = 19.259(9), c = 13.789(8) Å, β = 116.80(7)°. The asymmetric unit consists of one ethanol and two benzodiazepine molecules, linked together by hydrogen bonds. The heterocyclic seven-membered ring adopts a boat configuration; the two phenyl rings are planar, the obtuse angles between them being 106.6 and 99.1°.

THE role of 1,4-benzodiazepine (I) derivatives has special significance for the understanding of the biochemical mechanisms underlying various phychoses. Thus, in view of the interesting pharmacological properties (muscle relaxant, sedative, and some indications of efficacy against epileptic seizures) of these compounds, a number of homologues were synthesized and characterized on the basis of chemical and spectroscopic data.[1]



(I)

Since its introduction into medicine (1971) one of these compounds has been an extremely effective and widely used antianxiety agent, bearing the generic name lorazepam (marketed in Italy under the trade name Tavor). The present work gives the molecular structure of lorazepam, in order to form a basis for further studies on the interrelation between molecular structure and pharmacological activity; in particular, it was desired to determine the bond system and electron population of the seven-membered ring.

EXPERIMENTAL

The title compound was obtained as described in the literature [1] and recrystallized from ethanol. The i.r. and ^{1}H n.m.r. spectra were consistent with the presence of EtOH molecule; moreover, the elemental analysis supports a formulation in which one ethanol for two benzodiazepine molecules is present. [Calc. for $(C_{15}H_{10}N_2O_2Cl_2)_2 \cdot C_2H_5OH$: C, 55.85; H, 3.8; N, 8.15. Found: C, 55.75; H, 3.9; N, 7.95%]. Very fine bright white needles were grown by keeping an ethanolic solution at 40 °C for several days and then leaving it at room temperature to evaporate. A crystal (0.27 × 0.19 × 0.14 mm) was mounted with the a axis parallel to the ϕ-axis of the goniometer and data were collected on a Siemens AED automated four-circle diffractometer by use of nickel-filtered Cu-K_α radiation and a Na(Tl)I scintillation counter. Accurate cell dimensions and crystal orientation parameters were obtained from ϕ, χ, and 2θ angles measured for 30 high-angle reflections. Cell dimensions were obtained from a least-squares calculation.

Crystal Data.—$(C_{15}H_{10}N_2O_2Cl_2)_2 \cdot C_2H_5OH$, M = 688.4. Monoclinic, a = 13.446(15), b = 19.259(9), c = 13.789(8) Å, β = 116.80(7)°, U = 3 187.2 Å^3, D_m = 1.44 (by flotation), Z = 4 (assuming two benzodiazepines + one EtOH molecule in the asymmetric unit), D_c = 1.43 g cm^{-3}, $F(000)$ = 1 416. Space group, $P2_1/n$ (a non-standard orientation of $P2_1/c$, No. 14) from systematic absences, with the general equivalent positions $\pm(x,y,z)$; $\pm(1/2 + x, 1/2 - y, 1/2 + z)$. Cu-$K_\alpha$ radiation, λ = 1.541 78 Å; μ(Cu-K_α) = 37.7 cm^{-1}.

The intensities of 2 564 independent non-zero reflections were taken, by use of the five-points technique,[2] to the limit θ 45°. 2 024 reflections were considered observed, having $I \geqslant 2\sigma(I)$, and used in the refinement. The relatively high % of unobserved reflections was due to a rapid fall-off of intensities at higher θ values, already apparent in the preliminary Weissenberg photographs. A standard reflection (04$\bar{2}$), remeasured every twenty reflections, was used to normalize the intensities to a common basis, correcting for any systematic change in the instrument or the crystal. The normalization factor was essentially constant with time, with an overall variation of 2.7% in intensity. Intensities were corrected for Lorentz and polarization factors, but not for absorption, owing to the relatively low μR value (maximum 1.0).

