The Configurations of Active 2,3-Epoxybutane and erythro-3-Chloro-2-butanol

BY HOWARD J. LUCAS AND HAROLD K. GARNER

At the time when the lower boiling 2,3-epoxybutane was shown to be the *trans* isomer,[1] it was not possible to determine the configuration of the active form, since the configuration of the active 2,3-butanediols had not yet been established. Also the stereochemical relationships of the various compounds involved in passing from the glycol to the oxide, although correctly surmised, were not definitely determined until later.[2] Moreover, the sample of active oxide obtained in the earlier work was not optically pure, for it possessed only a relatively low rotation.

Now that levorotatory 2,3-butanediol has been obtained in a high state of optical purity,[3,4,5] and the configurations of the active forms have been established,[6,7] it has been possible to prepare an optically pure 2,3-epoxybutane by methods which establish its configuration. In the changes, which are shown by I to V in Fig. 1, the stereo relation-

chlorohydrin, through the bromoform reaction, to levorotatory α-chloropropionic acid, VI, which is known to have the L configuration.[8]

In D(−)-2,3-butanediol, I, each carbon atom has the D configuration.[6,7] When the glycol is converted to D(+)-2,3-diacetoxybutane, II, by acetic anhydride with either sulfuric acid or pyridine as a catalyst, the configuration of each carbon atom is still D. When II is converted to L(+)-*erythro*-3-chloro-2-butanol, III, by hydrochloric acid, the configuration of carbon atom C-3 is inverted, for a single Walden inversion has been shown to accompany the displacement of one of the acetoxy groups by chlorine in the change of DL-2,3-diacetoxybutane to DL-*erythro*-3-chloro-2-butanol.[9,10] In the last step, III to D(+)-*trans*-2,3-epoxybutane, IV, the configuration of carbon atom C-3 is again inverted, for a single Walden inversion accompanies the closing of the oxide ring. This has been shown to be the case when DL-*trans*-2,3-epoxybutane is formed from DL-*erythro*-3-chloro-2-butanol.[9,11] There could not have been an odd number of inversions, otherwise the final product would have been the optically inactive *cis* oxide, rather than the active *trans* oxide. Thus it seems reasonable to conclude, on the basis of the changes I to IV, that the configuration of each carbon in IV is D, since there has been no inversion at C-2, and two inversions at C-3.

The conversion of the chlorohydrin, III, to chloropropionic acid, VI, by establishing the configuration of carbon atom C-3 as L, presents additional proof that one inversion is associated with each of these changes, viz., II to III, and III to IV. In addition, it confirms the earlier evidence that the higher boiling chlorohydrin has the *erythro* configuration.[9]

The configuration of α-chloropropionic acid cannot be unequivocally established by relating it directly to hydroxy compounds such as lactic
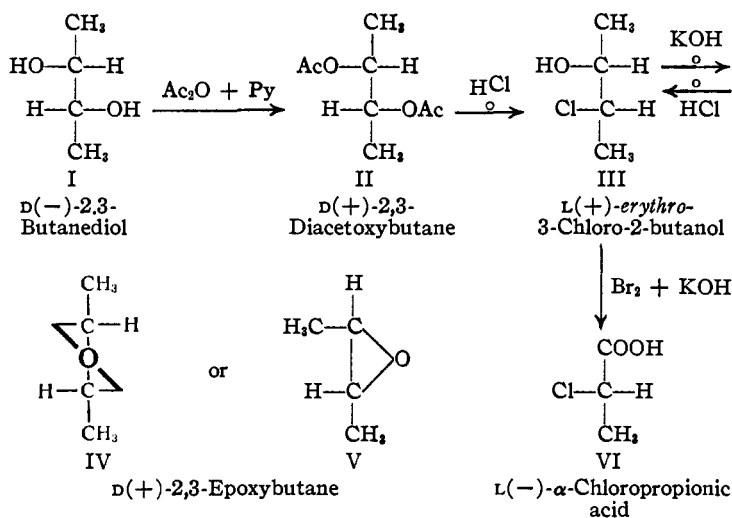

Fig. 1.—Configurational relationships of D(+)-2.3-epoxybutane and L(+)-*erythro*-3-chloro-2-butanol to D(−)-2,3-butanediol.

ships of the compounds involved are based upon previous results, as discussed below. In addition, the configuration of the C-3 carbon atom in dextrorotatory *erythro*-3-chloro-2-butanol has been independently established as L, by converting the

(1) C. E. Wilson and H. J. Lucas. THIS JOURNAL. 58, 2396 (1936).

