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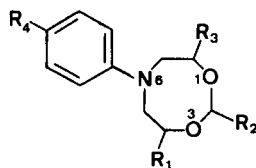
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Heterocyclic compounds of four 6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazines have been synthesized by condensation of the corresponding *N,N*-bis(2-hydroxyethyl)- or *N,N*-bis(2-hydroxypropyl)anilines with aldehyde or ketone in the presence of acid. The pmr and cmr spectra of these compounds were recorded to determine their stereochemical structures. On the basis of the chemical shifts due to the γ -effects, the stereochemical structures are discussed.

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Recently, the stereochemical structures of six-, seven-, and eight-membered ring heterocyclic compounds have been investigated by means of pmr and cmr spectroscopy. For example, detailed nmr studies for conformational analyses of cyclooctane [1], 1,3-dioxane [2], and 1,3-dioxepane [3] by using nmr have recently been reported. From these results, it was found that the compounds with rings larger than seven-membered ring have relatively low ring-torsional barriers [3,4] and that the barrier of a ring inversion becomes greater due to the introduction of bulky substituents or the replacement of methylene group in a ring by heteroatoms [1,5]. With these findings as a background, this paper describes the synthesis and spectral behavior of the following tetrahydro-1,3,6-dioxazine system.



- 1, $R_1=R_2=R_3=H$ $R_4=p\text{-Cl}$
- 2, $R_1=R_3=H$ $R_2=CH_3$ $R_4=p\text{-Cl}$
- 3, $R_1=R_3=R_4=H$ $R_2=di\text{-}CH_3$
- 4, $R_1=R_2=R_3=CH_3$ $R_4=p\text{-Cl}$

The series of compounds **1-4** was prepared by the reaction of the corresponding *N,N*-bis(2-hydroxyethyl)- or *N,N*-bis(2-hydroxypropyl)anilines with an aldehyde or a ketone in the presence of *p*-toluenesulfonic acid. The products of these reactions and their physical properties are summarized in Table 1.

Table 1

 Yields and Analytical Data of Compounds **1-4**

Compound No.	Yield %	Mp °C	Found (Calcd.) %		
			C	H	N
1	60	88.0-89.0	57.84 (58.03)	6.13 (6.20)	6.07 (6.15)
2	22	50.9-51.8	59.83 (59.63)	6.93 (6.67)	5.42 (5.79)
3	31	[a]	70.45 (70.56)	8.84 (8.65)	6.03 (6.33)
4a	8	[a]	61.98 (62.33)	7.66 (7.47)	5.28 (5.19)
4b	14	84.8-85.8	62.17	7.51	5.08

[a] Liquid.

In compound **4**, two isomers of **4a** and **4b** can be separated by the use of a silica gel column with hexane as the eluent, whereas compounds **1**, **2** and **3** were obtained as the sole product.

The pmr spectra of the heterocyclic protons of **1-4** are shown in Figure 1 and Table 2. Compounds **1** and **3** displayed similar sets of methylene protons on C-4, 8 and C-5,

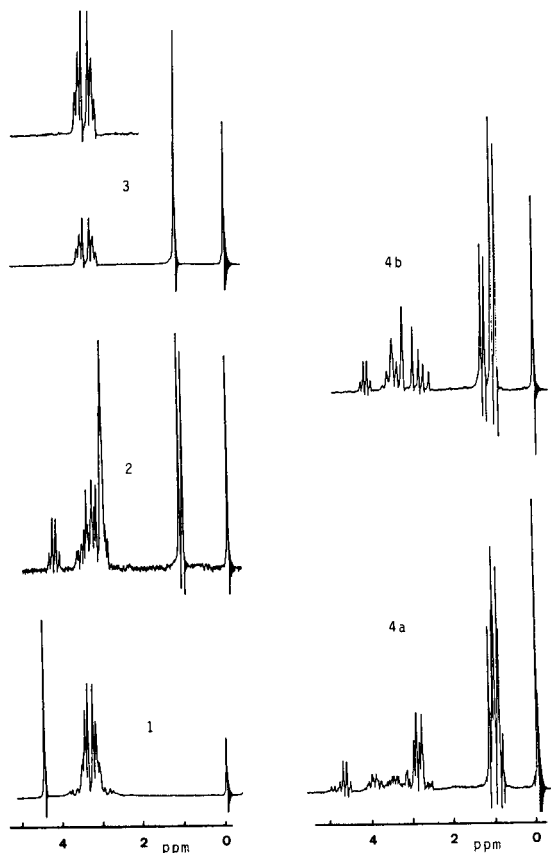


Figure 1. PMR Spectra of the Heterocyclic and Methyl Protons of **1-4** in perdeuteriobenzene.

