Stereochemistry of Benzodiazepinooxazoles: Crystal Structure and NMR Spectroscopic Investigations of New Conformational Variants of Mexazolam Analogues

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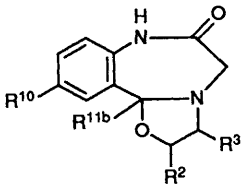
The varied stereochemistry of mexazolam analogues is described on the basis of six crystal-structure analyses of the 11b-hydro (**2**), methyl (**3** and **4**), phenyl (**5**) and 2′-chlorophenyl (**6**; mexazolam) derivatives of 3-methylbenzodiazepinooxazole and the benzodiazepinooxazole (**1**), all determined by X-ray diffraction techniques. Two new comformations for the benzodiazepinooxazole ring system have been found in these analyses, *i.e.*, a flat conformation Y_{II} in the case of **2** and **3**, and a skewed conformation Y_{I} in **1**. The usual 'boat-wing' conformation X_{I} has been found in compounds **4**–**6**. The solution-state ^{1}H NMR spectra of **1**, **3** and **4** at room temperature have been examined by phenyl ring-current effects and support retention of the three types of solid-state conformation. In polar solvents, all these compounds (except for **1**) show a diastereoisomeric equilibrium of *trans*⟷*cis* interconversion through epimerization at the 11b position. The diastereoisomeric and conformational differences in these compounds are discussed along with the steric interaction of the substituents.

Mexazolam (**6**)[1] is an established psychological drug of the 1,4-benzodiazepine class, and is marketed in Japan and some other countries. The chemical structure of **6**, 10-chloro-11b-(2′-chlorophenyl)-2,3,7,11b-tetrahydro-3-methyloxazolo[3,2-*d*]-[1,4]benzodiazepin-6(5*H*)-one, is known to consist of a seven-membered diazepine ring fused to a phenyl ring and a five-membered oxazolidine ring containing a methyl group at the 3



Compound	R^2	R^3	R^{10}	R^{11b}
1	H	H	H	H
2	H	CH_3	H	H
3, *trans*	H	CH_3	H	CH_3
4, *cis*	H	CH_3	H	CH_3
5	H	CH_3	Cl	C_6H_5
6, mexazolam	H	CH_3	Cl	2′-ClC_6H_4
7, oxazolam	CH_3	H	Cl	C_6H_5

position. An empirical correlation between the chemical structures of 1,4-benzodiazepine drugs and their pharmacological activity has been proposed;[2,3] however, little is known of the stereochemical features of the benzodiazepinooxazole drugs. The characterization of the conformation and configuration of these drugs is of paramount importance in probing stereospecific effects on the bioactivity, *i.e.*, structure–activity relationship.

We have reported remarkably different kinetic behaviour of **6** in the oxazolidine ring-opening and ring-closing reactions as compared with that of oxazolam (**7**),[4] which is another marketed benzodiazepinooxazole drug carrying a 2-methyl and an 11b-phenyl group (but no 2′-Cl group). The crystal structure of **7** has recently been determined.[5] Although the reaction mechanism was found to be complicated by conformational and stereochemical details with respect to the substituents, it is certain that the three-dimensional structure of benzodiazepinooxazoles affects the stability of the drug, and in turn, the bioavailability through solubility, and the biological effectiveness of these drugs on oral administration. It is also interesting in this context to note that stereospecific binding of the (+)-enantiomer of some benzodiazepine derivatives to receptors of the central nervous system has been discovered.[6]

In order to explore the possible correlations between the stereochemical structure, stability and biological activity of benzodiazepinooxazoles, a series of mexazolam analogues has been prepared and the molecular structures of the compounds determined by an X-ray method. Although we,[5,7] and others,[8,9] have demonstrated earlier the basic features of the benzodiazepinooxazole ring system, we have more systematically pursued stereochemical variants of mexazolam analogues with particular interest in the following points: (1) the conformational variations induced by the effect of the bulk of the 11b substituent on the ring conformation of benzodiazepinooxazole; (2) the composition of *cis* and *trans* isomers (referring to the 11b substituent and the 3-methyl group) in the solid state with relation to the conformation and the *trans*⟷*cis* equilibrium in solution; and (3) the 11b-(2′-chlorophenyl) ring orientation in **6** compared with the chloro-free phenyl ring in analogues.

We report herein two new conformations, flat and skewed, of benzodiazepinooxazoles found first in this work, and we also report the stereochemical characteristics of mexazolam which is believed[3] to have the best pharmacological properties among the derivatives in the present study.

Experimental

General.—All m.p.s were measured on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM GSX-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer with tetramethylsilane as an internal standard. Chemical shift and spin-spin coupling are given in ppm (δ) and Hz (J), respectively. The ratios of *trans*/*cis* isomers of each mexazolam analogue in

Table 1 Summary of crystal data and intensity collection parameters for mexazolam analogues

	1	2	3
Formula	$C_{11}H_{12}N_2O_2$	$C_{12}H_{14}N_2O_2$	$C_{13}H_{16}N_2O_2$
M	204.25	218.28	232.31
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$C2/c$	$P2_1/c$	$P\bar{1}$[b]
T/K	295	295	295
a/Å	17.126(21)	6.608(1)	6.703(1)
b/Å	5.902(1)	20.367(3)	12.130(1)
c/Å	19.655(2)	7.979(1)	16.045(1)
α/°	90.0	90.0	104.68(1)
β/°	97.75(5)	100.97(0)	102.06(1)
γ/°	90.0	90.0	106.03(1)
V/Å^3	1968	1054	1157
Z	8	4	4
D_x/g cm^{-3}	1.378	1.376	1.334
D_m/g cm^{-3}	—	1.380	1.339
Crystal size/mm	0.15 × 0.09 × 0.45	0.54 × 0.57 × 0.75	0.21 × 0.42 × 0.60
Diffractometer	Enraf-Nonius CAD4		
Radiation	Graphite monochromated Mo-Kα		
2θ range/°	3 – 50		
Scan technique	$\omega - 2\theta$		
Scan range (ω)/°	0.80 + 0.35 tan θ		
Criterion for observation	$F_o > 3\sigma(F_o)$		
Unique observed data	1133	1543	3978
R	0.077	0.046	0.055
R_w	0.087	0.043	0.054

