Chem. Pharm. Bull. 38(1) 249—251 (1990)

The Crystal and Molecular Structure of Racemic 11b-Methylbenzodiazepinooxazole

Keiichiro HATANO,[a] Yukihisa KURONO,*,[a] Tomonari KUWAYAMA,[b] Akimitsu MURAKAMI,[a] Tamotsu YASHIRO,[a] and Ken IKEDA[a]

Faculty of Pharmaceutical Sciences, Nagoya City University,[a] 3–1 Tanabe-dori, Mizuho-ku, Nagoya 467, Japan and Department of Pharmacy, NTT Tokai General Hospital,[b] 2–17–5 Matsubara, Naka-ku, Nagoya 460, Japan. *Received June 15, 1989*

The crystal structure of 11b-methylbenzodiazepinooxazole (MBDOZ) obtained from methanol solution was determined by X-ray diffraction techniques. MBDOZ crystallizes in space group P_{bca} with cell dimensions $a = 25.293$ (2) Å, $b = 8.483$ (1) Å, and $c = 10.307$ (1) Å. The centrosymmetric space group of P_{bca} with $Z = 8$ demands that molecules in the crystal lattice form a racemic pair. Two diazepine moieties form a dimer with a hydrogen-bond net between the amide hydrogen and carbonyl oxygen (O_6) of each molecule. The conformations of the benzodiazepinooxazole ring system are discussed.

Keywords X-ray analysis; 11b-methylbenzodiazepinooxazole; minor tranquilizer; dimer; hydrogen bonding; racemization; *R,S*-configuration; oxazolidine ring; diazepine ring; conformation

Benzodiazepinooxazoles (BDOZs) and diazepam, derivatives of 1,4-benzodiazepine, are established or potential drugs in the category of minor tranquilizers. BDOZ has a five-membered oxazolidine ring fused on the seven-membered diazepine ring. The conformational behavior of the two rings is of interest in connection with the stability of the drugs. We have demonstrated[1-3] that the oxazolidine ring of several BDOZs undergoes ring-opening and ring-closing reactions at the C_{11b}–O_1 bond through iminium cation formation and the reaction rates are affected by the pH of the aqueous solutions. The reactivities depend on the conformations of the two rings.[1,3] BDOZ in solution was considered to have three conformations: two with respect to the relative arrangement of the diazepine ring and oxazolidine ring are a planar one (conformation X) and a skewed one (conformation Y).[1,3] The conformation X can be divided into two subgroups with respect to the 11b-substituent and the lone pair of the N_4 atom, that is, the lone pair occupying the same side as the 11b-group (conformation X_I) and the opposite side (conformation X_{II}).[1,3] The ring-opening and -closing reaction implies a stereochemical interconversion at the asymmetric diazepine C_{11b} carbon along with the conformational modulation of the two rings. Actually, we and others[1-7] observed rapid racemization of stereoisomers of BDOZs in aqueous solution or even in alcoholic solution.

In order to investigate the relationship between the conformations and stability of these drugs, we have undertaken the determination of the structure of a fundamental derivative of racemic benzodiazepinooxazols, 11b(*R,S*)-methyl-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (11b-methylbenzodiazepinooxazole, MBDOZ), by the X-ray crystallographic method and report it herein. Only limited structural and stereochemical information on related compounds (having an 11b-phenyl group) has been published thus far by other workers.[7-9]

TABLE I. Summary of Crystal Data and Data Collection

Formula	$C_{12}H_{14}N_2O_2$	Absorption coefficient (cm^{-1})	0.7
M_r	218.28	$F(0, 0, 0)$	116×8
Space group	P_{bca}	Crystal size (mm^3)	0.4×0.4×0.2
a(Å)	25.293 (2)	Scan technique	ω–2θ scan
b(Å)	8.483 (1)	Scan range (deg)	$0.8+0.35\tan\theta$
c(Å)	10.307 (1)	2θ limit (deg)	$4<2\theta<55$
V(Å^3)	2211.5 (7)	No. of data measured	2571
Z	8	No. of data with $F_O \geqq 3\delta$ (F_O)	1497
D_{calc} ($g\cdot cm^{-3}$)	1.311	No. of variables	188
D_m ($g\cdot cm^{-3}$)	1.311	R_F (R_{wF})	0.072 (0.062)
Radiation	MoK_α		

