Syntheses of 4,7-Dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocin-2-ones and its Related Compounds

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Four isomeric 4,7-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocin-2-ones and four isomeric 4,7-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-oxides were prepared. On the basis of the nmr chemical shifts due to the γ-effect, the stereochemical structures are discussed.

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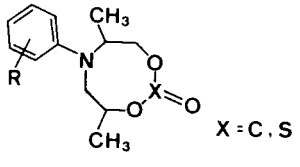
During the course of our studies concerning the synthesis of eight-membered heterocyclic systems, we have recently described the synthesis of two isomeric 4,8-dimethyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocin-2-ones [1] and two isomeric 4-methyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocine 2-oxides [2]. In order to extend our investigations to these heterocycles, we now wish to report the synthesis of similar compounds, 4,7-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocin-2-ones 1-2 and 4,7-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-oxides 3-4.



The 1,3,6-dioxathiazocin-2-oxides **1-2** and 1,3,2,6-dioxathiazocine 2-oxides **3-4** were prepared from the reaction with the appropriate amino alcohol and phosgene in acetic acid ethyl ester at -5° or with thionyl chloride in benzene at room temperature, respectively. A slight excess of pyridine or triethylamine was used as the proton acceptor.

The ir spectra of compounds **1-2** show absorption in the region at 1515-1600 cm^{-1} due to the stretching vibration of the C=O group, in addition compounds **3-4** show absorption around 1200 cm^{-1} due to the S=O group. Their analytical and spectral data of the **1-4** are in accord with the proposed structure.

In case of compounds **1** and **2**, two isomers **a** and **b** are formed which could be separated by column chromatography. The products of these reactions and their physical properties are indicated in Table 1. The product ratios of each isomers were determined by capillary gas chromatography.

Existence of isomeric pairs requires that these heterocyclic compounds possess an asymmetric carbon atom. This conclusion is reinforced by the synthesis of 6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocin-2-one having no 4- and 7-methyl groups in the heterocyclic ring. For a reaction of *N*,*N*-bis(2-hydroxyethyl)aniline with phosgene by a similar synthetic method to compounds **1** and **2**, the sole product was obtained. From the above results, it may be thought that the isomers **a** and **b** of compounds **1** and **2** are configurational isomers of either equatorial (eq)-eq, eq-axial (ax), or ax-ax 4,7-dimethyl groups.

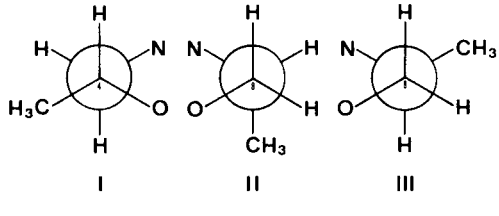
Table 1

Physical Properties of Compounds **1-4**

Compound No.	R	X	yield %	Mp °C	C	H	N
						(Calcd.)	
1a	H	C	20	[a]	66.10	7.18	5.98
					(66.36)	(7.28)	(5.95)
1b	"	"	41	75.0-77.9	66.44	7.35	5.85
2a	*p*-CH_3	C	32	[a]	67.20	7.35	5.46
					(67.45)	(7.68)	(5.62)
2b	"	"	44	119.4-119.9	67.21	7.74	5.41
3a	H	S	12	100.0-100.5	56.34	6.67	5.32
					(56.45)	(6.71)	(5.49)
3b	"	"	11	[a]	56.75	6.79	5.22
3c	"	"	25	105.0-105.5	56.53	6.66	5.43
3d	"	"	15	114.0-115.0	56.18	6.65	5.47
4a	*p*-CH_3	S	22	[a]	57.68	7.25	5.18
					(57.97)	(7.11)	(5.12)
4b	"	"	13	151.5-152.0	58.06	7.09	5.14
4c	"	"	18	155.5-156.0	58.29	6.98	5.11
4d	"	"	21	93.0-94.0	57.96	6.76	4.95

[a]:liquid.

The pmr spectra of the heterocyclic and methyl protons of compounds **1** and **2** are shown in Table 2. Their signals



Scheme 1. Possible configurations of compounds **1** and **2**.

Table 2.

PMR Chemical Shifts of Compounds **1** and **2**.