Solution and Refinement of the Structure.—The structure was determined by the symbolic-addition procedure for centrosymmetric crystals [3] using a multiple-solution program [4] adapted by us for the CDC 6600 computer. The scale of the $|F_o|$ data and the overall temperature factor were estimated from a Wilson plot. Scattering-factor curves employed in this and all other calculations were taken from ref. 5. The normalized structure factor amplitudes $|E_A|$ were calculated according to ref. 6. The signs of 309 reflections with $|E| \geqslant 1.5$ (corresponding to seven reflections per non-hydrogen atom) were deduced in terms of three signs for the origin-specifying reflections (33$\bar{2}$, 013, 49$\bar{6}$) and four symbolic signs (150, 753, 123, 23$\bar{1}$). For each of the sixteen solutions the consistency index, c, is evaluated and the E map corresponding to the largest value of c (0.77) revealed all the atomic positions, excluding those of the ethanol molecule (later this was ascribed to the high thermal motion of its constituent atoms). At this

[1] L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, 1962, **27**, 3788; S. C. Bell and S. J. Childress, *ibid.*, p. 1691; H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Chem. Ber.*, 1968, **101**, 4245; G. A. Archer and L. H. Sternbach, *Chem. Rev.*, 1968, 747 and references therein.

[2] W. Hoppe, *Acta Cryst.*, 1969, **A25**, 67.
[3] J. Karle and I. L. Karle, *Acta Cryst.*, 1966, **21**, 849.
[4] R. E. Long, Ph.D. Thesis, 1965, Part III, U.C.L.A.
[5] D. T. Cromer and J. T. Waber, *Acta Cryst.*, 1965, **18**, 104.
[6] J. Karle and H. Hauptmann, *Acta Cryst.*, 1956, **9**, 635.

stage, structure factors calculated for the trial model, assuming an overall isotropic temperature factor of 3.7 Å², gave R 0.26. Since the unit cell contained many atoms in the asymmetric unit and the number of parameters to be varied was quite large, a block-diagonal least-squares refinement procedure was then adopted. Three cycles of isotropic refinement (with unit weights) then reduced R value to 0.18. Anisotropic temperature factors of the form $\exp -(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + \ldots)$ were assigned to the four chlorine atoms, and two more cycles lowered R to 0.14. The positions of the atoms of the ethanol molecule were located in a difference-Fourier map. After this point, all atoms were assigned anisotropic thermal parameters, except those of the ethanol, since the ethyl group showed some tendency towards disorder, although evidence for this was now too weak. The anomalous dispersion corrections for chlorine [7] were included in the later stages of the refinement, as well as the full-matrix least-squares procedure (R 0.08). From a difference-Fourier synthesis only 17 hydrogen atom positions could be identified, being among the twenty strongest peaks (0.6—0.4 eÅ^{-3}). In the following cycles of refinement the contributions of the hydrogen atoms were included, but their parameters were kept constant at B 5.0 Å². The function minimized was $\Sigma w(k|F_o| - |F_c|)^2$, where k is the scale factor, while the weighting scheme used was the reciprocal of the best polynomial fitting of ΔF^2 as a function of $|F_o|$, *i.e.* $w^{-1} = a_i|F_o|^i$. The best fitting was not achieved *via* the usual least-squares method but, with better results, *via* orthogonal polynomials. The number and value of the a_i parameters were adjusted by a computer program (written by us: PESO) during refinement, so as to give approximately constant mean values of $w\Delta F^2$ for equally populated ranges of $|F_o|$. Four final cycles of refinement converged at R 0.066. During the final round of refinement, mean shifts in positional parameters were $< 1\sigma$, maximum of 0.50, and the mean σ of the atomic co-ordinates was 0.005 Å. A final difference-Fourier map was essentially featureless; the highest peaks were 0.40 eÅ^{-3}, but these could not be related unambiguously to the remaining nine hydrogen atom positions.