TABLE II. Final Atomic Parameters and Equivalent Thermal Parameters with Estimated Standard Deviations in Parentheses

Atom	x	y	z	B(Å^2)
O_1	0.7201 (1)	0.4421 (3)	0.2386 (4)	5.59 (7)
O_6	0.5327 (1)	0.3484 (3)	−0.0364 (3)	5.27 (7)
N_4	0.6523 (1)	0.3215 (3)	0.1341 (4)	3.58 (6)
N_7	0.5520 (1)	0.4929 (3)	0.1533 (4)	4.29 (7)
C_{Me}	0.6690 (2)	0.5446 (4)	0.0394 (6)	5.40 (1)
C_2	0.7356 (2)	0.3116 (4)	0.2356 (7)	6.80 (1)
C_3	0.6874 (2)	0.2345 (4)	0.2216 (6)	5.20 (1)
C_5	0.5966 (1)	0.2841 (4)	0.1564 (5)	4.07 (8)
C_6	0.5586 (1)	0.3775 (4)	0.0824 (5)	4.07 (8)
C_{7a}	0.5783 (1)	0.5327 (4)	0.2928 (5)	3.87 (8)
C_8	0.5486 (2)	0.5964 (4)	0.4064 (5)	4.70 (9)
C_9	0.5722 (2)	0.6354 (4)	0.5461 (5)	5.50 (1)
C_{10}	0.6252 (2)	0.6106 (4)	0.5710 (5)	5.20 (1)
C_{11}	0.6550 (2)	0.5500 (4)	0.4560 (5)	4.42 (9)
C_{11a}	0.6326 (1)	0.5113 (3)	0.3141 (4)	3.61 (7)
C_{11b}	0.6670 (1)	0.4541 (4)	0.1830 (5)	3.82 (8)
H_{7N}	0.5227	0.5443	0.1133	4.00

Experimental

Synthesis and the chemical and spectroscopic data of MBDOZ were described previously.[3,10] Among crystals obtained by recrystallization from methanol, a colorless plate crystal with dimensions of 0.4×0.4×0.2 mm was found to be suitable for X-ray examination. The cell parameters and axial photographs displayed an orthorhombic unit cell with eight molecule units. A summary of the crystal data and the intensity collection is given in Table I. Intensity data were corrected for Lorentz and polarization effects but not for absorption. The systematic absences of reflections are consistent with P_{bca} (No. 61[11a]) as the space group.

The structure was solved by the direct method and refined by full-matrix least-squares techniques.[12] Least-squares refinement was eventually carried to convergence with anisotropic thermal parameters for all non-hydrogen atoms and with idealized isotropic thermal parameters for hydrogen atoms. The final difference Fourier was judged to be essentially featureless: the largest peak had a height of 0.26 e/Å^3 and was located near the N_4 atom. The final positional coordinates with the estimated standard deviations and the isotropic equivalent temperature factors for the non-hydrogen atoms are given in Table II.

Results and Discussion

The single crystal of MBDOZ was obtained from methanol solution where the racemization reaction between two enantiomers, 11b(R)-MBDOZ and 11b(S)-MBDOZ, is rapid.[3,6,10] The centrosymmetric space group of P_{bca} with $Z=8$ (one molecule in an asymmetric unit) demands that molecules in crystal lattice form a racemic pair. Indeed, two diazepine moieties form a dimer with a hydrogen-bond net between amide hydrogen and carbonyl oxygen (O_6) of each molecule. A perspective view of the dimeric molecule with the thermal ellipsoids of 50% probability (except hydrogen atoms) is shown in Fig. 1. Figure 1 also shows the atomic labeling scheme on half of the dimer. The labeled half of the dimer is depicted as a molecule with R-configuration at the C_{11b} atom, hence, the other half must have S-configuration as shown in the figure. This racemic pair arrangement is actually present in the solid state since there is no disordered atom suggesting other configuration pairs (*e.g.*, S–S pair or R–R pair).

