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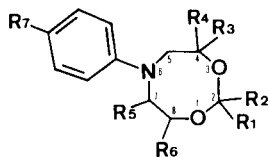
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The stereochemical properties of 2-, 4-, 7-, and 8-methyl substituted 5,6,7,8-tetrahydro-1,3,6-dioxazocines have been investigated by their pmr and cmr spectroscopy. On the basis of the coupling constant and  $\gamma$ -effects, the stereochemical structures are discussed.

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The conformation of medium-ring compounds containing heteroatoms has been studied by means of pmr and cmr spectroscopy [1-4]. For example, Anet *et al.* [5] obtained pmr and cmr data of 1,3-dioxocanes over the range of room temperature to  $-170^\circ$  and concluded that 1,3-dioxocanes exist exclusively in boat-chair (BC) with the oxygen in the BC-1,3 positions. On the other hand, solution studies [6] on azocines by dynamic cmr show that this compound exists as a BC conformation in which the nitrogen resides at the BC-1 position on the molecular plane of symmetry.

We report here the stereochemical structures in solution of 6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocine and its five methyl substituted derivatives, in which three methylene groups of cyclooctane have replaced with a nitrogen and two oxygens.



- 1, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>5</sub> = H, R<sub>4</sub> = R<sub>6</sub> = Me, R<sub>7</sub> = C<sub>1</sub>
- 2, R<sub>1</sub> = R<sub>3</sub> = R<sub>5</sub> = H, R<sub>2</sub> = R<sub>4</sub> = R<sub>6</sub> = Me, R<sub>7</sub> = C<sub>1</sub>
- 3, R<sub>3</sub> = R<sub>6</sub> = R<sub>7</sub> = H, R<sub>1</sub> = R<sub>2</sub> = R<sub>4</sub> = R<sub>5</sub> = Me
- 4, R<sub>3</sub> = R<sub>5</sub> = R<sub>7</sub> = H, R<sub>1</sub> = R<sub>2</sub> = R<sub>4</sub> = R<sub>6</sub> = Me
- 5, R<sub>1</sub> = R<sub>2</sub> = R<sub>5</sub> = H, R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = Me, R<sub>7</sub> = C<sub>1</sub>
- 6, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>5</sub> = R<sub>6</sub> = H, R<sub>7</sub> = C<sub>1</sub>

## EXPERIMENTAL

All the melting points are uncorrected. The pmr and cmr spectra were obtained on JEOL-GSX-400 spectrometer. Chemical shifts are referenced to the central peak of the deuteriochloroform: triplet at 77.00 ppm. Pmr spectra (for the deuteriochloroform solvent) are referenced to internal tetramethylsilane. Gas chromatography was performed on a Hewlett-Packard 5890A instrument fitted with an OV101 capillary column. *N,N*-Bis(2-hydroxyethyl) and *N,N*-bis(2-hydroxypropyl)anilines were prepared by the reaction of the corresponding aniline with ethylene oxide

or propylene oxide, respectively [7]. *N*-(2-Hydroxypropyl)-*N*-(2-hydroxyisopropyl)aniline was prepared from the reaction of aniline and ethyl lactate in the presence of sodium ethoxide and subsequently was treated with lithium aluminum hydride. These *N*-(2-hydroxypropyl)anilines were in turn treated with 2-chloropropionic acid methyl ester, followed by the treatment of lithium aluminum hydride.

## Results and Discussion.

The series of compounds **1-6** was prepared by the reaction of the corresponding anilinodiols with an aldehyde or ketone in methylene chloride over molecular sieves 3 Å at room temperature. In the case of compounds 1-3, two isomers of types **a** and **b** can be separated by the use of a silica gel column with hexane as an eluent. The products of these reactions and physical properties are summarized in Table 1.