TABLE 1

Final fractional atomic co-ordinates, with standard deviations in parentheses. Values for non-hydrogen atoms are $\times 10^4$, and for hydrogen atoms $\times 10^3$ *

	Molecule (*A*)			Molecule (*B*)		
	x/a	*y/b*	*z/c*	*x/a*	*y/b*	*z/c*
Cl(1)	−5 024(2)	−1 331(1)	617(2)	3 100(2)	1 485(2)	6 745(2)
Cl(2)	−978(2)	−250(1)	3 259(2)	1 277(2)	95(1)	2 689(2)
N(1)	−1 292(5)	−1(3)	189(5)	107(5)	2 016(3)	2 124(4)
C(2)	−1 228(6)	668(4)	−77(6)	371(6)	2 341(4)	1 435(5)
C(3)	−2 194(6)	1 128(4)	−190(5)	1 571(6)	2 530(4)	1 805(5)
N(4)	−2 050(4)	1 239(3)	924(4)	2 194(4)	1 895(3)	1 940(4)
C(5)	−2 325(5)	738(3)	1 364(5)	2 352(5)	1 506(3)	2 742(5)
C(6)	−3 588(6)	−280(4)	956(5)	2 603(6)	1 500(4)	4 632(6)
C(7)	−3 920(6)	−935(4)	529(6)	2 201(7)	1 601(4)	5 384(6)
C(8)	−3 371(7)	−1 279(4)	21(6)	1 122(7)	1 789(4)	5 064(6)
C(9)	−2 506(7)	−954(4)	−93(6)	450(7)	1 919(4)	3 991(6)
C(10)	−2 186(6)	−290(4)	309(5)	840(6)	1 861(3)	3 212(5)
C(11)	−2 716(5)	52(3)	851(5)	1 912(5)	1 629(3)	3 529(5)
O(12)	−418(4)	894(3)	−175(4)	−329(4)	2 483(3)	496(4)
O(13)	−2 231(4)	1 752(3)	−691(4)	1 678(4)	2 960(3)	1 035(4)
C(14)	−2 282(5)	881(3)	2 435(5)	3 030(6)	865(4)	2 891(5)
C(15)	−1 749(6)	444(4)	3 323(6)	2 640(6)	208(4)	2 895(6)
C(16)	−1 757(7)	567(5)	4 330(7)	3 259(8)	−389(5)	3 029(8)
C(17)	−2 309(7)	1 147(5)	4 410(7)	4 339(8)	−317(5)	3 150(9)
C(18)	−2 840(8)	1 600(5)	3 553(8)	4 780(8)	336(5)	3 141(9)
C(19)	−2 823(7)	1 462(4)	2 558(6)	4 127(7)	923(5)	3 010(7)
H(1)	−67	−36	18	−73	186	190
H(3)	−291	88	−51	193	277	258
H(6)	−386	−10	148	319	130	481
H(8)	−374	−182	−51	100	192	580
H(9)	−209 †	−122	−49	−33	198	380
H(13)	−150	202	−39	233	285	120
H(16)	−138	12	500	305	−101	299
H(17)	−233	131	530	484 †	−77	325
H(18)	−326 †	205	364	561 †	39	323
H(19)	−302	188	198	445	149	307
Ethanol						
O(43)	335(7)	2 209(4)	−1 143(7)			
C(44)	−28(13)	1 770(9)	−2 098(13)			
C(45)	−268(13)	2 058(8)	−3 034(12)			
H(43)	−12	258	−145			

* Numbered according to the atoms to which they are bonded. † Hydrogen atoms placed at calculated positions.

Final atomic parameters and their standard deviations are given in Table 1. Vibration parameters and their standard deviations and observed and calculated structure amplitudes are given in Supplementary Publication No. SUP 21531 (6 pp., 1 microfiche).*

Solution and refinement of the structure were carried out

* See Notice to Authors No. 7, in *J.C.S. Perkin II* 1975, Index issue.

[7] D. T. Cromer, *Acta Cryst.*, 1965, **18**, 17.

by use of the programs of ref. 8(*a*); calculations were carried out on a CDC 6600 computer at the Consorzio Interuniversitario dell'Italia Nord-Orientale, Casalecchio, Bologna.