Compound No.	Chemical shifts, δ (Coupling constants, Hz) 5H	8H	4H	7H	4Me	7Me
1a	3.27 (q, J gem = 15.1, J vic = 9.0) 3.45 (q, J vic = 3.7)	4.01 (q, J gem = 11.5, J vic = 2.4) 4.63 (q, J vic = 3.9)	4.80 (m)	3.87 (m)	1.35 (d)	1.27 (d)
1b	3.07 (q, J gem = 15.3, J vic = 10.6) 3.37 (q, J vic = 2.2)	4.02 (q, J gem = 11.7, J vic = 5.1) 4.34 (t, J vic = 11.7)	4.85 (m)	4.15 (m)	1.41 (d)	1.11 (d)
2a	3.17 (q, J gem = 15.0, J vic = 9.1) 3.40 (q, J vic = 3.4)	3.96 (q, J gem = 11.4, J vic = 2.4) 4.60 (q, J vic = 4.2)	4.75 (m)	3.74 (m)	1.32 (d)	1.26 (d)
2b	3.02 (q, J gem = 15.2, J vic = 10.6) 3.32 (q, J vic = 2.2)	3.98 (q, J gem = 11.0, J vic = 5.1) 4.29 (t, J vic = 11.0)	4.80 (m)	4.15 (m)	1.38 (d)	1.07 (d)

clearly separated into individual peaks and were unambiguously assigned based on the chemical shifts and the coupling pattern. The coupling constant $J_{4,5}$ of **1a** and **2a** are about 9.0 and 3.5 Hz, respectively. Similarly, the coupling constants $J_{4,5}$ of **1b** and **2b** are 10.5 and 2.2 Hz. From the above results, it may be thought that the preferred relationship between the 4H proton and the two 5H protons in isomer **a** is gauche and anti form **I** as shown in Scheme 1.

On the other hand, the coupling constants $J_{7,8}$ of **1a** and **2a** are about 2.4 and 4.1 Hz, whereas the same coupling constants $J_{7,8}$ of **1b** and **2b** are about 5.1 and 11.3 Hz. That is, the preferred geometry between the 7H proton and the two 8H protons in isomer **a** is gauche form **II**, whereas same geometry for isomer **b** is gauche and anti form **III** as shown in Scheme 1.

The configurations of isomers **a** and **b** are further illustrated by means of shielding effect by the adjacent 4- and 7-methyl groups. Anteunis *et al.* [3] have reported the pmr spectra of various substituted 1,3-dioxolanes. The shifts of the pseudo-axial hydrogen of 2,2,4-trimethyl-, *trans*-2,4-dimethyl- and *cis*-2,4-dimethyl-1,3-dioxolane appeares at higher field about 0.61, 0.46, and 0.74 ppm than that of pseudoequatorial hydrogen, respectively. This difference in chemical shift has been attributed to shielding of the axial hydrogen by the adjacent *cis*-methyl group. If this considerations can be extended to the 5- and 8-methyl-

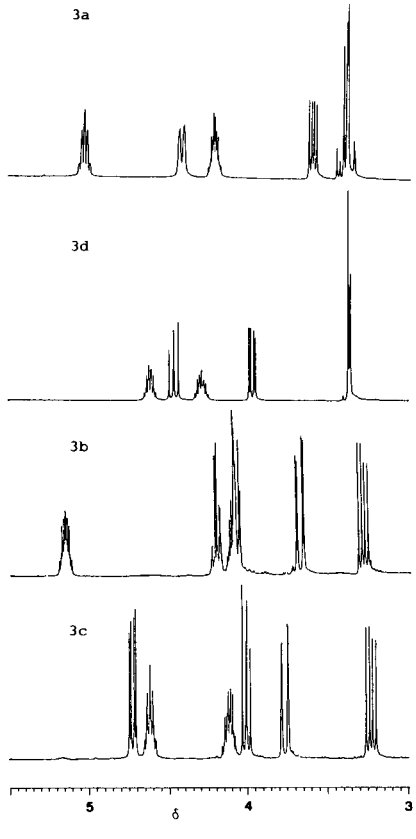


Figure 1. Pmr spectra of the compounds **3**.