Table 1  
Physical Properties of Compounds 1-6

Compound No.	Yield %	Mp °C	C	H (Calcd.)	N
<b>1a</b>	9	[a]	61.16 (61.05)	7.35 (7.09)	5.63 (5.48)
<b>1b</b>	15	87.0-88.0	61.16	7.12	5.39
<b>2a</b>	5	[a]	62.27 (62.23)	7.54 (7.47)	5.03 (5.19)
<b>2b</b>	7	84.8-85.5	62.17	7.51	5.08
<b>3a</b>	45	[a]	72.38 (72.25)	9.43 (9.30)	5.49 (5.62)
<b>3b</b>	8	[a]	72.45	9.48	5.55
<b>4</b>	42	[a]	72.04	9.41	5.51
<b>5</b>	18	134.0-135.2	61.93	7.40	5.30
<b>6</b>	60	88.0-89.0	57.84 (58.03)	6.13 (6.20)	6.07 (6.15)

[a] Liquid.

The pmr spectra of the heterocyclic protons of compounds **1a** and **1b** are displayed in Figure 1 and Table 2. The C-2 protons of compound **1a** give rise to a sharp singlet line at  $\delta$  4.72 and, the two quartets at  $\delta$  3.30 and 3.48 can be assigned to the C-5,7 protons, respectively. The multiplet signal at  $\delta$  3.91 belongs to the methine protons at C-4,8. In contrast, in compound **1b**, the methine protons for C-5,8 appeared at  $\delta$  3.91, and the resonance of the C-5,8 protons at  $\delta$  3.17 and 3.79. Striking differences in

Table 2  
PMR Chemical Shifts of Compounds 1-6

Compound No.	2-H		4,8-H	Chemical Shifts, $\delta$ 5,7-H		2-CH <sub>3</sub>	4,8-CH <sub>3</sub>
	ax	eq		ax	eq		
1a		4.72 (s)	3.91 (m)	3.30 (q)	3.48 (q)	—	1.26 (d)
1b	4.42 (d)	5.27(d)	3.91(m)	3.17 (g)	3.79(d)	—	1.23 (d)
2a	4.95 (q)	—	4.06 (m)	3.13 (q)	3.34 (d)	1.23 (d)	1.19 (d)
2b	4.55 (q)	—	4.26 (m)	3.34 (q)	3.46 (q)	—	1.22 (d)
3a	—	—	3.87 (m)	3.16 (q)	3.77 (d)	1.25 (d)	1.21 (d)
3b	—	—	4.15 (m)	3.08 (q)	3.77 (q)	1.36 (s)	1.17 (d)
4	—	—	4.11 (q)	4.15 (m)	4.15 (m)	1.39 (s)	1.28 (d) [a]
5	4.75 (d)	5.04 (d)	4.06 (m)	3.27 (q)	3.14 (d)	1.29 (s)	1.01 (d)
6	4.43 (s)	—	3.72 (t)	3.43 (q)	4.06 (m)	1.27 (s)	1.24 (d) [a]
			4.18 (m)	3.23 (q)	3.33 (q)	1.30 (s)	1.20 (d)
			3.99 (m)	3.22 (d)	3.74 (d) [b]	—	1.22 (d)
				3.05 (q)	3.55 (d)	—	1.19 (s)
				3.44 (q)	—	—	—

[a] Chemical shift of 7-CH<sub>3</sub>. [b] Values for ax and eq may be interchanged.

