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Crystal Structures of Four Solvates of Lorazepam*: with Ethanol (A), Acetone (B), Dioxane (C), and Cyclohexanone (D)

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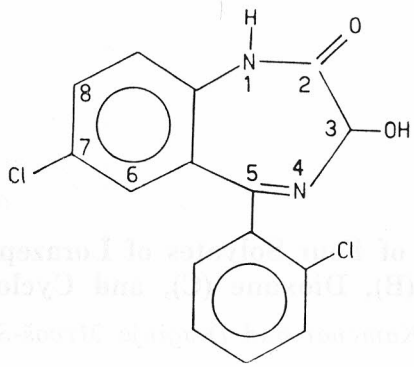
X-ray structure analysis of four solvates of lorazepam with ethanol (A), acetone (B), dioxane (C) and cyclohexanone (D) is described. All four crystallize in the triclinic system, space group $P\bar{1}$, and with the lorazepam molecules of essentially the same conformation. As common in other benzodiazepines, the seven-membered rings adopt a boat conformation. The four solvates have different kinds of hydrogen bonding. While in (A), (B) and (D) lorazepam molecules are interconnected either by N—H ... O (282 to 292 pm) or O—H ... O hydrogen bonds (289 pm) in (C) such bonding does not exist. The solvent molecules fill cavities in the crystal structures and are linked to the lorazepam molecules either by van der Waals interactions as in (A), (B) and (C) or by hydrogen bond of the O—H ... O type of 281 pm in (D). The investigated structures are compared with other lorazepam derivatives and solvates previously described in the literature.

INTRODUCTION

1,4-benzodiazepine derivatives are of special interest due to their pharmacological activity as tranquillizers, muscle relaxants, anticonvulsants and as hypnotic drugs. They show high affinity for stereospecific binding sites in the central nervous system. Although the solid state conformation of the drug molecules may differ in biological systems, structural data obtained by the X-ray diffraction methods are still the primary and most important source of structural information for pharmacologically active molecules. This is the reason why many benzodiazepine derivatives have been structurally studied and on the basis of the results their structure-activity relationship discussed.[1–10] Polymorphism and solvation of the drug molecules is another important problem in these studies. As part of our investigations of pharmacologically interesting compounds, we report here the structure of four

* 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one. Introduced into medicine in 1971. Marked in Yugoslavia either under its generic name Lorazepam or under the trade names Tavor and Lorsilan.



different solvates of lorazepam: with ethanol (A), acetone (B), dioxane (C) and cyclohexanone (D).[11,12] The first structure with ethanol was published twelve years ago but it was its monoclinic polymorph.[1] Now we decribe here its triclinic form.

EXPERIMENTAL

We were given the compounds by Dr. M. Oklobdžija from the Laboratory of Chemical Pharmacology »Podravka Institute«, Zagreb. Recrystallization from different solvents resulted in (A) lorazepam-ethanol 2 : 1 solvate, (B) lorazepam--acetone 1 : 1 solvate, (C) lorazepam-dioxane 1 : 1 solvate and (D) lorazepam-cyclohexanone 1 : 1 solvate.

Crystal Data

From rotation and Weissenberg photographs and from single crystal diffractometry:

(A) $C_{15}H_{10}O_2N_2Cl_2 \cdot 1/2C_2H_5OH$**, $M = 344.20$, triclinic, $a = 1.0624(4)$, $b = 1.6420(4)$, $c = 1.0192(2)$ nm, $\alpha = 90.52(3)$, $\beta = 113.93(2)$, $\gamma = 90.76(6)^\circ$, $V = 1.6247$ nm^3, $Z = 2$ (two benzodiazepines and one ethanol molecule in the asymmetric unit), $D_m = 1.38$ Mg · m^3 (by flotation), $D_c = 1.400$ Mg · m^3, space group $P\bar{1}$ (No. 2), $\mu(MoK_\alpha) = 3.8$ cm^{-1}, $\lambda = 71.07$ pm.

(B) $C_{15}H_{10}O_2N_2Cl_2 \cdot CH_3COCH_3$, $M = 379.24$, triclinic, $a = 1.2614(4)$, $b = 0.8632(4)$, $c = 0.8618(3)$ nm, $\alpha = 77.29(3)$, $\beta = 74.65(3)$, $\gamma = 78.85(2)^\circ$, $V = 0.8736$ nm^3, $Z = 2$, $D_m = 1.46$ Mg · m^3 (by flotation), $D_c = 1.44$ Mg · m^3, space group $P\bar{1}$ (No. 2), $\mu(MoK_\alpha) = 3.39$ cm^{-1}, $\lambda = 71.07$ pm.

