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The Effects of Neighboring Heteroatoms in Ring Opening of Epoxides*

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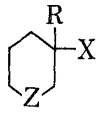
In connection with our studies on the roles of heteroatoms (N,S,O) in solvolytic reactions, the effects of the heteroatoms in ring openings of epoxides, methylenecyclohexane epoxide (**4**), 3-methylene epoxides of tetrahydropyran (**5**), N-methylpiperidine (**6**) and tetrahydrothiopyran (**7**), were examined. All epoxides were synthesized according to Corey's procedure from the corresponding cyclanones.

Ring-opening reactions of epoxides were carried out as follows: **a**) Reduction with lithium aluminum hydride, **b**) reduction with lithium metal in ethylenediamine, **c**) reduction with borane–lithium borohydride, **d**) acetic acid-catalyzed opening, **e**) hydrochloric acid-catalyzed opening, and **f**) reaction of **7** with Lewis acid (boron trichloride). No appreciable effects of heteroatoms were observed in the reactions **a** and **b** for **4**, **5**, and **6**. The reactions **c**, **d**, and **f** for **7** resulted in the predominant formation of ring-contracted 5-membered ring derivatives. These results strongly suggest that an enormous amount of participation, particularly by the sulfur atom, is also involved in the ring-opening reactions of epoxides as well as that observed in solvolysis.

Nucleophilic β-participation by heteroatoms (N,S,O) in solvolysis is relatively large and often observed as extremely fast rates except by oxygen atom.[2] Although the magnitude of participation varies with chemical structure, the N and S atoms usually cause the rates of solvolysis to increase by a factor of 10^5—10^9.[3] In contrast, the effect of the oxygen atom is usually small as compared with those of N and S, and its rate is relatively slow because of large inductive factor of oxygen. As we have already reported on solvolysis in medium-sized ring systems (**1**,**2**; Z=N or S), the two different ring compounds (**1**,**2**; halide for Z=NMe, ester for Z=S) undergo solvolysis in processes *via* intermediates (**3**; Z=NMe, S) and yield two products (**1**,**2**) in same ratios (30: 70 for Z=NMe, 82: 18 for Z=S).[3] These observations indicate that the reactions must be due to huge amount of β-S- and β-N-participations.



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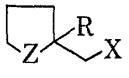

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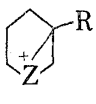

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Epoxides are recognized to be one of the most reactive classes with respect to attack by nucleophilic reagents and their ring-opening reactions, such as reduction, nucleophilic sub-

* Dedicated to the memory of Prof. Eiji Ochiai.

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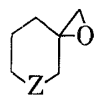
2) For reviews, see *a*) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Co., New York, N.Y., 1962, pp. 16—18, 103—120, *b*) B. Capon, *Quart. Revs.*, **18**, 45 (1964); *c*) K.-D. Gundermann, *Angew. Chem.*, **75**, 1194 (1963); *d*) E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N.Y., 1959, Chapter 14.

3) *a*) S. Ikegami, K. Uoji, and S. Akaboshi, *Tetrahedron*, **30**, 2077 (1974); *b*) S. Ikegami, T. Asai, K. Tsuneoka, S. Matsumura, and S. Akaboshi, *ibid.*, **30**, 2087 (1974).

stitution, and isomerization, have been well-known.[4] Nevertheless, much confusion has still surrounded the mechanism of these reactions. Several different mechanisms, S_N1 and S_N2, uncatalyzed or catalyzed by acids, have been called into play to explain the direction and stereochemistry of ring opening. The ring-opening reactions of heterocyclic epoxides often result in ring transformations which play an important role for synthesis of heterocycles.[5] Therefore, it is of interest to know the effects of heteroatoms in ring-opening reactions and whether or not same intermediate as solvolysis would be involved in ring opening. Compounds used in the present subject were monocyclic six-membered ring compounds (**4**—**7**) containing one heteroatom as related to the previous studies.[3,6] Reactions carried out are in the following six different procedures: 1. Reduction—**a**) with lithium aluminum hydride (LAH) in ether, **b**) with lithium in ethylenediamine, **c**) with borane–lithium borohydride; 2. Acid-catalyzed opening—**d**) with hydrochloric acid, **e**) with acetic acid, **f**) with Lewis acid (boron trichloride).



4 : Z=CH_2
5 : Z=O
6 : Z=NMe
7 : Z=S

Results

Syntheses of Epoxides

All of the methyleneoxy compounds (**4**—**7**) were synthesized from the corresponding ketones with dimethylsulfonium methylide prepared *in situ* according to Corey's procedure.[7] Tetrahydro-3-pyranone was synthesized from hydroboration-oxidation of dihydropyran followed by oxidation with sodium chromate–sulfuric acid under heterogeneous condition.[8] The preparation of the other ketones, N-methyl-3-piperidinone[9] and tetrahydrothiopyran-3-one,[3] have been reported previously. The results are summarized in Table I.

Table I. Results of Synthesis of Epoxides

Compd.	Yield, %	bp (°C/mmHg)	n_D^{20}
4[a]	92	67—68/50	1.4494
5	64	83—85/37	1.4496
6	54	60—63/14	1.4606
7	80	88—90/9	1.5196

a) See Ref. 21.

4) *a*) S. Winstein and R.B. Henderson, "Heterocyclic Compounds," Ed. by R.C. Elderfield, Vol. 1, John Wiley & Sons Inc., New York, N.Y., 1950, pp. 1—58; *b*) E.L. Eliel, "Steric Effects in Organic Chemistry," Ed. by M.S. Newman, John Wiley & Sons Inc., New York, N.Y., 1956, pp. 106—114; *c*) A. Rosowsky, "Heterocyclic Compounds," Ed. by A. Weissberger, Interscience Publishers, New York, N.Y., 1964. pp. 1—523.

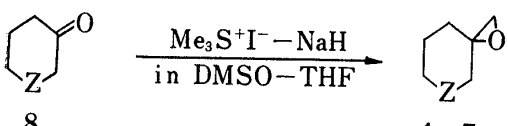
5) H.C. van der Plas, "Ring Transformations of Heterocycles," Vol. 1, Academic Press, London & New York, 1973, pp 1—121.

