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Studies of Cyclic Ethers. II.[1] Syntheses and Conformations of Two Isomers of 2,3,5,6-Tetramethyl-1,4-dioxane

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Two of five isomers of 2,3,5,6-tetramethyl-1,4-dioxane were isolated. Their configurations were assigned with the coupling constants of the methine protons of the 1,4-dioxane ring by nuclear magnetic resonance (NMR) spectrometry.

2, *cis*-3-Bis(Iodomethyl)-*cis*-5, *trans*-6-dimethyl-1,4-dioxane (IIa) and 2, *trans*-3-bis-(iodomethyl)-*trans*-5, *cis*-6-dimethyl-1,4-dioxane (IIb) were obtained by the cyclization reaction of *meso*- and *dl*-2,3-butanediol, respectively, and 1,3-butadiene with mercuric oxide and iodine. 2, *cis*-3, *cis*-5, *trans*-6-Tetramethyl-1,4-dioxane (IIIa) and 2, *trans*-3, *trans*-5, *cis*-6-tetramethyl-1,4-dioxane (IIIb) were obtained by reduction of IIa and IIb, respectively, with $LiAlH_4$.

The coupling constants and τ values of the methine protons of the 1,4-dioxane ring were 3.3, 9.0 Hz, 6.16, 6.30, 6.54, 6.76 τ for IIIa, and 9.0 Hz, 6.77 τ for IIIb.

Previously, we prepared the geometrical isomers of various 1,3-dioxolane derivatives by an acid catalyzed condensation reaction of 2,3-butanediol and some aliphatic aldehydes and clarified the configurations of these compounds.[1] The gas–liquid chromatogram (GLC) of the crude products of this reaction, however, showed the existence of many compounds besides the 1,3-dioxolanes, as shown in Fig. 1. When the 1,3-dioxolane derivatives had been removed by hydrolysis with dilute acid, the GLC of the small amount of the residue still showed several peaks, suggesting the formation of 2,3,5,6-tetramethyl-1,4-dioxanes (TMD). The existence of five isomers of TMD are expected, as shown in Fig. 2.

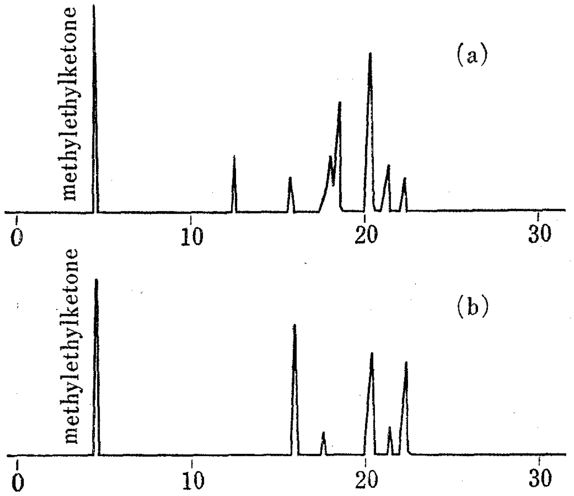

Fig. 1. Gas Chromatograms of (a): raw products of the acid catalyzed condensation reaction of 2,3-butanediol and paraldehyde, and (b): the residue after hydrolysis of (a) with dilute acid.

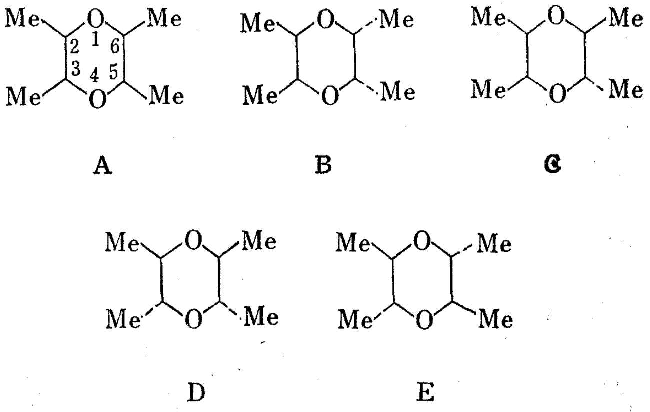

Fig. 2

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[1] Part I: F. Kametani and Y. Sumi, *Chem. Pharm. Bull.* (Tokyo), 20, 1479 (1972).

