Synthesis of 4,8-Dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocines

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Five 6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocines were synthesized by the reaction of the corresponding *N,N*-bis(2-hydroxypropyl)- and *N,N*-bis(2-hydroxyethyl)chloroanilines with paraformaldehyde in the presence of *p*-toluenesulfonic acid.

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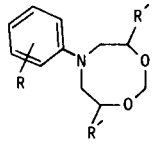
Reaction of diols with aldehydes has been known to give cyclic compounds (1 – 3). In a similar manner, 1,3-oxazines have prepared by the reaction of aminopropanol with aldehydes (4,5). Recently, a number of stereochemical studies of six-, seven- and eight-membered heterocycles containing the OCH_2O unit have been carried out by means of nmr spectroscopy (6 – 8).

In a previous paper, we reported the reaction of *N,N*-bis(2-hydroxyethyl)aniline with thionyl chloride giving the 6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-oxides and their conformation using nmr (9,10). From this study, it appears that the S = O bond constitutes a useful indicator to examine the geometry of the 1,3,2,6-dioxathiazocine 2-oxide system. With these findings as a background, we wish to report the synthesis of a new series of the 1,3,6-dioxazocine system which has no S = O in the cyclic ring.



1, R = *p*-Cl, R' = CH_3
2, R = *o*-Cl, R' = CH_3
3, R = *p*-Cl, R' = H

The 4,8-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocines (**1**,**2**) were prepared by the reactions of *N,N*-bis(2-hydroxypropyl)chloroanilines with paraformaldehyde in the presence of acid. In each reaction, two isomers of types **a** and **b** can be separated by the use of silica gel column with hexane as an eluent. The structure of **1** and **2** is supported by analytical and spectral data. The pmr spectra of the heterocyclic and methyl protons of **1a** and **1b** are shown in Figure 1. The pmr spectrum of **1a** consists of five distinct sets of multiplets, whereas **1b** consists of six distinct sets. Striking differences between compounds **1a** and **1b** are recognizable in the signals of the methylene protons attached to C – 2 carbon. That is, the two protons attached to C – 2 carbon for **1b** appeared at δ 4.38 (d) and 5.23 (d) because of magnetically nonequivalence, whereas the methylene protons of **1a** appeared at δ 4.63 (s). A second, albeit less dramatic, result is the chemical shift of methylene protons attached to C – 5 and/or C – 7. For the compound of **1b**, one of the hydrogens attached to C – 5 and/or C – 7 appeared in lower field compared with those of **1a**. The methyl and cyclic ring protons of **1a** and **1b** show one set of multiplets, respectively.

Regarded from the standpoint that these **a** and **b** are conformational isomers, it may consider that one isomer exists in equilibrium mixture of both isomers by elevating temperature. In order to ensure the thermal isomerization of **a** or **b**, we first attempted the treatments of **1a** and **1b**, respectively, at a refluxed temperature in benzene for 16 hours. Cosequently, the starting material was quantitatively recovered in each of **1a** and **1b**. Secondly, we tried the reaction of *N,N*-bis(2-hydroxyethyl)-*p*-chloroaniline having no asymmetic center with paraformaldehyde by a similar synthetic method to **1** or **2**. In the reaction, the sole pro-

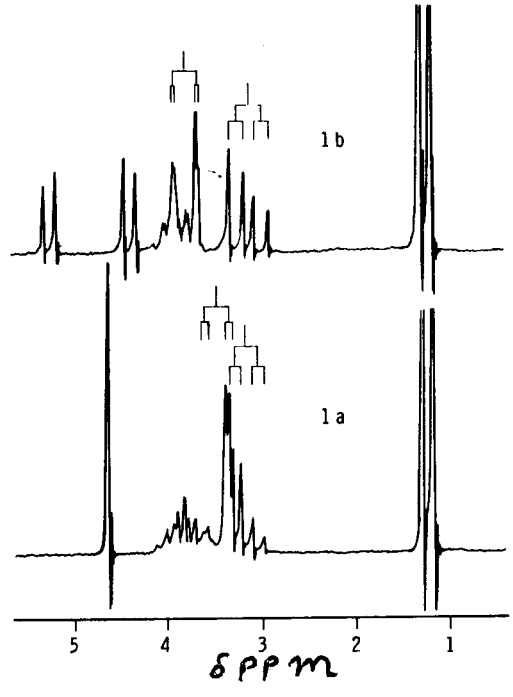


Figure 1. Nmr spectra of the compounds of **1a** and **1b**.

duct was obtained and the methylene protons at C−2 carbon appeared at δ 4.71 (s).