6) The occurrence of epoxides in substances of natural origin are known particularly in the plant kingdom and recognized also in the micro-organisms as an antibiotic mould metabolite (See Ref. 4*c*, pp. 24—30). Among them many kinds of epoxide possessing high mycotoxic activity against human or domestic animals, containing one of the epoxides subjected to the present work as a part of the structure, have been reported. They are called as the substances of scirpene and scirpenone species. Because of interest concerning carcinogenic or anti-carcinogenic activity, the epoxide we synthesized were assayed in a cell level by Dr. T. Tatsuno, The Institute of Physical and Chemical Research, Wako-shi, Saitama, whom we thank.

7) E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

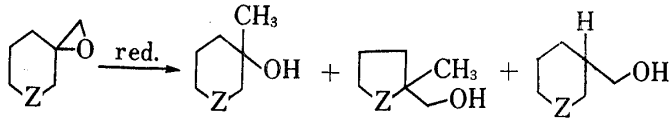
8) G. Zweifel and J. Plamondon, *J. Org. Chem.*, **35**, 898 (1970). We also examined the hydroboration-oxidation of dihydropyran and related derivatives. The results will be published.

9) R.E. Lyle, R.E. Adel, and G.C. Lyle, *J. Org. Chem.*, **24**, 342 (1959).



8 4—7

Chart 1



4—7 **9** **10** **11**

Z=CH2, O, NMe, S

Chart 2

Reduction of Epoxides

a) Reduction with Lithium Aluminum Hydride in Ether——Epoxides were reduced with 1.2 mequiv. of LAH in anhydrous ether. Products were analyzed by gas liquid partition chromatography (GLPC) and proton nuclear magnetic resonance spectroscopy (PMR). All epoxides yielded the corresponding tertiary alcohols (**9**) as a single product, which would be expected from attacking of a hydride anion at the less highly substituted position as would be anticipated for an S_N2 process.[10] Other product such as **10** and **11** could not be detected on GLPC and PMR analyses. The results are summarized in Table II.

b) Reduction with Lithium in Ethylenediamine——Since this reduction is considered to be reaction proceeding *via* a carbanion formed by the supply of electrons from metal a type of reduction would be apparently different from LAH-reduction.[11] Also, this type of reduction can be done in liquid ammonia[12] or ethylamine [11] and especially reduction of hindered epoxides by these procedures is superior to reduction with LAH.[13] Reduction was run in anhydrous ethylenediamine by adding three equimolar amounts of lithium metal. The compounds (**4—6**) yielded tertiary alcohols (**9**) quantitatively. The S-containing compound (**7**) gave 5,6-dihydro-4H-thiopyran-3-methanol (**20**) as an initial product, which immediately changed to various undetectable substances as a result of subsequent reactions. In order to confirm the structure of the initial product, the olefin alcohol (**20**) was prepared from the reaction with ethylenediamine lithium amide and characterized by PMR and mass spectroscopies. These results are summarized in Table II.

c) Reduction with Borane-Lithium Borohydride in Tetrahydrofuran (THF)——Generally, the oxirane ring is so sensitive to an acid, that the addition of Lewis acid may permit more favorably such a process as *via* a carbonium ion (S_N1 type) which would be resulted from an initial attack of borane at the oxygen of epoxide. Accordingly, reduction may occur at the more crowded position.[14]

Reductions were carried out using a 1:1 molar mixture of a freshly prepared borane–THF solution and lithium borohydride. The compounds (**4,5**) afforded the corresponding tertiary alcohols (**9**) quantitatively. Interestingly, **7** gave a mixture of the corresponding tertiary alcohol (**9**; Z=S) and a ring transformed product (**10**; Z=S) in a ratio of 37:63. A ratio of the 5-membered alcohol (**10**; Z=S) increased to 80% with the use of an excess of borane. Yields and products are illustrated in Table II.

Acid-catalyzed Opening of Epoxides

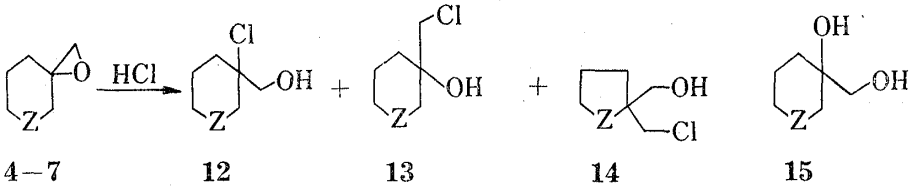
d) Reaction with Hydrochloric Acid——Reactions were run in 80% aqueous acetone at 25° or 50° for 15—20 hours after adding a slight excess of conc. hydrochloric acid. The reac-

10) *a*) H.O. House, "Modern Synthetic Reactions," 2nd Ed., W.A. Benjamin, Inc., Menlo Park, Calif., 1972, pp. 103—105; *b*) Ref. 4*c*, pp. 199—221.
11) Ref. 4*c*, pp. 181—187.
12) E.M. Kaiser, C.G. Edmonds, S.D. Grubb, J.W. Smith, and D. Tramp, *J. Org. Chem.*, **36**, 330 (1971).
13) H.C. Brown, S. Ikegami, and J.H. Kawakami, *J. Org. Chem.*, **35**, 3243 (1970).
14) *a*) H.C. Brown and N.M. Yoon, *J. Am. Chem. Soc.*, **90**, 2686 (1968); *b*) *Idem*, *Chem. Commun.* **1968**, 1549; *c*) P.T. Lansbury, D.J. Scharf, and V.A. Pattison, *J. Org. Chem.*, **32**, 1748 (1967); *d*) R.E. Lyle and W.E. Krueger, *ibid.*, **32**, 2873 (1967).