(2) (a) S. Winstein and H. J. Lucas. *ibid.*, 61. 1576 (1939); (b) 61, 1583 (1939).

(3) G. E. Ward. O. G. Pettijohn. L. B. Lockwood and R. D. Coghill, *ibid.*, 66, 541 (1944).

(4) A. C. Neish, *Can. J. Research*, 23B, 10 (1945).

(5) J. W. Knowlton, N. C. Schieltz and D. Macmillan, THIS JOURNAL. 68, 208 (1946).

(6) E. Grivsky. *Bull. soc. chim. Belg.*, 51, 63 (1942).

(7) S. A. Morell and A. H. Auernheimer. THIS JOURNAL. 66, 792 (1944).

(8) (a) K. Freudenberg and A. Lux. *Ber.*, 61, 1083 (1928); (b) K. Freudenberg. W. Kuhn and I. Bumann. *ibid.*, 63, 2380 (1930); (c) W. A. Cowdrey. E. D. Hughes and C. K. Ingold. *J. Chem. Soc.*, 1208 (1937); (d) W. A. Cowdrey. E. D. Hughes. C. K. Ingold. S. Masterman and A. D. Scott. *ibid.*, 1265 (1937).

(9) H. J. Lucas and C. W. Gould. THIS JOURNAL. 63, 2541 (1941).

(10) In the analogous change of DL-2,3-diacetoxybutane to DL-*erythro*-3-bromo-2-butanol by hydrobromic acid, the single Walden inversion has been located at the step where DL-*threo*-3-acetoxy-2-butanol is changed to DL-*erythro*-2-acetoxy-3-bromobutane.[2b]

(11) A single Walden inversion is known to be associated with closing of the epoxy ring when *cis*-2.3-epoxybutane is formed from DL-*threo*-3-bromo-2-butanol.[2a]

TABLE I
PHYSICAL CONSTANTS OF THE D AND L COMPOUNDS

	B. P., °C. (cor.)	Mm.	M. p., °C. (cor.)	d^{24}_4	$n^{25}D$	M_D Calcd.	M_D Obs.	$\alpha^{25}D$ obs. pure liquid	$[\alpha]^{25}D$ pure liquid
D(−)-2,3-Butanediol	77.5–77.6	10	19.4–19.7°	0.9869ᵇ	1.4308ᵇ	23.72	23.63	−13.00°	−13.17°ᶜ
D(+)-2,3-Diacetoxy-butane	82.2	10	25.7–25.9	1.0244	1.4134	42.45	42.34	+14.10°	+13.76°ᶜᵈ
L(+)-*erythro*-3-Chloro-2-butanol	56.0	30		1.061	1.4397	27.06	26.95	+ 9.47°	+ 8.92°
D(+)-2,3-Epoxybutane	53.5–53.7°	745		0.7998ᶠ	1.3705ᶠ	20.11	20.41ʰ	+47.23°	+59.05°

ᵃ Previous values³·⁵: 19°, 19°. ᵇ Ref. 5, also 3, 4; $n^{25}D$ 1.4307, 1.4318. ᶜ Previous values²·⁴·⁵·⁷: −13.0°, −13.19°, −13.34°, −12.85°. ᵈ $[\alpha]^{25}D$ +18.7° in CHCl₃; 0.9895 g. in 10 ml. CHCl₃; previous values¹³: $[\alpha]^{28}D$ 13.65°. ᵉ Previous value²ᵃ: *cis*-oxide, 59.7°, 742 mm.; DL-*trans* oxide, 53.5°, 742 mm. ᶠ Previous value²ᵃ: *cis*-oxide, 0.8226; DL-*trans* oxide, 0.8010. ᵍ Previous value²ᵃ: *cis*-oxide, 1.3802; DL-*trans* oxide, 1.3705. ʰ No correction for three-membered ring.