(C) $C_{15}H_{10}O_2N_2Cl_2 \cdot C_4H_8O_2$, $M = 409.30$, triclinic, $a = 1.0177(4)$, $b = 1.2891(21)$, $c = 0.8827(4)$ nm, $\alpha = 71.13(6)$, $\beta = 66.81(3)$, $\gamma = 80.96(2)^\circ$, $V = 1.0067$ nm^3, $Z = 2$, $D_m = 1.31$ Mg · m^3 (by flotation), $D_c = 1.22$ Mg · m^3 (crystals lose solvent), space group $P\bar{1}$ (No. 2), $\mu(Mok_\alpha) = 2.93$ cm^{-1}, $\lambda = 71.07$ pm.

(D) $C_{15}H_{10}O_2N_2Cl_2 \cdot C_6H_{10}O$, $M = 419.31$, triclinic, $a = 1.2887(3)$, $b = 1.0537(8)$, $c = 0.8396(3)$ nm, $\alpha = 66.04(9)$, $\beta = 72.31(5)$, $\gamma = 83.45(2)^\circ$, $V = 1.0516$ nm^3, $Z = 2$, $D_m = 1.34$ Mg · m^3 (by flotation), $D_c = 1.38$ Mg · m^3, space group $P\bar{1}$ (No. 2), $\mu(MoK_\alpha) = 2.93$ cm^{-1}, $\lambda = 71.07$ pm.

*Intensity Data, Structure Determinations and Refinement****

For each crystal, the intensity of every independent reflection within the range $2^\circ \leq \Theta \leq 30^\circ$ was measured on a fully automated Philips PW1100

** G. Bandoli and D. A. Clemente published the monoclinic form of the same solvate with $a = 1.3446(25)$, $b = 1.9259(9)$, $c = 1.3789(8)$ nm, $\beta = 116.80^\circ$, space group $P2_1/n$.[1] We were not able to prepare the monoclinic crystals.

*** Lists of the observed and calculated structure factors and anisotropic thermal parameters are obtainable from the authors on request.

diffractometer using graphite-monochromated MoK_α radiation, $\Theta - 2\Theta$ scan technique, scan width 1.20° [for (D) 1.0°], scan rate 0.04° s^{-1}. Reflections with $I \leq 3\sigma(I)$ [for (C) $I \leq 2\sigma(I)$], where σ is the standard deviation based on counting statistics, were not included in the calculations, which were based on the remaining 2812, 1926, 2914 and 1309 independent reflections for (A), (B), (C) and (D), respectively. The intensities were corrected for Lorentz and polarization effects but not for absorption.

All four structures were solved by direct methods MULTAN80.[13] Refinement was performed using the SHELX76 programme[14] by the least-squares procedure, minimizing $\Sigma w(|F_o| - |F_c|)^2$, assuming unit weights for all observations. In structures (A), (B) and (D) the hydrogen atoms were located either in the difference Fourier maps or generated at geometrically fixed positions. They were not refined but included in the structure factor calculations. In structure (C) the hydrogen atoms were not positioned due to the unsatisfactory refinement with a high final value of the R factor. Even atoms belonging to the dioxane molecule were not clearly resolved since the crystals were losing solvent during exposure to the X-rays. The refinements with anisotropic temperature factors for all non-hydrogen atoms converged at $R = 0.072$, 0.070, 0.17 and 0.064 for (A), (B), (C) and (D), respectively. Relatively high values of R factors for all structures, as well as the high temperature factors of the atoms belonging to the solvent molecules, indicate that all crystals were gradually losing solvent during the data collections. Of course, this effect was most significant for the structure of (C). To a certain extent similar effects were noticed also in the structures of the monoclinic lorazepam solvate with ethanol[1], water[5] and with isopropyl and isoamyl alcohol[9].

The atomic scattering factors were taken from International Tables for X-ray Crystallography.[15] All calculations were performed on the UNIVAC1100 computer of the Zagreb University Computing Centre.

Description of the Structures and Discussion

Final atomic coordinates are given in Table I, while Table II gives the comparative values of the interatomic distances and bond angles for all four structures.