Table II. Results of Reduction of Epoxides

Epoxide	Reactant					
	LAH in ether		Li in $(CH_2NH_2)_2$		BH_3–$LiBH_4$ in THF	
	Product	Purity, %	Product	Purity, %	Product	Purity, %
4	**9**(Z=CH_2)	~100	**9**(Z=CH_2)	~100	**9**(Z=CH_2)	98
5	**9**(Z=O)	~100	**9**(Z=O)	~100	**9**(Z=O)	~100
6	**9**(Z=NMe)	~100	**9**(Z=NMe)	~100	—	
7	**9**(Z=S)	~100	mixture		**9**(Z=S)	37
					10(Z=S)	63

tions of the epoxides (**5**, **6**) yielded the corresponding chlorohydrins (**12**; Z=O, Z=NMe) in good yields (Chart 3); in the case of **6** two mequiv. of hydrochloric acid was used. In order to identify their structures, these chlorohydrins were converted to the starting materials by treatment with sodium hydroxide solution. Both were identical with **5** and **6** respectively on GLPC analysis. For the determination of a position of a hydroxyl group, two chlorohydrins were converted into esters; *p*-nitrobenzoate for **12**; Z=O and acetate for 12; Z=NMe. The chemical shift of peak assignable to the methylene group for both derivatives, chlorohydrin and its ester, and the fragmentation in mass spectrum substantiate the structure of **12** to the chlorohydrins. Similarly, ring opening of **4** afforded mainly two kinds of chlorohydrin, **12**; Z=CH_2 and **13**; Z=CH_2, the latter as a major component, in a ratio of 32: 49. As a similar trend to reactions mentioned above, the reaction of the epoxide (**7**) gave quantitatively the corresponding diol (**15**) as a sole product. Probably, it would be produced as a result of solvolysis of an initially formed chlorohydrin (s) (**12**; Z=S and/or **14**; Z=S). These results are summarized in Table III.



4–7 12 13 14 15

Z=CH_2, O, NMe, S

Chart 3

e) **Reaction with Acetic Acid**——The epoxides (**4**,**5**) were relatively stable under the mild condition used, so that they unchanged in the reaction with three times excess of glacial acetic acid in refluxing deuteriochloroform for more than 10 hr. However, in the reaction of the N-containing epoxide (**6**) with four equimolar amounts of acetic acid, there was obtained diol monoacetate of 6-membered ring compounds, N-methyl-3-acetoxymethyl-3-piperidinol (**17**; Z=NMe), as a unique product (Chart 4). In speculating from the structure of the product, it may be seen that opening occurred at the terminal position (S_N2 type). If so, why opening of the epoxides (**4**,**5**) did not take place under the similar condition? Therefore, it is concluded that this easy opening would be due to the transannular effect of the nitrogen atom. It occurred in the usual S_N1 process and subsequently, an O–O acetyl shift gave the acetoxymethyl derivative as shown in Chart 4. Similarly, acid-catalyzed opening of the S-containing epoxide (**7**) yielded the two kinds of isomers, 3-acetoxymethyltetrahydrothiopyran-3-ol (**17**; Z=S) and tetrahydro-2,2-thiophenedimethanol acetate (**18**; Z=S), in a ratio of 1: 1.5. It is of particular interest that the sulfur atom showed strong nucleophilic effect to an electron deficient center by which the ring transformed.

The characterization of the structures was done by a spectroscopic method such as PMR and mass. Furthermore, the five-membered ring compound (**18**; Z=S) was converted to the diacetate, which was spectroscopically identical with an authentic sample prepared in another synthetic route.[3b]

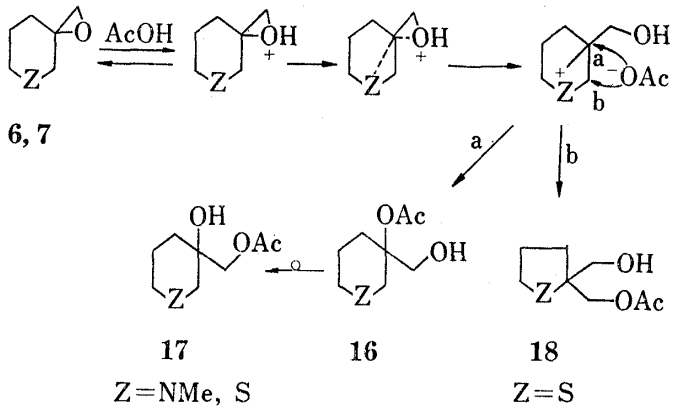


Chart 4

Table III. Results of Acid-catalyzed Opening of Epoxides

Epoxide	Reactant	
	aq. HCl, product	AcOH in $CHCl_3$, product
4	**12**(Z=CH_2):**13**(Z=CH_2)=32:49	unchanged
5	**12**(Z=O)	unchanged
6	**12**(Z=NMe)	**17**(Z=NMe)
7	**15**	**17**(Z=S):**18**(Z=S)=28:72

f) Reaction with Lewis Acid (Boron Trichloride)——Only the epoxide (**7**) of which ring transformation can be expected in this reaction was undertaken to the reaction with boron trichloride. The reaction was carried out in carbon tetrachloride by adding a slight excess of boron trichloride at 0° and found to be extremely fast. As soon as adding boron trichloride, a white solid came out, of which PMR spectrum in nitrobenzene showed to be a 2,2-bis(chloromethyl)tetrahydrothiophene boron trichloride complex (**19**).

Discussion

General aspects and surveys concerning reductions of epoxides with LAH and related complex metal hydrides have since been discussed by many excellent reviewers[4b,10,15] and it is well-known that this reduction is a bimolecular nucleophilic substitution of the classical S_N2 type, involving backside approach of a reagent and thus resulting Walden inversion.

The reduction of the present epoxides, in all cases, took place with the same trend without any observation of effects of heteroatoms and yielded the corresponding tertiary alcohols as a sole product. These are attributed to an attack at the less highly substituted terminal position of epoxides.