TABLE 2

Interatomic distances (Å), with standard deviations in parentheses *

	Molecule (*A*)	Molecule (*B*)
N(1)–C(2)	1.35(2)	1.31(2)
C(2)–O(12)	1.24(2)	1.24(1)
C(2)–C(3)	1.52(3)	1.50(2)
C(3)–O(13)	1.38(2)	1.40(2)
C(3)–N(4)	1.47(2)	1.45(3)
N(4)–C(5)	1.28(3)	1.27(2)
C(5)–C(11)	1.48(2)	1.47(2)
C(11)–C(6)	1.40(2)	1.40(2)
C(6)–C(7)	1.38(2)	1.38(2)
C(7)–Cl(1)	1.72(1)	1.73(1)
C(7)–C(8)	1.39(2)	1.36(3)
C(8)–C(9)	1.39(2)	1.37(2)
C(9)–C(10)	1.38(2)	1.40(2)
C(10)–N(1)	1.40(2)	1.41(2)
C(10)–C(11)	1.41(2)	1.38(3)
C(5)–C(14)	1.48(3)	1.49(2)
C(14)–C(15)	1.39(2)	1.37(2)
C(15)–Cl(2)	1.72(1)	1.74(1)
C(15)–C(16)	1.41(2)	1.38(3)
C(16)–C(17)	1.37(3)	1.39(2)
C(17)–C(18)	1.38(2)	1.39(2)
C(18)–C(19)	1.41(3)	1.39(3)
C(14)–C(19)	1.39(2)	1.41(3)
Mean C–H	1.06	1.04
Ethanol		
O(43)–C(44)	1.45(2)	
C(44)–C(45)	1.31(3)	
O(43)–H(43)	0.90	

* Taking into account the accuracy of cell parameters.

TABLE 3

Interatomic angles (°), with standard deviations in parentheses, for all non-hydrogen atoms

	Molecule (*A*)	Molecule (*B*)
C(2)–N(1)–C(10)	125.0(0.7)	125.8(0.6)
N(1)–C(2)–O(12)	122.1(0.7)	122.3(0.7)
C(3)–C(2)–O(12)	122.5(0.9)	119.7(0.9)
N(1)–C(2)–C(3)	115.2(0.8)	118.0(0.9)
C(2)–C(3)–O(13)	113.3(1.2)	110.3(0.9)
O(13)–C(3)–N(4)	110.8(0.6)	110.2(0.7)
C(2)–C(3)–N(4)	105.8(0.9)	108.1(0.8)
C(3)–N(4)–C(5)	117.0(0.8)	118.0(0.7)
N(4)–C(5)–C(11)	124.2(0.7)	125.6(0.6)
N(4)–C(5)–C(14)	116.4(0.6)	117.3(0.7)
C(14)–C(5)–C(11)	119.3(1.0)	117.2(0.8)
C(5)–C(11)–C(10)	121.1(0.7)	122.0(0.5)
C(5)–C(11)–C(6)	119.4(0.7)	118.9(0.6)
C 6)–C(11)–C(10)	119.4(0.6)	119.2(0.8)
C(11)–C(10)–N(1)	122.9(0.6)	122.5(0.8)
C(11)–C(10)–C(9)	120.3(0.8)	118.9(0.9)
N(1)–C(10)–C(9)	116.7(1.1)	118.6(0.9)
C(10)–C(9)–C(8)	119.7(0.9)	121.7(0.8)
C(9)–C(8)–C(7)	120.2(0.7)	119.2(0.9)
C(8)–C(7)–C(6)	120.4(0.8)	120.9(0.7)
C(8)–C(7)–Cl(1)	119.7(0.6)	120.5(0.8)
Cl(1)–C(7)–C(6)	119.9(0.9)	118.6(0.8)
C(7)–C(6)–C(11)	119.9(0.8)	119.9(0.7)
C(5)–C(14)–C(19)	119.0(0.6)	119.4(0.7)
C(5)–C(14)–C(15)	122.8(0.6)	123.5(0.7)
C(15)–C(14)–C(19)	118.1(0.9)	117.0(0.8)
C(14)–C(15)–Cl(2)	120.6(0.7)	119.5(0.6)
Cl(2)–C(15)–C(16)	116.9(0.6)	116.5(0.7)
C(14)–C(15)–C(16)	122.4(1.1)	124.0(0.9)
C(15)–C(16)–C(17)	117.3(0.8)	117.9(0.9)
C(16)–C(17)–C(18)	122.3(1.4)	120.9(0.9)
C(17)–C(18)–C(19)	119.1(1.4)	119.2(1.2)
C(18)–C(19)–C(14)	120.7(0.9)	121.0(0.9)
Ethanol		
O(43)–C(44)–C(45)	118.8(2.5)	

