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Optical Resolution and Configuration of *cis*-β-Phenylglycidic Acid[1]

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Synopsis. DL-*cis*-β-phenylglycidic acid was resolved using (−)-ephedrine. The configurations of α- and β-carbons of the resolved *cis*-(+)-glycidic acid were determined by oxydative and hydrogenolytic reactions.

The chemistry of epoxide has been studied extensively. Reviews have been presented in several articles.[2,3] Darzens' reaction in the synthesis of glycidic acids has been reviewed.[4] Several ammonolysis and aminolysis reactions of glycidic acids have been reported.[5-14]

In previous studies from this laboratory, racemic *trans*-2,3-epoxy-β-phenylpropionic acid,[15] *trans*-2,3-epoxybutyric acid,[16] and *trans*-2,3-epoxysuccinic acid[17] were optically resolved and their absolute configurations were determined.

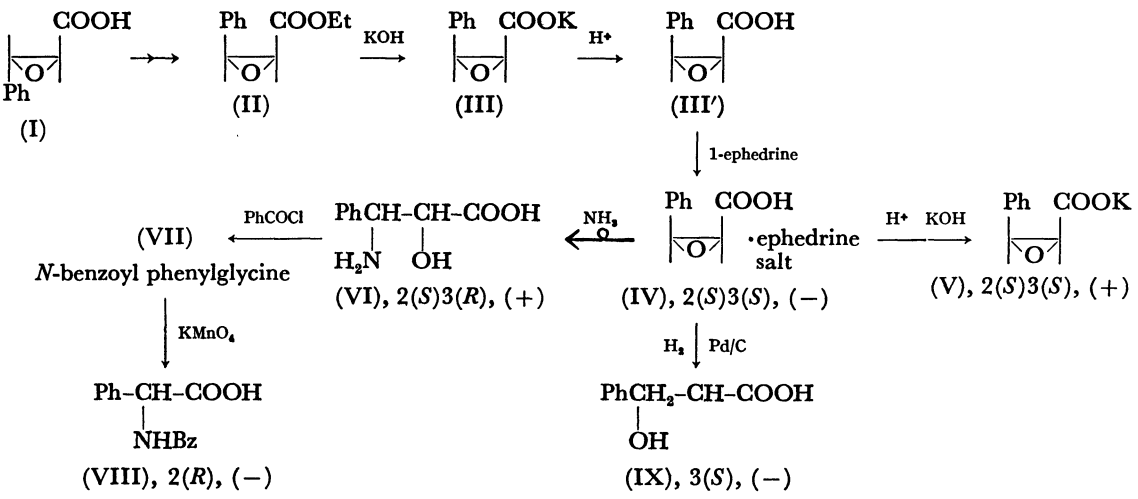
In the present study, *cis*-β-phenylglycidic acid (II) was prepared from the corresponding *trans*-β-phenylglycidic acid (I) [18] and the *cis*-glycidic acid was subjected to optical resolution. The phenylglycidic acid is an unstable compound in the free state and it decarboxylates easily to form phenylacetaldehyde at room temperature. However, by the use of rapid procedures under cold conditions, the resolution of the *cis*-glycidic acid was carried out without difficulty. The racemic *cis*-glycidic acid (III′) was resolved using (−)-ephedrine. The crystallized glycidic acid-(−)-ephedrine salt (IV) shows levorotatory $[\alpha]_D^{25}$ −27°. From this salt, optically active *cis*-phenylglycidic acid was precipitated as a potassium salt (V). The potassium salt of the *cis*-phenylglycidic acid (V) showed dextrotatory $[\alpha]_D^{25}$ +4.4°. The diastereomeric *cis*-(−)-glycidic acid-(−)-ephedrine salt was syrupy and could not be crystallized. The resolved *cis*-(+)-glycidic acid was treated with aqueous ammonia. Paper chromatography of the ammonolysis products using Shaw-Fox' solvent[19] and the results obtained by automatic amino acid analysis (Phoenix K-5000), indicated that the product was predominantly phenylisoserine (VI). The presence of a small amount of *threo*-phenylserine was confirmed in the reaction mixture by paper chromatography[19] and by amino acid analysis.

The phenylisoserine (VI) was benzoylated and the resulting *N*-benzoyl phenylisoserine (VII) was oxidized with potassium permanganate.[15] (*R*)-(−)-*N*-Benzoylphenylglycine (VIII) ($[\alpha]_D^{25}$ −119.3°) was obtained. Therefore, the configuration of the β-carbon of the phenylisoserine (VI) is (*R*). On the other hand, resolved *cis*-(+)-glycidic acid (IV) was hydrogenolyzed to convert it to (*S*)-(−)-α-hydroxy-β-phenylpropionic acid (IX). The results indicate that the configuration of the α-carbon of the *cis*-(+)-glycidic (V) is (*S*). These results obtained by the use of *cis*-(+)-glycidic acid, together with the consideration of the S_N2-type nucleophilic substitution of the β-carbon of the glycidic acid with ammonia, indicate that the configuration of the resolved (+)-glycidic acid (V) would be 2(*S*), 3(*S*), respectively. The reaction processes are summarized in Scheme 1.

Experimental

Ethyl (±)-cis-β-Phenylglycidate (II). The *cis*-glycidic acid ester (II) was prepared from ethyl *trans*-β-phenylglycidate (I) by the method described in the literature.[18] The compound (II) was gas chromatographically pure and the retention time was earlier than that of *trans*-β-phenylglycidate. bp 122—125 °C/4.2 mmHg.