From the above results, it may be thought that the isomers **1a** and **1b** are a pair of *cis-trans* configurational isomers, the one compound with both equatorial methyl groups and the other one with one axial and one equatorial methyl groups. In the cis isomer, the methyl group has a tendency to far away from the axial hydrogen at C−8 carbon, because of the steric repulsion between these hydrogens. Consequently, the axial hydrogen in the methylene protons at C−2 carbon comes very close to the nitrogen atom with lone-pair electrons compared with the equatorial hydrogen at C−2 carbon. Therefore, the two hydrogens at C−2 carbon of the cis-isomer are nonequivalence, as was proved by the data of pmr. From these results, we came to the conclusion that these isomers **a** and **b** are the trans and cis isomers, respectively.

EXPERIMENTAL

The ir spectra were recorded on a Shimadzu Model-27G spectrometer. Pmr spectra were run with 60 MHz JEOL-PMX-60 spectrometer in deuteriochloroform solution with tetramethyl silane as a reference material. Cmr spectra were obtained using a JNM-PS-100/EC-100 Fourier transform spectrometer operating at 25.15 MHz, with complete proton decoupling. *N,N*-bis(2-hydroxypropyl)- and *N,N*-bis(2-hydroxyethyl)chloroanilines were prepared by the reaction of the corresponding chloroaniline with propylene oxide or ethylene oxide (11). $Eu(dpm)_3$ was dried over phosphorus pentoxide *in vacuo* just before use.

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

A solution of *N,N*-bis(2-hydroxypropyl)-*p*-chloroaniline (5.09 g, 20.9 mmoles) and p-toluenesulfonic acid (1.78 g., 9.4 mmoles) in benzene (10 ml) was added to a stirred suspension of paraformaldehyde (4.06 g, 45.1 mmoles) in benzene (200 ml). This solution was heated to reflux equipment with a Dean-Stark trap. After stirring for 35 hours, the solvent was evaporated *in vacuo*. The excess paraformaldehyde which precipitated was filtered off and washed with small amounts of benzene. The filtrate was dried over sodium sulfate and evaporated to yield an oily product, which exhibited three main spots at R_f 0.72, 0.52 and 0.02 on an analytical tlc plate developed with methylene chloride. This oily product was separated on a column of silica gel (30 g.) using hexane as an eluent. The fraction with R_f 0.72 afforded **1a** as colorless oil (7% yield), and identified on the basis of spectral data; ir (neat): 2950 (s), 2910 (s), 2860 (s), 1580 (s), 1500 (s), 1450 (m), 1390 (m), 1379 (s), 1240 (s), 1190 (s), 1175 (s), 1130 (s), 1100 (s), 1164 (s), 1138 (s), 989 (m), and 807 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.23 (d, 6H, J = 6.0 Hz), 3.18 (q, 2H, J = 15.0 and 7.0 Hz), 3.48 (q, 2H, J = 15.0 and 2.0 Hz), 3.62 − 4.13 (m, 2H), 4.63 (s, 2H), 6.55 (d, 2H, J = 9.0 Hz), and 7.12 (d, 2H, J = 9.0 Hz); cmr (deuteriochloroform): δ 20.1 (CH_3), 56.7 (C−5 and/or C−7), 71.2 (C−4 and/or C−8), and 93.6 (C−2).

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; N, 5.48. Found: C, 61.16; H, 7.35; N, 5.63.

Similarly, the fraction with R_f 0.52 was evaporated to yield white crystals which were recrystallized (13% yield, mp 87.0 − 88.0°) and identified as **1b**; ir (potassium bromide): 2960 (s), 2920 (s), 2870 (s), 1592 (s), 1500 (s), 1460 (m), 1450 (m), 1385 (s), 1373 (s), 1296 (m), 1289 (m), 1246 (s), 1190 (s), 1142 (m), 1122 (m), 1055 (s), 1015 (s), 887 (m), 812 (s), and 795 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.23 (d, 6H, J = 6.0 Hz), 3.08 (q, 2H, J = 15.0 and 10.0 Hz), 3.78 (q, 2H, J = 15.0 and 2 Hz), 3.57 − 4.10 (m, 2H), 4.38 (d, 1H, J = 7.5 Hz), 5.23 (d, 1H, J = 7.5 Hz), 6.38 (d, 2H, J = 9.0 Hz), and 7.10 (d, 2H, J = 9.0 Hz); cmr (deuteriochloroform): δ 18.7 (CH_3), 59.2 (C−5 and/C−7), 73.1 (C−4 and/or C−8), and 96.5 (C−2).

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; N, 5.48. Found: C, 61.16; H, 7.12; N, 5.39.

The fraction with R_f 0.02 was evaporated to give an oil, which agreed in all the physical and spectral properties with the starting aminoalcohol.

