

Tableau 8. Distances (Å) du milieu M_4 du cycle ϕ_4 aux atomes d'hydrogène des chaînes éthoxycarboxyles et distances du milieu M_2 du cycle ϕ_2 aux hydrogènes H(21.1) et H(21.2)

Atomes	Distances	Atomes	Distances
M_4			
H(18.1)	3,79 (5)	H(21.1)	7,61 (4)
H(18.2)	5,09 (5)	H(21.2)	6,88 (4)
H(19.1)	4,98 (6)	H(22.1)	6,03 (6)
H(19.2)	5,92 (6)	H(22.2)	7,71 (6)
H(19.3)	5,97 (6)	H(22.3)	6,98 (6)
M_2			
H(21.1)	7,29 (4)	H(21.2)	7,34 (4)

Les résultats obtenus par radiocristallographie confortent la conformation proposée par données RMN protoniques principalement au niveau des substituants portés par les carbones 4 et 5. Les angles dièdres obtenus par l'étude des constantes de couplage sont fort voisins de ceux déterminés par la présente étude.

L'angle entre le plan du phényle en 4 et celui de la Δ -1-pyrroline est néanmoins plus faible [65 (1)°] que celui proposé à partir des données RMN (90°) mais il présente une valeur en accord avec l'anisotropie IR et la non équivalence magnétique des deux groupements éthoxycarboxyles.

Le cycle Δ -1-pyrroline présente une conformation sofa avec le carbone 4 pour sommet. Cette conformation est à rapprocher de celle de tétrahydrothiophène et du tétrahydrofuranne (Nahlovska, Nahlovsky & Seip, 1969; Touré, Lapasset, Xicluna & Bodot, 1981).

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Acta Cryst. (1982). **B38**, 1768–1772

Structure of 7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (Chlordiazepoxide)

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

Centro di Strutturistica Diffraattometrica, Università di Ferrara, Italy

AND P. A. BOREA

Istituto di Farmacologia, Università di Ferrara, Italy

(Received 23 November 1981; accepted 5 January 1982)

Abstract

$C_{16}H_{14}ClN_3O$ is triclinic, $P\bar{1}$, with $a = 15.786$ (4), $b = 13.155$ (3), $c = 15.496$ (4) Å, $\alpha = 104.56$ (3), $\beta = 102.43$ (3), $\gamma = 79.83$ (3)°, $M_r = 299.8$, $Z = 8$, $D_c = 1.32$ Mg m⁻³, $\mu(\text{Cu } K\alpha) = 2.15$ mm⁻¹. The structure has been solved by direct methods and refined by blocked-matrix least squares to an R value of 0.055 using 5829 observed diffractometer-collected reflections. The asymmetric unit consists of four mol-

ecules, all of the same conformational chirality, linked in pairs by hydrogen bonds. The diazepine ring adopts a boat conformation with different twist components in the four independent molecules. By comparing the present with previous structure determinations, the geometrical changes caused by protonation and N -oxide formation at the two N atoms of the diazepine ring are discussed.

Introduction

Since their discovery at the end of the nineteen fifties, 5-phenyl-1,4-benzodiazepines have been the subject of an ever-growing interest in consequence of their broad spectrum of biological activities. At present several of them are marketed worldwide as important anxiolytic, anticonvulsant and hypnotic agents (Randall, Schallek, Sternbach & Ning, 1974). The recent discovery of benzodiazepine receptors in the central nervous system (Squires & Braestrup, 1977) has rekindled interest in the mechanism of action of these drugs and in the geometrical features responsible for

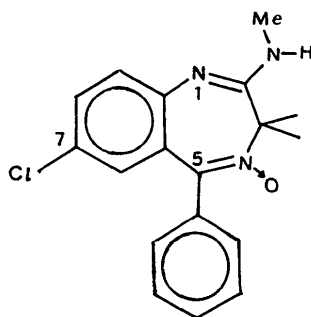
their stereospecific receptor binding. All benzodiazepines in clinical use may be reduced to three chemical classes: (I) 1,3-dihydro-2*H*-1,4-benzodiazepine-2-one, (II) 2,3-dihydro-1*H*-1,4-benzodiazepine and (III) 3*H*-1,4-benzodiazepine 4-oxide derivatives. While at least ten crystal structures of compounds belonging to class (I) have been determined so far (Galdecki & Glówka, 1980 and references therein; Sternbach, Sancilio & Blount, 1974; Frayer, Earley & Blount, 1977), only two molecular structures are known in class (II) (medazepam: Gilli, Bertolasi, Sacerdoti & Borea, 1978; medazepam hydrochloride: Chananont, Hamor & Martin, 1980) and just one in class (III) (chlor-

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

Thermal parameters are expressed as U_{eq} (Hamilton, 1959).