[2] Location: *Shomachi, Tokushima, 770, Japan.*

In the present investigation, we attempted to obtain these isomers authentically, to identify the peaks on the GLC. The method of Summerbell and Lestina[3] is very suitable for obtaining these isomers. That is, the reaction of ethyleneglycol with 1,3-butadiene gives *cis*- and *trans*-2,3-bis(iodomethyl)-1,4-dioxane (I) and favors formation of the *trans* isomer. Reduction of I with $LiAlH_4$ in ethereal solution gives *cis*- and *trans*-2,3-dimethyl-1,4-dioxane.[4]

Two isomers of 2,3-bis(iodomethyl)-5,6-dimethyl-1,4-dioxane (IIa and IIb) were synthesized *via* 2,3-bis(iodomercurimethyl)-5,6-dimethyl-1,4-dioxane (V), by the reaction of 2,3-butanediol and 1,3-butadiene with the mercuric salt as a condensation catalyst according to the method used to obtain I.[3] One of the isomers (IIa) was isolated from *meso*-2,3-butanediol and 1,3-butadiene, and the other isomer (IIb) from *dl*-2,3-butanediol and 1,3-butadiene. Two isomers of TMD (IIIa and IIIb) were obtained from IIa and IIb, respectively, using the method of Augdahl.[4] Their purities were checked on a GLC, as shown in Fig. 3. A mixture of reaction products (IIIc) was also obtained from the mother liquid of IIa by the same procedure. The GLC of IIIc, shown in Fig. 3 as a reference, indicates the existence of five isomers of TMD. However, the five isomers could not be clearly separated from each other because of the similarity in their physical properties and lack of any suitable functional group.

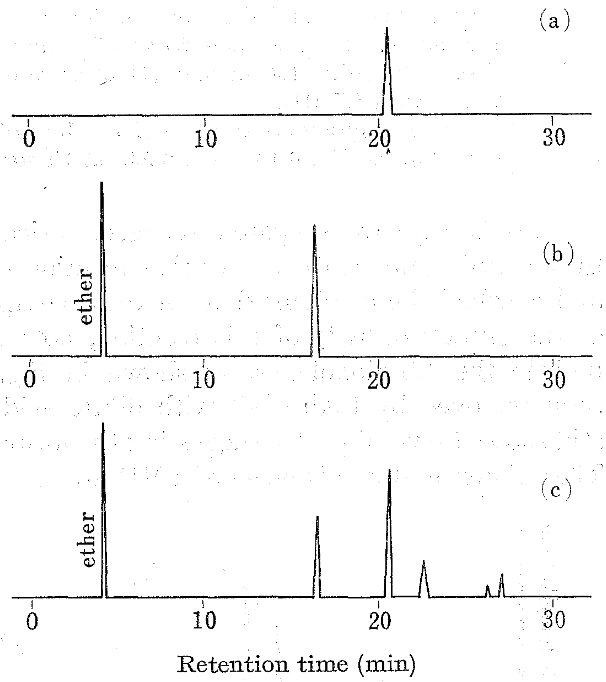

Fig. 3. Gas Chromatograms of (a): IIIa, (b): IIIb, (c): IIIc

The configuration of the two methyl groups of 2,3-butanediol should be retained in this cyclization reaction of 2,3-butanediol and 1,3-butadiene.[3] The configuration of the two methyl groups on the other side of the dioxane ring, which were constructed with 1,3-butadiene, could be either *cis* or *trans*. Thus three isomers each should be obtained from *meso*- and *dl*-2,3-butanediols. Compounds with structures A, B and C in Fig. 2 are expected to be synthesized by the cyclization reaction of *meso*-2,3-butanediol and 1,3-butadiene. However, only one isomer (IIIa) was isolated from the reaction of *meso*-2,3-butanediol. Compounds with structures C, D and E are also expected to be synthesized from *dl*-2,3-butanediol, but only one isomer (IIIb) was isolated. The configuration of the two methyl groups at position 2 and 3, which was constructed from those of *dl*-2,3-butanediol, would be retained as *trans*.