An attempt for applying lithium–aliphatic amine systems to epoxide reduction, particularly insteroidal epoxides, is tried chiefly by Hallsworth and Henbest.[16] This powerful re-

15) Reviews for reduction of epoxides with LAH, see; *a*) W.G. Brown, "Organic Reactions," Vol. 6, John Wiley & Sons, Inc., New York, N.Y., 1951, p. 478; *b*) N.G. Graylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N.Y., 1956; *c*) R.E. Parker and N.S. Isaacs, *Chem. Revs.*, **59**, 737 (1959).

16) A.S. Hallsworth and H.B. Henbest, *J. Chem. Soc.*, **1957**, 4604; *idem*, *ibid.*, **1960**, 3571.

agent is able to cleave highly hindered epoxide rings that are usually difficult in cleaving by LAH and openings often occur with high selectivities. An application of anhydrous ethylenediamine to this reduction as a solvent makes it practically more convenient because the amine can be handled in similar ways to other versatile reagents.[13]

In this convenient procedure, the reduction of the epoxides (**4**,**5**,**6**) resulted in a selective attack at the terminal position, indicating no effect of heteroatoms in this reaction. In contrast to these normal ways of reduction, the reduction of the S-containing epoxide (**7**) provided **20** as a result of eliminative epoxide opening, which could be isolated from the reaction under much milder condition. As drawn in Chart 5, lithium or a base (lithium amide) first attacks the α-proton and then by subsequent move of electrons as shown in an arrow to change to **20**. In this reaction, it may be seen that the sulfur atom does not contribute directly to the β-carbon with a nucleophilic character, but to stabilization of a carbanion formed at the α-position.

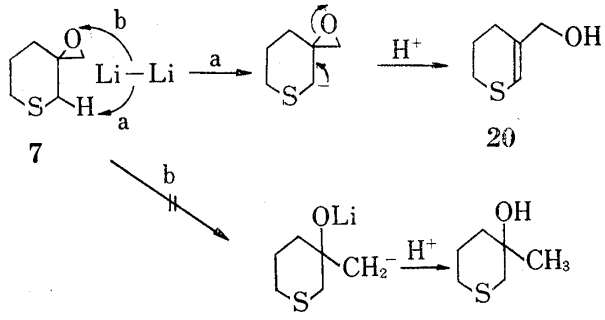
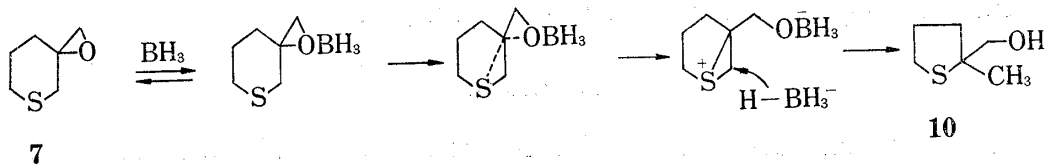


Chart 5

Evidence that the reduction of epoxides with complex metal hydride, particularly, in the presence of Lewis acid, increases a product ratio attacked at the more highly substituted carbon atom,[14] provided an interesting result for the reaction of **7**. In the cases of **4** and **5**, the reaction still occurred at the less hindered carbon, but the sulfur atom greatly affected the reduction to perform huge amount of neighboring participation. The preferred formation (63%) of the 5-membered ring alcohol (**10**), which increases 80% by using an excess of a reagent, is in good contrast to that of solvolysis of **1** and **2** (R=Me); solvolysis results in the predominant formation (98%) of the corresponding 6-membered alcohol.[3b,17] This contradictory result indicates that the mechanism must be different. Probably, the difference of intermediates, such as solvated or unsolvated episulfonium ion, and/or which is charge-localizing on sulfur or charge-delocalizing over the carbon atoms, might respond to the formation of different products. As illustrated in Chart 6, epoxide opening was easily initiated, by both the formation of borane-epoxide



7 **10**

Chart 6

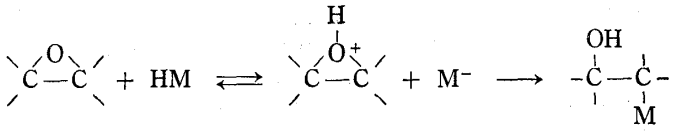
complex and the neighboring electron donation of sulfur from the backside, to form a stiff episulfonium ion, which was attacked preferentially at the less highly substituted postion by a borohydride anion. In other words, this mechanism might occur in more concerted feature, involving a total process of extended S_N2' type. In addition to the mechanism, this reaction is apparently of preparative value because of difficulty in the synthesis of such compound as **10**.

In an acetic acid-catalyzed opening, which much resembles solvolytic conditions, it was also observed that a major product from **7** was a 5-membered ring compound (**18**; Z=S). The mechanism of the opening would be identical with borane-lithium borohydride reduction just as mentioned, rather than solvolysis. As shown in Chart 4, the attack of an acetoxy anion

17) Our recent work concerning intramolecular sulfenyl chloride additions in the related systems also offers similar results. The work will be published soon.

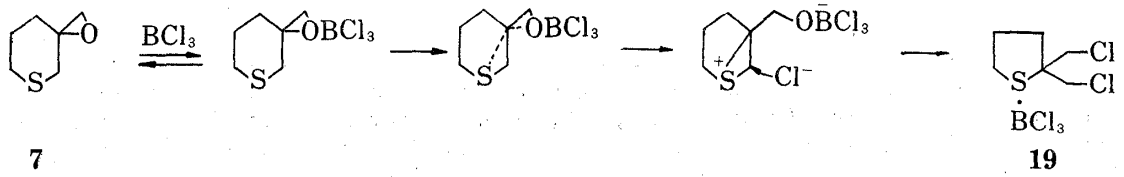
at the α-carbon atom (path b) is favorable for the S-containing epoxide (**7**), while the N-containing epoxide (**6**) undergoes exclusively an attack at the β-carbon (path a). Both glycol monoacetates (**16**; Z=NMe, S) immediately vanish by occurring an O,O-acetyl migration, which must be in the direction from a less acidic hydroxyl group (tertiary) to a more acidic one (primary), resulting the formation of more thermodynamically stable isomers (**17**; Z=NMe, S). On the other hand, this ring-opening reaction catalyzed by acetic acid resulted in failure for the epoxides (**4** and **5**). Thus it may be said that large amount of neighboring assistance must be required for cleaving epoxide rings.