	4	5	6
Formula	$C_{13}H_{16}N_2O_2$	$C_{18}H_{17}ClN_2O_2$·C_2H_5OH	$C_{18}H_{16}Cl_2N_2O_2$·C_2H_5OH
M	232.31	374.90	409.34
Crystal system	Monoclinic	Monoclinic	Monoclinic[a]
Space group	$P2_1/c$	$P2_1/c$	$C2/c$
T/K	295	295	295
a/Å	11.765(1)	15.427(1)	34.023(3)
b/Å	7.975(2)	7.719(1)	8.088(1)
c/Å	13.229(1)	16.411(1)	16.912(2)
α/°	90.0	90.0	90.0
β/°	95.90(0)	110.67(1)	117.17(2)
γ/°	90.0	90.0	90.0
V/Å^3	1235	1828	4140
Z	4	4	8
D_x/g cm^{-3}	1.249	1.362	1.314
D_m/g cm^{-3}	—	1.311	1.321
Crystal size/mm	0.21 × 0.33 × 0.69	0.27 × 0.33 × 1.26	0.21 × 0.27 × 0.72
Diffractometer	Enraf-Nonius CAD4		
Radiation	Graphite monochromated Mo-Kα		
2θ range/°	3 – 50		
Scan technique	$\omega - 2\theta$		
Scan range (ω)/°	0.80 + 0.35 tan θ		
Criterion for observation	$F_o > 3\sigma(F_o)$		
Unique observed data	1726	2043	4697
R	0.061	0.068	0.070
R_w	0.057	0.076	0.073

[a] This crystal was originally thought and solved as: $P\bar{1}$: a = 8.088(1) Å; b = 16.912(1) Å; c = 17.486(2) Å; α = 116.38(1)°; β = 103.38(1)°; γ = 89.99(1)°; V = 2070 Å^3; Z = 4. [b] This could not be reduced to the monoclinic space group $C2/c$.

solution were evaluated from the ^{1}H NMR signal integrations of the 3-methyl group with the aid of the lanthanide shift reagent [Eu(fod)$_3$-d$_{27}$]. IR spectra were recorded on a Perkin-Elmer FTIR-1600 as a KBr pellet.

Materials.—Mexazolam (**6**, lot No. 2) was supplied by the Sankyo Co., Ltd. Other compounds (**1**–**5**) were prepared by procedures similar to those reported by Deriege *et al.*,[10] Miyadera *et al.*,[3] and Lemke and Hanze.[11] Since the synthesis of a 3,11b-dimethyl derivative (**3** and **4**) has not been published, a typical preparation method and chemical data will be given below. All other chemicals were purchased commercially and used without further purification unless otherwise noted.

Preparation of 3,11b-*Dimethylbenzodiazepinooxazole* (**3** *and* **4**).—A mixture of 2-bromoacetamidoacetophenone (5.12 g, 0.02 mol) and 2-aminopropan-1-ol (3.76 g, 0.05 mol) in 10 cm^3 of dimethylformamide (DMF) was stirred for 3 h at room temperature. The reaction mixture was poured into ice–water and extracted with chloroform. The chloroform layer was washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting oily residue was dissolved in ethanol (10 cm^3) and the solution was refluxed for 2 h. Evaporation of the solution afforded a solid, crude product. Recrystallization of the solid product from ethanol gave microcrystals (1.15 g, yield 23.6%). The compounds **3** and **4** were fractionally crystallized from ethanol. **3**: m.p. 147–149 °C (Found: C, 67.0; H, 7.1; N, 12.05%. $C_{13}H_{16}N_2O_2$ requires C,

67.21; H, 6.96; N, 12.06%); ν_{max}(KBr)/cm^{-1} 3070 (NH) and 1660 (C=O); δ_H(400 MHz; $CDCl_3$) 1.08 (3 H, d, J = 5.9, 3-CH_3) and 1.45 (3 H, s, 11b-CH_3); δ_C($CDCl_3$) 57.3 [C(3)], 14.7 [C(M)], 51.2 [C(5)], 94.9 [C(11b)] and 21.7 [C(11M)]. **4**: m.p. 127–130 °C (Calc. for **4** is the same as for **3**. Found: C, 67.2; H, 6.8; N, 12.0%); ν_{max}(KBr)/cm^{-1} 3200 (NH) and 1690 (C=O); δ_H($CDCl_3$) 1.16 (3 H, d, J = 5.9, 3-CH_3) and 1.60 (3 H, s, 11b-CH_3); δ_C($CDCl_3$) 59.8 [C(3)], 16.1 [C(M)], 52.2 [C(5)], 96.4 [C(11b)] and 29.2 [C(11M)].

X-Ray Structure Determination and Refinement.—X-Ray quality single crystals of all mexazolam analogues were obtained by slow evaporation from solutions in ethanol. Since the crystals of **5** and **6** contained solvent molecules and effloresced solvent, these were sealed in a thin-walled capillary. All crystals were examined on an Enraf-Nonius CAD4 Kappa goniometer using Mo-Kα radiation. A summary of the crystal data and the intensity collection for the six mexazolam analogues is given in Table 1. Intensity data were corrected for Lorentz and polarization effects but not for absorption (μ < 1.0 cm^{-1}).

The structures were solved by direct methods and refined by difference Fourier and full-matrix least-squares techniques.* The most non-hydrogen atomic positions for each molecule could be located in initial E-maps. There were no critical disorder problems about the main part of all molecules, although two crystals (**5** and **6**) had disordered solvates. The final models, utilizing anisotropic thermal parameters for all non-hydrogen atoms and fixed parameters for idealized hydrogen atoms, were eventually carried to convergence by repeated least-squares refinement. Final difference Fourier syntheses for each molecule were judged to be essentially featureless.

Results and Discussion

Description of Molecular Structures.—Perspective views of six mexazolam analogues are displayed in Figs. 1–6 for compounds **1**–**6**, respectively. Entered on some Figures are the common atomic labellings for the ring framework. For all six compounds, hydrogen atom coordinates, temperature factors and individual bond lengths and angles for non-hydrogen atoms are provided as supplementary data.† Non-hydrogen atom coordinates are given in Table 5. An unusually short distance [1.330(6) Å] between O(1) and C(2) in **4** has been observed. There are no other unusual bond lengths and bond angles in any molecule. The equivalent bond lengths generally agree well in all six compounds. The average bond lengths in the framework of six molecules (including two independent molecules in **3** and excluding **4**) are given in Fig. 7 which displays formally the common benzodiazepinooxazole skeleton disregarding the conformations, diastereoisomers and substituents of each molecule. The small fluctuations in the values are indicated by the standard deviations, shown in parentheses in the least-significant digits, of the six equivalent bond lengths. Nevertheless, bond angles involved in the diazepinooxazole ring system are fairly varied in the seven molecules. The compounds are therefore divided into three groups depending on the conformation as described below, and average bond angles of the ring system in each group are listed in Table 2. The opened