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq} (Å ²)		<i>x</i>	<i>y</i>	<i>z</i>	U_{eq} (Å ²)
Molecule A					Molecule B				
C(1)	1313 (3)	4795 (4)	6406 (4)	65 (3)	8500 (3)	-948 (4)	4317 (4)	60 (4)	
C(2)	1775 (4)	4560 (4)	7212 (4)	62 (3)	7829 (3)	-1561 (4)	3905 (4)	61 (3)	
C(3)	2645 (4)	4164 (4)	7278 (3)	55 (3)	6984 (3)	-1078 (4)	3843 (4)	59 (3)	
C(4)	3091 (3)	3993 (4)	6543 (3)	46 (3)	6766 (3)	17 (4)	4178 (3)	50 (3)	
C(5)	2599 (3)	4216 (4)	5719 (3)	46 (3)	7460 (3)	625 (3)	4614 (3)	47 (3)	
C(6)	1706 (3)	4620 (4)	5662 (3)	57 (3)	8332 (3)	127 (4)	4667 (3)	53 (3)	
C(7)	4516 (3)	3774 (4)	6300 (3)	50 (3)	5574 (3)	1333 (4)	4046 (3)	50 (3)	
C(8)	4289 (3)	4619 (4)	5765 (3)	52 (3)	6127 (3)	2091 (4)	3912 (3)	51 (3)	
C(9)	2949 (3)	3993 (4)	4881 (3)	47 (3)	7338 (3)	1749 (4)	5102 (3)	46 (3)	
C(10)	5620 (4)	2418 (5)	6815 (5)	91 (5)	4141 (4)	1061 (5)	4203 (5)	85 (4)	
C(11)	2394 (4)	3575 (4)	4003 (3)	54 (3)	7938 (3)	2107 (5)	5959 (3)	59 (3)	
C(12)	1917 (4)	2757 (5)	3938 (4)	72 (4)	8189 (4)	1453 (6)	6564 (4)	93 (5)	
C(13)	1364 (4)	2370 (6)	3121 (6)	98 (5)	8772 (6)	1756 (12)	7365 (5)	151 (9)	
C(14)	1279 (5)	2830 (8)	2402 (5)	113 (6)	9100 (7)	2692 (13)	7540 (8)	180 (11)	
C(15)	1750 (5)	3644 (8)	2463 (4)	102 (6)	8859 (6)	3337 (8)	6970 (8)	146 (8)	
C(16)	2306 (4)	4007 (5)	3253 (4)	71 (4)	8271 (4)	3054 (5)	6147 (5)	92 (5)	
N(1)	3953 (3)	3534 (3)	6689 (3)	52 (3)	5881 (2)	372 (3)	4129 (3)	52 (3)	
N(2)	3745 (3)	4162 (3)	4894 (3)	47 (2)	6705 (3)	2427 (3)	4787 (3)	50 (3)	
N(3)	5336 (3)	3282 (4)	6369 (3)	65 (3)	4727 (3)	1703 (3)	4060 (3)	56 (3)	
O	4125 (2)	3903 (3)	4189 (2)	56 (2)	6520 (2)	3412 (3)	5210 (2)	62 (2)	