The general feature of the lorazepam molecules in all four solvates is similar [shown in Figure 1. for (A)] to that previously determined in the analogous 1,4-benzodiazepine derivatives (*e. g.* see ref. 5, 6 and 7). It is best described in terms of three planes: seven-membered diazepine ring, fused chlorophenyl ring and substituted chlorophenyl ring. The angles between the least-squares best plane through the basis plane N(1), C(2), N(4), C(5) of the seven-membered ring and the benzene rings, fused and substituted, are: 30.6 and 59.6°, and 20.6 and 88.6° (two independent molecules) in (A), 32.3 and 57.8° in (B), 31.2 and 51.1° in (C), and 10.4 and 69.7° in (D). The actual similarity between diazepine rings in the different solvates is probably best seen from Table III which lists the selected torsion angles in the rings compared to the corresponding values found in the monoclinic form of the ethanolic solvate[1] and diazepam derivative.[10,****] The diferences are

**** Well known under the trade name »Valium« (Roche).

TABLE,I Atomic Coordinates ($x10^4$, for H atoms $x10^3$) and Equivalent Isotropic Thermal Parameters (in pm^2) the non-H atoms ($x10^4$) with Estimated Standard Deviations in Parentheses.

$$Beq = \frac{4}{3}\sum_i\sum_j b_{ij}a_i a_j$$

Atom	Compound (A) Molecule I x/a	y/b	z/c	Beq	Compound (A) Molecule II x/a	y/b	z/c	Beq	Compound (B) x/a	y/b	z/c	Beq	Compound (C) x/a	y/b	z/c	Beq	Compound (D) x/a	y/b	z/c	Beq
Cl(1)	2177(3)	3154(2)	-1590(3)	5.6(1)	5226(3)	5635(2)	7001(3)	5.6(1)	1995(3)	7085(4)	9782(4)	3.8(1)	2951(4)	2220(3)	3802(5)	5.1(1)	2131(2)	6598(3)	1993(4)	5.0(1)
Cl(2)	238(4)	616(2)	1459(5)	10.6(2)	9691(3)	3441(2)	10318(4)	8.1(1)	3982(3)	1473(5)	6401(4)	5.4(1)	7635(5)	3742(4)	4528(5)	6.9(2)	3748(3)	2329(4)	6924(5)	7.0(2)
N(1)	3474(7)	-159(4)	756(7)	3.6(3)	6209(7)	2375(4)	9577(7)	3.6(3)	953(8)	1263(12)	8250(10)	3.1(3)	8123(10)	-566(8)	5458(11)	3.5(3)	491(7)	1816(8)	8561(13)	3.1(4)
C(2)	4363(8)	-363(5)	2085(9)	3.2(3)	6296(8)	2147(5)	10897(9)	3.4(3)	470(9)	1145(13)	7039(13)	2.8(4)	8184(11)	81(9)	7046(13)	3.1(4)	72(8)	1859(10)	10115(19)	3.3(5)
C(3)	5102(9)	339(5)	3070(9)	3.2(3)	6064(8)	2795(5)	11790(8)	3.6(3)	246(8)	2783(13)	5914(13)	2.9(3)	6769(11)	80(9)	8586(12)	3.1(4)	93(8)	3293(10)	10194(14)	3.1(5)
N(4)	4144(6)	733(4)	3521(7)	3.0(2)	7348(6)	3322(4)	12339(7)	3.5(2)	1311(7)	3167(9)	4899(10)	2.2(3)	6433(9)	1223(7)	8650(10)	3.0(3)	1242(7)	3566(8)	9964(12)	2.8(4)
C(5)	3224(8)	1179(5)	2609(9)	3.0(3)	7495(8)	3802(4)	11405(9)	2.0(3)	1953(8)	3664(12)	5556(12)	2.4(3)	5953(11)	1879(9)	7531(12)	3.0(4)	1858(8)	3942(9)	8421(16)	2.8(5)
C(6)	2717(8)	2058(5)	509(10)	3.5(3)	6330(9)	4625(5)	9247(9)	3.5(3)	1911(8)	5210(13)	7709(13)	2.6(3)	4510(20)	2008(13)	5719(23)	3.1(4)	1914(10)	5133(12)	5355(23)	3.1(6)
C(7)	2548(8)	2163(5)	-918(10)	3.8(3)	5548(9)	4677(5)	7810(10)	4.1(3)	1697(9)	5362(14)	9320(13)	2.9(4)	4488(14)	1764(10)	4207(15)	3.8(4)	1683(8)	5158(11)	3944(18)	3.4(5)
C(8)	2615(9)	1544(6)	-1761(10)	4.1(3)	5020(10)	3993(6)	6924(10)	4.4(4)	1259(9)	4193(14)	10594(13)	2.9(4)	5584(14)	1256(10)	3190(14)	3.9(4)	1101(8)	4089(12)	3994(17)	3.6(5)
C(9)	2931(9)	774(5)	-1211(10)	3.9(3)	5260(10)	3242(5)	7576(10)	4.5(4)	981(9)	2844(14)	10240(12)	3.0(4)	6748(15)	850(10)	3656(14)	3.5(4)	707(8)	3005(11)	5575(20)	3.3(5)