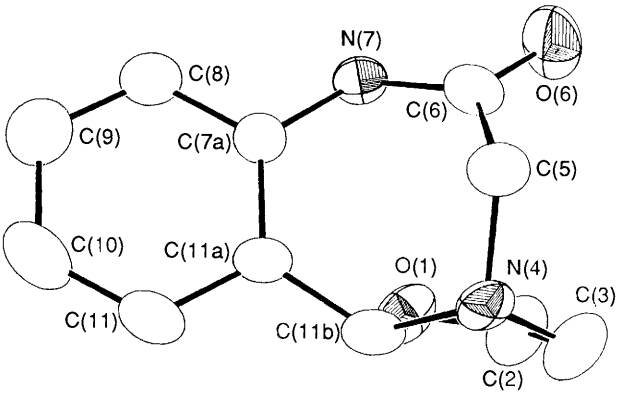


Fig. 1 Perspective view of the X-ray structure of **1** with the atomic labelling. Octant-shaded ellipsoids are heteroatoms, and all thermal ellipsoids are 50% probability. Hydrogen atoms are omitted for clarity.

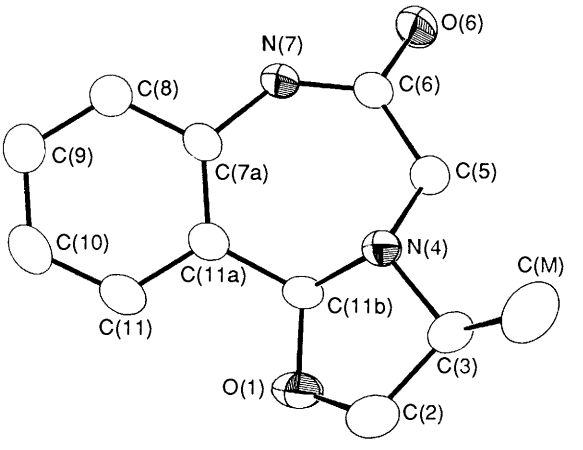


Fig. 2 ORTEP plot for **2** showing similar information as in Fig. 1

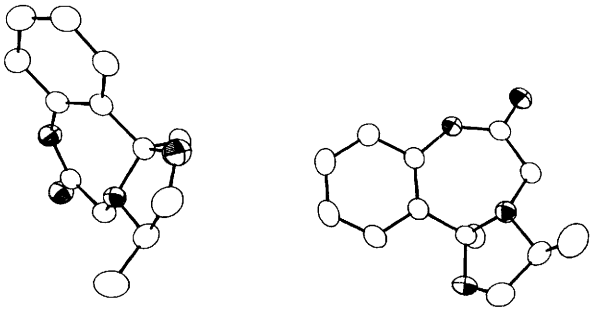


Fig. 3 Perspective view of two independent molecules of **3** in an asymmetric unit. The right molecule viewed in the same direction as **2** in Fig. 2 is the [3(*S*),11b(*S*)] *trans* isomer. The other is the [3(*R*),11b(*R*)] enantiomer. Atomic labellings and hydrogen atoms are omitted for clarity.

C(6)–N(7)–C(7a) and C(5)–C(6)–N(7) angles in the group Y_{II} are remarkable by comparison with the others, and suggest the ring expansion of the seven-membered diazepine moiety.

The bonding features around the two nitrogen atoms [N(4) and N(7)] of the diazepine ring are in marked contrast. The average C–N distances and the individual bond angles around the ternary N(4) nitrogen range from 1.454(8)–1.474(10) Å and from 103–118°, respectively, indicating sp^3 hybrid character of N(4) in all seven molecules. The N(4) atom is located at the apex of a trigonal pyramid in the bond network. On the other hand, the N(7) nitrogen bonds to C(6) with an average bond length of 1.347(10) Å. The shortened bond length is consistent with a partial double bond for C(6)–N(7) in the amide group.

* Programs of the Enraf-Nonius's SDP package were used. The package includes modified versions of Main, Hull, Lessinger, Germain, Declerq, Woolfson's MULTAN82 and Johnson's ORTEP II, and LSFM for full-matrix least-squares refinement.

† For details of the Cambridge Crystallographic Data Centre deposition scheme, see 'Instructions for Authors' (1992), *J. Chem. Soc., Perkin Trans. 2*, Issue 1. Structure factor tables are available from the authors on request.

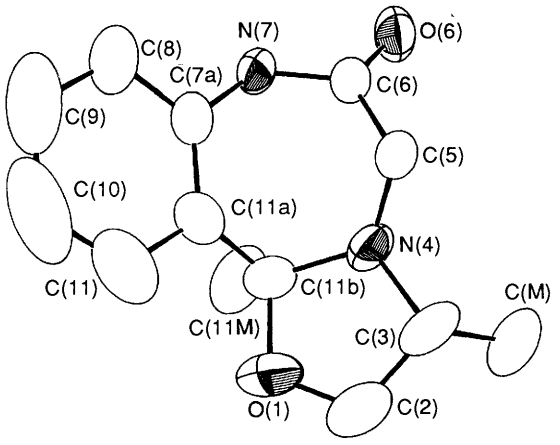


Fig. 4 ORTEP plot for **4** showing similar information as in Fig. 1

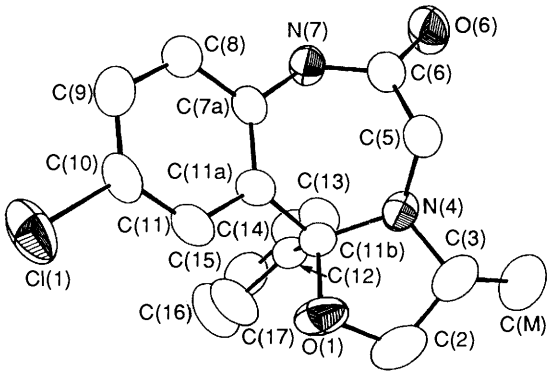


Fig. 5 ORTEP plot for **5** showing similar information as in Fig. 1

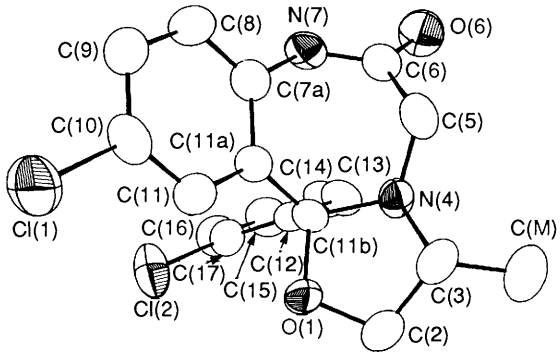


Fig. 6 ORTEP plot for **6** showing similar information as in Fig. 1

Conformation of the Benzodiazepinooxazole Ring System.— On the basis of Dreiding molecular models, we propose here* that there are four possible conformations for the benzodiazepinooxazole ring system *i.e.* there are two basic elements of conformational motion. The first element is ring inversion characterized by a motion of C(5) and the phenyl moiety passing through the central plane of the diazepine ring which normally adopts a cycloheptatriene-like boat conformation.[2,12] This ring inversion leads the equatorial–equatorial 'wing' disposition of the five-membered oxazolidine ring to the axial–axial skewed one in the boat, and it has been designated symbolically as the conformational conversion from X to Y. Molecular models suggest that the seven-membered diazepine moiety cannot adopt the chair form because of the strong rigidity imposed by a fused oxazolidine and a planar amide group. The other conformational element is a Walden-type

* Preliminary proposal for the conformation has been reported in refs. 4(*b*) and 7.