For the reaction of mineral acids to epoxides, a mode of addition may correspond to acid-catalyzed nucleophilic substitution process (S_N1, S_N2 or their mixture).
The direction and stereochemistry of ring opening often are affected by the reaction conditions that may be included such parameters as temperature, solvent polarity, and catalysis.



The ring opening of **4** catalyzed by aqueous hydrochloric acid took place easily by proceeding through both of two processes, S_N1 and S_N2, the latter being favorable and its ratio changable for varying reaction temperature. These results would be comparable to those of the additions of hypohalous acid to methylenecyclohexane.[18] In cases that are calable of neighboring participation, ring openings occurred with the single direction similar to solvolysis (compounds **5**, **6**, and **7** in Table III). The fact that only 6-membered glycol (**15**) was obtained from the S-containing epoxide (**7**) may indicate, as described previously, that reactive chloride(s) (**12** or **14** (Z=S)) initially formed were solvolyzed rapidly. In the case of the N-containing epoxide (**6**), protonation to the nitrogen atom of the product (**12**; Z=NMe) may prohibit to bring about further reactions.

As the most drastic difference compared with solvolysis, one can see in the reaction with boron trichloride which resulted in the formation of 5-membered dichloride (**19**) as a unique product (Chart 7). Successive chlorination at the second stage would be understood to be



7 **19**

Chart 7

a similar process to chlorination of alcohols which correspond to stabilized carbocation.[19] This selective formation of 5-membered derivative, as pointed out above, would be caused by more concerted process in which two different steps, nucleophilic participation by sulfur to the electron deficient β-carbon developed by ring opening and an attack of chloride anion intramolecularly or intermolecularly at the α-carbon, may take place at one time.

Finally, as one can expect the occurrence of neighboring group participation of heteroatoms, the nucleophilic effects of the N and S atoms greatly affect various reactions concerning ring opening of epoxides. Particularly, the effect by the S atom is different from that of solvolysis and would be rather large.

18) J.G. Traynham and O.S. Pascual, *Tetrahedron*, **7**, 165 (1959).
19) W. Gerrard and M.F. Lappert, *J. Chem. Soc.*, **1951**, 2545.

Experimental[20]

Preparation of Methyleneoxy Compounds——All of methyleneoxy compounds were synthesized from the corresponding ketones (**8**; Z=CH_2, O, NMe, S) with 20% excess of dimethylsulfonium methylide freshly prepared according to Corey's procedure.[7]

1,1-Methyleneoxycyclohexane (**4**)——An etherial extract from the reaction mixture of cyclohexanone (8.0 g, 82 mmoles) and dimethylsulfonium methylide (20% excess) left, after evaporating the solvent, 5.05 g (55.5%) of **4**, bp 67—68°/50 mmHg, n_D^{20} 1.4495. IR ν_{max}^{film}: 3030 cm^{-1}. Lit.[21] reports bp 66—68°/50 mmHg, n_D^{20} 1.4470.

3,3-Methyleneoxytetrahydropyran (**5**)——The reaction mixture of tetrahydropyran-3-one[22] (4 g, 40 mmoles) and dimethylsulfonium methylide gave 3.0 g of crude epoxide after continuing extraction with ether for 40 hr, which was distilled *in vacuo* to yield 2.61 g (57.2%) of colorless oil, bp 83—85°/37 mmHg, n_D^{20} 1.4496. IR ν_{max}^{film}: 3048 cm^{-1}. PMR: 2.68 (2H, s, C$\underline{H}_2$). Mass Spectrum *m/e*: 114 (M^+).

N-Methyl-3,3-methyleneoxypiperidine (**6**)——An etherial layer obtained from continuous extraction of the reaction mixture of N-methylpiperidin-3-one (**8**; Z=NMe)[9] (5.5 g, 50 mmoles) and dimethylsulfonium methylide was evaporated and distilled to give an oil which was contaminated with some of dimethyl sulfoxide (DMSO). In order to remove DMSO, the mixture was dissolved in ether, washed with satd. NaCl solution and dried. After evaporating the solvent, distillation of a residue gave a colorless oil; 3.4 g, 54%, bp 60—63°/4 mmHg. n_D^{20} 1.4607. IR ν_{max}^{film}: 3040 cm^{-1}. Mass Spectrum *m/e*: 127 (M^+).

3,3-Methyleneoxytetrahydrothiopyran (**7**)——The reaction mixture of tetrahydrothiopyran-3-one (**8**; Z=S)[23] (4.6 g, 40 mmoles) and dimethylsulfonium methylide was extracted with ether and the extract was dried over $MgSO_4$. Evaporation of the solvent left 4.2 g of crude material, which was distilled to give a colorless oil, 3.9 g (yield, 75%), bp 88—90°/9 mmHg, n_D^{20} 1.5196. IR ν_{max}^{film}: 3030 cm^{-1}. Mass Spectrum *m/e*: 130 (M^+).

General Procedure for Reduction with LAH——A suspended solution of 2.5 g of LAH in anhyd. ether (200 ml) was refluxed for 1 hr under N_2 atmosphere. After cooling, the solution was filtered by suction under N_2 stream and its concentration was determined volumetrically by measuring H_2 gas evolved from the reaction with H_2O. Under N_2 atmospheric pressure, to the LAH solution (13 ml, 6.7 mmoles) placed in a 50 ml two-necked round-bottomed flask equipped with a drying tubing ($CaCl_2$) was added, under ice-cooling, a solution of epoxide (5 mmoles) dissolved in 7 ml of anhyd. ether. After stirring for 30 min, the reaction mixture was decomposed by adding 10% NH_4Cl solution at 0° and stirred for additional 1 hr. White solid which came out was filtered and washed with ether a few times. The combined etherial solution was dried over $MgSO_4$ and used for GLPC analysis without further working up.

i) Reduction of **4**: GLPC analysis (column A, 80°, 120°, 180°) showed to be the tertiary alcohol (**9**; (Z=CH_2) by comparison with an authentic sample. No other peaks could be observed.