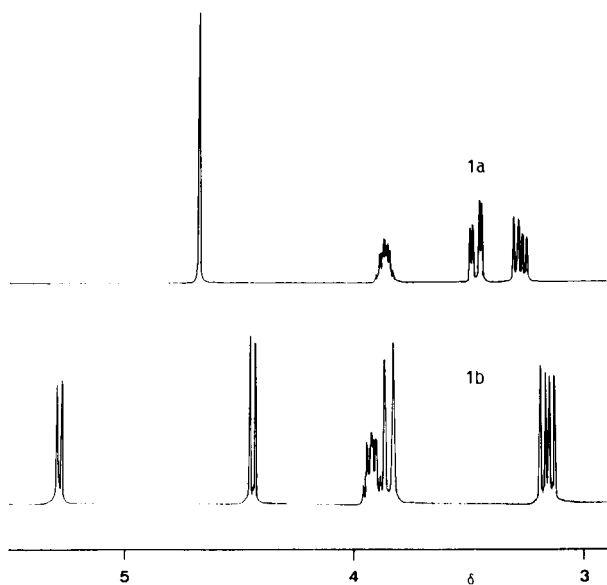


Figure 1. The pmr spectra of the heterocyclic protons of compounds 1a and 1b.

compound **1b** compared with **1a** are recognizable in the signals of the C-2 protons. That is, two sharp doublet peaks for compound **1b** appeared at  $\delta$  4.42 and 5.27. The presence of the two kinds of peaks can be expected to exist for diastereotopic protons with a symmetrical conformation, while the single methylene resonance for C-2 protons show time-averaged symmetry at room temperature. The pmr spectra of compound **1a** at various temperatures are shown in Figure 2. Below  $-100^\circ$ , the band of the C-2 protons for compound **1a** splits into two and at  $-120^\circ$  two well separated bands are found ( $\delta$  4.68 and 4.79). At  $-120^\circ$ , the four protons at C-5,7 give separate resonances at  $\delta$  2.98, 3.46, 3.89 and 3.96, whereas the C-4,8 protons remain unchanged at  $\delta$  3.76. The presence of two resonances each for the C-2 protons and the C-5,7 protons at low temperature indicates that this compound exists as a 1:1 mixture of mirror-image symmetrical conformations.

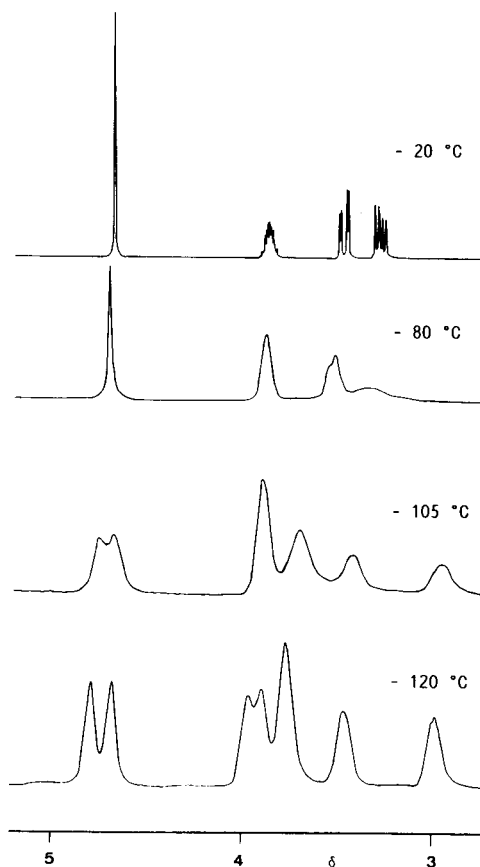
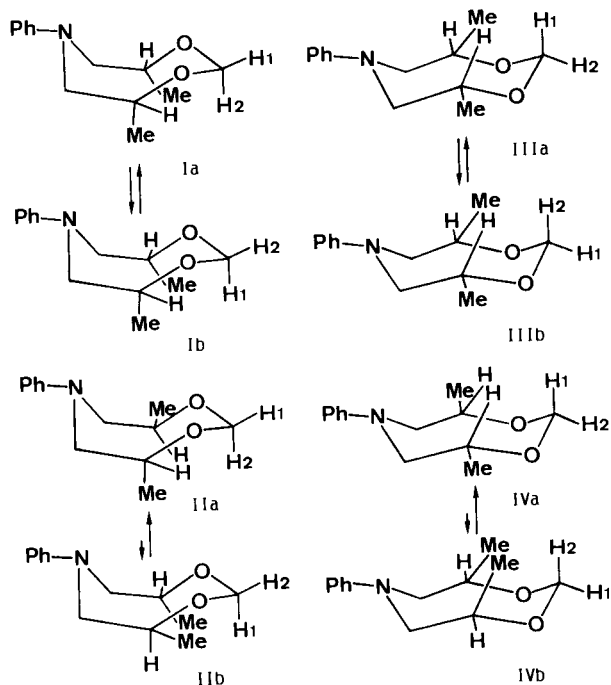


