Base Catalyzed Isomerization of Epoxides. I. The Isomerization of β-Chloroepoxides (1)

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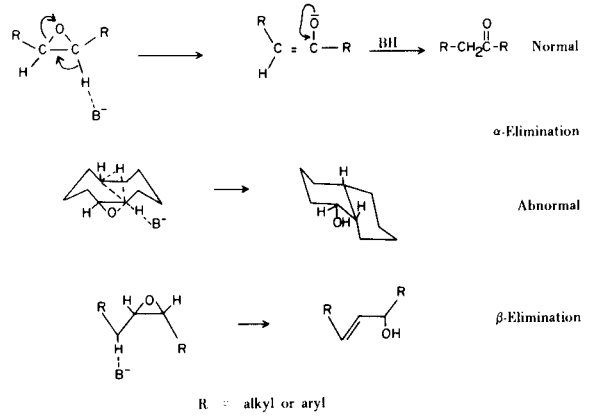
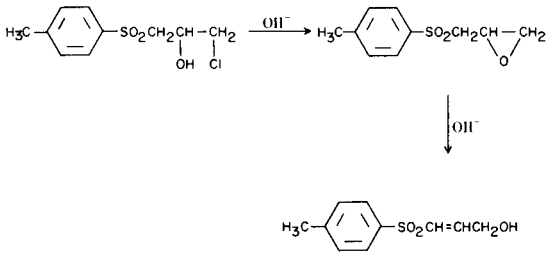
Dedicated to Professor Allan R. Day

The base catalyzed isomerizations of epichlorohydrin, 1-chloro-2,3-epoxy-2-methylpropane, 1-chloro-2,3-epoxybutane, and 3-chloro-1,2-epoxybutane have been studied, using lithium orthophosphate as the basic catalyst. Chloroketones and dichloro-alcohols are the major products. This is the first example of a compound with an electron withdrawing group attached to the carbon atom adjacent to the oxirane ring which undergoes the α-elimination pathway. A bi-directional mechanism is proposed to explain the experimental results. The stereochemistry of the hydrochlorination of 1-chloro-2,3-epoxybutane and 3-chloro-1,2-epoxybutane has also been studied.

Base catalyzed isomerizations of epoxides have been reported in the literature (2, 3). Two mechanisms have been established for this reaction. The rearrangement of an epoxide by abstraction of a proton directly attached to the oxirane ring is referred to as α-elimination, and the abstraction of the proton from the adjacent carbon is referred to as β-elimination. Two types of α-elimination have been observed. The normal α-elimination has been



found to occur in the rearrangement of epoxides of α,β-unsaturated ketones, *i.e.*, benzalacetophenone oxide (4). In this instance the oxirane proton is activated by the adjacent carbonyl group. However, when the carbonyl group is moved one carbon atom away from the oxirane ring, the proton on the β-carbon atom is activated, and undergoes β-elimination. For example, treatment of 1,2-epoxy-3-benzoyl-2-phenylcyclopentane with ethanolic sodium ethoxide gave 1-benzoyl-2-phenylcyclopenten-3-ol (5). Similarly, upon treatment with cold dilute alkali, 1-chloro-3-*p*-tolylsulphonylpropan-2-ol was converted into 3-*p*-tolylsulphonylprop-2-en-1-ol (6). The epoxide was assumed to be the intermediate.



The abnormal α-elimination has been shown to occur for *trans*-di-*t*-butylethylene oxide (7), norbornene oxide (8), and medium ring epoxides (9) which either possess no β-hydrogen or have a sterically hindered β-hydrogen.

We have studied the lithium orthophosphate catalyzed isomerization of β-chloro epoxides and found that chloroketones were the products. This is the first example of a compound with an electron withdrawing group attached to the carbon atom adjacent to the oxirane ring which follows the α-elimination pathway.

RESULTS AND DISCUSSION

Isomerization of Chloroepoxides.