ii) Reduction of **5**: Only 3-methyltetrahydropyran-3-ol (**9**; Z=O) could be detected by GLPC analysis (column A, 50°, 70°, 100°, 190°). After careful evaporation of ether there was obtained 423 mg (73%) of colorless oil, of which PMR spectrum was superimposable with that of an authentic sample.[3b] Distillation provided 272 mg or 47% of the pure material, bp 93—95°/40 mmHg.

iii) Reduction of **6**: Reduction was carried out in 2 mmoles scale of epoxide. Only one peak corresponding to the retention time of 1,3-dimethyl-3-piperidinol (**9**; Z=NMe) could be detected by GLPC analysis (column B, 70°, 100°, 180°). After careful evaporation of the solvent, a colorless oil was obtained (207 mg, yield, 80%). PMR spectrum showed to be identical with that of an authentic sample.[3a]

iv) Reduction of **7**: Only a single peak corresponding to 3-methyltetrahydrothiopyran-3-ol (**9**; Z=S)[3b] was detected by GLPC analysis (column A, 70°, 100°, 190°). Removal of ether left crude product (570 mg or yield, 89%). Distillation of a residue gave pure tertiary alcohol (352 mg), bp 97—98°/20 mmHg, of which PMR spectrum was found to be identical with that of an authentic sample.

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20) All melting points are corrected; boiling points, uncorrected. PMR spectra were recorded on a Varian 100 Mc (HA-100) spectrometer, in most cases, in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard and are given in ppm from TMS. Mass spectra were measured with a Hitachi mass spectrometer Model RMS-4 performed with 70 μA of the target current and 70 eV of the chamber voltage. Infrared (IR) spectra were taken by a JASCO spectrometer (IRS) and a Hitachi-Perkin Elmer spectrometer Model 225 (Grating).

Isomeric compositions and identification of structures were established, in most part, by GLPC analysis using a Varian gaschromatograph Model 1440 (single column, FID), in all cases under a flow rate of a carrier gas (N_2) controlled to 20 ml/min. The instrument was performed with 8 feet × 1/8″ glass spiral tubing packed with (A) 10% by weight of diethylene glycol adipate or (B) 5% by weight of carbowax 20M supported on acid-washed 80—100 mesh chromosorb W. Product ratios were determined by DISC integrator equipped with a recorder. Oven temperature performed is indicated at a given position in Experimental part.

21) G.B. Payne, *Tetrahedron*, **18**, 763 (1962).

22) D.S. Tarbell and J.R. Hazen, *J. Am. Chem. Soc.*, **91**, 7657 (1969).

23) E.A. Fehnel, *J. Am. Chem. Soc.*, **74**, 1569 (1952).

General Procedure for Reduction with Lithium-Ethylenediamine——To a solution of 2—3 mmoles of epoxide dissolved in ethylenediamine (freshly distilled, bp 116—117°, and stored over NaOH), three times equimolar amounts of lithium metal cut to small pieces were added portionwise under N_2 atmosphere. The reaction mixture was warmed at 55° and stirred vigorously for 1 hr until lithium metal disappeared completely. Then to the reaction mixture, after ice-cooling, 10 ml of ether and 0.5—1 ml of H_2O was added and resulting mixture was continued to stir for 1 hr. A colorless etherial layer separated by decantation from ethylenediamine hydrate was dried over $MgSO_4$ and used for GLPC analysis.

i) Reduction of **4**: Only a single peak whose retention time corresponded to that of 1-methylcyclohexanol (**9**; Z=CH_2) could be detected by GLPC analysis (column B, 50°, 80°, 180°). Careful removal of the solvent left an oil (286 mg or 84%), which was spectroscopically identical with **9** (Z=CH_2).

ii) Reduction of **5**: GLPC analysis (column B, 80°, 180°) indicated that a major product (99.7%) was 3-methyltetrahydropyran-3-ol (**9**; Z=O). After careful removal of the solvent, there was obtained an oil (143 mg or 56%).

iii) Reduction of **6**: GLPC analysis (column B, 70°, 180°) indicated that a single product was 1,3-dimethyl-3-piperidinol (**9**; Z=NMe). No other peak could be detected. Because of volatility, the product was isolated as its hydrochloride, of which PMR spectrum showed to be identical with that of an authentic sample.

iv) Reduction of **7**: The reduction of the epoxide (**7**) was carried out according to the general procedure described above, but no peak was detected by GLPC analysis (column B, 180°). There were appeared about ten spots on a silicagel thin-layer chromatography plate eluted with $CHCl_3$ and visualized by iodine vapor. All peaks on the PMR spectrum of the crude product were unassignable except a set of two feeble broad singlets (4.00 (2H), 6.08 (1H)), which might be assigned to hydroxymethyl protons and olefinic proton of 5,6-dihydro-4H-thiopyran-3-methanol (**20**). This set of signals appeared as one of main signals when reaction time shortened. Relatively pure **20** could be obtained by treatment with ethylenediamine lithium amide at 50° for 3 hr; yield, 44%, 35 mg of a faint yellow oil from 80 mg (0.62 mmole) of the epoxide (**7**). IR $\nu_{max}^{CHCl_3}$: 3400, 1657 cm^{-1}. PMR: 6.08 (1H, bs, olefinic H), 4.00 (2H, bs, $-C\underline{H}_2OH$). Mass Spectrum *m/e*: 130 (M^+), 113 (M^+-OH).