ene protons for isomers **a** and **b**, the following consideration are possible. The chemical shift differences between the 5H protons in compounds **1-2** and those of 8H protons in compounds **1b** and **2b** are 0.25 and 0.31 ppm, respectively. On the other hand, those chemical shift differences between 8H protons in compounds **1a** and **2a** are considerably large value, 0.63 ppm as can be seen in Table 2. This large chemical shift differences of 0.63 ppm is compatible with above arguments. Namely, one proton in 5H protons is shielded by adjacent *cis*-methyl group and another proton in 5H protons is essentially no effect due to the *trans* relationship for the 7-methyl group. The outline of the results of coupling constant and chemical shift of 5- and 8H protons will be explained as follows. The compounds of isomer **a** exist with 4-eq and 7-ax methyl groups, whereas the methyl groups of isomer **b** exist with 4-eq and 7-eq configuration.

On the other hand, the reaction of amino alcohol with thionyl chloride gave four isomers **a** and **d**. The pmr spectra of the heterocyclic protons of compounds **3a** to **3d** are shown in Figure 1. The pmr spectra of the isomers **a** and **d** displayed similar sets of 5H methylene protons multiplets of the representative A_2 pattern, whereas those of isomers **b** and **c** showed AB pattern. That is, the geometrical relationships between 4-methyl group and 5-methylene protons of isomers **a** and **d** and/or isomers **b** and **c** are almost similar situation, respectively. The C-4 chemical shifts (mean value) of isomers **a** and **b** appeared at 67.3 ppm, whereas those of isomers **c** and **d** appeared at 72.8 ppm. The upfield shifts of 5.5 ppm at the C-4 carbon of isomers **a** and **b** are due to the γ-gauche relationship between the axial S=O and the axial hydrogen at the C-4 carbon [4,5]. From the above results and examination of the molecular model, it is assumed that preferred structure of the isomers **a** and **d** exist in chair-chair form of 4-eq methyl group with the ax S=O and eq S=O group, respectively, whereas the isomers **b** and **c** exist in boat-chair form of 4-eq methyl group with the ax S=O and eq S=O group. On the other hand, the C-5 chemical shift of isomers **a**, **b** and **d** appeared at 50.9 ppm, whereas chemical shift of isomer **c** is 56.9 ppm. This can be interpreted in terms of the γ- steric shift of an axial methyl group on C-7 with syn-axial hydrogen on C-5. That is, the methyl group on C-7 of isomers **a**, **b** and **c** indicates the axial orientation but the methyl on C-7 for the isomer **c** exists an equatorial orientation.

Oxidation of **3** and **4** by ruthenium tetroxide [6,7] are now under study in order to explore more a detailed stereo structure of the dioxathiazocine 2-oxide skeleton.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were taken on a Perkin Elmer 1600 Ft spectrometer for potassium bromide discs (unless otherwise noted). The pmr and cmr spectra were recorded on a JEOL GSX-400 (400 MHz) spectrometer in deuteriochloroform solution with tetramethylsilane as an internal standard. *N*-(2-Hydroxypropyl)-*N*-(2-hydroxyisopropyl)anilines used in our study were prepared from the reactions of the corresponding anilines and ethyl lactate in the presence of sodium ethoxide and subsequently were 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.

4,7-Dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocin-2-ones **1a** and **1b**.

A solution of phosgene (3.14 ml, 30% in carbon tetrachloride, 14.27 mmoles) in ethyl acetate (20 ml) was added to a stirred solution of *N*-(2-hydroxypropyl)-*N*-(2-hydroxyisopropyl)aniline (1.97 g, 9.43 mmoles) and pyridine (1.9 g) in ethyl acetate (200 ml) at -5° for 2 hours and subsequently at room temperature. After stirring over night the resulting orange-colored solution was washed with water, dried over sodium sulfate and evaporated *in vacuo* to give 1.99 g (67% crude yield from gc) which exhibited two peaks on capillary gas chromatography. This oily product was separated on a column of silica gel using hexane-methylene chloride (6:1) as an eluent. The first fraction afforded **1a** as a colorless oil, and identified on the basis of spectral data; pmr data of **1-2** are shown in Table 2; ir (neat): 2982, 1748, 1598, 1504, 1370, 1267, 1216, 1130, 1071, 1048 and 752 cm^{-1}; cmr: δ 155.2 (C-2), 77.6 (C-4), 54.8 (C-5), 56.6 (C-7), 74.0 (C-8), 17.5 (4-CH_3) and 15.7 (7-CH_3).