Cl	228 (1)	5361 (2)	6354 (1)	117 (1)	9580 (1)	-1562 (1)	4401 (1)	90 (1)	
Molecule C					Molecule D				
C(1)	1716 (3)	-517 (4)	820 (3)	53 (3)	8383 (4)	3911 (4)	43 (4)	62 (4)	
C(2)	2421 (3)	-1199 (4)	1135 (4)	58 (3)	7818 (4)	4118 (4)	-723 (4)	67 (4)	
C(3)	3243 (3)	-894 (4)	1307 (4)	57 (3)	6948 (4)	4024 (4)	-816 (4)	61 (4)	
C(4)	3379 (3)	97 (4)	1200 (3)	47 (3)	6611 (3)	3728 (4)	-150 (3)	52 (3)	
C(5)	2643 (3)	774 (4)	881 (3)	44 (3)	7199 (3)	3583 (4)	657 (3)	49 (3)	
C(6)	1813 (3)	442 (4)	685 (3)	48 (3)	8095 (3)	3659 (4)	734 (3)	56 (3)	
C(7)	4448 (3)	1227 (4)	1683 (3)	55 (3)	5263 (3)	3691 (4)	200 (4)	55 (3)	
C(8)	3789 (3)	2135 (4)	2033 (3)	53 (3)	5529 (3)	4326 (4)	1155 (4)	60 (3)	
C(9)	2695 (3)	1791 (4)	666 (3)	44 (3)	6957 (3)	3284 (4)	1424 (3)	47 (3)	
C(10)	5915 (4)	653 (5)	1388 (5)	91 (5)	4225 (4)	2621 (5)	-861 (4)	81 (5)	
C(11)	2193 (3)	2054 (4)	-180 (3)	42 (3)	7610 (3)	2630 (4)	1966 (3)	48 (3)	
C(12)	2149 (3)	1245 (4)	-962 (3)	56 (3)	8110 (3)	1748 (4)	1533 (4)	59 (3)	
C(13)	1725 (4)	1448 (4)	-1794 (3)	63 (4)	8765 (4)	1151 (4)	2017 (4)	70 (4)	
C(14)	1323 (4)	2463 (5)	-1849 (4)	65 (4)	8925 (4)	1431 (5)	2956 (5)	77 (5)	
C(15)	1349 (4)	3262 (4)	-1083 (4)	63 (4)	8426 (4)	2305 (5)	3398 (4)	72 (4)	
C(16)	1785 (3)	3071 (4)	-248 (3)	53 (3)	7773 (3)	2895 (4)	2913 (3)	57 (3)	
N(1)	4244 (3)	273 (3)	1337 (3)	54 (3)	5762 (3)	3497 (3)	-401 (3)	56 (3)	
N(2)	3216 (3)	2449 (3)	1223 (3)	48 (3)	6187 (3)	3639 (3)	1650 (3)	50 (3)	
N(3)	5252 (3)	1454 (3)	1737 (3)	63 (3)	4487 (3)	3332 (4)	-7 (3)	66 (3)	
O	3303 (2)	3377 (3)	1108 (2)	56 (2)	5929 (2)	3387 (3)	2312 (2)	58 (2)	
Cl	679 (1)	-946 (1)	541 (1)	83 (1)	9498 (1)	3953 (1)	147 (1)	90 (2)	