Table 2
Proton Chemical Shifts of Compounds 1-4

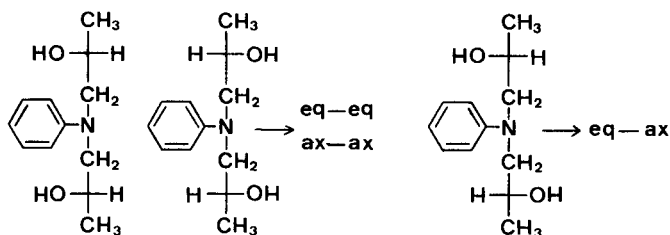
Compound No.	H-2		Chemical shifts, δ		2-CH ₃	4,8-CH ₃
	ax	eq	H-4,8	H-5,7		
1	4.43 (s)		3.44 (q)		—	—
2	4.24 (q)	—	2.92-3.70 (m)		1.16 (d)	—
3	—	—	3.55 (q)	3.21 (q)	1.20 (s)	—
4a	4.68 (q)	—	3.48 (m)	2.55-3.33 (m)	1.10 (d)	0.95 (d)
			3.95 (m)			0.98 (d)
4b	3.45 (q)	—	4.07 (q)	2.72 (q)	3.32 (q)	1.21 (d)
						0.96 (d)

7 at δ 3.4-3.5 (q) and 3.1-3.2 (q), for which a straightforward analysis was possible. In contrast, in the compound **2**, the methylene protons on C-4, 8 and C-5, 7 gave complicated multiplets due to overlap of the protons on C-4, 8 and C-5, 7. In the case of the 4,8-dimethyl compounds, striking differences between **4a** and **4b** are recognizable in the spectral pattern of the C-4, 8 and methyl groups. Compound **4a** shows two sets of methyl groups at δ 0.95 (d) and 0.98 (d), whereas compound **4b** shows one set of methyl groups at δ 0.96 (d). As can be seen in Table 3, similar phenomena is observed for the cmr spectra of the C-4, 8 methyl carbons. That is, the methyl carbons attached to C-4, 8 for **4a** appeared nonequivalently at δ 20.43 and 21.07, whereas those for **4b** appeared equivalently at δ 24.57. Similarly, the cmr spectra of C-4 and C-8 or C-5 and C-7 show a same chemical shift for **4b**.

Table 3
CMR Chemical Shifts of Compounds 1-4

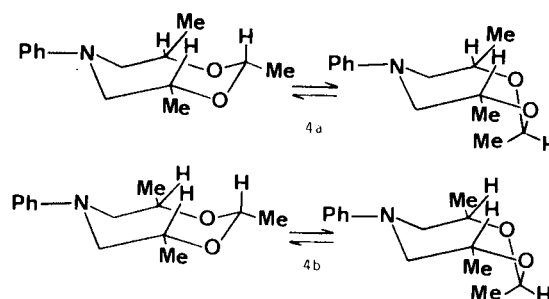
Compound No.	Chemical shifts, δ						
	C-2	C-4	C-5	C-7	C-8	2-CH ₃	4,8-CH ₃
1	97.50	66.37	51.99	51.99	66.37	—	—
2	102.81	64.67	52.17	52.17	64.67	21.37	—
3	100.07	59.64	50.64	50.64	59.64	24.88	—
4a	98.15	72.90	56.25	56.44	63.72	19.84	20.43 21.07
4b	104.85	73.05	59.61	59.61	73.05	19.54	24.57