C(10)	3189(7)	656(5)	274(8)	3.0(3)	5990(5)	3174(4)	9034(8)	3.2(3)	1183(9)	2697(15)	8680(13)	2.9(4)	6893(12)	979(9)	5112(13)	3.2(3)	895(8)	2966(10)	7043(18)	2.8(5)
C(11)	3066(7)	1277(4)	1098(8)	2.9(3)	6559(6)	3363(4)	9882(8)	3.1(3)	1664(8)	3848(13)	7320(12)	2.5(3)	5829(11)	1510(9)	6123(13)	3.1(3)	1536(7)	4014(9)	6951(16)	3.4(4)
O(12)	4530(6)	-1082(3)	2444(6)	4.3(2)	6531(5)	1431(3)	11260(6)	4.1(2)	254(7)	-78(10)	6813(10)	4.4(3)	9295(8)	-291(7)	7254(10)	4.5(3)	-310(6)	837(7)	11423(10)	4.4(3)
O(13)	6263(5)	82(3)	4261(6)	3.9(2)	5865(5)	2506(3)	12981(6)	4.3(2)	-467(6)	2650(9)	4928(9)	3.5(3)	6912(11)	-576(8)	119(11)	3.8(3)	-520(6)	3272(9)	11810(12)	4.2(4)
O(14)	2302(5)	1633(5)	3098(9)	3.1(3)	8773(5)	4350(5)	11972(10)	3.9(3)	3046(8)	4043(12)	4537(12)	2.4(3)	5510(12)	3013(9)	7638(14)	3.0(4)	2998(8)	4357(11)	8105(13)	3.2(4)
C(15)	838(10)	1422(6)	3638(11)	5.0(4)	9804(10)	4205(7)	11495(11)	5.5(4)	4035(9)	3120(14)	4792(13)	3.2(3)	6207(16)	3599(11)	6333(17)	4.8(5)	3902(9)	3700(11)	7444(15)	4.5(5)
C(16)	76(10)	1842(8)	3122(13)	6.4(4)	11009(14)	4701(11)	12041(17)	8.8(6)	5053(9)	3423(16)	3793(15)	4.0(4)	5829(21)	4982(12)	6453(24)	7.0(8)	4954(10)	4092(15)	7200(17)	6.0(7)
C(17)	566(11)	2487(7)	4051(11)	5.2(4)	11113(16)	5289(10)	13004(13)	9.0(7)	5082(10)	4595(19)	2486(16)	4.9(5)	4713(22)	5118(13)	7921(25)	6.8(8)	5089(10)	5165(17)	7617(19)	6.6(7)
C(18)	1953(11)	2717(7)	4521(12)	5.6(5)	10118(17)	5444(7)	13491(14)	8.1(5)	4111(10)	5646(15)	2225(14)	3.8(4)	4019(20)	4237(13)	9218(24)	5.7(7)	4230(11)	5561(14)	8265(18)	6.3(7)
C(19)	2775(10)	2271(6)	4045(11)	4.6(4)	8889(11)	4947(6)	12956(11)	5.4(4)	3103(9)	5312(14)	3235(13)	3.0(4)	4447(16)	3196(12)	9068(18)	4.4(5)	3168(9)	5432(13)	8517(15)	4.5(6)
H(1)	337	-65	2		617	197	887		97	37	931						43	99	841	
H(3)	544	66	244		605	344	1154		-19	364	665						-21	401	926	
H(6)	247	269	33		675	517	988		229	611	675						236	593	542	
H(8)	244	165	-287		445	405	578		114	432	1185						97	411	285	
H(9)	279	25	-198		495	270	693		92	192	1120						29	213	565	
H(13)	594	23	489		663	215	1335		-26	152	466						-58	253	1242	
H(16)	-99	168	275		1181	461	1166		581	270	403						563	353	671	
H(17)	9	281	445		1209	561	1347		587	493	167						590	552	739	
H(18)	237	323	525		1019	596	1418		414	665	123						434	668	863	
H(19)	385	344	444		808	501	1334		235	606	301						247	536	904	
	Ethanol								Acetone				Dioxane				Cyclohexanone			
O(43)	8645(24)	1753(19)	7568(29)	27(2)					2917(11)	-281(13)	451(14)	8.6(5)	-120(57)	3115(54)	7669(59)		1186(10)	-1213(11)	4812(14)	10.0(5)
C(44)	8028(40)	1970(19)	6286(26)	24(2)					3168(11)	313(14)	1438(18)	4.2(5)	570(61)	2338(47)	8797(95)		1994(13)	-425(18)	4086(28)	8.6(9)
C(45)	7830(10)	1600(7)	4973(10)	5.1(4)					2758(14)	-329(20)	3244(19)	6.5(7)	1041(60)	3222(53)	9056(84)		2537(18)	-119(31)	5107(32)	19(2)
C(46)									3879(15)	1565(20)	952(20)	6.5(6)	-770(79)	4191(39)	9034(84)		3674(20)	8(35)	4489(39)	16(2)
C(47)													-1495(41)	3444(56)	8888(78)		4012(21)	862(26)	2656(42)	15(2)
C(48)																	3546(24)	301(32)	1650(27)	18(2)
C(49)																	2335(19)	305(22)	2258(29)	14(1)
O(50)													-286(56)	3252(52)	10387(47)					