diazepoxide hydrochloride: Herrnstadt, Mootz, Wunderlich & Möhrle, 1979). The present paper reports the crystal structure of chlordiazepoxide free base (CDZO) belonging to class (III) and corresponding to the following structural formula:



Experimental

A quantity of the product was kindly provided by the firm Prodotti Roche, Milan, and recrystallized from ethanol. 7568 reflection intensities were collected from a crystal of dimensions 0.10 × 0.12 × 0.21 mm on a Siemens AED diffractometer with Ni-filtered Cu $K\alpha$ radiation and an $\omega/2\theta$ scan ($\theta \leq 55^\circ$). Only 5829 reflections having $I_o \geq 3\sigma(I_o)$ were used in the refinement.

The structure was solved by direct methods (Sheldrick, 1976) and refined by blocked-matrix least squares (four blocks) with anisotropic temperature factors for the non-H atoms and unit weights (XRAY 72, Stewart, Kruger, Ammon, Dickinson & Hall, 1972). The H atoms were given calculated positions and thermal parameters 10% greater than those of the bonded atoms. The final disagreement factor was 0.055. Scattering factors were taken from *International Tables for X-ray Crystallography* (1974).

Final positional and isotropic thermal parameters (Hamilton, 1959) for the four independent molecules are reported in Table 1.*

Discussion

The crystal structure consists of a van der Waals packing of two similar but crystallographically non-equivalent dimers built up by the pairs *A, B* and *C, D* of independent molecules in the asymmetric unit. Each pair of molecules is linked by two hydrogen bonds $O \cdots H(N3')-N(3')$ and $O' \cdots H(N3)-N(3)$, which define a 12-membered ring, the relevant distances

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36642 (35 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

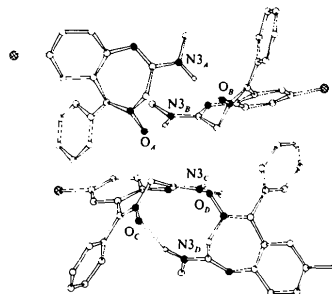


Fig. 1. The four molecules of the asymmetric unit projected on the plane *ac*. The H atoms not involved in intermolecular hydrogen bonding have been omitted.

being $O(A) \cdots N(3B) = 2.853(5)$, $O(B) \cdots N(3A) = 2.910(7)$, $O(C) \cdots N(3D) = 2.788(7)$ and $O(D) \cdots N(3C) = 2.795(6)$ Å (Fig. 1).

Owing to the boat conformation of the diazepine ring the molecule displays conformational chirality, the two enantiomers interchanging by ring reversal. The associated energy barrier can be expected to be relatively high as a seven-membered ring having three double bonds is easily shown to be rigid; that is it cannot change its conformation without deforming the bond angles. Such a barrier has been estimated by dynamic NMR techniques to be 63.8 kJ mol⁻¹ for chlordiazepoxide (Bley, Nuhn & Benndorf, 1968; Sadee, 1969). In the present case all the four molecules *A-D* are found to belong to the same absolute configuration,

Table 2. Mean values of the interatomic distances (Å) and angles (°), with *e.s.d.*'s in parentheses, of the four independent molecules of the asymmetric unit

C(1)-Cl	1.745 (5)	C(8)-N(2)	1.478 (2)
C(1)-C(2)	1.383 (2)	C(9)-C(11)	1.477 (4)
C(1)-C(6)	1.377 (3)	C(9)-N(2)	1.314 (2)
C(2)-C(3)	1.372 (2)	C(10)-N(3)	1.438 (2)
C(3)-C(4)	1.414 (2)	C(11)-C(12)	1.390 (3)
C(4)-C(5)	1.417 (2)	C(11)-C(16)	1.392 (5)
C(4)-N(1)	1.384 (2)	C(12)-C(13)	1.392 (5)
C(5)-C(6)	1.409 (2)	C(13)-C(14)	1.383 (5)
C(5)-C(9)	1.476 (5)	C(14)-C(15)	1.376 (8)
C(7)-C(8)	1.510 (3)	C(15)-C(16)	1.387 (7)
C(7)-N(1)	1.299 (2)	N(2)-O	1.310 (3)
C(7)-N(3)	1.339 (2)		
Cl-C(1)-C(2)	118.6 (4)	C(5)-C(9)-C(11)	119.6 (2)
Cl-C(1)-C(6)	119.5 (4)	C(5)-C(9)-N(2)	120.6 (3)
C(2)-C(1)-C(6)	121.8 (3)	C(11)-C(9)-N(2)	119.8 (1)
C(1)-C(2)-C(3)	118.8 (3)	C(9)-C(11)-C(12)	118.8 (5)
C(2)-C(3)-C(4)	122.2 (2)	C(9)-C(11)-C(16)	122.3 (5)
C(3)-C(4)-C(5)	117.8 (1)	C(12)-C(11)-C(16)	118.7 (3)
C(3)-C(4)-N(1)	115.8 (1)	C(11)-C(12)-C(13)	120.8 (3)
C(5)-C(4)-N(1)	126.1 (2)	C(12)-C(13)-C(14)	119.5 (1)
C(4)-C(5)-C(6)	119.5 (1)	C(13)-C(14)-C(15)	120.1 (3)
C(4)-C(5)-C(9)	124.2 (2)	C(14)-C(15)-C(16)	120.6 (1)
C(6)-C(5)-C(9)	116.2 (2)	C(11)-C(16)-C(15)	120.1 (4)
C(1)-C(6)-C(5)	119.9 (1)	C(4)-N(1)-C(7)	120.0 (3)
C(8)-C(7)-N(1)	122.4 (3)	C(8)-N(2)-C(9)	120.5 (5)
C(8)-C(7)-N(3)	116.7 (3)	C(8)-N(2)-O	115.2 (3)
N(1)-C(7)-N(3)	120.9 (2)	C(9)-N(2)-O	124.3 (4)
C(7)-C(8)-N(2)	106.8 (3)	C(7)-N(3)-C(10)	121.3 (3)

Mean values (X_m) and their standard errors (σ_m) have been calculated from the individual values (x_i ; σ_i) according to the formulae: $X_m = \sum (x_i/\sigma_i^2) / \sum (1/\sigma_i^2)$; $\sigma_m = \{ \sum [(x_i - X_m)^2/\sigma_i^2] / (N-1) \sum (1/\sigma_i^2) \}^{1/2}$.