Scheme 1



Judging from an examination of molecular models, cyclocondensation of meso amino alcohols I and II with acetaldehyde gave the equatorial (eq)-eq and axial (ax)-ax methyl groups, respectively, while an analogous condensation with III gave the eq-ax methyl group, as can be seen in the Scheme 1. Therefore, **4a** has the structure of eq-ax methyl groups and **4b** has either eq-eq or ax-ax methyl groups. The configuration of the 4,8-diaxial methyl groups is unlikely because of nonbonded interactions between the 4,8-diaxial methyl groups and the lone pair electrons attached to the nitrogen or oxygen atoms or methine proton on C-2. Therefore, it can be considered that **4b** has the structure of eq-eq methyl groups. From the above considerations, some possible stereoisomers of **4a** and **4b** are illustrated in Scheme 2.

Scheme 2



The orientation of 4,8-dimethyl groups for **4a** and **4b** is further illustrated by means of the cmr spectra at C-2. The shift differences of C-2 for **4a** and **4b** are consistent with the above arguments. The C-2 for **4a** appeared at δ 98.15, whereas these for **4b** appeared at δ 104.85. The relationship between the C-2 and the axial methyl group in **4a** is gauche, whereas the same relationship in **4b** is anti. That is, the upfield shift of 6.7 ppm at the C-2 for **4a** relative to **4b** is due to the gauche γ relationship between the axial methyl group and the C-2 for **4a**.

In order to determine the orientation of a monosubstituted methyl group at C-2 for **2** and **4**, the cmr chemical shifts for **2** with one substituent at C-2 are compared with **3** having the axial and equatorial methyl groups at C-2. The chemical shifts of C-4, 8 in **3** appeared at δ 59.64, whereas those in **2** appeared at δ 64.67. The C-4, 8 chemical shift of **3** appeared at higher field (about 5 ppm) than those of **2**. Therefore it can be considered that the geometrical relationship of **3** between C-4, 8 and the axial methyl group attached to C-2 is γ -gauche, whereas the same relationship of **2** is anti. From the results mentioned above, equilibrium between the 2-equatorial and 2-axial orientations of **2** is shifted well over the 2-equatorial conformation. Similarly, it can be considered that the preferred orientation of the methyl group at C-2 for **4a** and **4b** is the equatorial form.

EXPERIMENTAL

All the melting points are uncorrected. The pmr spectra were determined in deuteriobenzene- d_6 with JEOL JNM-PMX-60 and JNM-PS-100 spectrometers using tetramethylsilane as an internal standard. The cmr spectra were recorded on a Hitachi R-90H FT spectrometer operating at 22.6 MHz with complete proton decoupling. Pulse width and repetition time were 12 μ s for 45° pulse and 4 s, respectively. The spectra were observed as a deuteriochloroform solution and their chemical shifts were referred to the internal tetramethylsilane. *N,N*-Bis(2-hydroxyethyl)- and *N,N*-bis(2-hydroxypropyl)anilines employed as the starting materials were prepared by the reaction of the corresponding aniline with ethylene oxide or propylene oxide, respectively [6].

6-(*p*-Chlorophenyl)-5,6,7,8-tetrahydro-4H-1,3,6-dioxazine (1).

A solution of *N,N*-bis(2-hydroxyethyl)-*p*-chloroaniline (5.0 g, 23.2 mmoles) and *p*-toluenesulfonic acid (1.8 g, 9.4 mmoles) in benzene (10 ml) was added to a stirred suspension of paraformaldehyde (4.5 g 49.5 mmoles) in benzene (50 ml). This solution was heated to reflux and the condenser was equipped with a Dean-Stark trap. After stirring 20 hours, the solvent was evaporated *in vacuo*. The excess paraformaldehyde which precipitated was filtered off and washed with a small amount of benzene. The filtrate was dried over sodium sulfate and evaporated to yield a pale yellow crystalline solid which exhibited two main spots at R_f 0.36 and 0.01 on an analytical tlc plate developed with methylene chloride. The spot with R_f 0.01 is the starting amino alcohol. Recrystallization from a mixture of hexane and benzene afforded **1** as white crystals, identified on the basis of the spectral data shown in Tables 1, 2 and 3; ir (potassium bromide): 2945 (m), 2880 (m), 2852 (m), 1590 (s), 1502 (s), 1392 (m), 1358 (s), 1258 (m), 1234 (m), 1188 (m), 1179 (m), 1167 (m), 1130 (s), 1112 (s), 1078 (m), 1042 (s), 1005 (s), 979 (s), 811 (s) and 800 (s) cm^{-1} .