TABLE II Interatomic Distances and Angles with Estimated Standard Deviations in Parentheses

Distances/pm	(A) Molecule I	(A) Molecule II	(B)	(C)+	(D)
N(1) - C(2)	134.8(9)	136(1)	137(2)	140(2)	134(2)
C(2) - O(12)	124(1)	123(1)	119(2)	122(1)	123(1)
C(2) - C(3)	151(1)	148(1)	155(1)	154(1)	154(2)
C(3) - O(13)	141(4)	140(1)	142(2)	139(1)	141(2)
C(3) - N(4)	143(1)	150(1)	145(1)	147(2)	148(1)
N(4) - C(5)	128.5(9)	130(1)	128(2)	128(1)	128(1)
C(5) - C(11)	149(1)	147(1)	150(2)	148(2)	146(2)
C(11) - C(6)	141(1)	139(1)	140(2)	150(2)	141(2)
C(6) - C(7)	140(2)	136.4(2)	137(1)	148(3)	137(3)
C(7) - Cl(1)	175.3(9)	175.5(9)	175(1)	171(2)	176(1)
C(7) - C(8)	135(1)	140(1)	139(2)	136(2)	140(2)
C(8) - C(9)	138(1)	138(1)	139(2)	138(2)	139(2)
C(9) - C(10)	144(1)	138(1)	142(2)	141(2)	138(3)
C(10) - N(1)	142(1)	141.4(9)	143(2)	139(2)	140(1)
C(10) - C(11)	136(1)	139.0(9)	139(1)	140(2)	142(2)
C(5) - C(14)	147(1)	152(1)	148(1)	148(2)	149(2)
C(14) - C(15)	142(1)	139(2)	139(1)	138(2)	139(2)
C(15) - Cl(2)	172(1)	170(1)	175(1)	173(1)	173(2)
C(15) - C(16)	135(2)	141(2)	138(2)	142(2)	139(2)
C(16) - C(17)	136(2)	134(3)	139(2)	141(3)	137(3)
C(17) - C(18)	140(2)	136(3)	138(2)	142(2)	136(2)
C(18) - C(19)	137(2)	143(2)	138(2)	138(2)	141(2)
C(19) - C(14)	136(1)	136(1)	138(1)	136(2)	138(2)

	Ethanol	Acetone	Cyclohexanone
O(43) - C(44)	126(4)	123(2)	120(2)
C(44) - C(45)	140(3)	152(2)	148(4)
C(44) - C(46)		144(2)	
C(45) - C(46)			140(3)
C(46) - C(47)			146(4)
C(47) - C(48)			153(5)
C(48) - C(49)			149(4)
C(44) - C(49)			144(3)