General Procedure for Reduction with Borane (BH_3)-Lithium Borohydride ($LiBH_4$)——The 1:1 mixed solution of freshly prepared BH_3–THF solution (1.50 mmole/ml) and $LiBH_4$–THF solution (1.47 mmole/ml) were used for reductions. In a flask immersed into an ice-water bath, 1 ml of BH_3–THF solution and 1 ml of $LiBH_4$–THF solution were placed under N_2 atmosphere. A solution of 1 mmole of epoxide dissolved in 1 ml of anhyd. THF was added to the BH_3–$LiBH_4$ solution with stirring. After additional stirring for 1 hr, the solution was hydrolyzed by adding a mixture of 0.75 ml of 1M H_2SO_4 and 0.75 ml of THF and then dehydrated with K_2CO_3. The mixture thus obtained was used for GLPC analysis.

i) Reduction of **4**: GLPC analysis (column A, 100°, 120°, 180°) indicated that a major product was **9** (Z=CH_2) having 98% purity.

ii) Reduction of **5**: GLPC analysis (column A, 120°, 180°) characterized **9** (Z=O) as a sole product.

iii) Reduction of **7**: GLPC analysis (column A, 120°, 180°) observed two peaks which were separated completly. A peak having shorter retention time corresponded to **9** (Z=S) (37%) and the other having longer one was trapped by preparative GLPC, which was characterized spectroscopically to be **10** (Z=S) (67%). PMR: 1.40 (3H, s, $C\underline{H}_3$), 3.45 (2H, s, $C\underline{H}_2OH$). Mass Spectrum *m/e*: 132 (M^+), 117 (M^+-CH_3), 101 (M^+-CH_2OH). The use of a 20% excess of borane to $LiBH_4$ increased a product ratio to **20** (**9**; Z=S): 80 (**10**; Z=S).

General Procedure for Reaction with HCl——To a solution of epoxide (0.5—1.5 mmole) dissolved in 80% aq. acetone (2 ml) was added a slight excess of conc. HCl and the mixture, if necessary, was warmed at 50° for 15—20 hr. After cooling the reaction mixture was diluted by adding ether, dehydrated with K_2CO_3 and used for GLPC analysis.

i) Reaction of **4**: GLPC analysis (column A, programed from 80° to 180° with a rate of 4°/min.) indicated that the reaction at room temperature provided four kinds of products in a ratio of 11:8:49:32 for the order of retention time. The first peak, however, could not be observed from the reaction at 0°. The other three peaks, which were completely separable, were trapped by preparative GLPC and their structures were characterized by spectroscopical technique. The second peak corresponded to 1-cyclohexenemethanol. PMR: 3.98 (2H, s, $C\underline{H}_2OH$), 5.68 (1H, bs, olefinic H). Mass Spectrum *m/e*: 112 (M^+), 94 (M^+-H_2O), 81 (M^+-CH_2OH). The third peak was determined to be **13** (Z=CH_2). PMR: 3.52 (2H, s, $C\underline{H}_2Cl$). Mass Spectrum *m/e*: 150 and 148 (M^+), 132 and 130 (M^+-H_2O), 99 ($C_6H_{11}O$). The last peak was found to be identical with **12** (Z=CH_2). PMR: 3.65 (2H, s, $C\underline{H}_2OH$). Mass Spectrum *m/e*: 118 and 116 (M^+-CH_3OH), 119 and 117 (M^+-CH_2OH). The last two peaks, which were corresponded to **13** and **12** (Z=CH_2), could be converted into the epoxide (**4**) by treatment with a base; **13** (Z=CH_2) underwent the conversion more easily than **12** (Z=CH_2). It is considered that the preferred formation of **13** and **12** (Z=CH_2), also in their relative ratios, is consistent with observations for the addition reaction of HOX to methylene cyclohexane.

ii) Reaction of **5**: A single peak was observed by GLPC analysis (column B, 100°, 120°, 150°) and characterized spectrometrically to be chlorohydrin (**12**; Z=O). Careful removal of the solvent left an oil (**12**; Z=O) in 93% yield, which was purified by preparative GLPC. IR $\nu_{max}^{CHCl_3}$: 3550 cm^{-1}. PMR: 1.5—2.0 (4H, m), 3.5—3.8 (6H, m, $C\underline{H}_2O$). Mass Spectrum *m/e*: 152 and 150 (M^+), 120 and 118 (M^+-CH_3OH).

Conversion of **12** (Z=O) into the epoxide (**5**) by treatment with aq. NaOH in warm MeOH was carried out and its formation was confirmed on GLPC. Furthermore, **12** (Z=O) was converted to *p*-nitrobenzoate, mp 85.5—87° (recrystallized from ether). IR $\nu_{max}^{CHCl_3}$: 1728, 1530, 1355 cm^{-1}. PMR: 8.23 and 8.26 (4H, q of AB type, J=9 Hz, aromatic H), 4.16 and 4.18 (2H, q of AB type, J=5 Hz, $C\underline{H}_2OCO$).

iii) Reaction of **6**: Reaction was performed in H_2O instead of aq. acetone. Crude crystals of chlorohydrin (**12**; Z=NMe) HCl salt were obtained after removal of H_2O (yield, 96%). Recrystallization from iso PrOH gave pure salt, mp 163.5—164°, of which PMR spectrum in D_2O was unchangable as compared with that of the crude product. PMR (D_2O, TMS as an external standard): 3.35 (3H, s, $NC\underline{H}_3$), 4.15 (2H, s, $C\underline{H}_2OH$). Free amine (**12**; Z=NMe) was obtained after purification by preparative GLPC of a neutralized product. IR $\nu_{max}^{CHCl_3}$: 3450 cm^{-1}. PMR: 2.30 (3H, s, NCH_3), 3.58 (2H, s, $C\underline{H}_2OH$). Mass Spectrum *m/e*: 165 and 163 (M^+), 128 (M^+-Cl). Conversion of **12** (Z=NMe) into the epoxide (**6**) by treatment with aq. NaOH solution easily proceeded and a product was characterized by GLPC analysis in the similar procedure to the case of **5**. Chlorohydrin (**12**; Z=NMe) was also converted into the corresponding acetate, of which purification was carried out on preparative GLPC. IR ν_{max}^{film}: 1740 cm^{-1}. PMR: 2.08 (3H, s, $C\underline{H}_3CO$), 2.27 (3H, s, $NC\underline{H}_3$), 4.09 (2H, s, $C\underline{H}_2O$). Mass Spectrum *m/e*: 170 (M^+-Cl), 164 and 162 (M^+-CH_3CO).

