Chemistry of 1,3-Glycol Derivatives. II. Lithium Aluminium Hydride and Meerwein-Ponndorf-Verly Reductions of 6,6-Dimethylspiro[2.5]octane-4,8-dione

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Lithium aluminium hydride reduction of 6,6-dimethylspiro[2.5]octane-4,8-dione in tetrahydrofuran gave *cis*- and *trans*-6,6-dimethylspiro[2.5]octane-4,8-diols. Almost the same ratio of *cis*: *trans*$=1:2$ was obtained with various substrate-reagent ratios. In the case of Meerwein-Ponndorf-Verly reduction, however, *cis*-diol was obtained almost exclusively. It is clear that the former reduction gave kinetically-controlled products and that the latter gave thermodynamically-stable products. Unusual results were obtained by changing the hydrolysis conditions for the lithium aluminium hydride reduction products and these are explained assuming that the intermediate aluminium alkoxide is oxidized by acid.

The reduction of 6,6-dimethylspiro[2.5]octane-4,8-dione (**1**) produces *cis*- and *trans*-6,6-dimethylspiro[2.5]-octane-4,8-diols (*cis*- and *trans*-**2**). Because of the special structure of **1**, a study of the steric course will provide a convenient tool for examining the mechanism for various reducing reagents and the spectral data of the resulting diol will be useful in stereochemistry. In this article, the results of lithium aluminium hydride and Meerwein-Ponndorf-Verly reductions of **1** are reported.

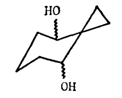
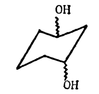
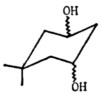
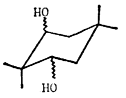
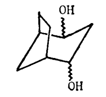
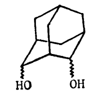
Lithium aluminium hydride reduction of **1** in tetrahydrofuran at 0 °C gave two kinds of diols, A and B, which were separated by fractional recrystallization from chloroform. As mentioned below, it was concluded that A (mp 166—168 °C) is *cis*-**2** and B (mp 119—121 °C) is *trans*-**2**.

The melting points of the *cis*- and *trans*-isomers of 1,3-cyclohexanediols appear to be related to the conformations. The melting points of the *cis*-isomers which can form intramolecular hydrogen bonds are higher than those of the *trans*-isomers, but this relation is reversed in cases where the intramolecular hydrogen bond is difficult to form due to steric repulsion. Related data are shown in Table 1. Applying this conclusion to the present case, it appears likely that A and B are *cis*- and *trans*-**2** respectively.

Finegold and Kwart have discussed the conformation of the 1,3-cyclohexanediol system and concluded that the hydroxyl groups of the *cis*-isomer are diaxial forming an intramolecular hydrogen bond when C-5 has no substituent, and are diequatorial when C-5 is substituted with two methyl groups because of the 1,3-diaxial repulsion between the hydroxyl and methyl groups.$^{1)}$ Therefore, two hydroxyl groups of the present *cis*-**2** should also be diequatorial.

The NMR spectra can be explained reasonably well in terms of the above conformations. Protons of the two methyl groups at the C-6 position of *trans*-**2** gave only one singlet at $\delta=1.09$, since rapid ring-inversion renders the two methyl groups equivalent. In the case of *cis*-**2**, two singlets were observed at $\delta=1.00$ (axial) and at $\delta=1.13$ (equatorial), since ring inversion is restricted. Cyclopropane ring protons of *trans*-**2** gave a multiplet of A_2B_2 type centered at $\delta=0.52$. The same protons of *cis*-**2** gave a singlet at $\delta=0.54$, since the cyclopropane ring is perpendicular and symmetrical to the plane of C-1, C-4, and C-8 which includes the two C–OH bonds. Assignments of the signals due to the cyclohexane ring protons are as follows. In the case of *cis*-**2**, a doublet ($J=12.0$ Hz) of doublets ($J=8$ Hz) centered at $\delta=1.45$ can be assigned to the signals of the two axial

Table 1. Melting points and IR absorptions due to the hydroxyl group of 1,3-diols