Angles (°)	(A) Molecule I	(A) Molecule II	(B)	(C)+	(D)
C(2) -N(1) -C(10)	124.3(6)	125.8(7)	126.7(9)	125.9(8)	125(1)
N(1) -C(2) -O(12)	121.6(7)	119.5(8)	124(1)	122.4(9)	123(1)
C(3) -C(2) -O(12)	122.8(7)	124.4(9)	123(1)	122(1)	121(1)
N(1) -C(2) -C(3)	115.6(7)	116.1(7)	112(1)	116.1(9)	116.0(8)
C(2) -C(3) -O(13)	112(5)	114.1(7)	109(1)	110(1)	111.2(8)
O(13)-C(3) -N(4)	111(2)	107.7(6)	110.5(8)	110(1)	108(1)
C(2) -C(3) -N(4)	108.2(7)	106.1(7)	107.2(8)	107.1(8)	106.0(8)
C(3) -N(4) -C(5)	117.8(8)	115.5(6)	117.9(9)	117(1)	115(1)
N(4) -C(5) -C(11)	123.6(9)	126.6(7)	123.5(9)	123(1)	126(1)
N(4) -C(5) -C(14)	118.1(8)	115.4(7)	118.4(9)	119(1)	117(1)
C(14)-C(5) -C(11)	118.3(6)	117.9(8)	118(1)	118(1)	117.5(9)
C(5) -C(11)-C(10)	123.5(7)	121.6(6)	122(1)	124(1)	122.3(9)
C(5) -C(11)-C(6)	116.8(7)	119.0(6)	118.6(9)	116(1)	119(1)
C(6) -C(11)-C(10)	119.7(8)	119.2(7)	119(1)	120(1)	118(2)
C(11)-C(10)-N(1)	123.6(8)	123.0(6)	121(1)	121(1)	123(1)
C(11)-C(10)-C(9)	121.1(7)	120.3(7)	122(5)	119(1)	120(1)
N(1) -C(10)-C(9)	115.1(7)	116.5(6)	117.3(9)	119(1)	117(1)
C(10)-C(9) -C(8)	118.3(9)	121.4(8)	118(1)	123(1)	122(1)
C(9) -C(8) -C(7)	120.1(9)	117.1(8)	120(1)	119(1)	118(2)
C(8) -C(7) -C(6)	122.9(8)	122.8(8)	122(1)	124(2)	123(1)
C(8) -C(7) -Cl(1)	120.7(8)	117.5(7)	119.0(9)	122(1)	119(1)
Cl(1)-C(7) -C(6)	116.3(7)	119.7(6)	118.7(8)	114(1)	118(1)
C(7) -C(6) -C(11)	117.8(8)	119.2(7)	119.3(9)	114(1)	120(1)
C(5) -C(14)-C(19)	121.5(8)	119(1)	119.8(9)	120.5(9)	119(1)
C(5) -C(14)-C(15)	122.2(8)	118.3(8)	122.2(8)	121(1)	123(1)
C(15)-C(14)-C(19)	116(1)	122.4(9)	117.9(9)	119(1)	118(1)
C(14)-C(15)-Cl(2)	118.4(9)	122.6(8)	118.7(8)	122(1)	120(1)
Cl(2)-C(15)-C(16)	120.9(8)	119(1)	119.0(9)	117(1)	118(1)
C(14)-C(15)-C(16)	120.7(9)	119(1)	122(1)	121(1)	122(1)
C(15)-C(16)-C(17)	122(1)	119(2)	119(1)	121(1)	119(1)
C(16)-C(17)-C(18)	118.9(2)	123.9(4)	120(1)	116(2)	122(1)
C(17)-C(18)-C(19)	118(1)	118(1)	120(1)	122(1)	119(2)
C(18)-C(19)-C(14)	123.6(9)	118(1)	121(1)	122(1)	121(1)

	Ethanol	Acetone	Cyclohexanone
O(43)-C(44)-C(45)	133(3)	117(1)	120(2)
O(43)-C(44)-C(46)		123(1)	
O(43)-C(44)-C(49)			124(2)
C(45)-C(44)-C(46)		120(2)	
C(45)-C(44)-C(49)			116(2)
C(44)-C(45)-C(46)			118(3)
C(45)-C(46)-C(47)			111(3)
C(46)-C(47)-C(48)			112(2)
C(47)-C(48)-C(49)			109(2)
C(48)-C(49)-C(44)			111(2)

+ The values for dioxane molecule are not given due to uncertainty of the atomic positions belonging to it (see text).