Selected bond lengths and bond angles are entered in Figs. 1 and 2. Other individual bond lengths and angles may be found in Table III.[13] Figure 2 illustrates the perpendicular displacement of each atom, in units of 0.01 Å (thick letters), from the bottom plate (*vide infra*) as well as selected bond lengths in Å and bond angles (inside of the rings) in degrees. Atoms with negative values are toward the back of the paper. Bonding features around the two nitrogen atoms (N_4 and N_7) of the diazepine ring are contrasting. The ternary N_4 nitrogen atom is bonding equally to three adjacent carbons with the average N–C distance of 1.471 Å and average bond angles of 111.0°. The N_4 atom occupies the apex of a trigonal pyramid of the bond net and has sp^3 hybrid orbital character, the lone pair thus being toward the back side. On the other hand, the amide nitrogen (N_7) is bonding to C_{7a} and C_6 with bond lengths of 1.419(4) and 1.344(4) Å, respectively. The shortened C–N bond lengths for the amide group are consistent with partial carbon–nitrogen double bonds and quasi-planar nitrogen atom geometry (sp^2 hybrid). The dimeric hydrogen bonds make an approximately planar bond net between the two amide groups with an O_6–$N_7{}'$ atomic distance of 2.871(6) Å, where the prime indicates the symmetrically related position (translation; x, $-y+1/2$, $z+1/2$). All other bond lengths, angles, and thermal ellipsoids in the molecule are usual as compared with standard values[11b] and related molecular structures reported.[7-9]

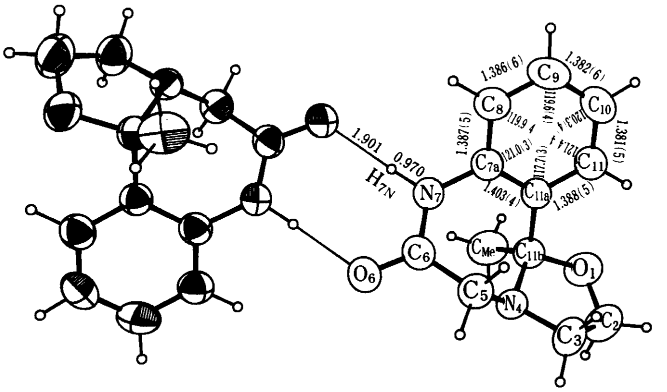

Fig. 1. Perspective View of Dimeric MBDOZ with Thermal Ellipsoids at 50% Probability and the Atomic Numbering

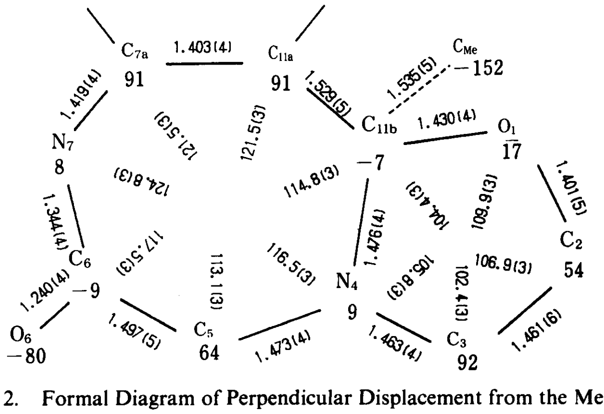

Fig. 2. Formal Diagram of Perpendicular Displacement from the Mean Plane of the 4-Atom Bottom Plate