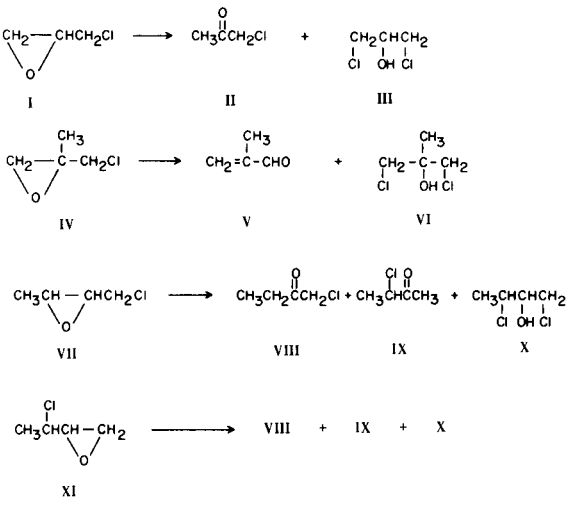
The isomerizations of epichlorohydrin (I), 1-chloro-2,3-epoxy-2-methylpropane (IV), 1-chloro-2,3-epoxybutane (VII), and 3-chloro-1,2-epoxybutane (XI) were studied.

Lithium orthophosphate (10, 11) was used as the basic catalyst. In a typical experiment, a solution of the epoxide in benzene was passed through a heated column packed with lithium orthophosphate pellets. The products were collected in a cold trap, and analyzed by instrumental methods. Most products were identified by comparing their glpc retention, ir and nmr spectra with authentic materials. Epichlorohydrin (I) gave a 72% yield of chloroacetone (II) and 1,3-dichloro-2-propanol (III) in a 3:1 ratio. 1-Chloro-2,3-epoxy-2-methyl propane (IV) gave two major products in approximately equal amounts, namely methacrolein (V) and 1,3-dichloro-2-methyl-2-propanol (VI). 1-Chloro-2,3-epoxybutane (VII) and 3-chloro-1,2-epoxybutane (XI) gave 1-chloro-2-butanone (VIII), 3-chloro-2-butanone (IX), and 1,3-dichloro-2-butanol (X) as the products (Table I). A mixture of *cis* and *trans* VII in a mole ratio of 28:72 gave 76% of VIII, IX, and X in a ratio of 29.6:44.5:25.9. Compound X consisted of two isomers (erythro and threo) in a 60:40 ratio. A mixture of erythro and threo XI in a mole ratio of 50:50 gave 80% of VIII, IX, and X in a ratio of 24.3:63.3:12.4. The ratio of erythro and threo X was 39:61.

TABLE I

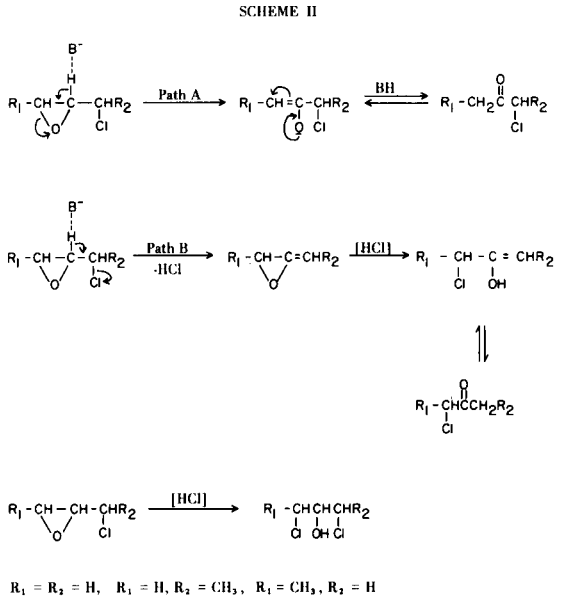
Reactant	Product (Relative Ratio)	Yield %
I	II:III = 3.4:1.0	72
IV	V:VI = 1.0:1.0	64
VII	VIII:IX:X = 1.1:1.7:1.0	80
XI	VIII:IX:X = 2.0:5.0:1.0	78