To elucidate their structures, the nuclear magnetic resonance (NMR) spectra of IIa, IIb, IIIa and IIIb were measured and are shown in Fig. 4, 5, 6 and 7, respectively.

The NMR spectrum of IIa has two unequivalent methyl signals indicating different geometrical relation between the iodomethyl groups and methyl groups. On the other hand, the spectrum of IIb has equivalent methyl signals, indicating the same spatial relation between the two pairs of methyl and iodomethyl groups.

Since the spectrum of IIIa was complicated, it was analyzed by the double resonance method. As shown in Fig. 6, when the methyl signals were irradiated, four doublets were

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[3] R.K. Summerbell and G.J. Lestina, *J. Am. Chem. Soc.*, **79**, 3878 (1957).

[4] E. Augdahl, *Acta Chem. Scand.*, **9**, 1237 (1955).

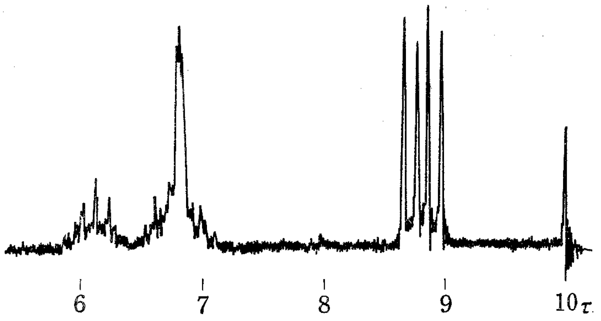

Fig. 4. NMR Spectrum of IIa

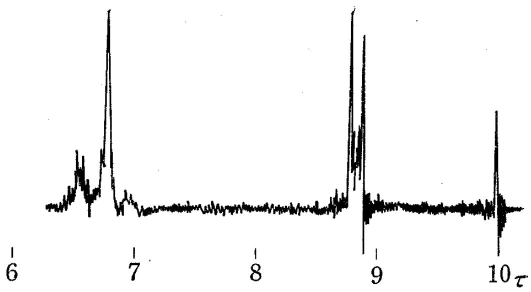

Fig. 5. NMR Spectrum of IIb

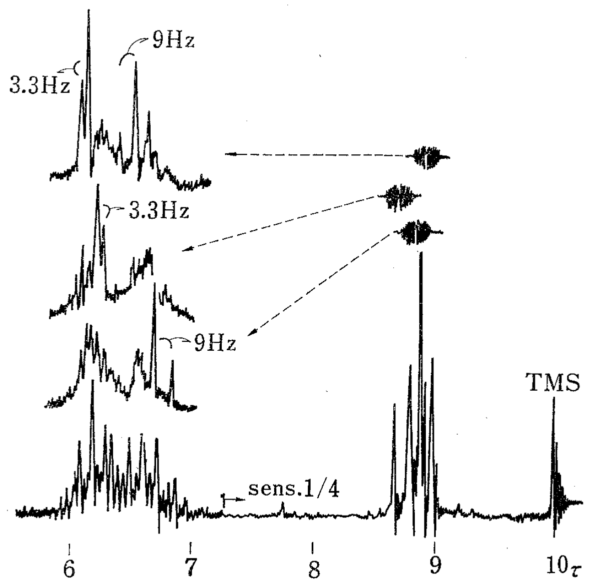

Fig. 6. NMR Spectrum of IIIa

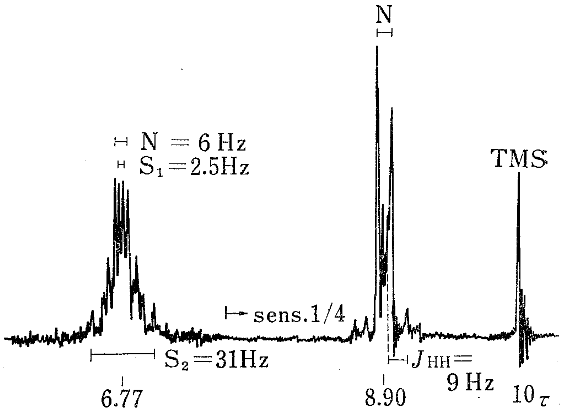

Fig. 7. NMR Spectrum of IIIb

observed. These doublets were analyzed as two AB type spectra. $J_{HH}=3.3$ and 9.0 Hz, $\tau_H=6.16$, 6.30, 6.54 and 6.76 were obtained using the equation[5]

$$C = \frac{1}{2}[(\nu_0\delta)^2+J^2]^{1/2}$$

in which $\nu_0\delta$ is a chemical shift and J is a spin coupling constant.

The spectrum of IIIb, shown in Fig. 7, was symmetrical which suggests that the structure of IIIb is also symmetrical. This spectrum was analyzed as a type of $X_3AA'X'_3$. Values of $J_{HH}=9.0$ Hz, $J_{HMe}=6.6$ Hz, $J_{HMe'}=-0.4$ Hz and $\tau_H=6.77$ were obtained using the following equations[6]