acid by reactions not involving the asymmetric center. Neither can the Walden inversions in the steps II to III, III to IV, and IV to III be proven unequivocally, although there is no reason to doubt that they occur. Nevertheless, the evidence presented here is consistent with the accepted configuration of α-chloropropionic acid, and with the assumption that one inversion accompanies each of the changes mentioned above. We believe that there can, therefore, no longer be any doubt in regard to the configuration of the active α-chloropropionic acids, for the satisfactory way in which active 3-chloro-2-butanol forms a configurational link with active 2,3-butanediol confirms the conclusions reached by Freudenberg, Ingold, *et al.*[8]

When the carbon chain is written vertically, the configuration of the dextrorotatory oxide is correctly represented by IV. However, since this is an awkward looking formula, it seems preferable to write the oxide ring on one side, as shown by V. This, therefore, is the preferred way of writing the configuration of D(+)-*trans*-2,3-epoxybutane, or more simply, D(+)-2,3-epoxybutane, since there are only two active isomers of 2,3-epoxybutane. Structures IV and V are equivalent.

The configurations of the dextrorotatory oxide and the dextrorotatory chlorohydrin are reasonably certain, since carbon atom C-2 is unaffected during the changes, and the configuration of carbon atom C-3 in the chlorohydrin is established by its conversion to levorotatory α-chloropropionic acid. The designation of these compounds as D or L is somewhat arbitrary, however, since there are no rules of nomenclature which specifically apply in this case. Either of the two asymmetric centers in the molecule might be taken as the point of reference. It seems preferable to take carbon atom C-3 as the point of reference, so as to correlate the nomenclature with that of the carbohydrates.[12] This is in agreement with the designation of the 2,3-butanediols given by Morell and Auernheimer.[7] On this basis, the configuration of the highest numbered asymmetric carbon atom determines the family to which the compound be-

(12) This has been done in conformity with the third progress report of the Committee on Carbohydrate Nomenclature, Charles D. Hurd, Chairman.

longs. Thus I, II and IV belong to the D family, since in these the functional group at carbon atom C-3 lies on the right, and III belongs to the L family, since the functional group lies on the left, as a result of inversion during its formation from II.

The oxide is believed to be of high optical purity for the following reasons: (1) the active glycol used as starting material had one of the highest optical rotatory powers recorded for this compound in the literature; (2) the reactions involved have been shown to yield configurationally pure compounds; (3) absence of *cis* oxide was indicated by agreement in physical properties with previously prepared DL-oxide²ᵃ; (4) rotations of two preparations agreed well, *viz.*, 58.65 and 59.05°.

The importance of (3) as an argument for optical purity is based on the assumption that if any reaction proceeded otherwise than with 100% retention or inversion of the configuration of carbon atom C-3, the resulting diastereomeric compound would lead to the presence of some *cis*-oxide in the final product. This would be the main contaminant, not the L(−)-oxide. In order for the latter to be formed there would have to be inversion at carbon atom C-2, as well as at C-3.

Rotations and some other physical constants of the compounds involved are shown in Table I. The rotation of the cyclic oxide is one more example of the well-known effect of ring structure in enhancing rotations.

The specific rotation of the chlorohydrin prepared by the action of hydrochloric acid on the active oxide was +8.87°, only 0.05° less than that of the chlorohydrin prepared from the diacetate, +8.92°. This indicates that in going from III to IV and back to III, the reactions proceed with essentially 100% inversion of configuration.

The sample of optically active 2,3-butanediol was furnished by the Northern Regional Research Laboratory, Peoria, Illinois. The authors express their appreciation to the Laboratory and especially to Dr. A. F. Langlykke for this courtesy.

Experimental

D(−)-2,3-Butanediol.—Dr. A. F. Langlykke of the Northern Regional Research Laboratory stated that the glycol was produced in a fermentation of starch induced by *Bacillus polymyxa*. The glycol contained a small amount

of water and had an observed rotation, $-12.4°$. This became $-13.00°$ ($[\alpha]^{25}$D $-13.17°$) after one distillation at reduced pressure.

