The Stereochemistry of 4,8-Dimethyl-6-phenyl-5,6,7,8-tetrahydro-4H-1,3,6-dioxazocin-2-ones Using NMR

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Two isomeric 4,8-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4H-1,3,6-dioxazocin-2-ones were prepared, and their pmr and cmr spectra were examined. From the tris(dipivaloylmethanato) europium (Eu(dpm)₃) shift reagent and the dihedral angle, the title compounds are found to exist in the eq-ax and eq-eq methyl groups with boat-chair form.

Recently, the stereochemical structures of six-, seven- and eight-membered ring heterocyclic compound are well investigated by means of pmr and cmr spectroscopies. For example, detailed nmr studies for conformational analyses of 1,3-dioxane [1], 1,3-dioxepane [2] and 1,3,2-dioxathiane 2-oxide [3] have been reported. From these results, it is known that the large ring compounds than seven-membered ring have relatively low ring-torsional barriers [2,3], but the barrier of a ring inversion increases as the introduction of bulky substituents or replacement of a ring methylene group by hetero atoms [1,5]. Buchanan [3] reported that 4-phenyl-1,3,2-dioxathiane 2-oxide exists in two stereochemical isomers and that the assignment of these isomers could be made by the use of nmr and ir spectroscopies.

In our previous papers [6,7], we have reported the syntheses and the stereochemical structures of 4,8-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4H-1,3,2,6-dioxathiazocine 2-oxides. In continuation of our studies concerning the stereochemistry of eight-membered heterocyclic compounds, this paper will describe the stereochemical structures of 4,8-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4H-1,3,6-dioxazocin-2-ones, which had a similar to that of dioxathiazocine skeleton.
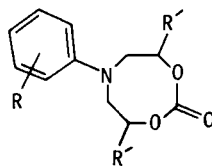
1, R=H, R′=CH₃
2, R=m-CH₃, R′=CH₃
3, R=p-CH₃, R′=CH₃
4, R=m-Cl, R′=CH₃
5, R=p-Cl, R′=CH₃
6, R=p-CH₃, R′=H

EXPERIMENTAL

meters in deuteriochloroform. Cmr spectra were obtained using Hitachi R-90H FT spectrometer operating at 22.6 MHz, with complete proton decoupling. The pulse width and repetition time were 12 µs for 45° pulse and 4 s respectively. N,N-bis(2-Hydroxypropyl)anilines were prepared by the reaction of the corresponding anilines with ethylene oxide or propylene oxide [8].

Result and Discussion.

Transformation of amino alcohols to 4,8-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4H-1,3,6-dioxazocin-2-ones **1-5** was accomplished by the reaction with phosgene in ethyl acetate. A slight excess of pyridine was used as the proton acceptor. The products of these reactions and their physical properties are summarized in Table 1. The structure of **1-5** is supported by analytical and spectral data. In each

Table 1

Physical Properties of Compounds **1-6**

Compound No.	Yield %	Mp °C	Found (Calcd) %			IR C=O
			C	H	N	ν cm⁻¹
1a	19	87.7-88.4	66.24 (66.36)	7.31 (7.28)	5.88 (5.95)	1735
1b	26	110.8-111.6	66.37	7.32	5.81	1740
2a	18	- [a]	67.85 (67.45)	7.92 (7.68)	5.71 (5.62)	1740
2b	19	104.4-105.2	67.34	7.71	5.46	1735
3a	20	68.6-69.2	67.42	7.74	5.52	1730
3b	24	144.3-145.2	67.11	7.70	5.61	1730
4a	13	81.5-82.4	57.92 (57.88)	5.98 (5.98)	5.08 (5.19)	1750
4b	26	87.7-88.5	58.19	6.07	5.05	1735
5a	17	99.1-100.1	57.85	6.02	5.08	1740
5b	26	134.0-135.0	58.11	6.05	5.15	1735
6	11	105.2-106.0	64.96 (65.14)	6.79 (6.83)	6.33 (6.27)	1732

[a] Liquid.

reaction, two isomers of types a and b can be separated by the use of silica-gel column with benzene as an eluents. Existence of isomeric pairs requires that these heterocyc-

lic compounds possess an asymmetric carbon atom. This conclusion is reinforced by the compound **6**. Thus, we tried the reaction of *N,N*-bis(2-hydroxyethyl)-*p*-toluidine having no 4,8-disubstituted methyl groups with phosgene by a similar synthetic method to **1-5**. In this reaction, the sole product was obtained because of lack carbon asymmetry. From the above results, it may be thought that the isomers a and b are configurational isomers of either equatorial(eq)-eq, eq-axial(ax), or ax-ax methyl groups.