$$L = |J_{AX}-J_{AX'}| \qquad N = |J_{AX}+J_{AX'}|$$
$$S_1 = (L^2+J_{HH}{}^2)^{1/2}-J_{HH}$$
$$S_2 = N + J_{HH} + (4L^2+J_{HH})^{1/2}$$

in which N, S_1 and S_2 were obtained on the NMR spectrum, as shown in Fig. 7, L was calculated from S_1 and J_{HH}. In the present example, J_{AX} and $J_{AX'}$ (for the long-range coupling) should be denoted as J_{HMe} and $J_{HMe'}$, respectively.

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[5] J.A. Pople, W.G. Schneider and H.J. Bernstein, "Highresolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, 1959, p. 120.

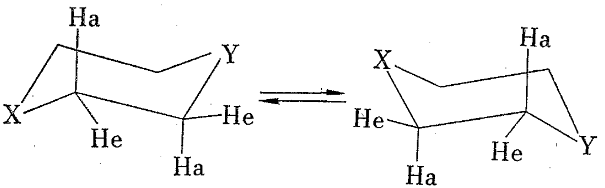
[6] R.K. Harris and N. Sheppard, *J. Chem. Soc.* (*B*), **1966**, 200.

In six-membered rings, there are three possible types of J_{HH} for a single conformation, depending on whether the two protons are both axial, both equatorial or one of each. These coupling constants will be denoted J_{aa}, J_{ee} and J_{ae}, respectively. Consideration of the chair conformation of the general molecule IV reveals that the two coupling constants between the ring protons may be measured when ring inversion is rapid. These two coupling constants are defined in the following equation.[7]

$$J_{trans} = \frac{1}{2}(J_{aa}+J_{ee}) \qquad (1)$$

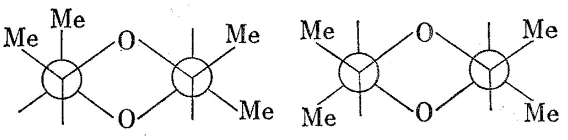
$$J_{cis} = \frac{1}{2}(J_{ae}+J_{ea}) \qquad (2)$$

The values of J_{ae} and J_{aa} of 1,4-dioxane were 2.7 and 9.4 Hz, respectively, assuming that J_{ee} equals J_{ae}.[8] Other values for 1,4-dioxane are 6.1 and 2.8 for J_{rrans} and J_{cis}, respectively.[9] Based on the same assumption, even it is not wholly justified, J_{ae} and J_{aa} of 1,4-dioxane are calculated to be 2.8 and 9.4 Hz, from the values of J_{trans} and J_{cis}.