SCHEME I



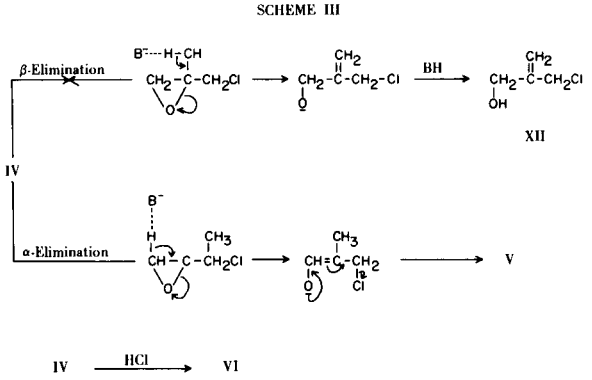
The formation of VIII and IX from the isomerization of VII or XI indicates that a chlorine migration is involved in this reaction. The formation of X suggests loss of the elements of hydrogen chloride from the reactant. A bidirectional mechanism is proposed to explain the experimental results. The first step is direct proton abstraction from the oxirane ring, referred to in the literature as α-elimination. This is followed by redistribution of bond electrons in two possible ways. In Scheme II, path A shows the rearrangement of the carbon-oxygen bond to give the enolate anion which upon protonation yields the expected chloro ketone. Path B shows that chloride ion is eliminated, which can either add to the allene oxide intermediate to give the α-chloro ketone formed by chlorine migration, or add to the starting epoxide to give the dichloroalcohol.

SCHEME II



Compound IV undergoes primarily α-elimination to give V and VI as the major products. No β-elimination product XII was detected in any significant amount. These results indicate that the protons attached to the oxirane ring are highly activated by the neighboring chloromethyl group, and, as a result, only α-elimination has occurred.

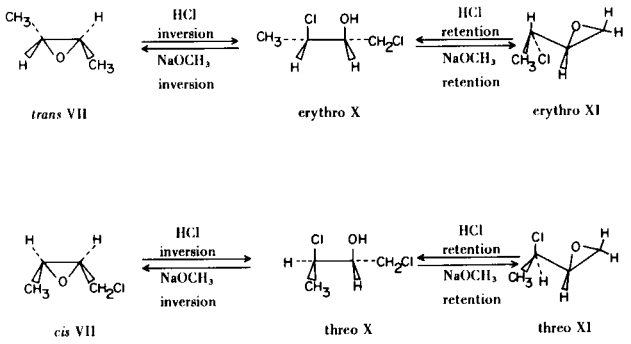
SCHEME III



Hydrochlorination of β-Chloroepoxides.

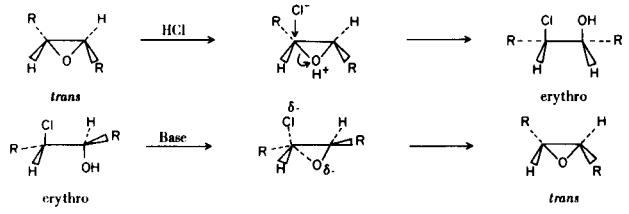
Hydrochlorination of VII and XI gave X as the product. When a mixture of *trans* and *cis* VII in a ratio of 74:26 was treated with hydrogen chloride in ether, it gave 75% erythro and 25% threo X. *Trans* and *cis* VII can be separated by glpc (150 ft., Carbowax 20M). The *trans* isomer has a shorter retention time than the *cis* isomer as expected from the differences in dipole moment. In the ir the characteristic C-O bond of the *trans*-epoxide appeared at higher frequency (1258 cm^{-1}) than that of the *cis*-epoxide (1240 cm^{-1}) consistent with values reported in the literature for *trans*- and *cis*-epoxides (12). Erythro and threo X can also be separated easily by glpc as the erythro isomer has the shorter retention time. The structures were confirmed by regenerating *trans*- and *cis*- VII with base.

SCHEME IV

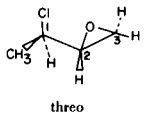


The mechanism and the stereochemistry of the hydrochlorination of *trans*- and *cis*-epoxides and the formation of epoxides by the reactions of halohydrins with base are well established (13, 14). The former involved the "borderline S_N2" type mechanism, and the latter involved an intramolecular displacement as shown in Scheme V.

SCHEME V



When a mixture of threo and erythro IX in ratios of 38:62 and 91:9 were reacted with hydrogen chloride, threo and erythro X in ratios of 38:62 and 90:10 respectively were obtained. The assignment of configuration of XI can be made from the following facts. Threo XI has this structure due to the configuration about C_1



and C_2. Hydrochlorination does not involve any inversion at C_1 or C_2; thus configuration is unchanged.

When erythro X was treated with sodium methoxide in ethanol, it gave 85% *trans* VII and 15% erythro XI. With a mixture of erythro and threo X in a ratio of 74:26, a product mixture of 72.4% *trans* VII, 8.2% *cis* VII, 2.2% erythro XI, and 17.2% threo XI was obtained. These results indicate that erythro X converts mainly to *trans* VII while threo X converts preferably to threo XI. The differences in reactivity of the two isomers can be explained by considering the steric factors operating in the pertinent transition states.