The cmr chemical shifts of compounds **1-6** are shown in Table 2. The cmr spectra of C-4 and C-8 or C-5 and C-7

Table 2

CMR Chemical Shifts of Compounds **1-6**

Compound No.	C-4,8	C-5,7	4,8-Me	C=O	R
1a	77.1	58.0	18.0	154.0	–
1b	76.1	58.5	16.8	154.8	–
2a	77.1	61.6	17.9	154.0	22.0
2b	76.3	58.7	17.0	154.8	21.9
3a	76.9	58.2	17.9	154.0	20.1
3b	76.3	59.2	16.9	154.9	20.3
4a	76.8	58.0	18.0	154.6	–
4b	75.8	58.4	17.0	153.8	–
5a	76.8	58.2	18.0	153.8	–
5b	76.0	58.7	16.9	154.8	–
6	68.7	52.1	–	155.7	20.3

show a same chemical shift for types a or b. It can therefore be considered that the structure of 1,3,6-dioxazocin-2-ones exists in a symmetry form. Judging from the examination of the molecular model, configuration of 4,8-diaxial methyl groups with symmetry form is unlikely because of nonbonded interactions between the 4,8-diaxial methyl groups and the lone pair electrons attached to the nitrogen atom or carbonyl oxygen atom. Therefore, it can be considered that the isomers a and b are configurational isomers of either eq-eq or eq-ax methyl groups.

Although Eu(dpm)₃ has electron donors such as ethers and esters, it can be considered that carbonyl oxygen atom of 1,3,6-dioxazocin-2-ones affords the only favored site for complexation with Eu(dpm)₃ because of its much greater Lewis basicity than 1,3-oxygen atoms. Assuming that the europium atom complexes on the exocyclic 2-oxygen atom, it can be expected that chemical shift differences of 4,8-dimethyl groups with eq-ax isomer are more affected than that of the eq-eq isomer due to the closer relationship between the ax methyl group and carbonyl oxygen atom than that of the eq methyl group in the complexed state with Eu(dpm)₃. In contrast, the chemical shift differences of 4,8-methine protons for the eq-eq isomer are larger than that of the eq-ax isomer. The chemical shift differences by Eu(dpm)₃ shift reagent *vs.* [Eu(dpm)₃]/[compound 1] are plotted in Figure 1. It is evident from Figure 1 that the
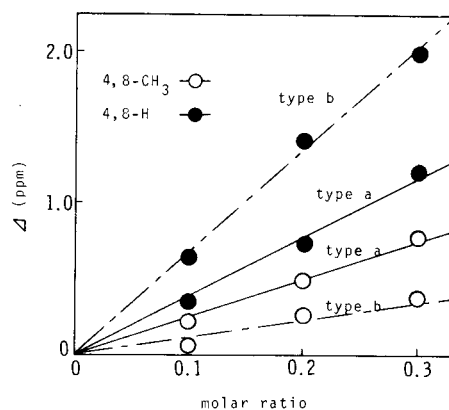

Figure 1. Variation of induced shift with molar ratio of [Eu(dpm)₃]/[compound 1] in perdeuteriobenzene.

4,8-methyl protons of type a are more deshielded than that of type b over the concentration range of Eu(dpm)₃, whereas the 4,8-methine protons of type b are more deshielded than that of type a. From the above considerations, the

Table 3

PMR Chemical Shifts and Dihedral Angles of Compounds **1-5**

Compound No.	H-4,8	H-5 and H-7 ax-H	H-5 and H-7 eq-H	4,8-CH₃	Dihedral angle ψ
1a	4.72 (m)	3.71 (q, J_{gem} = 15.6, J_{vic} = 3.0) [a]	2.96 (q, J_{vic} = 9.8)	1.33 (d, J = 6.3)	16
1b	4.71 (m)	3.23 (q, J_{gem} = 13.5, J_{vic} = 5.0)	2.89 (q, J_{vic} = 9.8)	1.20 (d, J = 6.3)	31
2a	4.80 (m)	3.83 (q, J_{gem} = 16.0, J_{vic} = 2.8)	3.04 (q, J_{vic} = 9.3)	1.44 (d, J = 6.0)	15
2b	4.72 (m)	3.27 (q, J_{gem} = 13.5, J_{vic} = 4.8)	2.93 (q, J_{vic} = 10.1)	1.23 (d, J = 6.0)	29
3a	4.76 (m)	3.79 (q, J_{gem} = 15.3, J_{vic} = 2.8)	3.07 (q, J_{vic} = 8.7)	1.41 (d, J = 6.6)	17
3b	4.75 (m)	3.32 (q, J_{gem} = 14.0, J_{vic} = 5.0)	2.97 (q, J_{vic} = 10.1)	1.25 (d, J = 6.0)	30
4a	4.75 (m)	3.76 (q, J_{gem} = 16.0, J_{vic} = 3.0)	3.02 (q, J_{vic} = 9.2)	1.40 (d, J = 6.0)	17
4b	4.62 (m)	3.25 (q, J_{gem} = 15.0, J_{vic} = 4.1)	2.91 (q, J_{vic} = 10.5)	1.20 (d, J = 6.0)	23
5a	4.70 (m)	3.74 (q, J_{gem} = 15.8, J_{vic} = 3.0)	3.03 (q, J_{vic} = 9.0)	1.39 (d, J = 6.4)	18
5b	4.70 (m)	3.35 (q, J_{gem} = 14.0, J_{vic} = 4.1)	2.99 (q, J_{vic} = 10.0)	1.31 (d, J = 6.4)	25