Diol			Mp, °C	IR absorption, cm^{-1}
	a)	*cis* *trans*	166—168 119—121	3610 (free) 3610 (free)
	b)	*cis* *trans*	86—87 116—116.5	3619 (free), 3544 (bonded) 3625 (free)
	c)	*cis* *trans*	147—148 102—104	
	d)	*cis* *trans*	205—206 107—108	3635 (free) 3637 (free)
	e)	*cis* *trans*		3615 (free), 3575 (bonded) 3615 (free)
	f)	*cis*		3616 (free), 3530 (bonded)

a) Determined in carbon tetrachloride. b) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1956). c) H. Finegold and H. Kwart, *J. Org. Chem.*, **27**, 2361 (1962). d) H. Favre and J. C. Richer, *Can. J. Chem.*, **37**, 411 (1959). A. W. Allan, R. P. A. Sneeden, and J. M. Wilson, *J. Chem. Soc.*, **1959**, 2186. e) J. G. Durocher and H. Favre, *Can. J. Chem.*, **42**, 260 (1964). f) D. Lenoir and P. von R. Schleyer, *Chem. Commun.*, **1971**, 26.

hydrogens at C-5 and C-7, a doublet (J=12 Hz) of doublets (J=4 Hz) centered at δ=1.65 to those of the two equatorial hydrogens, and a doublet (J=8 Hz) of doublets (J=4 Hz) centered at δ=3.67 to the two methine protons at C-4 and C-8, respectively. In the case of *trans*-**2**, a doublet (J=13 Hz) of doublets (J=7 Hz) centered at δ=1.45 can be assigned to the two axial protons at C-5 and C-7, a doublet (J=13 Hz) of doublets (J=4 Hz) centered at δ=1.16 to those of the two equatorial protons, and a doublet (J=7 Hz) of doublets (J=4 Hz) centered at δ=3.77 to the two methine protons, respectively. The protons of the hydroxyl groups gave a rather sharp singlet at δ=1.54 in the case of *cis*-**2**, and a rather broad singlet at δ=1.61 which overlapped with the signals of the axial protons in the case of *trans*-**2**.

Lithium aluminium hydride reduction of **1** in tetrahydrofuran at 0 °C followed by hydrolysis gave *cis*- and *trans*-**2** in a ratio of 37: 63. In contrast, aluminium isopropoxide reduction in 2-propanol under reflux followed by hydrolysis gave *cis*-**2** almost exclusively (the *cis*- to *trans*-**2** ratio was 99: 1). These results are in accordance with the conclusions of Dauben *et al.* that the Meerwein-Ponndorf-Verly reduction gives thermodynamically more stable products (product development-control) and that lithium aluminium hydride reduction gives sterically approach-controlled products.[2)]

Attacks by aluminium isopropoxide on **1** appear to occur to form the less hindered diequatorial intermediate leading to *cis*-**2**. Because the reduction is reversible, thermodynamic stabilities of the products determine the product distribution. The possibility that one aluminium isopropoxide molecule reacts with two carbonyl groups of the same molecule leading to *cis*-**2** appears to be unlikely because of the steric repulsion with cyclopropyl group.

In the case of lithium aluminium hydride, the reduction process is not reversible. In the intermediate of the attack on the first carbonyl, the $-OAlH_3^-$ group will take the equatorial position, prohibit ring inversion, and fix the conformation. The less hindered reaction path for second carbonyl group reduction appears to proceed from the opposite side of the axial methyl group at C-5 and results in *trans*-**2** preferentially.

Unusual results were obtained during the course of the attempts to obtain the hydroxy ketone by the half reduction of dione **1**. In tetrahydrofuran at 0 °C, **1** was treated with a 1/3 mole equivalent of lithium aluminium hydride. After one hour, 2 M-HCl was added. In one experiment, the reaction mixture was heated to 40—50 °C to remove the solvent using a rotary evaporator immediately after the addition of hydrochloric acid. In another experiment, the solvent was evaporated after standing at room temperature for two days. The former experiment gave 2-(2-chloroethyl)-3-hydroxy-5,5-dimethyl-2-cyclohexanone (**3**), which is the enol form of 2-(2-chloroethyl)-5,5-dimethyl-1,3-cyclohexanedione (**4**) and is the cleaved product of the cyclopropane ring of **1** with hydrochloric acid. The latter gave diol **2**. Related results are shown in Table 2. Since the experiments were carried out on a small scale because of the limited amount of **1** available and the product separations were performed by column chromatography, the data are not quantitative.