Theoretical Calculations.—We have carried out a CNDO/2 calculation, according to the method of ref. 9, adapted for the CDC 6600 computer. The orthogonal co-ordinates of all atoms were derived by applying to the fractional co-ordinates (Table 1) the *L* transformation matrix.[8b] The two ' missing ' H(9) and H(18) atoms were placed at their geometrically expected positions (Table 1).

TABLE 4

Interatomic angles (°) for all bonds involving hydrogen atoms

	Molecule (*A*)	Molecule (*B*)
H(1)–N(1)–C(2)	117	121
H(1)–N(1)–C(10)	117	113
H(3)–C(3)–O(13)	113	111
H(3)–C(3)–C(2)	112	112
H(3)–C(3)–N(4)	100	105
H(6)–C(6)–C(7)	118	119
H(6)–C(6)–C(11)	121	121
H(8)–C(8)–C(7)	122	110
H(8)–C(8)–C(9)	116	130
H(9)–C(9)–C(8)		123
H(9)–C(9)–C(10)		115
H(13)–O(13)–C(3)	115	96
H(16)–C(16)–C(15)	118	124
H(16)–C(16)–C(17)	123	118
H(17)–C(17)–C(16)	117	
H(17)–C(17)–C(18)	120	
H(19)–C(19)–C(14)	118	115
H(19)–C(19)–C(18)	119	124
Ethanol		
H(43)–O(43)–C(44)	99	

DISCUSSION

The asymmetric unit consists of one ethanol and two lorazepam molecules, which are almost identical. (There is only a small difference in the orientation of the benzene rings which is probably due to crystal packing forces.) Bond distances and angles are shown in Tables 2—4 [for comparison, all values are given for the two molecules of the asymmetric unit labelled (*A*) and (*B*)]. No corrections have been made for thermal motion. Standard deviations range from 0.01 Å for Cl–C bonds to 0.03 Å for C–C bonds. For the angles, the standard deviations are of the order of 0.6—1.2°.

The general shape of the lorazepam molecules (conformation and the magnitudes and the shapes of the atomic thermal ellipsoids) can be seen in Figure 1. The drug may be regarded as a non-planar, seven-atom heterocyclic hydroxy-ketone fused to a planar chlorophenyl ring and substituted with another planar chlorophenyl group. As expected from models and from known structures of seven-membered rings,[10] the benzodiazepine ring adopts a boat conformation with the C(3) atom as bow atom, in which there are three almost planar areas. The bow angles [between the plane through C(2)—(4) and the least-squares plane through N(1),C(2),N(4),C(5) (basis plane)] are 62° in molecule

[8] (*a*) J. M. Stewart, F. A. Kundell, and J. C. Baldwin, ' *X*-Ray ' System of Programs, University of Maryland, Technical Report TR6 46, version of June 1970. (*b*) ' Computing Methods and the Phase Problem in Crystallography,' Pergamon Press, Oxford, 1965.

[9] J. A. Pople and D. L. Beveridge, ' Approximate Molecular Orbital Theory, ' McGraw-Hill, New York, 1970.

[10] B. Jensen, *Acta Cryst.*, 1972, **B28**, 774, and references therein.