The seven-membered diazepine ring has a boat conformation with the C_5 atom as the bow and the C_{7a}–C_{11a} bond as the stern. Thus, the mean plane of the N_7, C_6, C_{11b}, and N_4 atoms can be compared to the bottom board. The boat form of the diazepine ring is probably due to the partial diene-like structure within the ring and the steric effect of the oxazolidine ring. The five-membered oxazolidine ring is attached approximately parallel to the bottom plate like a wing conformation X; the dihedral angle of the two mean planes is 22.8°. The conformation (X_1) of the two rings and the N_4 lone pair position can be readily seen in the formal diagram of displacement from the mean plane of the 4-atom plate (Fig. 2). The phenyl ring plane makes a dihedral angle of 43.8° against the bottom board, resembling a sail. This conformation imposes non-equivalence on all methylene hydrogens at C_2, C_3, and C_5 with respect to methyl group or phenyl ring. In fact, the proton nuclear magnetic resonance (NMR) spectrum[10] of this compound shows complicated multiplet[14] in region of 2.78—4.16 ppm, suggesting the maintenance of this conformation in chloroform solution.

The intermolecular atomic distances (except the hydrogen bonds) show no unusual contact smaller than 3.357 Å which is observed between C_5 and $O_6{}'$.

Acknowledgments We are greatly indebted to Dr. M. Goto, Associate Professor of the Dept. of Chemical Reaction Engineering, Nagoya City University, for the valuable suggestions and comments on this work, and also to Mr. M. Saburi, Director of the Dept. of Pharmacy, NTT Tokai General Hospital, for his kind encouragement.

References and Notes

1) Y. Kurono, T. Kuwayama, K. Kamiya, T. Yashiro, and K. Ikeda, *Chem. Pharm. Bull.*, **33**, 1633 (1985).
2) Y. Kurono, K. Kamiya, K. Kuwayama, Y. Jinno, T. Yashiro, and K. Ikeda, *Chem. Pharm. Bull.*, **35**, 3831 (1987).
3) Y. Kurono, T. Kuwayama, Y. Jinno, K. Kamiya, E. Yamada, T. Yashiro, and K. Ikeda, *Chem. Pharm. Bull.*, **36**, 732 (1988).
4) Y. Kurono, Y. Jinno, T. Kuwayama, N. Sato, T. Yashiro, and K. Ikeda, *Chem. Pharm. Bull.*, **37**, 1044 (1989).
5) Y. Okada, T. Takebayashi, M. Hashimoto, S. Kasuga, S. Sato, and C. Tamura, *J. Chem. Soc.*, *Chem. Commun.*, **1983**, 785.
6) Y. Okada and T. Takebayashi, *Chem. Pharm. Bull.*, **36**, 3787 (1988).
7) Y. Okada, T. Takebayashi, and S. Sato, *Chem. Pharm. Bull.*, **37**, 5 (1989).
8) S. Sato, N. Sakurai, T. Miyadera, C. Tamura, and R. Tachikawa, *Chem. Pharm. Bull.*, **19**, 2501 (1971).
9) T. A. Hamor and I. L. Martin, "Progress in Medicinal Chemistry,"

Vol. 20, ed. by G. P. Ellis and G. B. West, Elsevier Science Publishers, B. V., 1983, pp. 157—223.

10) T. Kuwayama, S. Kato, Y. Kurono, T. Yashiro, and K. Ikeda, *Yakugaku Zasshi*, **108**, 641 (1988).

11) *a)* N. F. M. Henry and K. Lonsdale, "International Tables for X-Ray Crystallography," Vol. I, Kynoch Press, Birmingham, England, 1962; *b)* *Idem*, *ibid.*, Vol. III, p. 276.

12) Programs of Enraf-Nonius's SDP package were used. The package includes modified versions of Main, Hull, Lessinger, Germain, Declerg, and Woolfson's MULTAN, Johnson's ORTEP II, and LSFM for full-matrix least-squares refinement.

13) Final tables of the individual bond lengths and angles, hydrogen atomic positions, anisotropic thermal parameters for non-hydrogen atoms, and structure amplitude (F_o and F_c) are available on request.

14) Complete resolution and assignment of the signals are in progress.