These results show that the reduction intermediate, aluminium alkoxide, decomposes to give **3** at a higher temperature, 40—50 °C, and hydrolyzes slowly to give **2** at room temperature. The addition of hydrochloric acid to the intermediate alkoxide results in the rapid hydrolysis of the hydrides bonded to aluminium. The hydrolysis of the Al–O bond, however, appears to be not always fast. For example, it is well known that the B–O bond in the borohydride reduction intermediate is sometimes hydrolyzed only slowly with acid. Rickborn and Quartucci have suggested the possibility that the intermediate of lithium aluminium hydride reduction of epoxide could be oxidized to ketone by a hydride acceptor (AlH_3).[3)] In the present case, oxidation back to ketone **1** and its subsequent decomposition by hydrochloric acid cannot explain the results, because **1** does not react with hydrochloric acid under the same conditions, but does react giving 6,6-dimethyl-2,3,4,5,-6,7-hexahydrofuran-4-one (**5**) instead of **3** under tetrahydrofuran refluxing. The formation of **3**, therefore, follows some other reaction path. The most probable scheme is depicted in Fig. 1 together with those of related reactions. The oxidation step with hydrochloric acid might be intramolecular, if both or either of the H^+ and Cl^- ions come from the ligands of aluminium. However, further detailed experiments are required to examine this interesting possibility.

The unusual results were obtained only in runs with smaller lithium aluminium hydride to **1** ratios (1: 2—1: 3), and no formation of the expected hydroxy ketone was observed. These results appear to show that the oxdation of alkoxide with acid occurs only in the case of an $RO-AlH_2-OR$ type alkoxide where the hydrolysis of Al–O bond is strongly hindered by two bulky R groups.

Some of the chemical properties of **3** were investigated. The reaction with equimolar sodium carbonate in 75% ethanol at 40 °C for 24 h gave **1**. The changes of **3** in pyridine were followed by NMR at 40 °C (NMR-probe temperature). Into 0.5 ml of pyridine were dissolved 30 mg of **3** and the spectra were determined immediately

TABLE 2. THE EFFECTS OF HYDROLYSIS CONDITION ON THE PRODUCT DISTRIBUTION[a)]

Run No.	1/$LiAlH_4$ mole ratio	Duration time of hydrolysis	Product
1	0.6/1	10 min	**2**
2	3.0/1	48 h	**2**
3	3.0/1	40 min	**3** and a trace of **2**
4	3.0/1	10 min	**3**
5[b)]	2.3/1	1 h	**3**

a) **1** (3 mmol in runs 1 and 5 and 5 mmol in runs 2, 3, and 4, respectively) was reduced with lithium aluminium hydride in 30 ml of tetrahydrofuran at 0 °C for 1 h. The reaction mixtures were treated with 4 ml of 2M-HCl to hydrolyze the products at room temperature for the duration times given in the table. b) Diethyl ether (30 ml) was used in place of tetrahydrofuran.

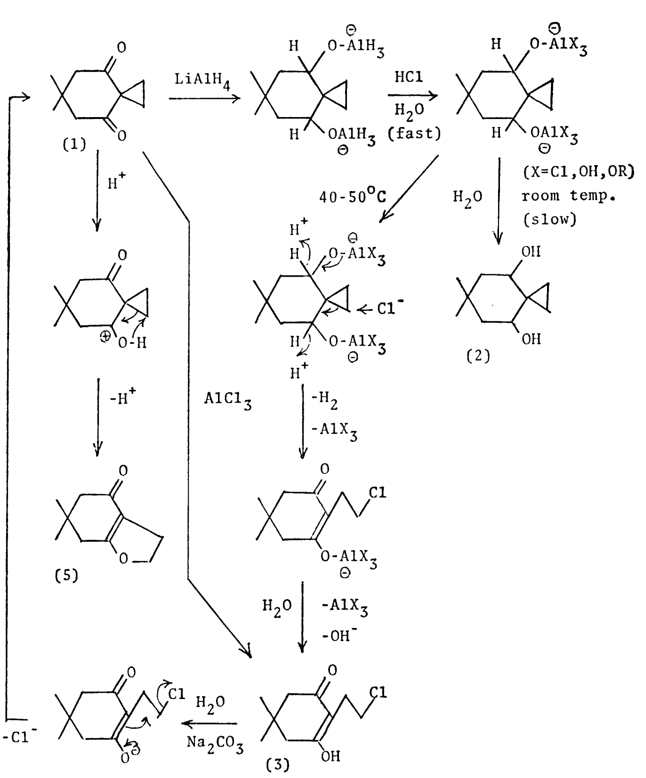


Fig. 1. Reaction of **1** and related reaction scheme.

