

# Resolution of Racemic Phenylsuccinic Acid Using (-)-Proline as a Resolving Agent

## An Introductory Organic Chemistry Experiment

Ralph Stephani and Victor Cesare

Department of Chemistry and Pharmaceutical Sciences, St. John's University, Jamaica, NY 11432

Described below is the procedure for the resolution of racemic phenylsuccinic acid. Isolation of the (+)-enantiomer has been successfully completed in our undergraduate organic laboratory for the past four years by more than 1500 students. The success of this resolution is due to the preferential formation and precipitation of the (+)-phenylsuccinic acid-bis proline salt from 2-propanol—that is, two molecules of (-)-proline are associated with one molecule of (+)-phenylsuccinic acid. This procedure has been adapted from that published by Shiraiwa et al. (1).

This experiment offers several advantages over other resolution procedures that use toxic alkaloids, such as brucine (2), or unpleasant smelling amines, like  $\alpha$ -phenylethylamine (3). It utilizes (-)-proline as the resolving agent and ( $\pm$ )-phenylsuccinic acid as the compound to be resolved; both are relatively nontoxic solids that are easy to work with. The procedure for isolating optically pure (+)-phenylsuccinic acid can be completed in about two hours and can also serve to introduce the reflux and recrystallization techniques. The specific rotation of (+)-phenylsuccinic acid is high,  $[\alpha]_D = +173.3^\circ$  (*c* 1.8235, acetone) (1); therefore, less sample is needed to measure the actual rotation, and pooling of students' products is not necessary to obtain an optical rotation reading.

Although we have never tried this resolution on a microscale, we are confident that this procedure, owing to the high yield and optical rotation value, would easily adapt to such experiments. At St. John's University, the students use the model SR-6 Polarimeter manufactured by Polyscience. The cell used with this polarimeter requires approximately 10 mL of solution; therefore, several hundred milligrams of sample is required. If a more sensitive polarimeter is available, employing a cell that requires approximately 1 mL of solution, then 10 to 20 mg of sample will suffice and a microscale version of the procedure to follow should work nicely.

### Procedure

No special drying of solvents is necessary. Dissolve 1.94 g (0.01 mol) of racemic phenylsuccinic acid (Aldrich) in 50 mL of 2-propanol in a clean, dry 250-mL round-bottom flask. Add 1.15 g (0.01 mol) of finely ground (-)-proline (Aldrich). Mix the contents of the flask for 2–3 min with a stirring rod and then reflux for 30 min. During the reflux, as all of the proline dissolves, the (+)-bis proline salt usually begins to precipitate out of solution.

Air cool the flask for 15–20 min to approximately 30 °C. If the (+)-salt has not crystallized at this point, seeding the solution with another student's salt and vigorous stirring

will initiate crystallization. Filter and wash the solid twice with 15 mL of acetone. Let the aspirator run for several minutes after the second acetone wash and then dry the salt between several pieces of filter paper. To isolate the (+)-phenylsuccinic acid in one lab period, the salt is hydrolyzed even though it is not completely dry. If desired, one may take the melting point and optical rotation of the salt (mp 160–161 °C,  $[\alpha]_D = +13.5^\circ$  (*c* 1.00, methanol), by spreading the crystals on a clean filter paper and allowing it to thoroughly dry (ca. 60 min).

Add all of the (+)-salt to 10 mL of 6M HCl that is being cooled in an ice water bath. Stir this mixture for 5 min. Filter and wash the solid twice with 15 mL of cold water. After the solid is allowed to air dry for at least 24 hours, the average yield per student is 0.39 g, 40%;  $[\alpha]_D = +151^\circ$  (*c* 4.0, acetone). Recrystallization from water will yield optically pure (+)-phenylsuccinic acid, with a melting point of 185–186 °C and  $[\alpha]_D = +171^\circ$  (*c* 4.0, acetone).

To isolate (-)-phenylsuccinic acid, evaporate the filtrate after filtering out the (+)-salt. To simply demonstrate that (-)-phenylsuccinic acid was in the filtrate, stir the remaining residue with 10 mL of 6M HCl for 10 min. Filtration of this mixture will yield optically active (-)-phenylsuccinic acid: 0.61 g, mp 169–171 °C,  $[\alpha]_D = -67^\circ$  (*c* 4.0, acetone). Alternatively, if optically pure (-)-phenylsuccinic acid is desired, the residue is dissolved in 40 mL of absolute ethanol. Add 0.39 g of (-)-proline and stir at room temperature for 30 min. Evaporate off the ethanol to isolate the (-)-mono-proline salt. Add 20 mL of acetone to the (-)-salt and stir for 2–3 min. Filter, and then dry the salt between several pieces of filter paper. (If the salt is allowed to dry thoroughly, typical results of the (-)-salt are 1.14 g, mp = 142–144 °C,  $[\alpha]_D = -96^\circ$  (*c* 1.00, methanol)). Add all of the (-)-salt to 10 mL of 6M HCl and stir at 0 °C for 5 min. Filter and wash the solid twice with 15 mL of water. Let the (-)-phenylsuccinic acid air dry: 0.57 g, mp 176–179 °C,  $[\alpha]_D = -160^\circ$  (*c* 4.0, acetone). Recrystallization from water will yield optically pure (-)-phenylsuccinic acid, 0.38 g (39%), mp 185–186 °C, and  $[\alpha]_D = -170^\circ$  (*c* 4.0, acetone).

### Literature Cited

- Shiraiwa, T.; Sado, Y.; Fujii, S.; Nakamura, M.; Kurokawa, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 824–827.
- Brewster, R. Q.; Vanderwerf, C. A.; McEwen, W. E. *Unitized Experiments in Organic Chemistry*, 4th ed.; Wadsworth: Belmont, CA, 1977; pp 301–306.
- Roberts, R. M.; Gilbert, J. C.; Rodewald, L. B.; Wingrove, A. S. *Modern Experimental Organic Chemistry*, 4th ed.; Saunders: Philadelphia, 1985; pp 184–187.