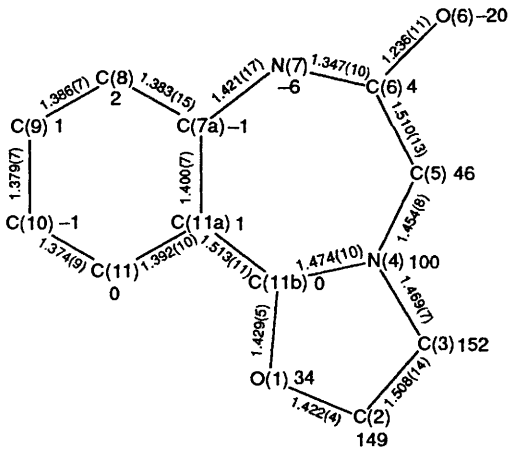


Fig. 7 Average bond lengths of the benzodiazepinooxazole skeleton in six molecules. The number following the atom label is the perpendicular displacement of each atom, in units of 0.01 Å, from the 9-atom mean plane of **2** (Y_{II}).

Table 2 Average bond angles/° for the diazepine-oxazolidine ring

Compound[a]	**1**[b] (Y_I[d])	**2**, **3**[c] (Y_{II})	**4**–**6** (X_I)
Oxazolidine ring			
C(11b)–O(1)–C(2)	110.0(3)	109.3(2)	108.1(31)
O(1)–C(2)–C(3)	104.4(3)	104.8(2)	105.8(28)
C(2)–C(3)–N(4)	105.6(3)	100.1(3)	101.9(11)
C(3)–N(4)–C(11b)	103.2(3)	106.2(5)	107.4(2)
N(4)–C(11b)–O(1)	105.2(3)	105.2(8)	104.9(2)
Diazepine ring			
C(11b)–N(4)–C(5)	113.8(3)	113.9(13)	117.6(5)
N(4)–C(5)–C(6)	115.0(3)	116.6(3)	110.4(7)
C(5)–C(6)–N(7)	115.6(3)	123.7(2)	116.9(8)
C(6)–N(7)–C(7a)	126.6(3)	135.0(2)	124.3(6)
N(7)–C(7a)–C(11a)	122.3(3)	125.8(3)	121.7(14)
C(7a)–C(11a)–C(11b)	121.8(3)	121.7(2)	122.9(6)
C(11a)–C(11b)–N(4)	116.6(3)	108.6(15)	115.5(12)

[a] Conformation in parentheses. [b] One molecule. [c] Two molecules. [d] Numbers in parentheses are estimated standard deviations from the refinement matrix for this group.

inversion of the N(4) atom, which is best distinguished by a *syn* or *anti* relationship between the 11b-substituent and the lone-pair orbital of the N(4) atom. The *syn* and *anti* orientations are denoted by subscripts I and II, respectively. Thus, a normal boat-wing conformation of the benzodiazepinooxazole ring system found in earlier studies[7–9] can be symbolized by X_I. The N(4) reorientation of X_I leads to the twisted boat X_{II}. The subsequent ring inversion from X to Y results in the flat form [except for N(4)] of the benzodiazepine nucleus. Although the oxazolidine ring keeps the distorted 'wing' disposition during these conversions, the flat form of the diazepine moiety is, for the sake of convenience, designated by the symbol Y_{II}. Consequently, four conformations, X_I(normal boat), X_{II}(twisted boat), Y_I(skewed ring system) and Y_{II}(flat form), are introduced in the model study with the coupling of two basic motional elements. The twisted boat form X_{II}, however, has not been given consideration owing to the close intramolecular contact of 11b-substituents with the carbonyl group. In fact there is some difficulty in discriminating it completely from Y_{II} in real situations, as mentioned below. Only the conformation X_I has, to our knowledge, been realized so far in the *solid state of the* benzodiazepinooxazole ring system. In this study we found two new conformations Y_I and Y_{II} by X-ray analyses; Y_I in **1** and Y_{II} in **2** and **3**. Meanwhile, **4** and both **5** and **6** adopt the conformation X_I. It is likely, therefore, that the steric effects of

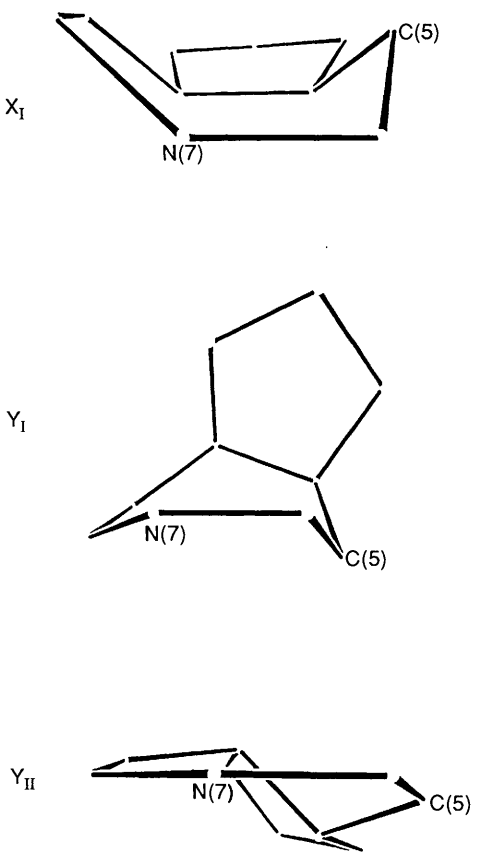


Fig. 8 Schematic drawings for the three realized conformations of the seven-membered diazepine and five-membered oxazolidine ring system. X_I, boat-wing; Y_I, skewed form; Y_{II}, flat form.