(*A*) and 58° in molecule (*B*); the stern angles [between the least-squares plane through N(1),C(5),C(11),C(10) and the basis plane] are both 33°. This situation parallels that of similar seven-membered 1,4-benzodiazepine rings.[11-20] The shortening of the C(10)–N(1) bond from the C–N single bond value (1.47 Å) [21] suggests that there is some electron delocalization between the chlorophenyl ring and the adjacent amide group, in accordance with the situation in diazepam,[11] but in contrast with another 1,4-benzodiazepine,[13] where the nitrogen corresponding to N(1) displays a configuration which is very close to tetrahedral. Moreover, it is well known that nitrogen atoms adjacent to *e.g.* C=O, C=S, and C=C, tend to be planar with foreshortened C–N bond lengths ranging from 1.40—1.34 Å, while those adjacent to the group CHR are pyramidal, with C–N 1.51 Å.[22] In the lorazepam molecules C(2)–N(1) bonds are 1.35 [molecule (*A*)] and 1.31 Å [molecule (*B*)] and the carbonyl distances C(2)=O(12), both 1.24 Å, are somewhat longer than those in ketones. Other bond lengths and angles are as expected for such a molecule. Thus, in agreement with the data reported in Table 7 of ref. 23 and Table 5 of ref. 24, the mean of the four C–Cl distances is 1.73 Å.

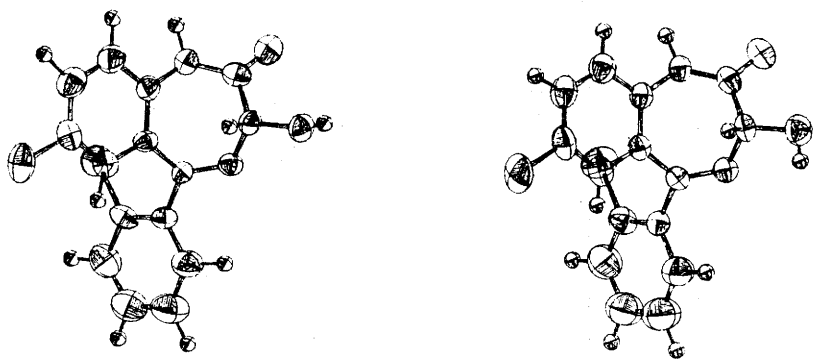


FIGURE 1 Molecular conformation of molecules (*A*) and (*B*) of lorazepam projected on the basis plane. Non-hydrogen atoms are represented by 50% probability thermal epillsoids. Hydrogen atoms are drawn artificially small for clarity.

TABLE 5

(*a*) Interplanar angles (°)*

(1): C(6)—(11)	(1)—(2)	73.4 (81.0)	(4)—(5)	72.2 (68.2)
(2): C(14)—(19)					
(3): C(5), C(11), C(10)	(1)—(3)	4.0 (2.5)	(5)—(6)	76.8 (71.9)
(4): N(1), C(2), C(3)					
(5): C(2), C(3), N(4)	(2)—(3)	77.1 (82.4)	(6)—(2)	53.6 (59.2)
(6): C(3), N(4), C(5)	(3)—(4)	42.4 (40.2)		

(*b*) Torsion angles (°)

C(11)–C(10)–N(1)–C(2)	42.8 (41.2)
C(10)–N(1)–C(2)–C(3)	3.2 (3.9)
N(1)–C(2)–C(3)–N(4)	72.2 (68.2)
C(2)–C(3)–N(4)–C(5)	76.8 (71.9)
C(3)–N(4)–C(5)–C(11)	3.3 (2.9)
C(5)–C(11)–C(10)–N(1)	2.2 (2.0)
C(11)–C(5)–C(14)–C(15)	51.9 (58.3)
C(11)–C(15)–C(14)–C(19)	53.8 (56.9)
N(4)–C(5)–C(14)–C(15)	49.5 (59.1)
N(4)–C(5)–C(14)–C(19)	51.5 (57.7)

* Values are given for molecule (*A*), those for molecule (*B*) in parentheses

A number of least-squares planes through parts of the molecules (*A*) and (*B*) have been calculated (Table 5), and show that the benzene rings are planar, but deviations as big as 0.13 Å, are found for atoms bonded directly to the phenyl groups. The deviations of the chlorine atoms from coplanarity with the benzene rings appear to be associated with the thermal factors; chlorine atoms have large thermal factors and large deviations.