Figure 2. Patrial 400-MHz pmr spectra of compound 1a in dichlorodifluoromethane at several temperatures.

Judging from an examination of molecular models, cyclo-condensation of meso-anilindiols with paraformaldehyde gave the equatorial (eq)-eq and axial (ax)-ax methyl groups, while an analogous condensation with racemic anilindiols gave the eq-ax methyl groups. Some possible stereoisomers of types **a** and **b** are

illustrated in Scheme 1. Isomers **Ia** and **Ib** are the eq-ax isomers with BC form, whereas **IIa** and **IIb** are the eq-eq and ax-ax isomers. Similarly, **IIIa** and **IIIb** are the eq-ax isomers with chair (CC) form, whereas **IVa** and **IVb** are the eq-eq and ax-ax isomers. The configurations of **IIb** and **IVb** are unlikely because of non-bonded interactions between the 4,8-diaxial methyl groups. In the case of configurations **I** and **III**, the C-2 protons are diastereotopic protons, while the C-2 protons of configurations **II** and **IV** are enantiotopic protons.

Scheme 1. Possible stereoisomers of compounds **1a** and **1b**.



In the chair form of cyclohexane, typical coupling constants [8] span the following ranges:  $J_{aa} = 9.5\text{--}12.5$  Hz;  $J_{ea} = 3.0\text{--}4.5$  Hz;  $J_{ee} = 2\text{--}3$  Hz. Eliel [9] has also reported that  $J_{aa}$  and  $J_{ea}$  for *cis*-4,6-dimethyl-1,3-dioxane with chair form are 9.5 and 3.1 Hz. The vicinal coupling constants between the C-4,5 protons and the C-7,8 protons are given in Table 3. Compound **1b** shows a vicinal coupling constant of 9.77 Hz ( $J_{aa}$ ). This value is a coupling constant for Hax and quite incompatible with the presence of Heq in

Table 3  
Coupling Constants,  $J_{4,5}$ , of Compounds 1-5

Compound No.	Coupling Constant, Hz		
	cis	trans	geminal
<b>1a</b>	3.54	7.69	14.93
<b>1b</b>	0.00	9.77	15.39
<b>2a</b>	2.56 (2.19)	9.71 (7.88)	15.02 (15.38) [a]
<b>2b</b>	0.00	9.34	15.57
<b>3a</b>	3.29	6.02	15.76
	3.29	6.59	12.56 [a]
<b>3b</b>	0.00	7.33	16.49
	5.49	11.73	11.73 [a]
<b>4</b>	2.93	8.42	14.65
<b>5</b>	—	—	15.39
	0.00	9.53	14.89 [a]

[a] Coupling constants of  $J_{7,8}$ .

the positions C-4,8. On the other hand, the vicinal coupling constant for compound **1a** is smaller than that of **1b** and intermediate in magnitude between  $J_{aa}$  and  $J_{ea}$  for typical coupling constants of cyclohexane.

