Note

Preparation of D-*p*-Hydroxyphenylglycine. Optical Resolution of DL-*p*-Hydroxyphenylglycine with *d*-3-Bromocamphor-8-sulfonic AcidShigeki YAMADA,* Chikara HONGO,
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Optically active D-*p*-hydroxyphenylglycine is used for the preparation of semisynthetic penicillins and cephalosporins.¹⁻³⁾ To develop a convenient method for the production of D-*p*-hydroxyphenylglycine (D-*p*-HPG), we have investigated the optical resolution of synthesized DL-*p*-hydroxyphenylglycine (DL-*p*-HPG). In our previous paper,⁴⁾ some sulfonates of DL-*p*-HPG were reported to be resolvable by preferential crystallization procedure. If we can find any readily available chiral agents which form separable diastereomeric salts with DL-*p*-HPG, it will provide the other advantageous resolution method. Unsubstituted DL-*p*-HPG has been reported to be resolvable *via* of *d*-3-bromocamphor-10-sulfonate.⁵⁾ This procedure, however, is inconvenient to isolation of D-*p*-HPG, because the salt consisting of that sulfonic acid and the undesired L-*p*-HPG is less soluble than the salt containing D-*p*-HPG.

In the present work, unsubstituted DL-*p*-HPG was found to be resolved by using *d*-3-bromocamphor-8-sulfonic acid (*d*-BCS), which is easily derived from natural *d*-camphor, as a resolving agent. In this case, the salt consisting of the desired D-*p*-HPG and *d*-BCS was advantageously less soluble, and furthermore the difference in solubility between the two diastereomeric salts was extremely large. Consequently, DL-*p*-HPG could be almost completely resolved. D-*p*-Hydroxyphenylglycine·*d*-3-bromocamphor-8-sulfonate (D-*p*-HPG·*d*-BCS) obtained by this resolution method was easily converted to optically pure D-*p*-HPG without racemization. The optically impure L-*p*-HPG recovered from mother liquor was racemized by heating and was reused for optical resolution. Scheme 1 shows the flowsheet for D-*p*-HPG production from DL-*p*-HPG. The simple optical resolution method presented here may provide a workable procedure for the industrial production of D-*p*-HPG, if combined

with proper synthetic methods for DL-*p*-HPG and *d*-BCS.

EXPERIMENTAL

Materials. DL-*p*-HPG manufactured by our company, Tanabe Seiyaku Co., Ltd., was used. *d*-BCS was prepared from commercial *d*-camphor ($[\alpha]_D^{20} + 44.0^\circ$, $c=7.5$, in EtOH) by the method of Kipping and Pope.^{6,7)} Namely, bromine (320 g) was added dropwise to *d*-camphor (304 g) at 80°C over a period of 3 hr under stirring and the liquified reaction mixture was kept at the same conditions for 3 hr. After hydrogen bromide was releasing by bubbling, the reaction mixture was poured into iced water (3 liters) and the resulting precipitate was recrystallized from ethanol (230 ml) to give *d*-3-bromocamphor (302 g), mp 76°C, $[\alpha]_D^{20} + 134.6^\circ$ ($c=10$, EtOH). *d*-3-Bromocamphor (231 g) was dissolved in chloroform (400 ml) and chlorosulfonic acid (233 g) was added dropwise to this solution over 1 hr at 50°C. The reaction mixture was refluxed for 12 hr and poured into iced water (1 liter). The water layer and washings were neutralized with Ca(OH)₂ (120 g) and the precipitated CaSO₄ was filtered off. To the filtrate (NH₄)₂CO₃ (128 g) was added and the precipitated CaCO₃ was removed. The filtrate was concentrated and crystallized crude ammonium *d*-BCS (152 g) was recrystallized from water (270 ml) to give ammonium *d*-BCS (102 g), mp 270~272°C (dec.), $[\alpha]_D^{20} + 85.3^\circ$ ($c=2$, water), [lit, $[\alpha]_D^{20} + 85.3^\circ$ ($c=4$, water),⁸⁾ $[\alpha]_D^{20} + 84.5^\circ$ ($c=1.6$, water)⁹⁾]. *Anal.* Found: C, 36.55; H, 5.60; N, 4.25. *Calcd.* for NH₄·C₁₀H₁₄O₄SBr: C, 36.59; H, 5.53; N, 4.27%. Ammonium *d*-BCS obtained above was passed through Amberlite IR-120, and the effluent was concentrated to dryness and used as free *d*-BCS·monohydrate.