IV

Fig. 8



IIIa IIIb

Fig. 9

Of the observed coupling constants for IIIa, 3.3 Hz was assigned to the couple of methine protons at positions 2 and 3, which are axial-equatorial, *cis*, and 9.0 Hz was assigned to the other couple of protons at positions 5 and 6, which are diaxial, *trans*. Therefore, IIIa has structure C, shown in Fig. 2 and the conformation shown in Fig. 9. On the other hand, the coupling constant 9.0 Hz for IIIb showed that the two couples of protons at positions 2, 3 and 5, 6 were diaxial, both being *trans*. IIIb has structure D in Fig. 2 and the conformation shown in Fig. 9.

Thus it was confirmed that IIIa is 2, *cis*-3, *cis*-5, *trans*-6-tetramethyl-1,4-dioxane and IIIb is 2, *trans*-3, *trans*-5, *cis*-6-tetramethyl-1,4-dioxane.

Experimental

meso-2,3-Butanediol was a product of Wako Chem. Ind. Ltd. (first grade reagent). *dl*-2,3-Butanediol (bp 87.5—88.7° at 24 mmHg, Lit. bp 86° at 16 mmHg) was obtained from *meso*-2,3-butanediol by the method of Lucas, *et al.*[10] The purities of *meso*- and *dl*-2,3-butanediol were calculated from the relative areas of the peaks of three isomers of 2,4,5-trimethyl-1,3-dioxolane on a GLC. The three isomers were derived from *meso*- and *dl*-2,3-butanediol with paraldehyde by an acid-catalyzed cyclization reaction.[1] They were each estimated to be 98% pure.

2,3-Bis(iodomercurimethyl)-5,6-dimethyl-1,4-dioxane (V), Va was prepared from *meso*-2,3-butanediol with 1,3-butadiene and mercuric oxide by the method of Summerbell and Lestina,[3] mp 133—137°, yield 51%. Vb was prepared by the same method from *dl*-2,3-butanediol, mp 140—142°, yield 59%.

2,3-Bis(iodomethyl)-5,6-dimethyl-1,4-dioxane (II), IIa was obtained by refluxing Va for 12 hr with iodine in chloroform using a method similar to that of Summerbell and Lestina.[3] On recrystallization from absolute methanol, white needles of IIa were obtained, mp 84.5—87.5°. *Anal.* Calcd. for $C_8H_{14}O_2I_2$: C, 24.26; H, 3.56. Found: C, 24.19; H, 3.73. IIb was obtained as white needles from Vb using a similar

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[7] W.B. Smith and B.A. Shoulders, *J. Phys. Chem.*, **69**, 579 (1965).

[8] A.D. Cohen, N. Sheppard and J.J. Turner, *Proc. Chem. Soc.*, **1958**, 118.

[9] J.B. Lambert, *J. Am. Chem. Soc.*, **89**, 1836 (1967).

[10] H.J. Lucas, F.W. Mitchell, Jr. and H.K. Garner, *J. Am. Chem. Soc.*, **72**, 2138 (1950).

method, mp 115—116°. Yield 60%. *Anal.* Calcd. for $C_8H_{14}O_2I_2$: C, 24.26; H, 3.56. Found: C, 24.55; H, 3.63. Crystals of the mixture (IIc) were obtained from the mother liquid of IIa.

2,3,5,6-Tetramethyl-1,4-dioxane (III), IIIa, IIIb and IIIc were obtained by heating IIa, IIb and IIc, respectively, with $LiAlH_4$ in ethyl ether on a water bath for eight days following the method of Augdahl.[4] IIIa was a colorless liquid, bp 151.5°, d_4^{20} 0.9225, n_D^{20} 1.4262. *Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.33; H, 11.22. IIIb gave colorless crystals, mp 39.0—40.4°. *Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.35; H, 11.06. A small amount of IIIc was obtained in ether solution.

NMR spectra were obtained with a Hitachi H-60 (60 MHz) instrument in deuterochloroform, containing TMS as an internal reference.

The isomers obtained were checked to see that they gave only one peak on a GLC, using a Hitachi gas chromatograph, Model F-6, and a Golay Column (Squalane 45 m) at 65°. Nitrogen was used as carrier gas.

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