Table 3 Conformations and diastereoisomers of mexazolam analogues characterized by X-ray structure

Compounds	Conformation	Diastereoisomer
1	Y_I	—
2	Y_{II}	*trans*
3	Y_{II}	*trans*
4	X_I	*cis*
5	X_I	*cis*
6	X_I	*cis*

3- and 11b-substituents control the conformation in the mexazolam analogues. The three realized conformations of the seven- and five-membered ring system are schematically illustrated in Fig. 8. The conformations of each molecule determined in this study are listed in Table 3.

The new conformation Y_I seems very unique and particular to unhindered **1**. Since the crystal system of **1** is centrosymmetric, the configuration of C(11b) must be racemic for this molecule. The NMR spectrum of **1** indicated the presence of a major single species together with very small unidentified signals in deuteriochloroform at 23 °C. The signal assignment of the major one is consistent with retention of the solid-state conformation Y_I of **1** (see NMR section). This means that if the facile racemic conversion occurs in solution through the ring-opening and re-closing reaction of the oxazolidine moiety,[13–15] both the ring inversion and the N(4) reorientation must be associated with the racemization of **1**. Thus we suggest that the conformation Y_I is uniquely stable in energy for unhindered **1** and that the direct inversion from Y_I of **1** to X_I or Y_{II} has a high barrier comparable with the activation energy of the racemization reaction in solution. Indeed, a similar inversion barrier calculated for diazepam has been reported[16] to be 17.6(3) kcal mol^{-1}.* On the other hand, if the minor signals which were too weak to assign (at most, 2% of one proton of the major species) could be attributed to X_I or Y_{II} of **1**, the free energy difference should be, at least, more than 2.4 kcal mol^{-1} in favour of Y_I. For **1**, the dihedral angle between the central plane of the boat [C(6), N(7), N(4), C(11b)] and the oxazolidine plane is 85.4°; thus, this conformation is really skewed.

Y_I is no longer the most stable conformation after the introduction of a methyl group at the 11b- or 3-position of **1**. 11b-Methylbenzodiazepinooxazole has been shown to adopt X_I,[7] which probably circumvents the steric hindrance between the methyl group and the C(11) hydrogen in the conformation Y_I. Compound **2** adopts another new conformation (Y_{II}), which prevents close contact of the methyl group with the equatorial hydrogen of C(5) in Y_I.

The conformation Y_{II}, also discovered first in this work, shows a flat benzodiazepine moiety except for the C(5) and N(4) atoms. The perpendicular displacement of each atom from the mean plane of 9 atoms [C(6), N(7), C(7a), C(8), C(9), C(10), C(11), C(11a) and C(11b)] of benzodiazepine is given, typically for **2**, in Fig. 7. Both independent molecules in an asymmetric unit of **3** also adopt Y_{II} and have similar disposition as in **2**. The displacement of C(5) from the plane is somewhat large (0.46 Å) for the ideal Y_{II} of the model; this conformation may therefore include some constituents of X_{II}. It is unclear whether the strict discrimination of Y_{II} from X_{II} in the model study can be adapted for the real molecule or not. As mentioned above, this conformation could not be attained directly from Y_I by simple N(4) reorientation, but may be bypassed through epimerization and ring inversion.

^{1}H *NMR Chacterization of the Three Conformations in Solution.*—Our discussion will focus on whether the three conformations characterized in the solid state retain these forms in solution. A complete analysis of the ^{1}H NMR spectra of all molecules is thus in progress. The C(5) methylene proton signals of **1**, **3** and **4** have been examined for the identification of conformations in solution, since these seem most sensitive to conformational variations, and their chemical shifts will be least dependent on chemical modifications, *i.e.*, methylation and epimerization and/or the magnetic anisotropy of neighbouring bonds. In these three molecules, the C(5) methylene proton resonances usually appear as an **AB** quartet with a geminal 11–17 Hz spin–spin coupling and a chemical shift difference of *ca.* 0.3 ppm (120 Hz), and are hence readily assignable. The differences in the C(5) methylene chemical shift are considered to be dominated by the ring-current effect of the phenyl moiety in these molecules. According to Johnson and Bovey,[17] the relative chemical shift of each proton due to the ring current can be calculated by the cylindrical coordinates ρ and z of the proton, expressed in units of ring radius a. Each conformation has significantly different ρ and z values for protons of C(5). The calculation was based on the literature parameters,[17] the complete ellipic integrals K and E from the table,[18] and the idealized positions of protons. The results are summarized and compared with the observed chemical shifts in Table 4. The calculations were justified by excellent fits to the positions on the 'isoshielding' line map.[17] The calculated relative shifts are appropriate for use in theoretical predictions of the chemical shift depending on the conformation. The prediction is that the largest down-field shift is for H_{eq} of **3** (Y_{II}) and the largest up-field shift is for H_{ax} of **4** (X_I), which agrees well with the observed chemical shifts, 3.81 and 2.91 ppm, respectively. Other

* 1 cal = 4.184 J.

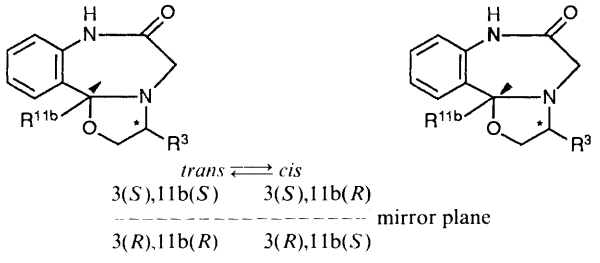
Table 4 Calculation of the relative chemical shift affected by the ring current and observed chemical shift for protons of the C(5) methylene group

	1 (Y_I)		**3** (Y_{II})		**4** (X_I)	
Compound[a]	H_{ax}[b]	H_{eq}[b]	H_{ax}	H_{eq}	H_{ax}	H_{eq}
z[c]	1.544	1.588	1.053	0.103	1.535	1.680
ρ[c]	1.845	3.112	3.540	3.561	1.787	3.054
δ[d]	+0.20	−0.09	−0.15	−0.22	+0.25	−0.07
δ(obs.)	3.22	3.57	3.55	3.81	2.91	3.37
^2J/Hz	14.1		17.0		11.0	

[a] Conformation in parentheses. [b] The equatorial hydrogen (H_{eq}) is distinguished by a larger ρ value than that of the axial hydrogen (H_{ax}). [c] The cylindrical coordinates expressed in units of 1.39 Å. Hydrogen positions are idealized by 1.08 Å for C–H. [d] The relative chemical shift in ppm from the resonance peak for the proton in which no ring current is assumed to exist. Signs are in accordance with the literature.[17]

observed chemical shifts agree qualitatively with the theoretical prediction if it is assumed that the chemical shift is 3.3–3.5 ppm for the non-shielded C(5) methylene protons. The differences between the two proton resonances [$\Delta = |\delta(H_{ax}) - \delta(H_{eq})|$] for each conformation are calculated to be 0.32, 0.29 and 0.07 ppm for X_I, Y_I and Y_{II}, respectively, and these are consistent with the observed ones in the order 0.46, 0.35, 0.26 ppm. These semi-quantitative agreements between the observed and calculated values support the idea that the conformations in the crystal are generally retained in solution. In the case of Y_{II}, the observed large difference in Δ may be due to a large contribution of the X_{II} type in solution.