iv) Reaction of **7**: Spectroscopically pure diol (**15**) was obtained in 81% yield after solvent was removed. PMR (C_5H_5N): 1.6—2.3 (4H, m), 2.48 (2H, t, J=5 Hz, $C\underline{H}_2$ at the 6 position), 2.87 and 3.05 (2H, q of AB type, J=13 Hz, $C\underline{H}_2$ at the 2 position), 3.93 and 4.14 (2H, q of AB type, J=11 Hz, $C\underline{H}_2OH$). There could not be observed signals to be corresponded to tetrahydrothiophene-2,2-dimethanol. Purification of the diol (**15**) was undertaken by elution with EtOAc over a silica gel column to give pure material. PMR: 1.2—2.1 (4H, m), 2.52 (2H, t, J=6 Hz, $C\underline{H}_2$ at the 6 position), 2.68 (2H, s, $C\underline{H}_2$ at the 2 position), 3.18 (2H, s, vanished by adding D_2O), 3.55 (2H, s, $C\underline{H}_2OH$). Mass Spectrum *m/e*: 148 (M^+), 117 (M^+-CH_2OH). The diol (**15**) was acetylated in C_5H_5N with an equimolar amount of Ac_2O to yield monoacetate, of which PMR spectrum was identical with that of one (**17**; Z=S) of monoacetates obtained by AcOH-catalyzed opening as described later.

Reaction with Acetic Acid (AcOH)——i) Reaction of **4** with AcOH: A solution of the epoxide (**4**) in $CDCl_3$ containing an equimolar amount of AcOH was refluxed for 17 hr and then left for 13 days at room temperature, but no change on PMR spectrum was observed.

ii) Reaction of **5** with AcOH: Epoxide (**5**) was reacted with three times equimolar amounts of AcOH in $CDCl_3$ under reflux for 12 hr and then for 4 days at room temperature, but no change on a PMR spectrum was observed.

iii) Reaction of **6** with AcOH: Epoxide (**6**) (22 mg, 0.19 mmole) was reacted with AcOH (44 mg, 0.73 mmole) in $CDCl_3$ (0.3 ml). The reaction was pursued by a PMR spectrum at room temperature. Peaks assignable to the acetate (**17**; Z=NMe) appeared and unchanged even after standing on for 87 hr. A pure sample of **17** (Z=NMe) was obtained by preparative GLPC using a column B controlled at 180° after neutralization of the crude material. IR $\nu_{max}^{CHCl_3}$: 3480, 1755 cm^{-1}. PMR: 2.11 (3H, s, $C\underline{H}_3CO$), 2.28 (3H, s, $NC\underline{H}_3$), 4.00 and 4.10 (2H, q of AB type, J=12 Hz, $C\underline{H}_2O$).

iv) Reaction of **7** with AcOH: Epoxide (**7**) (520 mg, 4 mmoles) was reacted with AcOH (360 mg, 6 mmoles) in 4 ml of $CHCl_3$ under reflux for 1.5 hr. The reaction mixture was diluted by adding ether after cooling, washed with satd. $NaHCO_3$ and dried over $MgSO_4$. Removal of the solvent under reduced pressure left a colorless oil, 600 mg (79%), of which GLPC analysis (column B, 180°) indicated that products consisted of two kinds of glycol monoacetate (**17** and **18** (Z=S)) in a ratio of 1: 1.46. Two isomers were separated by preparative GLPC and characterized as follows: **17** (Z=S), having shorter retention time; IR $\nu_{max}^{CCl_4}$ 3500, 1745 cm^{-1}. PMR: 2.15 (3H, s, $C\underline{H}_3CO$), 4.12 (2H, s, $C\underline{H}_2O$). Mass Spectrum *m/e*: 190 (M^+), 148 (M^+-CH_2CO), 130 (M^+-CH_3COOH), 117 ($M^+-CH_2OCOCH_3$). **18** (Z=S), having longer retention time; PMR: 2.07 (3H, s, $C\underline{H}_3CO$), 2.89 (2H, t, J=6 Hz, $C\underline{H}_2$ at the 5 position), 3.59 and 3.68 (2H, q of AB type, J=12 Hz, $C\underline{H}_2OH$), 4.10 and 4.32 (2H, q of AB type, J=12 Hz, $C\underline{H}_2OAc$). Mass Spectrum *m/e*: 190 (M^+), 159 (M^+-CH_2OH), 117 ($M^+-CH_2OCOCH_3$). 5-Membered ring isomer (**18**; Z=S) was acetylated in the usual manner to yield the corresponding diacetate, tetrahydrothiophene-2,2-dimethanol diacetate, of which spectral data are as follows: PMR: 2.03 (6H, s, $2\times C\underline{H}_3COO$), 2.87 (2H, t, J=6 Hz, $C\underline{H}_2$ at the 5 position), 4.07 and 4.22 (4H, q of AB type, J=11 Hz, $2\times C\underline{H}_2OAc$).

The reduction of diethyl tetrahydrothiophene-2,2-dicarboxylate that we synthesized previously[3b], gave the corresponding diol, mp 112.5—114.5° (recrystallized from ether), Mass Spectrum *m/e*: 148 (M^+). PMR (C_5H_5N): 4.12 and 4.13 (4H, q of AB type, J=11 Hz, $2\times C\underline{H}_2OH$). Acetylation of the diol yielded the corresponding diacetate, of which PMR spectrum was identical with that of diacetate derived from **18** (Z=S).

Reaction of 7 with Boron Trichloride (BCl_3)——A slight excess of BCl_3-solution in CCl_4 was added to a solution of **7** (50 mg, 0.38 mmole) dissolved in CCl_4. White precipitate came out immediately. Relatively pure material of **19** was obtained in 89% yield (104 mg) after removing the solvent under reduced pressure. PMR ($C_6H_5NO_2$): 1.8—2.3 (4H, m), 2.88 (2H, t, J=6.5 Hz, $C\underline{H}_2$ at the 5 position), 3.83 and 3.86 (4H, q of AB type, J=11 Hz, $2\times C\underline{H}_2Cl$).

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