In order to obtain more precise information on the possible orientation of the 4,8-dimethyl groups for **1a** and **1b**, cmr spectra at C-2 was examined. As can be seen in Table 4, the shift differences of C-2 for **1a** and **1b** are consistent with the above arguments. The C-2 for **1a** appeared at 93.6 ppm, whereas these for **1b** appeared at 96.5 ppm, very close to the parent compound **6**. The upfield shift of 2.9 ppm at C-2 in **1a** relative to **1b** is due to the  $\gamma$ -gauche relationship [10] between the axial methyl group at C-4 or C-8 and the C-2 ring carbon. That is, one of the methyl groups on C-4 or C-8 of **1a** indicates the axial orientation but two methyl groups on C-4,8 for **1b** exist in the diequatorial orientation.

From the above results, it may be thought that the geometry of compound **1b** is **IIa** or **IVa** in Figure 1, and the equilibrium between eq-eq and ax-ax methyl groups lies very much on the side of the eq-eq conformation. On the other hand, compound **1a** is a mixture of interconverting eq-ax forms of either **I** or **III**.

Aromatic solvent shifts provide confirmatory evidence in support of the BC conformation in compound **1**. Since it has been experimentally well established that aromatic systems like benzene

Table 4  
Carbon-13 Chemical Shifts of Compounds 1-6

Compound No.	Chemical Shifts, $\delta$							
	C-2	C-4	C-5	C-7	C-8	2-CH <sub>3</sub>	4,8-CH <sub>3</sub>	7-CH <sub>3</sub>
<b>1a</b>	93.6	71.3	56.8	56.8	71.3	—	20.2	—
<b>1b</b>	96.5	73.0	59.2	59.2	73.0	—	18.7	—
<b>2a</b>	98.2	72.9	56.4	56.3	63.7	19.8	20.4, 21.1	—
<b>2b</b>	104.9	73.0	59.6	59.6	73.0	19.5	24.6	—
<b>3a</b>	100.2	67.1	53.4	64.3	54.3	25.3, 25.1	20.5	14.7
<b>3b</b>	100.5	67.6	51.3	63.3	51.4	26.0, 24.2	20.3	13.0
<b>4</b>	100.2	65.9	55.9	55.9	65.9	25.6	20.5	—
<b>5</b>	89.6	75.8	61.2	61.0	73.4	—	18.9, 25.2	—
<b>6</b>	97.5	66.4	52.0	52.0	66.4	—	—	—

are capable of coordinating at electron-deficient sites within a solute molecule [11-13], solute protons coordinated in the vicinity of the aromatic solvent should experience large shielding effects. For example, the C-3,4 methylene protons for tetrahydrofuran should be strongly shielded while the remaining protons may be only marginally affected [14]. Assuming that collision complexes of a similar geometry are formed between solvent benzene molecules and the two oxygens and a nitrogen atom in the 1,3,6-dioxazocine system, then the geometry of the association differs in the two isomeric 1,3,6-dioxazocines (I-IV in Scheme 1). The following considerations are presented. For the I-IV conformations, aromatic solvent association should take place from the C-5,7 protons. Consequently, the C-2 protons are only marginally affected in the I and II conformations, while the remaining ring protons and the methyl groups are shielded. In the III and IV conformations, the ax-methyl and the ax-hydrogen(s) on the C-4 and/or C-8 and the C-2 protons are only marginally affected.

The benzene-induced shift ( $\Delta = \delta$  deuteriochloroform -  $\delta$  perdeuteriobenzene) of compound **1a** showed that the C-4,8, C-5,7 protons and the C-4,8 methyl protons are shielded (+0.28, +0.31 and +0.23 ppm, respectively) while the C-2 protons are only marginally affected (+0.14 ppm). For compound **1b**, the C-4,8 (+0.34 ppm), C-5,7 protons (+0.33 and +0.42 ppm) and the C-4,8 methyl protons (+0.28 ppm) are shielded while Heq (+0.11 ppm) and Hax (+0.25 ppm) protons on the C-2 are only marginally affected. Only structures of I and II in Figure 1 are compatible with these observations. It may be concluded that the preferred structure of **1a** is considered to take the BC conformation with ax-eq methyl groups. In contrast, the preferred structure of **1b** exists in the BC conformation with eq-eq methyl groups.

