Optical Resolution and Configuration of *trans*-2, 3-Epoxybutyric Acid[1, 2]

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The direct epoxidation of the double bond of α, β-unsaturated acids by peroxy acid or by hydrogen peroxide has been known to be generally very slow. (±)-*trans*-2, 3-Epoxybutyric acid (epoxy acid I) was successfully synthesized from crotonic acid (*trans*) by epoxidation with hydrogen peroxide and sodium tungstate.³⁾ Liwschitz et al.⁴⁾ reported the amination of I by treating with benzylamine or ammonia in which they reported the synthesis of (±)-allothreonine.

In the present study, the epoxy acid (I) was resolved by brucine. To determine the configuration of the resolved (−)-*trans*-2, 3-epoxybutyric acid [(−)-epoxy acid] (III), it was treated with benzylamine or ammonia, as was done by Liwschitz et al. The resulting *N*-benzyl allothreonine (IV) was hydrogenolyzed by the use of palladium on charcoal. The isolated amino acid was found to be optically pure (+)-allothreonine (V) and it did not contain any threonine or other amino acid, even in the reaction mixture. This was examined paper chromatographically⁵⁾ and also by the automatic amino acid analyzer. This fact suggests that the amination proceeds with a typical S_N2 mechanism and no racemization occurs during the reaction. The configuration of the resulting (+)-allothreonine (V) is known as: 2(s), 3(s). Therefore, the configuration of (−)-*trans*-2, 3-epoxybutyric acid would be 2(R), 3(s). The reaction products of epoxy acid and ammonia showed a large allothreonine peak and a little peak at about the alanine area in the automatic amino acid analyzer, (ratio allo : unknown=99.4 : 0.6). The latter peak might be α-hydroxy β-amino butyric acid (isothreonine) which is a possible ammonolysis product. Attempts to obtain optically active α-hydroxybutyric acid by reduction of (−)-epoxy acid (III) with sodium borohydride and by catalytic hydrogenation were unsuccessful. In each case, mainly β-hydroxybutyric acid was isolated by column chromatography.⁶⁾

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1) Stereochemistry of Glycidic Acid. II, Part I of this series, K. Harada, *J. Org. Chem.*, **31**, 1407 (1966).

2) Aided by Grant no. NsG-689 of the National Aeronautics and Space Administration. Contribution No. 061 of the Institute of Molecular Evolution, University of Miami.

3) G. B. Payne and Paul H. Williams, *J. Org. Chem.*, **24**, 54 (1959).

4) Y. Liwschitz, Y. Rabinsohn and D. Perera, *J. Chem. Soc.*, **1962**, 1116.

5) K. N. F. Shaw and S. W. Fox, *J. Am. Chem. Soc.*, **75**, 3421 (1953). *n*-butanol : acetone : conc. ammonia : H_2O=100 : 12.5 : 12.5 : 75.

6) E. F. Phares, E. H. Mosbach, F. W. Denison, Jr., S. F. Carson, M. V. Long and B. A. Gwin, *Anal. Chem.*, **24**, 660 (1952).

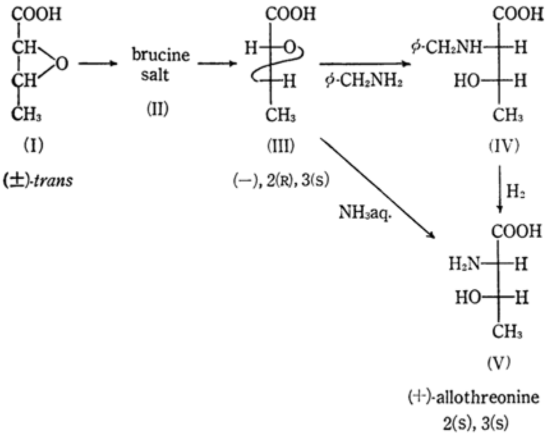

Fig. 1.

Experimental

(±)-*trans*-2, 3-Epoxybutryic Acid (I).—The epoxy acid was prepared by the method of Payne and Williams.[3] M. p. 83°C.