The trans *and* cis *Diastereoisomers of Mexazolam Analogues.*—Except for **1**, there are two chiral carbons in the present mexazolam analogues, *i.e.*, C(3) and C(11b). We have demonstrated that these diastereoisomers in polar solvents generally undergo facile epimerization at C(11b) just like a racemization for **1**, and the configuration of the C(3) carbon atom should be intact during the reactions.[13–15] The stereochemical situation in the reaction can be summarized using the symbols *R* and *S* on the basis of IUPAC rules, adapting the 11b-substituent always to be the smallest group.



From the spatial relationship between the transannular 3-methyl and 11b-substituents with respect to the oxazolidine ring plane, the epimerization reaction in solution can be chemically named as a *trans*⟷*cis* isomerization. Thus, racemic substances in solution will, in general, be a mixture of two *trans* and two *cis* isomers, *i.e.*, the *trans* isomer contains 3(*R*)-11b(*R*) and 3(*S*)-11b(*S*) enantiomers, and the *cis* isomer has 3(*R*)-11b(*S*) and 3(*S*)-11b(*R*) enantiomers. The *trans*/*cis* isomer ratios for each compound in solution can be determined from integration of the ^{1}H NMR signals of the 3-methyl group and have been reported to be 0.3 and 0.09 for **2** and **6**, respectively.[19] The ratios are dependent mainly on the substituents at the 11b-position for mexazolam analogues and are probably dependent on solvents, temperature and some other unidentified factors such as impurities. Regardless of the distribution of isomers at equilibrium, single crystals of all derivatives were crystallized in one polymorph from ethanol, where the rates of isomerization are estimated, from the case of oxazolam,[15] to be fast on the timescale for crystal formation. In the case of the racemic 3,11b-dimethyl derivative, two different

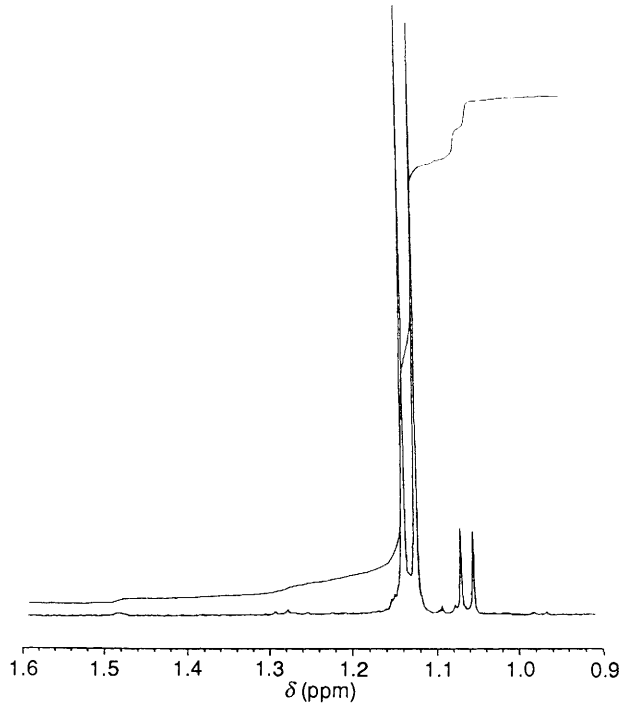


Fig. 9 ^{1}H NMR spectrum of **3** and **4** in the 3-methyl region

crystal systems appeared independently from ethanol. Although conditions which permit a choice between the two systems have not yet been identified, the solubility of isomers in solvent systems used for recrystallization seems to be crucially important. The X-ray molecular structure analyses for all derivatives in this work have revealed that each single crystal contains exclusively one diastereoisomer, *i.e.*, there is no disorder problem attributable to the *trans*–*cis* mixture.[5] The identification of diastereoisomers is also summarized in Table 3. There is a perfect correlation in the solid state between the choices of diastereoisomer and conformation, *i.e.*, the *trans* isomer always adopts Y_{II} while the *cis* isomer adopts X_I. Isolation and crystallization of the counterpart isomer are so far unsuccessful except for **3** and **4** because of the rapid isomerization reactions which occur during the separating processes, *e.g.*, chromatography. It is surprising that **2** gives only the *trans* isomer in the crystal in spite of the three to four fold excess of *cis* isomer in solvents such as ethanol, methanol, chloroform, *etc.*[19] This may be due to the much lower solubility of the *trans* isomer than the *cis* isomer in these solvents.

Most interesting is the case of racemic 3,11b-dimethyl derivatives (**3** and **4**) in this context. The ^{1}H NMR spectrum in the 3-methyl range at *trans*–*cis* equilibrium of this compound in CD_3OD is given in Fig. 9. The relative intensity of the *trans* to *cis* isomer is a function of time after either the *trans* or *cis* isomer

Table 5 Atomic coordinates for compounds 1–6 (esds in parentheses)