In the case of compounds **4** and **5**, the sole product was obtained while two isomers of types **a** and **b** can be separated for compounds **2** and **3**. The existence of isomeric pairs is readily rationalized in terms of steric effects associated with diaxial interaction. If one assumes, that the methyl group on C-4 and/or C-8 for compound **4** is an axial orientation, there is steric repulsion between the axial methyl group on C-4 and/or C-8 and the axial methyl group on C-2. Since two methyl groups on C-4,8 exist in only the equatorial configuration. The methyl group on C-8 for compound **5** exists in the equatorial configuration for the same reason.

In accordance with the foregoing arguments, compounds **2a** and **2b** should exist in the configuration with a 2-eq methyl

group. Therefore, it can be considered that compound **2a** exists in the BC conformation with 2,4-dieq and 8-ax methyl groups, whereas the methyl groups of **2b** exist with 2,4-dieq and 8-eq configuration. The nmr data are compatible with this supposition. The upfield shifts of 6.7 ppm at the C-2 carbon of isomer **2a** are due to the  $\gamma$ -gauche relationship between the ax methyl group on C-8 and the axial hydrogen at the C-2 carbon. Moreover, the pmr spectra of compounds **2a** and **2b** displayed similar coupling patterns to compounds **1a** and **1b** as shown in Tables 2 and 3.

The compounds **3** exist in the configuration in which the C-4 methyl group would avoid the axial position because of an interaction between the 2-ax methyl group. The coupling constants  $J_{7,8}$  for compounds **3a** and **3b** are 6.59 and 11.73 Hz, respectively. The coupling constant of 11.73 Hz is for Hax protons and quite incompatible with the presence of Heq proton on the C-7 position. That is, the preferred structure of compounds **3a** and **3b** exist in the BC conformation in which the 4- and 7-methyl groups are equatorial and axial, in which the 4- and 7-methyl groups are equatorial and equatorial, respectively.

#### REFERENCES AND NOTES

- [1] F. A. L. Anet and M. Ghiaci, *J. Org. Chem.*, **45**, 1224 (1980).
- [2] H. Faucher, A. C. Guimaraes and J. B. Robert, *Tetrahedron*, **37**, 689 (1981).
- [3] N. J. Leonard, J. W. Milligan and T. L. Brown, *J. Am. Chem. Soc.*, **82**, 4075 (1960).
- [4] J. B. Lambert and S. A. Khan, *J. Org. Chem.*, **40**, 369 (1975).
- [5] F. A. L. Anet, P. J. Degen and J. Krane, *J. Am. Chem. Soc.*, **98**, 2059 (1976).
- [6] J. B. Lambert and S. A. Khan, *J. Org. Chem.*, **40**, 369 (1975).
- [7] K. D. Petrov, *Sb. Statei Khim., Akad. Nauk SSSR*, **1**, 374 (1953); *Chem. Abstr.*, **49**, 997g (1955).
- [8] A. C. Huitric, J. B. Carr, W. F. Trager and B. J. Nist, *Tetrahedron*, **19**, 2145 (1963).
- [9] E. L. Eliel and M. C. Knoeber, *J. Am. Chem. Soc.*, **90**, 3444 (1968).
- [10] S. H. Grove, J. P. Guthrie, J. B. Stothers and C. T. Tan, *J. Magn. Reson.*, **10**, 227 (1973).
- [11] J. W. ApSimon, W. G. Craig, P. V. DeMarco, D. W. Mathieson and W. B. Whalley, *Tetrahedron*, **23**, 2375 (1967).
- [12] W. Amann and G. Kresge, *Tetrahedron Letters*, 4909 (1968).
- [13] E. J. Strom, B. S. Snowden and P. A. Toldan, *Chem. Commun.*, 50 (1969).
- [14] T. Ledaal, *Tetrahedron Letters*, 1683 (1968).