Analyses. All samples were dried overnight *in vacuo* at 40°C. Melting points were measured with a Yamato MP-21 melting point apparatus in an unsealed capillary tube and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter.

Optical resolution of DL-*p*-hydroxyphenylglycine with *d*-3-bromocamphor-8-sulfonic acid. A mixture of DL-*p*-HPG (30.0 g) and *d*-BCS·monohydrate (59.1 g) was dissolved in water (290 ml) at 95°C and was stirred at 25°C for 2 hr. The precipitated crystals were filtered, washed with a small amount of cold water, and dried to give crude D-*p*-HPG·*d*-BCS (40.2 g), $[\alpha]_D^{25} + 4.9^\circ$ ($c=1$, 1N HCl). The crude salt (40.0 g) was recrystallized from 0.5% *d*-BCS aqueous solution (300 ml) to give D-*p*-HPG·*d*-BCS (35.5 g), $[\alpha]_D^{25} + 2.9^\circ$ ($c=1$, 1N HCl), mp 243~245°C (dec.). *Anal.* Found: C, 45.17; H, 5.11; N, 2.93; S, 6.94. *Calcd.* for

SCHEME 1. Flowsheet for Preparation of D-*p*-Hydroxyphenylglycine.

Figures in [] are weight. Substances in () were used in the next process without separation.

$C_{18}H_{21}O_7NSBr$: C, 45.20; H, 5.06; N, 2.93; S, 6.70%. The product was optically and chemically pure. The specific rotation of a mixture of DL-*p*-HPG and equivalent amount of *d*-BCS was $[\alpha]_D^{25} + 54.7^\circ$ ($c=1$, 1N HCl), and that of an authentic D-*p*-HPG·*d*-BCS was $[\alpha]_D^{25} + 2.9^\circ$ ($c=1$, 1N HCl).

Preparation of D-*p*-hydroxyphenylglycine. The pure D-*p*-HPG·*d*-BCS (30.0 g) obtained above was dissolved in water (250 ml) at 95°C. The solution was adjusted at pH 6 with 2N NaOH (ca. 31 ml), concentrated to about 70 g, and stirred at 5°C for 2 hr. The precipitated crystals were filtered, washed with water, and dried to give D-*p*-HPG (9.6 g), $[\alpha]_D^{25} - 158.3^\circ$ ($c=1$, 1N HCl). Anal. Found: C, 57.70; H, 5.41; N, 8.33. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38%.

Recovery of optically impure L-*p*-hydroxyphenylglycine. After the separation of less soluble D-*p*-HPG·*d*-BCS in the above resolution process, the mother liquor was adjusted at pH 6 with 2N NaOH, concentrated to about 130 g, and stirred at 5°C for 2 hr. The precipitated crystals were filtered, washed with water, and dried to give optically impure L-*p*-HPG (12.6 g). $[\alpha]_D^{25} + 129.3^\circ$ ($c=1$, 1N HCl).

Racemization of optically impure L-*p*-hydroxyphenylglycine. Optically impure L-*p*-HPG (10.0 g) obtained by the above procedure was dissolved in 2N HCl (30 ml). The mixture was heated in an autoclave at 140°C for 12 hr. After the reaction, the mixture was adjusted at pH 6 with 2N NaOH and was stirred at 5°C for 2 hr. The precipitated crystals were filtered, washed with water, and dried to give DL-*p*-HPG (9.2 g),

$[\alpha]_D^{25} \pm 0.0$ ($c=1$, 1N HCl). The racemized *p*-HPG could be reused for resolution.

Reuse of d-3-bromocamphor-8-sulfonic acid. Sodium salt of *d*-BCS contained in the mother liquors after the separations of D- and L-*p*-HPG could be reused as resolving agent by addition of equivalent amount of hydrochloric acid. In the mother liquor after the separation of D-*p*-HPG (9.6 g) in the preceding procedure, DL-*p*-HPG (9.1 g) and 2N HCl (31 ml) were added. The mixture was heated at 95°C for dissolution and was stirred at 25°C for 2 hr. The precipitated crystals were filtered, washed with a small amount of cold water, and dried to give crude D-*p*-HPG·*d*-BCS (14.7 g), $[\alpha]_D^{25} + 3.9^\circ$ ($c=1$, 1N HCl).

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