The favourable hydrogen bonding pattern appears to be a major reason for the presence of two lorazepam molecules in the asymmetric unit in this case. The geometry of these hydrogen bonds is summarized in Table 6 and shown in Figure 2. Intermolecular hydrogen bonding occurs (i) between the NH group of molecule (*A*) and the ketone group of the same molecule at $\bar{x},\bar{y},\bar{z}$ and *vice versa*, to form a ring of eight atoms with a symmetry centre in the middle, (ii) between the hydroxy-group of molecule (*A*) and the ketone group of (*B*), and (iii) between the NH group of molecule (*B*) and

[11] A. Camerman and N. Camerman, *J. Amer. Chem. Soc.*, 1972, **94**, 268.
[12] R. F. Dunphy and H. Lynton, *Canad. J. Chem.*, 1971, **49**, 3401.
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the unsaturated nitrogen atom N(4) of (*A*). In addition, the ethanol molecule is hydrogen-bonded to the ketone group of molecule (*B*) only, and thus there is no extended network of hydrogen bonds.

range of energetically possible conformational modes of the drug molecule.[25] In fact, the premise that it is possible for the drugs to adopt conformations at the receptor sites in which the stereochemical similarities

TABLE 6

(*a*) Geometry of the hydrogen bonds [distances (Å), angles (°)]

	X–H	Y · · · H		X · · · Y	X–H · · · Y
O(13)–H(13)	1.02	O(12′) · · · H(13)	1.74	2.73	161.9
N(1)–H(1)	1.10	O(12^{II}) · · · H(1)	1.78	2.88	175.7
N(1′)–H(1′)	1.07	N(4) · · · H(1′)	2.06	3.01	150.0
O(43)–H(43)	0.90		O(43) · · · O(12′)	2.83	81.2

(*b*) Selected intra- and inter-molecular distances (Å) between non-hydrogen atoms which are <3.5 Å *

Molecule (*A*)		(*A*) · · · (*B*)		Molecule (*B*)	
O(12) · · · O(13)	2.76	O(12) · · · O(12′)	3.18	O(12′) · · · O(13′)	2.62
O(12) · · · O(43)	3.23	O(12) · · · C(2′)	3.42	O(13′) · · · O(43)	3.08
O(12) · · · C(44)	3.38	C(3) · · · O(12′)	3.44	O(12′) · · · C(6′^{III})	3.16
Cl(2) · · · C(11)	3.14	Cl(1) · · · Cl(1′^{I})	3.40		
		C(9) · · · N(4′^{II})	3.30		
		O(13) · · · C(11′^{III})	3.33		
		O(13) · · · C(3′^{III})	3.38		
		O(13) · · · C(6′^{III})	3.42		

X = Donor atom, Y = acceptor. Roman numerals as superscripts refer to atoms in the equivalent positions, relative to the reference molecule at x,y,z:

I $\bar{x},\bar{y},1-z$ II $\bar{x},\bar{y},\bar{z}$ III $-\frac{1}{2}+x,\frac{1}{2}-y,-\frac{1}{2}+z$

There are no other significant contacts between molecules (*A*) and (*B*), except for the ordinary van der Waals contacts (Table 7).