In the formation of epoxide from erythro X, the bulky CH_3 and CH_2Cl groups would be oriented *trans* in the transition state (R_1 = CH_2Cl, R_2 = H) whereas the corresponding transition state for ring closure of threo X has a *cis* arrangement of bulky groups (R_1 = H, R_2 = CH_2Cl).

EXPERIMENTAL

General.

Infrared spectra data were obtained with a Perkin-Elmer Infracord, and nuclear magnetic resonance spectra with a Varian A-60 spectrometer. Gas-liquid partition chromatography was conducted using a Perkin-Elmer Model 226. A 100 ft. x 0.01 inch stainless steel capillary column coated with carbowax 1540 was used. Reagent grade chemicals were used when available without further purification. Epoxides were prepared either by the peracetic acid method (15) or the molybdenum catalyzed hydroperoxide oxidation method (16). Lithium orthophosphate was prepared according to the procedure of Denton (10).

Chloro acetone (II) and methacrolein (V) were identified by comparing their physical constants with commercially available authentic samples. The dichloro alcohols were identified by comparing glpc retention, ir and nmr spectra with the materials prepared by hydrochlorination of the corresponding β-chloroepoxides.

Isomerization of Epichlorohydrin (I).

A solution of 2.5 g. of epichlorohydrin in 2.5 g. of benzene was passed, using nitrogen as the carrier through an 8″ x 0.5″ column packed with lithium orthophosphate pellets at 230-240° at a rate of approximately 0.1 ml./min. The product (4.3 g.), collected in an ice-water trap, was shown by glpc analysis to consist of 32.5% chloroacetone (II), 9.5% 1,3-dichloro-2-propanol (III), and 58% benzene. About 0.7 g. of the material was lost,

probably due to the absorption on the pellets. The total yield of II and III was 72%.

1-Chloro-2,3-epoxy-2-methylpropane (IV).

Compound IV was isomerized under similar conditions, but without benzene solvent. Eighty-two percent of the materials were collected and glpc analysis showed that the product contained 31% methacrolein (V), 37% 1,3-dichloro-2-methyl-2-propanol (VI), 13% unreacted IV, and 19% of several unidentified by-products.

1-Chloro-2,3-epoxybutane (VII).

A solution of *cis* and *trans* VII in a mole ratio of 28:72 in benzene gave 2.4% of unreacted VII, 10.5% of 1-chloro-2-butanone (VIII), 15.8% of 3-chloro-2-butanone (IX), 9.2% of 1,3-dichloro-2-butanol (X), and a small amount of unidentified by-products. Compound X consisted of two isomers (erythro and threo) in a 60:40 ratio. Compounds VIII and IX were separated by fractional distillation and identified by ir and nmr spectra. The nmr spectrum of VIII showed a two-proton singlet at 5.74 τ, a two-proton quartet at 7.35, and a three-proton triplet at 8.94. The nmr spectrum of IX displayed a one-proton quartet at 5.59, and three-proton singlet at 7.74, and a three-proton doublet at 8.48.

Anal. Calcd. for C_4H_7ClO: C, 45.08; H, 6.57. Found: C, 45.38; H, 6.50, (VIII). C, 45.24; H, 6.63 (IX).

3-Chloro-1,2-epoxybutane (XI).

Similarly, a solution of erythro and threo XI in a mole ratio of 50:50 in benzene gave 9.8% of VIII, 25.5% of IX, 5% of X, and a small amount of by-products. The ratio of erythro and threo X was 39:61.

Hydrochlorination of Epichlorohydrin (I).

A solution of 5 g. of epichlorohydrin in 50 ml. of anhydrous ether was placed in a 100 ml. 3 neck flask equipped with a thermometer, a condenser, a magnetic stirrer, and a gas inlet. Hydrogen chloride gas was introduced into the solution with stirring at 5° for 1 hour. The solution was stirred continuously for an additional hour. After the ether was removed by flash-evaporation, the residue weighed 6.6 g. (94% yield). Pure III was obtained by distillation, b.p. 62°/11 mm. (lit. (17) b.p. 177°), ir, 3400 cm^{-1}; nmr, τ 6.04 (1H), 6.45 (4H).