Potassium cis-β-Phenylglycidate (III). The compound (II) (10.0 g) in 20 ml of absolute ethanol was added slowly to a solution of potassium hydroxide (5.0 g) in 30 ml of absolute ethanol under cooling. The agitation was continued



Scheme 1

for 3 hr. The precipitated potassium salt was filtered and washed with ethanol repeatedly. Yield, 9.4 g, mp 191—193 °C (decomp.).

Optical Resolution of cis-*β-Phenylglycidic Acid (III').* Potassium β-phenylglycidate (III) (8.3 g) was dissolved in 60 ml of water. Crushed ice and 40 ml of ether were added to the solution. To this mixture, 40 ml of 1 M hydrochloric acid was added and the liberated free glycidic acid was extracted with ether. Two additional ether extractions (40 ml×2) were carried out. The combined ether solution was dried with anhydrous sodium sulfate. To the dried ether solution, 6.78 g of (−)-ephedrine in 20 ml of ether was added. The mixture was kept at room temperature overnight. The resulting salt seemed to be amorphous; however, crystallization took place. After evaporation of ether, the syrupy residue which contained crystalline salt was digested with 30 ml of acetone and filtered. White crystals (IV) were obtained, yield 3.45 g; mp 138—140 °C. This was recrystallized from ethanol. Yield, 3.0 g; mp 145–146 °C, $[\alpha]_D^{25}$ −27.2° (*c* 2.77, ethanol). Additional crystals (1.18 g) were obtained from the salt mixture.

The resolved (−)-salt (1.0 g) in 15 ml of water was acidified to pH 2 with 6 M hydrochloric acid under ice cooling. The liberated free glycidic acid was extracted with ether. The ether solution was dried with anhydrous sodium sulfate and the solvent was evaporated. The residual oil was dissolved in 5 ml of ethanol. To this, potassium hydroxide (0.17 g) in 1 ml of ethanol was added. The precipitated potassium salt of optically active *cis*-phenylglycidic acid (V) was collected by filtration. Yield, 150 mg; mp 203—204 °C (decomp.), $[\alpha]_D^{25}$ +4.4° (*c* 0.98, H_2O).

Ammonolysis of (+)-β-Phenylglycidic Acid. The crystallized (+)-β-phenylglycidic acid-(−)-ephedrine salt (IV, 3.0 g) was dissolved in 70 ml of concentrated aqueous ammonia. The solution was kept at room temperature for 6 days. The reaction mixture was evaporated to dryness under reduced pressure. Paper chromatography using Shaw-Fox solvent[19] indicates that the major product is *threo*-β-phenylisoserine (R_f 0.33). A small amount of *threo*-β-phenylserine (R_f 0.53) was identified. Amino acid analysis showed that the ratio of phenylisoserine and phenylserine is 29.2: 1. The evaporated reaction mixture was dissolved in a minimum amount of water and the pH was adjusted to 6 using 6 M hydrochloric acid. The precipitated (+)-*threo*-β-phenylisoserine (VI) was recrystallized from water. The VI was paper chromatographically pure. Yield, 1.1 g; mp 256—257 °C (decomp.); $[\alpha]_D^{25}$ +14.9° (*c* 0.737, 6 M HCl).

Found: C, 59.41; H, 6.17; N, 7.65%. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73%.

It has been known that Shaw-Fox' paper chromatographic solvent[19] resolves diastereomers of threonine and phenylserine. This study indicates that the solvent also resolve diastereomers of phenylisoserine (*threo*-phenylisoserine, R_f 0.33; *erythro*-phenylisoserine, R_f 0.26).

threo-(+)-N-*Benzoylphenylisoserine (VII).* *threo*-(+)-Phenylisoserine (VI) was benzoylated by the usual Schotten-Baumann procedure. The yield was 65% after recrystallization from ethanol–water (3: 7). mp 168—169 °C, $[\alpha]_D^{25}$ +36.5° (*c* 1.45 EtOH).

Found: C, 67.35; H, 5.26; N, 4.79%. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91%.

Oxidation of N-*Benzoyl*-threo-(+)-*phenylisoserine (VII).* A weight of 0.85 g of VII was dissolved in a mixture of 3 ml of 1 M sodium hydroxide and 5 ml of water. To this, 0.948 g of powdered potassium permanganate was added slowly in a period of 35 min with stirring and cooling. After an additional 15 min of stirring, 0.8 g of sodium sulfite was added and the reaction mixture was stirred for 10 min. The reaction product was treated in a similar way as described in an earlier study.[15] Crude *N*-benzoylphenylglycine (VIII) (200 mg) was obtained. mp 178—182 °C. This was recrystallized from a mixed solvent of water and ethanol (4: 6). Yield, 120 mg; mp 196.5—198 °C; $[\alpha]_D^{25}$ −119.3° (*c* 0.845, ethanol).

Found: C, 70.62; H, 5.15; N, 5.43%. Calcd for $C_{15}H_{13}O_3N$: C, 70.58; H, 5.13; N, 5.49%.

(S)-(−)-α-*Hydroxyphenylpropionic Acid (IX).* The crystallized optically active phenylglycidic acid (−)-ephedrine salt (IV, 1.0 g) in 25 ml of water was hydrogenated with 1.0 g of 5% palladium on charcoal for 2 hr at room temperature. From the reaction mixture, 380 mg of crude (*S*)-(−)-α-hydroxy-β-phenylpropionic acid (IX) was obtained. mp 120—122 °C. This was recrystallized from benzene. Yield, 340 g, mp 123—124 °C; $[\alpha]_D^{25}$ −20.7° (*c* 2.11, H_2O).

Found: C, 65.26; H, 6.17%. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07%.

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