[a] Coupling constants, Hz.
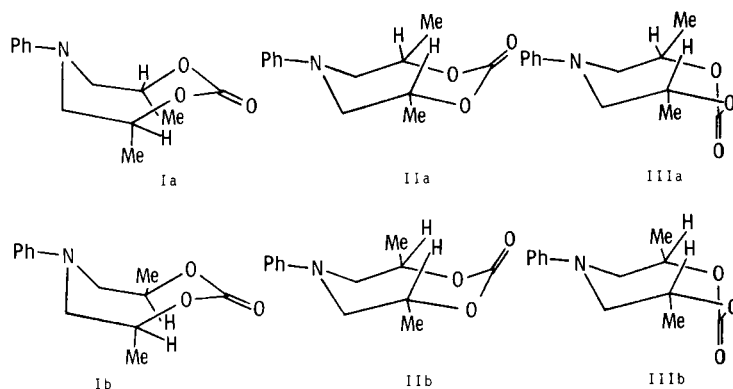
Scheme 1. Possible conformations of 1,3,6-dioxazocin-2-ones

possible conformations of 1,3,6-dioxazocin-2-ones are illustrated in Scheme 1. Isomer Ia is the eq-ax isomer with boat-chair form, whereas Ib is the eq-eq isomer with boat-chair form. Isomer IIa and IIb are the eq-ax and eq-eq isomers with chair-chair form, respectively. Similarly, IIIa and IIIb are the eq-ax and eq-eq isomers with chair-boat form, respectively. Judging from experiment of Eu-(dpm)₃ shift reagent, conformation of III is unlikely. That is, it is it is considered that chemical shift differences of the 4,8-methine protons are smaller than that of the 4,8-methyl protons because of far away from carbonyl oxygen atom. But, chemical shift values of the 4,8-methine protons are more deshielded than that of the 4,8-methyl protons, as can be seen in Figure 1. We have therefore suggested that the preferred conformation of 1,3,6-dioxazoxin-2-ones are the structures of boat-chair (I) or chair-chair (II) forms.

The conformations of 1,3,6-dioxazocin-2-ones are further illustrated by means of dihedral angle (ψ). Coupling constant between protons on vicinal atoms depend not only on the dihedral angle, but also on the electronegativity of substituents [9-11]. The large variation of coupling constant with dihedral angle, a $\cos^2 \phi$ function, give the very familiar Karplus curve [12]. Lambert [13,14] reported that the ratio(R) of the average J_{trans} to the average J_{cis} in six-membered ring has been found to be nearly independent

of the electronegativity of substituents. Therefore, R becomes a direct measure of conformational effects. The possible Newman projections of the structures Ia and IIa are illustrated in Scheme 2 (Newman projection along C-4-C-5 bond). The dihedral angle of boat-chair and chair-chair forms can be estimated as about 0°-60° and 60°-110° from molecular model. Moreover, there will be repulsive van der Waals interaction between the axial 4-methyl group and the axial 8-methine proton for the eq-ax form which will decrease dihedral angle as compared with the eq-eq form, as can be seen in Scheme 1. The dihedral angle of compounds 1-5 calculated from Lambert equation is given in Table 3 with pmr data. The dihedral angle of all compounds 1-5 lies in the range from 11° to 31°. On the other hand, the dihedral angle of the type a with eq-ax form is smaller than that of the type b with eq-eq form.

Therefore, it can be considered that preferred structure of type a exists in the eq-ax methyl groups with boat-chair form(Ia), whereas type b exists in the eq-eq methyl groups with boat-chair form(Ib).

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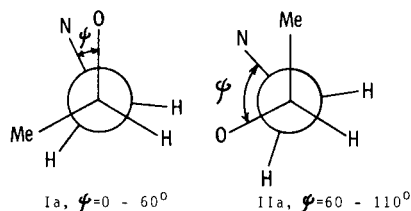
Scheme 2. Newman projections of Ia and IIa

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