Brucine Salt of (+)-*trans*-2, 3-Epoxybutyric Acid (II).—Epoxy acid (I), 20.4 g. (0.2 mol.), and brucine, 78.8 g. (0.2 mol.), were dissolved in 200 ml. of hot methanol. The solution was filtered and the solvent was evaporated in vacuo. The residual syrup was dissolved in a hot mixture of methanol (20 ml.) and acetone (180 ml.). After cooling, crystallization of brucine salt began by seeding with an authentic specimen which was obtained in another crystallization experiment. After standing overnight at room temperature, the crystals were filtered and were washed with cold acetone. The crystals, 35.0 g., were recrystallized from a hot mixture of methanol (5 ml.) and acetone (95 ml.). Yield, 32.0 g., m. p. 173°C, $[\alpha]^{25}_{D}=-26.0°$ (*c* 2.1, H_2O).

(−)-*trans*-2, 3-Epoxybutyric Acid (III).—Brucine salt (II), 14.3 g. (0.03 mole), was dissolved in 100 ml. of water. To this solution, 1 N sodium hydroxide solution, 33 ml., was added. The precipitated brucine was separated by filtration. The filtrate was extracted with benzene three times to remove the residual brucine. Concentrated hydrochloric acid was used to bring the pH of the aqueous solution to 2.5. After saturation of the solution with sodium chloride, the epoxy acid was extracted with ether five times (100 ml. × 5). The ether solution was dried with anhydrous sodium sulfate. After evaporation of ether, 1.80 g. (60%) of crude III was obtained. This was recrystallized from benzene. 1.20 g. (40%), m. p. 61°C. $[\alpha]^{25}_{D}=-82.5°$ (*c* 0.59, benzene). Neut. equiv. Found: 102. Calcd. for $C_4H_6O_3$.

(+) *N*-Benzyl-allothreonine (IV).—A mixture of III, 1.53 g., water, 5 ml., and benzylamine, 2 ml., was refluxed for 2 hr. After cooling, the excess benzylamine was removed by ether extraction and the pH of the aqueous solution was brought to 5.5 by the addition of concentrated hydrochloric acid. Precipitated IV was washed with acetone and then with ether. The crude product, 2.2 g. (70%), was recrystallized from *N, N*-dimethylformamide. Yield, 2.0 g. (67%). m. p. 245°C (decomp.), $[\alpha]^{25}_{D}=+12.2°$ (*c* 1.9, 5 N hydrochloric acid).

Found: C, 63.42; H, 7.20; N, 6.68. Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.69%.

(+)-Allothreonine (V). — (+)-*N*-Benzyl-allothreonine (IV), (2.09 g.), was dissolved in 50 ml. of 50% ethanol. To this solution, 1.0 g. of 5% palladium on charcoal was added and the hydrogenolysis was carried out at room temperature. When the hydrogen uptake ceased, the catalyst was removed by filtration. The filtrate was concentrated in vacuo. The crystalline residue was recrystallized from water and ethanol. Yield, 1.13 g. (95%). This was repurified from water (1) and ethanol (9). Yield, 0.95 g. (80%). M. p. 285°C, $[\alpha]^{25}_{D}=+32.9°$ (*c* 1.9, N hydrochloric acid).[7]

Found: C, 40.09; H, 7.48; N, 11.57. Calcd. for $C_4H_9O_3N$: C, 40.33; H, 7.62; N, 11.76%.

(+)-Allothreonine (V) by Ammonolysis of III.—A mixture of 1.53 g. (0.015 mol.) of III and 50 ml. of concentrated ammonia (sp. gr. 0.90) was kept at room temperature. After 4 days the reaction mixture was concentrated in vacuo. A weight of 1.43 g. (80%) of crude V was obtained.[8] This was recrystallized from water. Yield, 0.50 g. (28%). m. p. 285°C (decomp.), $[\alpha]^{25}_{D}=+33.5°$ (*c* 2.0, N hydrochloric acid).[7]

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[7] D. F. Elliot, *J. Chem. Soc.*, **1950**, 62. (+)-Allothreonine, $[\alpha]^{25}_{D}=+32.5°$ (*c* 8.2, N HCl).

[8] The crude V contains some impurity which is ninhydrin negative. It decomposes at 238°C and shows specific rotation $[\alpha]^{25}_{D}=+27.2°$ (*c* 2.1, N HCl).