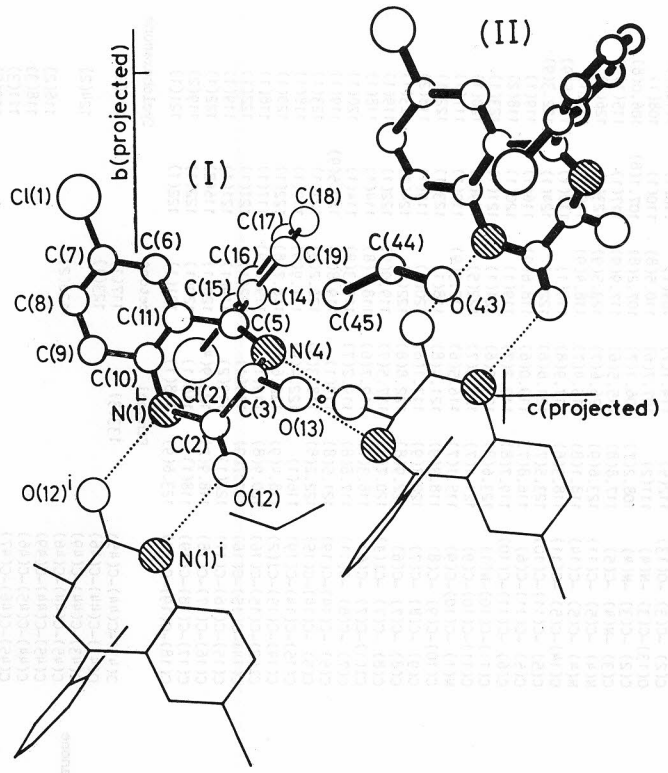


Figure 1. The structure of the 2 : 1 lorazepam-ethanol solvate showing atom numbering for the crystallographically independent molecule (I). The analogous numbering scheme for molecule (II) has been omitted for clarity. The hydrogen bonds are denoted by dotted lines.

most probably due to the packing conditions caused by the solvate molecules and different hydrogen bonding. As usual, the seven-membered rings adopted boat conformations. The angles between the least-squares best plane through the basis plane N(1), C(2), N(4), C(5) and the planes through C(2), C(3), N(4) and C(5), C(11), C(10) are: 61.9 and 32.4, and 83.4 and 23.8° (two independent molecules in the asymmetric unit) in (A), 62.7 and 35.1 in (B), 60.2 and 37.3° in (C), and 83.4 and 14.6° in solvate (D). Again, such values are in agreement with the values found in the previously determined structures, *e. g.* in the monoclinic form of the lorazepam solvate with ethanol where the bow angles amounted to 62 and 58° and both stern angles 33° for two independent molecules.

However, the four solvates have different systems of hydrogen bonding. In (A) all molecules are three-dimensionally held together by hydrogen bonds N(1)—H . . . O(12^i) of 292 pm and N(1^i)—H . . . 0(12) of 282 pm [$i = 1 - x$, $\bar{y}$, $1 - z$] acting between molecules (I) and (II) and 0(13) — H . . . N(4) of 282 pm acting between centrosymmetrical pairs of molecules (I). (Figure 1.). In contrast to the structure of the monoclinic form of the same solvate[1], as well as to the solvates with isopropyl and isoamyl alcohols[9], in the present tri-

TABLE III Torsion Angles in the Diazepine Ring for Compounds (A), (B), (C) and (D) Compared to Monoclinic Ethanolic Solvate and Diazepam

TORSION ANGLES /°	(A)*		(B)	(C)	(D)	Ethanolic solvate (monoclinic form)[1]		DIAZEPAM[10]
	Molecule I	Molecule II				Molecule I	Molecule II	
C(10)-N(1) -C(2) -C(3)	1.6	3.6	-3.9	-5.0	-2.5	3.2	3.9	-13.5
N(1) -C(2) -C(3) -N(4)	-74.2	-110.8	-72.9	-69.5	-73.2	72.2	68.2	-65.0
C(2) -C(3) -N(4) -C(5)	74.5	96.1	75.7	75.3	77.2	76.8	71.9	74.7
C(3) -N(4) -C(5) -C(11)	-2.9	-0.9	-0.8	-4.8	-4.6	3.3	2.9	-2.9
N(4) -C(5) -C(11)-C(10)	-39.7	-31.8	-43.4	-44.0	-42.6	-	-	-40.2
C(5) -C(11)-C(10)-N(1)	1.0	1.8	-0.8	-4.9	-2.6	2.2	2.0	-3.3
C(11)-C(10)-N(1) -C(2)	39.8	25.5	45.1	41.1	41.4	42.8	41.2	51.9
N(4) -C(5) -C(14)-C(15)	109.4	91.7	111.0	116.7	-51.2	49.5	59.1	-
N(4) -C(5) -C(14)-C(19)	-69.2	-85.3	-65.9	-60.2	130.0	51.5	57.7	157.3
C(11)-C(5) -C(14)-C(15)	-71.9	-88.3	-67.6	-62.7	-60.1	51.9	58.3	-
C(11)-C(5) -C(14)-C(19)	109.4	94.7	115.4	120.4	121.1	53.8	56.9	-25.5
C(9) -C(10)-N(1) -C(2)	-145.0	-157.0	-139.5	-142.2	-143.1	-	-	-130.2
C(6) -C(11)-C(5)- N(4)	142.0	151.9	138.1	140.7	140.0	-	-	138.1