Atom	*x*	*y*	*z*
Compound **1**			
O(1)	0.311 1(3)	0.153 2(8)	0.727 3(2)
O(6)	0.446 4(3)	−0.071 3(8)	0.611 4(3)
N(4)	0.338 8(3)	0.390 6(7)	0.640 7(2)
N(7)	0.315 2(3)	−0.128 4(8)	0.603 8(3)
C(2)	0.387 5(5)	0.239(1)	0.750 8(4)
C(3)	0.400 4(4)	0.424(1)	0.699 4(4)
C(5)	0.363 1(3)	0.254 6(9)	0.584 7(3)
C(6)	0.379 8(3)	0.004(1)	0.602 1(3)
C(7a)	0.237 5(3)	−0.059 9(9)	0.598 1(3)
C(8)	0.180 3(3)	−0.194(1)	0.565 7(3)
C(9)	0.102 4(4)	−0.133(1)	0.558 0(3)
C(10)	0.081 1(4)	0.075(1)	0.583 8(4)
C(11a)	0.216 0(3)	0.150 6(9)	0.626 5(3)
C(11)	0.138 1(3)	0.212(1)	0.617 2(3)
C(11b)	0.273 9(4)	0.290(1)	0.672 2(3)
Compound **2**			
O(1)	−0.143 5(3)	0.163 2(1)	0.794 3(3)
O(6)	0.565 6(3)	0.024 4(1)	0.718 8(3)
N(4)	0.201 3(3)	0.149 1(1)	0.787 5(3)
N(7)	0.283 3(3)	0.054 5(1)	0.534 6(3)
C(M)	0.348 1(5)	0.247 1(2)	0.951 8(4)
C(2)	−0.032 0(5)	0.218 1(2)	0.876 1(4)
C(3)	0.187 4(4)	0.193 6(1)	0.930 6(4)
C(5)	0.363 1(4)	0.100 7(2)	0.832 7(4)
C(6)	0.405 5(4)	0.057 5(1)	0.689 9(3)
C(7a)	0.084 7(4)	0.079 2(1)	0.460 7(3)
C(8)	0.030 2(4)	0.070 0(2)	0.284 4(4)
C(9)	−0.162 9(5)	0.088 4(2)	0.196 2(4)
C(10)	−0.302 3(4)	0.116 5(2)	0.283 8(4)
C(11a)	−0.055 0(4)	0.108 0(1)	0.549 2(3)
C(11b)	−0.003 3(4)	0.119 0(1)	0.739 4(4)
C(11)	−0.247 9(4)	0.126 2(2)	0.458 0(4)
Compound **3**			
O(1)	0.243 7(3)	0.465 9(2)	0.790 2(1)
O(6)	−0.441 3(3)	0.582 6(1)	0.614 1(1)
N(4)	−0.108 0(3)	0.464 8(2)	0.751 0(1)
N(7)	−0.278 9(3)	0.452 7(2)	0.565 4(1)
C(2)	0.136 1(5)	0.422 9(2)	0.848 9(2)
C(3)	−0.046 7(4)	0.473 5(2)	0.846 3(2)
C(M)	−0.233 3(5)	0.402 1(3)	0.872 8(2)
C(5)	−0.237 4(3)	0.538 3(2)	0.731 0(2)
C(6)	−0.321 0(3)	0.525 8(2)	0.633 2(2)
C(7a)	−0.132 1(3)	0.387 2(2)	0.560 4(2)
C(8)	−0.173 9(4)	0.305 4(2)	0.475 3(2)
C(9)	−0.035 6(4)	0.241 4(2)	0.458 2(2)
C(10)	0.142 4(4)	0.257 7(2)	0.527 5(2)
C(11b)	0.095 5(3)	0.490 6(2)	0.725 4(2)
C(11a)	0.046 6(3)	0.403 5(2)	0.631 2(2)
C(11)	0.181 1(4)	0.336 7(2)	0.612 5(2)
C(11M)	0.204 6(4)	0.622 3(2)	0.732 1(2)
O(1)*	0.011 8(3)	−0.034 7(2)	0.289 8(1)
O(6)*	0.638 1(3)	0.082 9(2)	0.114 2(1)
N(4)*	0.324 5(3)	−0.035 0(2)	0.251 1(1)
N(7)*	0.296 7(3)	−0.047 4(2)	0.065 5(1)
C(2)*	0.136 1(5)	−0.076 9(3)	0.349 3(2)
C(3)*	0.366 2(4)	−0.026 3(2)	0.346 2(2)
C(M)*	0.509 0(5)	−0.097 6(3)	0.373 1(2)
C(5)*	0.505 9(3)	0.038 4(3)	0.231 1(2)
C(6)*	0.480 3(3)	0.025 5(2)	0.133 3(2)
C(7a)*	0.080 2(3)	−0.112 7(2)	0.061 0(2)
C(8)*	−0.045 8(4)	−0.194 7(2)	−0.025 0(2)
C(9)*	−0.264 5(4)	−0.258 7(2)	−0.041 3(2)
C(10)*	−0.357 4(4)	−0.242 5(2)	0.027 2(2)
C(11b)*	0.120 4(3)	−0.009 5(2)	0.225 5(2)
C(11M)*	0.150 2(4)	0.122 2(2)	0.232 1(2)
C(11)*	−0.231 5(4)	−0.163 4(2)	0.112 6(2)
C(11a)*	−0.012 2(3)	−0.096 9(2)	0.131 0(2)

Table 5 (*continued*)