Similarly, a second fraction was evaporated to yield white crystals, which was recrystallized and identified as **1b**; ir: 2976, 1747, 1599, 1498, 1459, 1382, 1339, 1272, 1205, 1142, 1095, 1079, 1054, 1033, 867 and 760 cm^{-1}; cmr: δ 155.2 (C-2), 79.9 (C-4), 52.4 (C-5), 53.9 (C-7), 70.5 (C-8), 17.0 (4-CH_3) and 11.5 (7-CH_3).

4,7-Dimethyl-6-(*p*-tolyl)-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocin-2-ones **2a** and **2b**.

The products **2a** and **2b** were obtained by the reaction of *N*-(2-hydroxypropyl)-*N*-(2-hydroxyisopropyl)-*p*-toluidine with phosgene by a similar way to that for the preparation of compounds **1**; **2a**; ir (neat): 2980, 1752, 1615, 1572, 1514, 1456, 1369, 1299, 1266, 1213, 1130, 1073, 1048, 1012, 970, 813 and 762 cm^{-1}; cmr: δ 155.6 (C-2), 78.0 (C-4), 55.9 (C-5), 57.1 (C-7), 73.7 (C-8), 17.5 (4-CH_3) and 15.9 (7-CH_3); **2b**, ir: 2971, 1738, 1517, 1384, 1340, 1331, 1291, 1272, 1244, 1207, 1144, 1092, 1074, 1053, 870, 818 and 795 cm^{-1}; cmr: δ 155.3 (C-2), 80.0 (C-4), 52.5 (C-5), 54.5 (C-7), 70.6 (C-8), 17.0 (4-CH_3) and 11.4 (7-CH_3).

4,7-Dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-Oxides **3a**, **3b**, **3c** and **3d**.

A solution of thionyl chloride (2.05 g, 19.9 mmoles) in benzene (20 ml) was added dropwise to a stirred solution of *N*-(2-hydroxypropyl)-*N*-(2-hydroxyisopropyl)aniline (2.09 g, 10.0 mmoles) and triethylamine (2.5 g) in benzene (70 ml) cooled at 0-5°. After stirring 1 hour and subsequently at room temperature for 2 hours, water was added and worked up to give 2.4 g of the crude products, which showed four peaks on gas chromatography. Separation of the products by the use of column chromatography eluted with hexane-methylene chloride (6:1) afforded four isomers. The first fraction was concentrated and subsequent recrystallization afforded **3a** as white crystals; ir: 2994, 2982, 1601, 1507, 1445, 1382, 1372, 1356, 1344, 1279, 1254, 1187, 1064, 1036, 968, 945, 931, 905, 847, 830, 750 and 701 cm^{-1}: cmr: δ 66.7 (C-4), 49.2 (C-5),

50.3 (C-7), 63.4 (C-8), 19.0 (4-CH_3) and 14.0 (7-CH_3).

A second fraction was isolated as a colorless oil and identified as **3b** on the basis of the spectral properties described below; ir (neat): 2977, 2932, 1598, 1504, 1452, 1381, 1346, 1240, 1202, 1034, 995, 953, 897, 862, 750 and 708 cm^{-1}; cmr: δ 67.6 (C-4), 52.7 (C-5), 54.6 (C-7), 64.9 (C-8), 20.0 (4-CH_3) and 14.9 (7-CH_3).

A third fraction was evaporated to yield white crystals and identified as **3c**; ir: 2965, 2924, 1602, 1509, 1384, 1350, 1335, 1242, 1206, 1056, 1034, 971, 906, 847, 755 and 715 cm^{-1}; cmr: δ 71.9 (C-4), 56.2 (C-5), 57.6 (C-7), 62.4 (C-8), 19.3 (4-CH_3) and 15.9 (7-CH_3).

A fourth fraction was isolated as white crystals and identified as **3d**; ir: 2968, 2928, 1601, 1500, 1452, 1439, 1407, 1386, 1342, 1262, 1199, 1105, 1065, 1040, 976, 956, 913, 868, 845, 724 and 700 cm^{-1}; cmr: δ 73.3 (C-4), 50.4 (C-5), 51.3 (C-7), 64.9 (C-8), 18.8 (4-CH_3) and 12.8 (7-CH_3).