* Calculated from centrosymetrically related coordinates

clinic structure we have no evidence of any hydrogen bonding between the solvent and benzodiazepine molecules, the closest contact between the ethanolic O and keto O(12^{i}) from molecule (I) is 358 pm. In the structure of (B) there is a hydrogen bond O(13)—H . . . O(12^{i}) [$i = \bar{x}, \bar{y}, 1 - z$] of 289 pm between the lorazepam molecules, but again there are no such bonds between lorazepam and solvent molecules. The closest contact between the solvent molecule [acetonic O(43)] and amide N(1) from the lorazepam molecule amounts to 341 pm. This is even more obvious in the structure of the solvate with dioxane (C) in which the loss of dioxane during the data collection and consequently, the unresolved atoms of the solvent molecule in a different Fourier map indicate a lack of any efficient cohesion in the crystal. However, the solvate (D) is different: apart from the hydrogen bonding between the amide and keto groups N(1)—H . . . O(12^{i}) [$i = \bar{x}, \bar{y}, 1 - z$] of the lorazepam molecules amounting to 285 pm, there is also a hydrogen bond O(13)—H . . . O(43^{i}) of 281 pm between cyclohexanone O and the benzodiazepine OH group. This better cohesion in this crystal structure may account for the best resolution of the atoms belonging to the solvent cyclohexanone molecule as well as for the best value of the reliability factor R.

The different kinds of hydrogen bonds, as well as their magnitudes observed in the investigated solvates, are consistent with those described earlier in the papers considering the possible roles of such hydrogen bondings in the benzodiazepine-biological receptor interactions. They are associated with the C=O group in position (2) and N(4) as hydrogen bonding acceptors and with N(1)H and OH at the carbon atom C(3) as hydrogen bonding donors.[16,17]

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REFERENCES

1. G. Bandoli and D. A. Clemente, *J. Chem. Soc. Perkin Trans II*, (1976) 413.
2. G. Gilli, V. Bertolasi, M. Sacerdoti, and P. A. Borea, *Acta Cryst.* **B33** (1977) 2664.
3. G. Gilli, V. Bertolasi, M. Sacerdoti, and P. A. Borea, *Acta Cryst.* **B34** (1978) 2826.
4. G. Gilli, V. Bertolasi, M. Sacerdoti, and P. A. Borea, *Acta Cryst.* **B34** (1978) 3793.
5. P. Chananont, T. A. Hamor, and I. L. Martin, *Acta Cryst.* **B36** (1980) 1690.
6. P. Chananont, T. A. Hamor, and I. L. Martin, *Acta Cryst.* **B37** (1981) 1372.
7. H. Butcher, T. A. Hamor, and I. L. Martin, *Acta Cryst.* **C39** (1983) 1469.
8. H. Butcher and T. A. Hamor, *Acta Cryst.* **C41** (1985) 1081.
9. J. Rambaud, J. L. Delarbre, B. Pauvert, L. Maury, A. Dubourg, and J. P. Declercq, *Acta Cryst.* **C43** (1987) 2195.
10. A. Camerman and N. Camerman, *J. Am. Chem. Soc.* **94** (1972) 268.
11. B. Kamenar, D. Matković, and A. Nagl, *Croat. Chem. Acta* **56** (1983) 87.
12. B. Kamenar, D. Mrvoš, A. Nagl, D. Matković-Čalogović, and M. Oklobdžija, *5th Italian-Yugoslav Crystallographic Congress*, Padova 3—6 June 1986, Book of Abstracts p. C 20.

13. P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, MULTAN 80, *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*, 1980, Univs. of York, England and Louvain, Belgium.
14. G. M. Sheldrick, SHELX76, *A Program for Crystal Structure Determination*, 1976, Univ. of Cambridge, England.
15. *International Tables for X-ray Crystallography*, Vol. **IV**, Birmingham, Kynoch Press, 1974, p. 72.
16. G. Gilli, V. Bertolasi, and M. Sacerdoti, *Biochemical Pharmacology*, **31** (1982) 889.
17. P. A. Borea, G. Gilli, V. Bertolasi, and V. Ferretti, *Molecular Pharmacology* **31** (1987) 334.

SAŽETAK

Kristalne strukture lorazepamskih solvata s etanolom, acetonom, dioksanom i cikloheksanom

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Izvedena je rendgenska analiza četiri solvata lorazepama i to s etanolom, acetonom, dioksanom i cikloheksanonom. Određene strukture su uspoređene sa strukturama drugih lorazepamskih derivata i solvata koje su već opisane u literaturi.