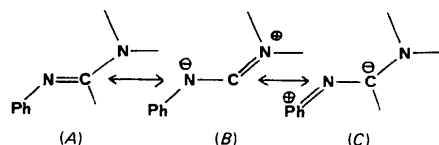
the corresponding enantiomers being those related by the crystallographic centre of inversion. One reason for such a complex packing pattern could be the lower energy associated with the hydrogen-bonded dimer formed between molecules of the same chirality, when compared with that of the dimer having both chiralities. This is in agreement with the fact that dimers of chiral molecules are in fact diastereoisomers, which can differ as far as their total energy is concerned. Mean bond distances and angles are reported in Table 2.

An ORTEP view (Johnson, 1971) of molecule *A* is shown in Fig. 2. The four molecules do not differ significantly as far as bond distances and angles are concerned. The comparison of the mean geometry of the present molecule with those of chlordiazepoxide hydrochloride (CDZO.HCl: Herrnstadt *et al.*, 1979), medazepam (MDZ: Gilli *et al.*, 1978), nitrazepam (NTZ: Gilli, Bertolasi, Sacerdoti & Borea, 1977) and 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepin-3-ol (CDZ: Chananont *et al.*, 1980) allows one to study the geometrical changes caused by two different donor-acceptor interactions, that is $\text{>N:} + \text{H}^+$ and $\text{>N:} + \ddot{\text{O}}:$ at N(1) and N(2), respectively, which both take place *via* dative-bond formation and without rehybridization of the donor. In the latter the *N*-oxide formation is associated with a small lengthening of 0.034 Å of the C(9)–N(2) bond and a widening of 2.70° of the C(9)–N(2)–C(8) angle, while the N(2)–C(8) distances are not significantly different.* The change in bond length is consistent with the decreased C–N bond order caused by the resonance

$\text{>C=N}^{\ominus}\text{--O}^{\ominus} \leftrightarrow \text{>C}^{\ominus}\text{--N}^{\oplus}=\text{O}$ and that in bond angle with a decreased VSEPR (Gillespie, 1970) of the nitrogen lone pair consequent to the formation of the N → O bond. As regards protonation at N(1), bond distances and the planarity of the C(4), N(1), C(7), N(3), C(10) moiety in the free base are indicative of

* Differences obtained by comparing the weighted averages over (CDZ, MDZ, NTZ) and (CDZO, CDZO.HCl) for >N and >N--O , respectively. E.s.d.'s are 0.002 Å and 0.4°.

resonance between the main canonical forms *A*, *B* and *C*, with decreasing contributions.



Protonation causes a lengthening of the C(4)–N(1) and N(1)–C(7) bonds of 0.036 and 0.023 Å respectively, a shortening of the C(7)–N(3) bond of 0.034 Å and a widening of the C(4)–N(1)–C(7) angle of 2.0.* The observed geometry changes are in agreement with an effect of stabilization of form *B* through partial removal of the negative charge and a decrease of VSEPR of the lone pair at N(1), both caused by protonation. Moreover, the suggested resonance in the non-protonated form would account for the otherwise inexplicable fact that protonation occurs at the imino instead of the amino N.

As regards a comparison of the conformations adopted by the four independent molecules of the asymmetric unit, the relevant torsion angles are given in Table 3. The rotation angle of the C(11)–C(16) phenyl

* Differences obtained by comparing the weighted averages over (CDZ, CDZO) and actual values of CDZO.HCl for >N and $\text{>N}^{\oplus}\text{--H}$, respectively. E.s.d.'s are 0.004 Å and 0.4°.

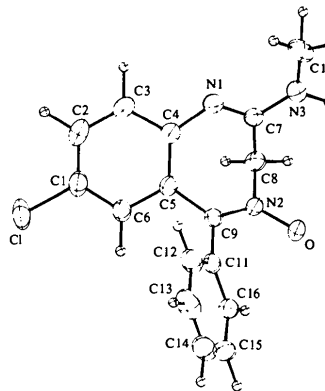


Fig. 2. An ORTEP (Johnson, 1971) view of molecule *A* showing the thermal ellipsoids at 40% probability.