The CNDO/2 results on the molecule in the ground state shows that significant charge densities are localized

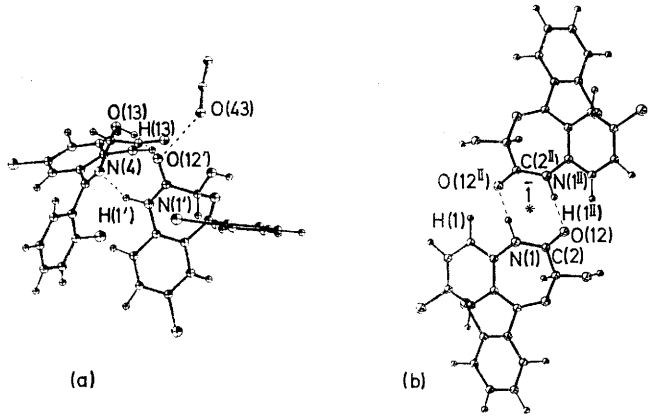

FIGURE 2 (a) View down the *b* axis showing the content of the asymmetric unit and three hydrogen bonds (b) The hydrogen bond between the NH group of molecule (*A*) and the CO group of molecule (*A*) at $\bar{x},\bar{y},\bar{z}$. Drawings were performed by use of the program ORTEP (Johnson, 1970)

at O(12) (−0.34) and O(13) (−0.26) atoms, whereas both nitrogen atoms show a charge of −0.19 and the charge at C(2) atom is markedly reduced (0.32) (Figure 3 and Table 7).

In the context of structure–activity relationships, unfortunately solution of the molecular structure in the crystal gives only one conformation and other physical and theoretical methods must be employed to study the

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present in the solid state are maintained is too simple. However, a preliminary study *via* space-filling models

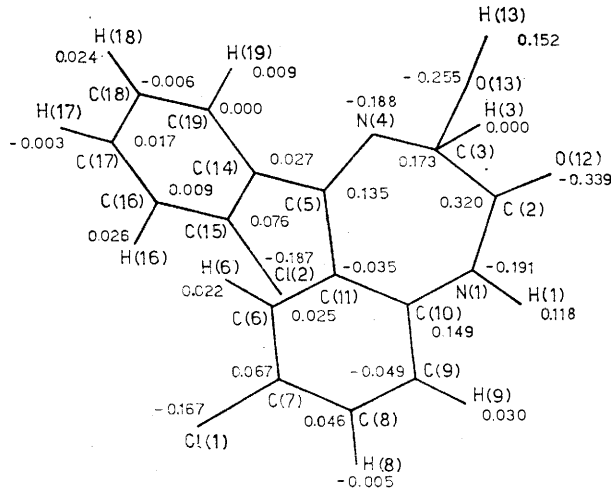

FIGURE 3 Charge densities of the atoms

TABLE 7

Some electronic configurations from the CNDO/2 calculation

		2*s*	2p_x	2p_y	2p_z
Seven-membered ring	N(1)	1.213	1.116	1.350	1.512
	C(2)	1.031	0.948	0.843	0.859
	C(3)	0.977	0.972	0.958	0.919
	N(4)	1.476	1.102	1.504	1.107
	C(5)	1.002	0.944	0.967	0.953
	C(11)	0.983	1.003	0.998	1.051
	C(10)	0.984	0.912	1.005	0.950
	O(12)	1.740	1.336	1.611	1.652
	O(13)	1.643	1.661	1.454	1.497
	Cl(1)	$3s^{1.907}$	$3p^{5.088}$	$3d^{0.172}$	
	Cl(2)	$3s^{1.906}$	$3p^{5.103}$	$3d^{0.178}$	

shows that on steric grounds the lorazepam molecule is sufficiently 'flexible,' and, for example, an alternate

conformation (chair) is possible for the seven-membered ring (large contacts). Indeed, results about the ' barriers to ring reversal in diazepam derivatives ' [26] indicate that the boat structure is the more stable.

Finally, in a recent paper on 1,4-benzodiazepines Sternbach *et al.*[27] have shown that ' conformational similarities of molecules do not necessarily indicate similar biological properties ' and so studies of drug potency should be discussed in the light of a drug-receptor complex, which is necessary in the process of mediating a membrane permeability change.

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