4,7-Dimethyl-6-(*p*-tolyl)-5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-Oxides **4a**, **4b**, **4c** and **4d**.

In a similar manner to that described for compounds **3**, treatment of *N*-(2-hydroxypropyl)-*N*-(2-hydroxyisopropyl)-*p*-toluidine with thionyl chloride gave a mixture of products. The mixture was chromatographed on silica gel with hexane-methylene chloride (6:1) as an eluent to give a compounds **4a**, **4b**, **4c** and **4d**. **4a**; pmr: δ 1.15 (3H, d, J = 6.8 Hz, 7-CH_3), 1.30 (3H, d, J = 6.6 Hz, 4-CH_3), 2.22 (3H, s, *p*-CH_3), 3.27-3.38 (2H, m, 5-H), 3.52 (1H, q, J = 6.9, 12.1 Hz, 8-H), 4.08-4.12 (1H, m, 7-H), 4.34 (1H, q, J = 3.7 12.1 Hz, 8-H), 4.96-4.99 (1H, m, 4-H), 6.50 (2H, d, ph-H) and 7.01 (2H, d, Ph-H); cmr: δ 66.8 (C-4), 49.3 (C-5), 50.4 (C-7), 63.4 (C-8) 19.0 (4-CH_3), 14.1 (7-CH_3) and 20.1 (*p*-CH_3); **4b**; ir (neat): 2973, 2930, 1617, 1522, 1447, 1386, 1367, 1344, 1257, 1241, 1199, 1125, 1101, 1058, 973, 952, 909, 868, 848, 807, 760 and 743 cm^{-1}; pmr: δ 1.27 (3H, d, J = 6.8 Hz, 7-CH_3), 1.32 (3H d, J = 6.6 Hz, 4-CH_3), 2.25 (3H, s, *p*-CH_3), 3.27 (1H, q, J = 8.3, 15.6 Hz, 5H), 3.65 (1H, q, J = 3.5, 15.6 Hz, 5-H), 4.02-4.09 (2H, m, 7- and 8-H), 4.17 (1H, q, J = 7.8, 12.2 Hz, 8-H), 5.12-5.16 (1H, m, 4-H), 6.74 (2H, d, Ph-H) and 7.03 (2H, d, Ph-H); cmr: δ 68.1 (C-4), 53.2 (C-5), 54.9 (C-7), 65.3 (C-8), 19.9 (4-CH_3) 14.9 (7-CH_3) and 20.3 (*p*-CH_3); **4c**, pmr: δ 1.25 (3H, d, J = 6.8 Hz, 7-CH_3), 1.31 (3H, d, J = 6.4 Hz, 4-CH_3), 2.26 (3H, s, *p*-CH_3), 3.20 (1H, q, J = 8.5, 15.7 Hz, 5-H), 3.71 (1H, q, J = 2.4, 15.7 Hz, 5-H), 3.95-4.05 (2H, m, 7- and 8-H), 4.58-4.62 (1H, m, 4-H), 4.69 (1H, q, J = 3.4, 11.2 Hz, 8-H), 6.74 (2H, d, Ph-H) and 7.04 (2H, d, Ph-H); cmr: δ 72.5 (C-4), 57.0 (C-5), 57.8 (C-7), 63.5 (C-8), 19.1 (4-CH_3), 15.9 (7-CH_3) and 20.3 (*p*-CH_3); **4d**, pmr: δ 1.07 (3H, d, J = 6.6 Hz, 7-CH_3), 1.40 (3H, d, J = 6.6 Hz, 4-CH_3), 2.25 (3H, s, *p*-CH_3), 3.25-3.34 (2H, m, 5-H), 3.95 (1H, q, J = 4.5, 12.4 Hz, 8-H), 4.18-4.22 (1H, m, 7-H), 4.40 (1H, q, J = 10.3, 12.4 Hz, 8-H), 4.56-4.62 (1H, m, 4-H), 6.60 (2H, d, Ph-H), and 7.06 2H, d, Ph-H); cmr: δ 73.5 (C-4), 50.4 (C-5), 51.7 (C-7), 65.7 (C-8), 18.6 (4-CH_3), 12.6 (7-CH_3) and 20.1 (*p*-CH_3).

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