4,8-Dimethyl-6-(*o*-chlorophenyl)-5,6,7,8-tetrahydro-4*H*-1,3,6-dioxazocine (**2a** and **2b**).

The products **2a** (25% yield) and **2b** (27% yield) were obtained by the reaction of *N,N*-bis(2-hydroxypropyl)-*o*-chloroaniline with paraformaldehyde by a similar way to that for the preparation of **1**. The reaction mixture exhibited three main spots at R_f 0.65, 0.50, and 0.04 on an analytical tlc plate developed with methylene chloride. By the use of a column of silica gel (110 g) eluted with hexane, the fraction with R_f 0.65 afforded **2a** as an oil; ir (neat): 2960 (s), 2929 (s), 2870 (s), 1582 (s), 1479 (s), 1443 (s), 1375 (s), 1259 (m), 1229 (m), 1190 (m), 1172 (m), 1130 (s), 1100 (s), 1043 (s), 984 (m), 879 (m), and 750 cm^{-1}; pmr (deuteriochloroform): δ 1.10 (d, 6H, J = 6.4 Hz), 3.08 (q, 2H, J = 14.2 and 6.0 Hz), 3.40 (q, 2H, J = 14.2 and 4.0 Hz), 3.70 − 4.26 (m, 2H), 4.87 (s, 2H), and 6.75 − 7.12 (m, 4H); pmr (benzene-d_6, **2a**: $Eu(dpm)_3$ = 1: 0.12 mole): δ 1.38 (d, 6H), 3.25 (q, 2H), 3.62 (q, 2H), 3.98 − 4.47 (m, 2H), 5.56 (s, 2H), and 6.66 − 7.86 (m, 4H); cmr (deuteriochloroform): δ 18.4 (CH_3), 62.9 (C−5 and/or C−7), 75.4 (C−4 and/or C−8), and 93.0 (C−2).

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; N, 5.48. Found: C, 61.29; H, 7.31; N, 5.61.

Similarly, **2b** was isolated from the fraction with R_f 0.50, and was identified on the basis of the spectral data; ir (neat): 2965 (s), 2930 (s), 2890 (s), 1584 (s), 1481 (s), 1448 (s), 1378 (s), 1231 (m), 1185 (s), 1145 (s), 1050 (br), 1010 (m), 884 (m), and 752 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.15 (d, 6H, J = 6.5 Hz), 3.12 (q, 2H, J = 14.2 and 8.5 Hz), 3.40 (q, 2H, J = 14.2 and 4.0 Hz), 3.83 − 4.35 (m, 2H), 4.82 (d, 1H, J = 7.0 Hz), 5.12 (d, 1H, J = 7.0 Hz), and 6.73 − 7.40 (m, 4H); pmr (benzene-d_6, **2b**: $Eu(dpm)_3$ = 1: 0.10 mole): δ 1.39 (d, 6H), 3.37 (d, 2H), 3.40 (d, 2H), 4.87 − 5.39 (m, 2H), 6.04 (d, 1H), 6.38 (d, 1H), and 6.50 − 7.37 (m, 4H); cmr (deuteriochloroform): δ 18.8 (CH_3), 60.5 (C−5 and/or C−7), 73.1 (C−4 and/or C−8), and 94.2 (C−2).

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; N, 5.48. Found: C, 61.00; H. 7.09; N, 5.45.

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

The product **3** was obtained by the reaction of *N,N*-bis(2-hydroxyethyl)-*p*-chloroaniline (5.01 g, 23.2 mmoles) with paraformaldehyde (4.46 g, 49.5 mmoles) by a similar way to that for the preparation of **1**. The reaction mixture 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 starting aminoalcohol. After the mixture had been stirred for 20 hours at refluxed temperature, the solvent was removed *in vacuo* to give a pale yellow crystal. Recrystallization from a mixture of hexane and benzene afforded white crystals (60% yeild, mp 88.0 − 89.0°), which were identified as **3** on the basis of following properties; 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 (m), 979 (s), 811 (s), and 800 (s) cm^{-1}; pmr (deuteriochloroform): δ 3.96 − 3.55 (m, 8H), 4.71 (s, 2H), 6.57 (d, 2H, J = 9.0 Hz), and 7.19 (d, 2H, J = 9.0 Hz); cmr (deuteriochloroform): δ 5.19 (C−5 and/or C−7), 66.3 (C−4 and/or C−8), and 97.5 (C−2).

Anal. Calcd. for $C_{11}H_{14}ClNO_2$: C, 58.03; H, 6.20; N, 6.15. Found: C, 57.84; H, 6.13; N, 6.07.

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