D($+$)-2,3-Diacetoxybutane; Acid Catalyzed Reaction.—The diacetate could be prepared, as previously described for the inactive diacetate,[1] from the glycol and acetic anhydride using as catalyst one drop of sulfuric acid per 0.5 mole of glycol. Vacuum fractionation of the reaction mixture gave a 90% yield of material with an observed rotation of $+13.8°$. On standing at room temperature (approximately 22°) overnight, about two-thirds of the material crystallized in large, clear prisms. The liquid was decanted from these, and the solid recrystallized from 30–60° petroleum ether and redistilled. The diacetate thus obtained melted at 25.7–25.9° and had an observed rotation of $+14.10°$. These values could not be raised by further purification. Additional amounts of pure diacetate could be obtained by crystallization and distillation of the liquid fraction. The total yield of purified diacetate was 70%.

The amount of sulfuric acid used to catalyze the acetylation should not exceed two drops per mole and the temperature should not rise above 80°; otherwise some optical inversion may occur.

Pyridine Catalyzed Reaction.—In a 1-liter Erlenmeyer flask were placed 90.0 g. (1 mole) of redistilled active 2,3-butanediol and 400 g. (5 moles) of redistilled anhydrous pyridine. The contents were thoroughly mixed, and then 224 g. (2.2 mole) of acetic anhydride were added slowly from a dropping funnel with stirring. As the mixture warmed, cooling was supplied to keep the temperature below 40°. After the reaction had subsided, the mixture was allowed to stand overnight, and was then fractionally distilled at reduced pressure, the final cut being taken at 82.1–82.2° (cor.), at 10 mm. The product weighed 170 g. (98%) and had an observed rotation of $+13.94°$. This material could be further purified so that finally α^{25}D obs. $+14.06°$ and $[\alpha]^{25}$D $+13.72°$; but this was found to be unnecessary since the chlorohydrin and oxide prepared from it had the same rotation as those from the more highly purified material.[13]

L($+$)-erythro-3-Chloro-2-butanol.—This was prepared as previously described for the inactive chlorohydrin,[9] from the active diacetate and concentrated aqueous hydrochloric acid saturated with dry hydrogen chloride at $-20°$. The crude material isolated in 70% yield from the reaction mixture contained some 3-chloro-2-acetoxybutane. Three fractionations of a portion of the crude product gave a pure sample of the chlorohydrin for the measurement of physical properties, but it is not necessary to separate the chlorohydrin from the chloroacetate in the preparation of 2,3-epoxybutane, since both are converted into the oxide.

D($+$)-2,3-Epoxybutane.—This was prepared, as previously described for the inactive oxides,[1] from active chlorohydrin and concentrated potassium hydroxide. The material was dried over potassium hydroxide and purified by fractional distillation; no trace of the higher boiling cis-oxide was detected. The over-all yield of purified active oxide from the glycol was 49%. The rotations of two preparations were $[\alpha]^{25}$D, 59.05° and 58.65°.

DL-α-Chloropropionic Acid.—Inactive 3-chloro-2-butanol was prepared, in the manner previously described,[8] from a supply of inactive oxide (mixture of cis and trans) and concentrated hydrochloric acid. The yield was 79%.

A three-necked 1-liter flask was fitted with a mechanical stirrer and two dropping funnels. In the flask was placed 27 g. (0.25 mole) of the inactive chlorohydrin, and in the two separatory funnels 160 g. (1.00 mole) of liquid bromine and 195 g. of potassium hydroxide (Baker C.P., 86%; 3 moles) dissolved in 500 ml. of water, respectively. The stirrer was started, and the bromine added rapidly, about fifteen minutes being required for the addition. When about one quarter of the bromine had been added, the addition of the base was begun and continued at such a rate that the bromine was always present in the reaction mixture in good excess. The mixture became hot, and cooling was supplied with an ice-bath to keep the temperature around 50°. After all the bromine was in, addition of the base was continued until the reaction mixture became colorless, and then a slight excess was run in. A yellow color developed in the presence of the excess base.