Table 3. Selected torsion angles (°) with e.s.d.'s in parentheses

	Molecule <i>A</i>	Molecule <i>B</i>	Molecule <i>C</i>	Molecule <i>D</i>
C(2)–C(3)–C(4)–N(1)	–176.4 (4)	–175.0 (4)	–175.8 (4)	–169.7 (5)
C(1)–C(6)–C(5)–C(9)	176.3 (5)	172.9 (5)	176.5 (4)	178.7 (5)
C(5)–C(4)–N(1)–C(7)	T_1 38.1 (7)	36.1 (7)	39.7 (7)	39.3 (7)
C(4)–C(5)–C(9)–N(2)	T'_1 –40.1 (7)	–39.6 (7)	–44.3 (7)	–35.6 (7)
C(4)–N(1)–C(7)–C(8)	T_2 6.2 (7)	5.6 (7)	6.6 (7)	9.8 (7)
C(5)–C(9)–N(2)–C(8)	T'_2 –2.1 (7)	–3.1 (7)	3.9 (7)	1.0 (7)
N(1)–C(7)–C(8)–N(2)	T_3 –74.9 (5)	–72.9 (6)	–76.0 (6)	–75.5 (6)
C(9)–N(2)–C(8)–C(7)	T'_3 70.3 (5)	69.0 (5)	66.5 (5)	64.7 (6)
C(3)–C(4)–C(5)–C(6)	1.8 (7)	2.2 (7)	0.0 (7)	–4.7 (7)
N(1)–C(4)–C(5)–C(9)	T_0 –0.7 (8)	0.9 (8)	–1.4 (7)	–8.3 (8)
C(5)–C(9)–C(11)–C(12)	–45.4 (7)	–40.3 (7)	–40.4 (6)	–45.1 (7)

Table 4. Least-squares planes, their χ^2 values and interplanar angles

χ^2 values Plane		Molecules			
		A	B	C	D
P1	C(1)–C(6)	12.0	11.8	13.8	59.3
P2	C(4), C(5), N(1), C(9)	0.5	1.2	3.7	86.0
P3	N(1), C(9), C(7), N(2)	13.2	7.8	125.6	230.4
P4	C(7), C(8), N(2)	–	–	–	–
P5	C(11)–C(16)	5.9	1.6	4.9	2.8
Interplanar angles (°)					
P1–P2		4.6 (3)	6.7 (2)	5.1 (3)	7.4 (2)
P2–P3		34.3 (2)	33.1 (3)	36.9 (3)	32.8 (2)
P3–P4		57.8 (2)	56.3 (4)	56.7 (4)	55.4 (3)

ring around the C(9)–C(11) bond is similar in all molecules, ranging from 40.3 to 45.4°.

The diazepine ring adopts an approximate boat conformation, but with different twist components, in the four independent molecules. This can be defined through an asymmetry parameter (Duax, Weeks & Rohrer, 1976): in a perfect boat conformation the ring should have C_s symmetry and the asymmetry parameter $\Delta C_s = \{[T_0^2 + \sum_{i=1}^3 (T_i + T_i')^2]/4\}^{1/2}$, where T_i are the torsional angles shown in Table 3, should be zero. The actual values of the calculated ΔC_s are 3.2 (4), 2.9 (5), 7.5 (5) and 8.9 (6)° for molecules A, B, C and D respectively, indicating that the last two molecules are appreciably twisted. The twisting occurs in different ways in molecules C and D, as can be seen from the least-squares planes through the diazepine atoms (Table 4). In molecule C atoms C(4), C(5), N(1), C(9) lie on the plane P2 within experimental errors, while atoms N(1), C(7), C(9), N(2) are not coplanar; in molecule D neither group of atoms defines a plane. Conversely all atoms of molecules A and B can be considered to lie, without significant error, on the four intersecting planes P1–P4; the diazepine ring adopts an almost perfect boat conformation with bow angles (angles P3–P4) of 55–58° and stern angles (angles P2–P3) of 33–37°. These results can be interpreted by postulating that the potential-energy surface is rather flat near the minimum, allowing several conformations which can occur without significant strain of the bond angles.

The authors thank Mr G. Bertocchi for technical assistance. Work was carried out with the financial support of Progetto Finalizzato CNR Chimica Fine e Secondaria, Rome.

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