2-Methyl-6-(*p*-chlorophenyl)-5,6,7,8-tetrahydro-4H-1,3,6-dioxazine (2).

The product **2** was obtained by the reaction of *N,N*-bis(2-hydroxyethyl)-*p*-chloroaniline (5.0 g, 23.2 mmoles) with acetaldehyde (2.3 g, 51.1 mmoles) in a similar manner to that for the preparation of **1**. The reaction mixture exhibited two main spots at R_f 0.48 and 0.02 on an analytical tlc plate developed with methylene chloride. By the use of a column of silica gel eluted with hexane, the fraction with R_f 0.48 was evaporated to yield colorless crystals which were recrystallized and identified as **2**; ir (potassium bromide): 2920 (s), 2874 (s), 1588 (s), 1498 (s), 1378 (s), 1350 (s), 1278 (m), 1237 (m), 1189 (m), 1132 (s), 1060 (s), 1007 (m), 921 (m), 865 (m), 798 (m) and 735 (m) cm^{-1} .

2,2-Dimethyl-6-phenyl-5,6,7,8-tetrahydro-4H-1,3,6-dioxazine (3).

A mixture of 5.0 g (27.6 mmoles) of *N,N*-bis(2-hydroxyethyl)aniline, 3.4

ml (23.9 mmoles) of 2,2-dimethoxypropane, 2.0 ml of acetone, 50 ml of benzene and a catalytic amount of *p*-toluenesulfonic acid were heated near 65° for 3 hours to allow some methanol, benzene and acetone to distill off. Dry benzene was added periodically to the reaction flask. The remaining benzene was then evaporated to yield a pale yellow oil, which exhibited two main spots at R_f 0.40 and 0.01 on an analytical tlc plate developed with methylene chloride. By the use of a column of silica gel eluted with hexane, the fraction with R_f 0.40 was evaporated to yield colorless oil and identified as **3**; ir (neat): 2990 (m), 2910 (m), 2856 (m), 1594 (s), 1499 (s), 1455 (m), 1375 (s), 1358 (s), 1275 (m), 1246 (m), 1205 (s), 1150 (s), 1074 (m), 1050 (s), 1030 (m), 1005 (m), 895 (m), 852 (m), 795 (m), 740 (s) and 688 (s) cm^{-1} .

2,4,8-Trimethyl-6-(*p*-chlorophenyl)-5,6,7,8-tetrahydro-4H-1,3,6-dioxazine (4a and 4b).

The products of **4a** and **4b** were obtained by the reaction of *N,N*-bis(2-hydroxypropyl)-*p*-chloroaniline with acetaldehyde in a similar manner to that for the preparation of **1**. The reaction mixture exhibited three main spots at R_f 0.42, 0.28 and 0.02 on an analytical tlc plate developed with methylene chloride. The reaction mixture was separated on a column of silica gel using hexane as an eluent. The fraction with R_f 0.42 afforded **4a** as colorless oil and identified on the basis of the spectral data shown in Table 1, 2 and 3; ir (neat): 2962 (s), 2925 (m), 1595 (s), 1498 (s), 1449 (m), 1392 (s), 1370 (s), 1330 (m), 1238 (m), 1188 (s), 1165 (m), 1132 (s), 1065 (s), 990 (m), 978 (m), 805 (s) and 749 (s) cm^{-1} .

Similarly, the fraction with R_f 0.28 was evaporated to yield white crystals which were recrystallized and identified as **4b**; ir (potassium bromide): 2960 (s), 2915 (s), 2880 (m), 1590 (s), 1495 (s), 1449 (m), 1383 (s), 1366 (s), 1325 (s), 1239 (s), 1190 (s), 1178 (s), 1139 (s), 1120 (s), 1061 (s), 982 (s), 805 (s) and 773 (w) cm^{-1} .

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