Stirring was continued for about fifteen minutes, after which the mixture was transferred to a separatory funnel, and the heavy layer of bromoform drawn off. The aqueous layer was washed once with 50 ml. of chloroform, and then acidified with 50% sulfuric acid, a 20-ml. excess of the acid being used. The bromine which formed was destroyed with formic acid, and the solution extracted five times with 100-ml. portions of ethyl ether. Following removal of the ether by ordinary distillation, the α-chloropropionic acid was distilled at 30 mm., b. p. 100–105°, yield, 3.5 g. (13%). The product was redistilled at atmospheric pressure, the fraction boiling at 184–186° being collected. The product gave a strong positive test for chlorine and had a neutralization equivalent of 115 (theoretical, 108.5). Its anilide melted at 89.5–90.5° (cor.),[14] and its salt with phenylhydrazine at 95–96° (cor.).[15]

Other modifications of the above procedure were tried, but no improvement of the yield could be realized. It is important that there be no excess of base until all of the bromine has been added; otherwise considerable amounts of the chlorohydrin are lost by conversion to oxide.

L($-$)-α-Chloropropionic Acid.—The active chlorohydrin used in the oxidation was prepared from the active oxide and concentrated hydrochloric acid as previously described for the inactive compound,[8] and had the following constants: b. p. 55.9–56.0° (cor.) at 30 mm.; α^{25}D $+9.42$; $[\alpha]^{25}$D $+8.87°$; n^{25}D 1.4394. The yield was 75%.

The oxidation of the active chlorohydrin was carried out similarly to that of the inactive material. From 12.0 g. of chlorohydrin was obtained 1.9 g. (16%) of α-chloropropionic acid, b. p. 100–102° (cor.) at 30 mm.; 184–187° (cor.), at 745 mm.; neutralization equivalent, 108 (theoretical, 108.5). The rotations were as follows: pure liquid, α^{25}D $-14.2°$, $[\alpha]^{25}$D $-11.3°$; aqueous soln. (0.0433 g. in 2.00 ml. water soln.), $[\alpha]^{25}$D $-9.1°$; sodium salt (0.0736 g. made up to 2.00 ml. with 3.94 f NaOH) $[\alpha]^{25}$D $+3.8°$.[16,17]

Summary

Optically active 2,3-epoxybutane has been prepared through the following series of reactions: D($-$)-2,3-butanediol → D($+$)-2,3-diacetoxybutane → L($+$)-erythro-3-chloro-2-butanol → D($+$)-2,3-epoxybutane. In addition, the configuration of carbon atom C-3 in the chlorohydrin has been established by conversion to L($-$)-α-chloropropionic acid.

It has been possible to assign absolute configurations to the compounds prepared, since levorotatory 2,3-butanediol is known to belong to the D series, and the mechanisms of all the reactions used are known. Thus dextrorotatory 2,3-diacetoxybutane and dextrorotatory 2,3-epoxybutane belong to the D series, while dextrorotatory erythro-3-chloro-2-butanol belongs to the L series.

(13) K. A. Clendenning, Can. J. Research. 24B, 269 (1946), gives these values for active diacetate: n^{25}D 1.4132; d^{20}₄ 1.029; $[\alpha]^{18}$D 13.65°.

(14) R. L. Shriner and R. C. Fuson. "Identification of Organic Compounds," second ed., John Wiley and Sons, Inc.. New York. N. Y.. 1940. p. 181. give the m. p. of the anilide as 92°.

(15) G. Stempel and G. Schaffel. THIS JOURNAL, 64, 470 (1942), give the m. p. of the phenylhydrazine salt as 95°.

(16) P. Levene and H. Haller. J. Biol. Chem.. 81, 703 (1929), observed that the sign of rotation changed in going from acid to basic solution.

(17) K. Freudenberg. W. Kuhn and I. Bumann[b] report the rotation of L-α-chloropropionic acid as α_{578} = $-19.30°$; $[\alpha]_{578}$ = $-15.4°$. pure liquid.