Atom	*x*	*y*	*z*
Compound **4**			
O(1)	0.167 6(2)	−0.216 9(3)	0.504 6(2)
O(6)	0.512 6(2)	−0.187 1(2)	0.262 9(2)
N(4)	0.314 1(2)	−0.294 7(3)	0.410 9(2)
N(7)	0.377 5(2)	0.003 5(3)	0.288 1(2)
C(M)	0.328 8(5)	−0.585 4(5)	0.472 2(4)
C(2)	0.179 5(4)	−0.382 0(5)	0.515 4(4)
C(3)	0.249 7(4)	−0.446 2(4)	0.436 7(3)
C(5)	0.331 3(3)	−0.292 1(3)	0.304 1(2)
C(6)	0.415 4(2)	−0.156 8(3)	0.282 9(2)
C(7a)	0.264 1(2)	0.049 9(3)	0.301 7(2)
C(8)	0.217 3(3)	0.178 6(4)	0.240 0(2)
C(9)	0.107 5(3)	0.231 8(5)	0.249 3(3)
C(10)	0.045 2(3)	0.159 2(5)	0.319 7(4)
C(11b)	0.256 9(3)	−0.147 6(4)	0.452 4(2)
C(11)	0.092 8(3)	0.033 1(5)	0.381 7(3)
C(11a)	0.203 7(2)	−0.023 6(3)	0.374 6(2)
C(11M)	0.339 3(4)	−0.057 4(4)	0.529 1(3)
Compound **5**			
Cl	0.940 41(9)	0.050 7(3)	0.678 8(1)
O(1)	0.877 7(2)	—0.408 5(6)	0.869 4(2)
O(6)	0.503 4(3)	—0.331 1(6)	0.768 5(3)
N(4)	0.723 7(3)	—0.451 0(6)	0.847 2(3)
N(7)	0.612 3(3)	—0.141 6(6)	0.765 5(3)
C(M)	0.732 8(6)	—0.741(1)	0.914 1(5)
C(2)	0.870 4(4)	—0.570 6(9)	0.907 9(4)
C(3)	0.771 7(5)	—0.620 6(8)	0.863 2(4)
C(5)	0.645 8(3)	—0.448 1(8)	0.764 7(3)
C(6)	0.581 5(3)	—0.303 4(8)	0.765 2(3)
C(7a)	0.694 9(3)	—0.096 8(7)	0.750 0(3)
C(8)	0.688 2(3)	0.037 3(8)	0.692 1(3)
C(9)	0.764 1(4)	0.087 3(8)	0.671 2(3)
C(10)	0.845 8(3)	—0.003 0(8)	0.708 0(3)
C(11b)	0.794 6(3)	—0.316 9(7)	0.862 6(3)
C(11)	0.854 0(3)	—0.134 1(8)	0.766 2(3)
C(11a)	0.779 2(3)	—0.183 3(7)	0.790 3(3)
C(12)	0.809 9(3)	—0.224 5(7)	0.949 2(3)
C(13)	0.742 6(4)	—0.218 7(9)	0.985 5(3)
C(14)	0.759 0(4)	—0.134(1)	1.063 9(4)
C(15)	0.841 9(5)	—0.057(1)	1.107 3(4)
C(16)	0.909 0(5)	—0.065(1)	1.072 3(4)
C(17)	0.894 3(4)	—0.146(1)	0.993 6(4)
Compound **6**			
Cl(1)	0.015 47(3)	0.218 1(2)	0.626 46(7)
Cl(2)	−0.078 15(3)	0.684 1(2)	0.488 47(6)
O(1)	−0.056 37(7)	0.723 8(3)	0.687 0(2)
O(6)	−0.204 29(8)	0.435 8(4)	0.661 2(2)
N(4)	−0.108 95(8)	0.634 4(4)	0.727 9(2)
N(7)	−0.160 42(9)	0.356 7(4)	0.600 9(2)
C(M)	−0.087 3(2)	0.797 6(8)	0.864 6(3)
C(2)	−0.052 4(1)	0.816 1(5)	0.761 8(2)
C(3)	−0.072 2(1)	0.707 3(6)	0.805 7(2)
C(5)	−0.126 3(1)	0.483 6(5)	0.747 2(2)
C(6)	−0.166 8(1)	0.424 1(5)	0.666 1(2)
C(7a)	−0.117 7(1)	0.327 3(5)	0.606 5(2)
C(8)	−0.109 1(1)	0.174 7(5)	0.583 2(2)
C(9)	−0.068 1(1)	0.137 9(5)	0.589 2(2)
C(10)	−0.036 4(1)	0.260 4(5)	0.620 3(2)
C(11)	−0.044 0(1)	0.413 6(5)	0.644 1(2)
C(11a)	−0.085 8(1)	0.453 6(4)	0.635 5(2)
C(11b)	−0.095 7(1)	0.626 3(5)	0.655 5(2)
C(12)	−0.131 5(1)	0.711 8(4)	0.570 9(2)
C(13)	−0.126 3(1)	0.740 5(5)	0.495 4(2)
C(14)	−0.158 4(1)	0.815 9(6)	0.420 1(3)
C(15)	−0.196 5(1)	0.871 7(6)	0.420 6(3)
C(16)	−0.202 4(1)	0.848 9(5)	0.494 5(3)
C(17)	−0.170 5(1)	0.771 0(5)	0.568 8(2)
O(E)	0.270 5(1)	0.789 5(5)	0.434 3(2)
C(20E)	0.271 0(2)	0.894 4(9)	0.366 1(4)
C(21E)	0.234 5(4)	0.993(2)	0.323 0(9)
C(22E)	0.290 1(6)	0.819(3)	0.334(1)

is dissolved, since an isomerization reaction occurs in CD_3OD. The *trans*/*cis* ratio eventually reaches 1:6.9, regardless of the original isomer, after being allowed to stand for 1 day at room temperature. This ratio corresponds to a free energy difference of 1.1 kcal mol^{-1} in favour of X_I for **4**. Since NMR signals attributable to other isomer conformations such as *trans*-X_I or *cis*-Y_{II} were not detected, the free energy difference of conformations in the same isomer should be larger than this value: it should be $> 1.1 + 2.4$ kcal mol^{-1}. In fact, the Arrhenius activation energy of the isomerization from **3** to **4** is found to be *ca.* 15 kcal mol^{-1}, which corresponds well to the barrier of conformational change as referred to **1**. The rate-limiting step of the isomerization therefore involves the two elements of conformational change. A similar effect will be one of the causes of the different kinetic behaviour of mexazolam[4] distinguished from *trans* and *cis* oxazolams which adopt only X_I.

The fairly high conformational barrier should be an important factor for distinguishing **3** and **4** crystallized in the respective independent systems. IR spectra of **3** and **4** show distinctively different absorption patterns in the fingerprint region, 1000–1400 cm^{-1}, as is expected from the bond angle characterization in Table 2 which refers to the difference between the conformations Y_{II} and X_I. However, the introduction of methyl groups into the ring system should induce a change in the conformation. Therefore, the steric effect of the methyl group has a comparable factor in energy with the conformational change. This consideration leads to the somewhat equivocal statement that the reverse correlation of diastereoisomer with conformation, *e.g. cis* isomer of **2** to be X_I, can not be made easily. A complete systematic characterization of spectroscopic and kinetic studies, including these conformational and steric aspects with various substituents, is in progress and will be published elsewhere.[20]

Complementary Notes for Crystal Structures of Mexazolam Analogues.—The phenyl ring orientation may be significant as an extra factor for probing the pharmacological activity of **5**–**7**. The 11b-phenyl ring orientation is evaluated by the torsion angle of N(4)–C(11b)–C(12)–C(17) [or C(13)] ranging from $-90°$ to $+90°$ toward the C(3) to C(5) side. The observed orientations, $+25°$ in **5** and $-6°$ in **6** with 2′-Cl in the stern side of the boat conformation, can be compared with $+22°$ and $+41°$ in the respective 2(*S*)- and 2(*R*)-oxazolams.[5] The 2′-Cl of mexazolam is almost in the bisectional plane of the O(1)–C(11b)–C(11a) angle.

Some benzodiazepinooxazoles are known to make a dimer in the solid state.[5,7] In the present study, the molecules of **2** and **3** form a dimer with a O(6)–N(7′) (*ca.* 2.9 Å) hydrogen bond. Molecules of **1** are arranged in a line along the *b* axis through the N(7)–N(4′) (2.94 Å) hydrogen bonds. Molecules of **4** and **5** make a polymeric spiral chain through N(7)–O(6′) (*ca.* 2.9 Å) hydrogen bonds. Two molecules of **6** form a dimeric interaction with solvate ethanol as the bridge through N(7)–O(E) (2.78 Å) and O(E)–O(6′) (2.75 Å) hydrogen bonds. Hydrogen bonding has been suggested to influence the comformation of cyclic phosphorinanes,[21] but may not be effective in the present mexazolam analogues since the hydrogen bonding in the solid state should be disorganized in solution.

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