after preparation of the solution, and at 24 and 48 h after preparation. When one drop of D_2O was added to the sample, the spectra showed that **3** was transformed to **1** after 24 h and further to **5** after another 24 h. When no D_2O was added, the changes were much slower. The reaction of **1** with a half mol of aluminium chloride in chloroform at room temperature gave **3**.

Experimental

Materials. The preparation of **1** has been reported previously.[4] Aluminium isopropoxide was prepared by a method reported in the literature.[5] Commercial tetrahydrofuran and 2-propanol were dried over calcium hydride and distilled before use. Other reagents were commercial ones of analytical grade.

Reduction of 1 with Lithium Aluminium Hydride. The following examples show typical experimental procedures. Into a tetrahydrofuran (20 ml) solution of lithium aluminium hydride (0.379 g, 10 mmol) was added a tetrahydrofuran (10 ml) solution of **1** (1.68 g, 10 mmol) over a period of 5 min at 0 °C. After 2 h, 2 M-HCl (5 ml) was added. After standing for 24 h, the solvent was evaporated with a rotary evaporator (bath temperature, 40—50 °C) and the residue was dissolved in ethyl ether, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. After evaporation of the ether, a colorless solid of **2** (1.58 g) was obtained. The *cis-* to *trans-* **2** ratio in the crude **2** was determined to be about 1: 2 by measuring the proton ratio of the NMR spectra in pyridine. The solid was dissolved in ether and passed through Wakogel C-200, $2\phi\times 3$ cm, to remove inorganic salts. After evaporating the solvent the product was recrystallized from chloroform (20 ml) to give fraction A, mp 166—168 °C (Found: C, 70.54; H, 10.54%. Calcd for $C_{10}H_{18}O_2$: C, 69.93; H, 10.54%) and fraction B, mp 119—121 °C (Found: C, 69.85; H, 10.56%).

1 (0.83 g, 5 mmol) was reduced with lithium aluminium hydride (0.062 g, 1.63 mmol) by the same procedure as described above, except that tetrahydrofuran was removed from the reaction mixture just after the addition of 2 M-HCl using a rotary evaporator at 45—50 °C. The evaporation required about 10 min. A work-up gave crystals of **3**, mp 144—145 °C (0.524 g, 52% yield). Found: C, 58.83; H, 7.21; Cl, 17.21%. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.46; Cl, 17.59%. NMR in dimethyl-d_6 sulfoxide δ: 0.95 (s, 6H, methyl), 2.23 (s, 4H, cyclohexane ring methylene), 2.62 (t, $J=7.0$ Hz, 2H, branched α-methylene), 3.49 (*t*, $J=7.0$ Hz, 2H, branched β-methylene), and 4.10 (s, broad, 1H, hydroxyl). IR (KBr disc): 3350 (ν_{O-H}), 2470 ($\nu_{C=O\cdots H-O}$), 1635 ($\nu_{C=O}$), and 1558 cm^{-1} ($\nu_{C=C}$).

Meerwein-Ponndorf-Verly Reduction of 1. According to the reported method,[5] **1** (1.0 g, 6 mmol) was reduced with aluminium isopropoxide (4.08 g, 20 mmol) in dry 2-propanol (9.0 g, 150 mmol). **2** was obtained in a yield of 98% (0.98 g). Gas-chromatographic analysis could not be applied to **2**. However, application of the trimethylsilylation method[6] gave satisfactory results, although the detector was damaged after repeated analyses. The ratio of *cis-* to *trans-***2** was found to be 99: 1.

The NMR spectra were recorded on a Varian Associates HR-220 spectrometer at 220 MHz at room temperature or on a Jeol PMX-60 spectrometer. The IR spectra were recorded on a Hitachi EPI-G2 spectrometer. The gas-chromatographic analyses were carried out by Yanaco GC-550 TPH chromatograph with a 1.5 m OV-17 column.

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