1-Chloro-2,3-epoxy-2-methylpropane (IV).

Hydrochlorination of IV under similar conditions gave 94% yield of VI. Compound VI, b.p. 48°/5.5 mm; ir, 3350 cm^{-1}; nmr, τ 6.39 (4H), 6.58 (1H), 8.62 (3H).

Anal. Calcd. for $C_4H_8Cl_2O$: C, 33.55; H, 5.59; O, 11.19; Cl, 49.67. Found: C, 34.00; H, 5.59; O, 11.44; Cl, 49.80.

1-Chloro-2,3-epoxybutane (VII).

Hydrochlorination of a mixture of *trans* and *cis* VII in a ratio of 74:26 gave 97% yield of erythro and threo X in a ratio of 75:25. The erythro and threo X were separated easily by glpc (150 ft. carbowax), as the erythro isomer has the shorter retention time. The physical constants are almost identical for both isomers, b.p. 63°/12 mm; ir, 3330 cm^{-1}; nmr, τ 6.14 (4H), 8.45 (3H).

Anal. Calcd. for $C_4H_8Cl_2O$: C, 33.55; H, 5.59; O, 11.19; Cl, 49.67. Found for threo: C, 33.96; H, 5.49; O, 11.46; Cl, 49.46. Found for erythro: C, 34.03; H, 5.51; O, 11.54; Cl, 49.44.

3-Chloro-1,2-epoxybutane (XI).

Similarly, a mixture of threo and erythro XI in a ratio of 38:62 and 91:9 gave a 90% yield of threo and erythro X in a ratio of 38:62 and 90:10.

Treatment of Erythro- and Threo-1,3-dichloro-2-butanol (X) with Base.

Erythro X (2.85 g., 0.02 mole) was dissolved in 40 ml. of 95% ethanol and the mixture was cooled in an ice bath. A solution of 1.08 g. of sodium methoxide (0.02 mole) in 15 ml. of methanol was added dropwise with stirring over a period of 10 minutes. Stirring was continued for 1 hour. The reaction mixture was filtered, and the solid (sodium chloride) was washed with a small amount of methanol. Glpc analysis of the filtrate showed that *trans* VII and erythro X had formed in a ratio of 85:15 and a yield of 59%. Similarly, a mixture of erythro and threo X in a ratio of 74:26, gave 65% yield of a mixture of 72.4% *trans* VII, 8.2% *cis* VII, 2.2% erythro XI, and 17.2% threo XI.

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REFERENCES

(1) Dedicated to Professor Allan R. Day.

(2) Rosowsky in "Heterocyclic Compounds with Three- and Four-Membered Rings", Part 1, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp. 262-270.

(3) A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev.*, **20**, 119 (1966).

(4) W. G. H. Lake and S. Peat, *J. Chem. Soc.*, 1069 (1939).

(5) H. H. Wasserman and M. J. Gorbunoff, *J. Am. Chem. Soc.*, **80**, 4568 (1958).

(6) C. C. J. Culvenor, W. Davies, and W. E. Savige, *J. Chem. Soc.*, 2198 (1949).

(7) J. K. Crandall and L. H. C. Lin, *J. Am. Chem. Soc.*, **89**, 4526 (1967).

(8) J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964).

(9) A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sherman, *J. Am. Chem. Soc.*, **82**, 6370 (1960).

(10) W. I. Denton, U. S. Patent, 2,986,585 (1961).

(11) E. Charles, M. E. D'egeorges, and A. Thizy, U. S. Patent, 3,255,258 (1966).

(12) K. Matsumoto, *Tetrahedron*, **24**, 6851 (1968).

(13) Rosowsky in "Heterocyclic Compounds with Three- and Four-Membered Rings", Part 1, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp. 352-357, pp. 94-95.

(14) S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 1576 (1939); H. J. Lucas and C. W. Gould, Jr., *ibid.*, **63**, 2541 (1941).

(15) B. Phillips and P. S. Starcher, Brit. Patent, 784,620 (1957).

(16) M. N. Sheng and J. G. Zajacek, "Oxidation of Organic Compounds II", p. 418, in Advances in Chemistry Series, No. 76, 1968.

(17) A. J. Hilla and E. J. Fischer, *J. Am. Chem. Soc.*, **44**, 2582 (1922).

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