



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

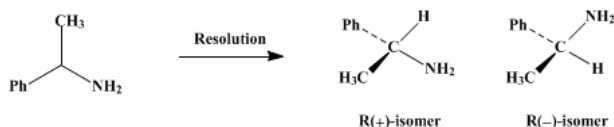
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

R(+)- AND S(-)- α -PHENYLETHYLAMINE

[Benzylamine, α -methyl]



Submitted by Addison Ault¹
Checked by Martin Gall, Elia J. Racah, and Herbert O. House.

1. Procedure

A. (*S*)-(-)- α -Phenylethylamine. A mixture of 31.25 g. (0.208 mole) of (+)-tartaric acid and 450 ml. of methanol is placed in a 1-l. Erlenmeyer flask and heated to boiling. To the hot solution is added, cautiously to avoid foaming, 25.0 g. (26.2 ml., 0.206 mole) of racemic α -phenylethylamine (Note 1) and the resulting solution is allowed to cool. Since crystallization occurs slowly, the solution should be allowed to stand at room temperature for approximately 24 hours. The (-)-amine (+)-hydrogen tartrate salt separates as white prismatic crystals (Note 2). The product (18.1–19.3 g.) should be collected on a filter and washed with a small volume of methanol. The combined mother liquor and methanol washings should be concentrated to a volume of 175 ml. with a rotary evaporator. The resulting mixture is then heated to boiling, and the solution is allowed to cool and stand at room temperature for approximately 24 hours. In this way an additional crop (2.0–3.8 g.) of the (-)-amine (+)-hydrogen tartrate salt may be separated as white prisms (Note 2). The combined methanolic mother liquors and washings from these crystallizations are concentrated to dryness on a rotary evaporator. The crude residual salt is used for the preparation of the (+)-amine.

The combined crops of crude (-)-amine (+)-hydrogen tartrate are pulverized in a mortar and redissolved in 450–500 ml. of boiling methanol. The resulting hot solution is concentrated to 350 ml. (Note 3) and then allowed to cool and stand for 24 hours. After the initial crop (14.3–16.2 g.) of pure (-)-amine (+)-hydrogen tartrate has been collected as white prisms (Note 2) (m.p. 179–182° dec.), the mother liquors and washings are concentrated to 75 ml. and again allowed to stand for 24 hours. In this way a second crop (2.9–3.6 g.) of the pure (-)-amine salt is obtained. The total yield of the pure (-)-amine salt is 17.9–19.1 g. (64–68%).

A mixture of the pure (-)-amine salt (17.9–19.1 g.) and 90 ml. of water is treated with 15 ml. of aqueous 50% sodium hydroxide and the resulting mixture is shaken with four 75-ml. portions of ether. After the combined ether extracts have been washed with 50 ml. of saturated aqueous sodium chloride and dried over magnesium sulfate, the bulk of the ether is distilled from the mixture through a 30-cm. Vigreux column and the residual liquid is distilled under reduced pressure. The (-)-amine is collected as 6.9–7.2 g. (55–58%) of colorless liquid, b.p. 94–95° (28 mm.), n_D^{25} 1.5241–1.5244, $[\alpha]_D^{29}$ –39.4° (neat) (Note 4), (Note 5).

B. (*R*)-(+)- α -Phenylethylamine. The residual salts (approximately 35 g.) obtained by concentration of the methanolic mother liquors from the initial crystallization of the (-)-amine (+)-hydrogen tartrate are treated successively with 160 ml. of water and 25 ml. of aqueous 50% sodium hydroxide. After the resulting mixture has been extracted with ether, the extract is dried, concentrated, and distilled as previously described. The recovered amine amounts to 12.5–14.1 g. of colorless liquid, b.p. 79–80° (18 mm.), $[\alpha]_D^{28}$ +23.8 to +24.7° (neat). From the weight and specific rotation data for this amine sample and the reported² specific rotation, $[\alpha]_D^{25}$ +40.6° (neat), for the pure (+)-amine, the amount of excess (+)-amine present in the recovered amine sample is calculated. Typical values range from 0.06 to 0.07 mole of excess (+)-amine. A solution of this partially resolved amine in 90 ml. of 95% ethanol is heated to boiling and then treated with 180 ml. of an ethanolic solution containing a sufficient amount (0.03–0.035 mole) of concentrated sulfuric acid to convert the excess (+)-amine to its neutral sulfate salt (Note 6). The hot solution is allowed to cool to room temperature, and the crude (+)-amine sulfate which separates as white needles (7.8–9.3 g.) is collected on a filter and washed with 95% ethanol. The combined ethanolic mother liquors and washings are concentrated and allowed to cool to separate a second crop (1.2–1.4 g.) of the crude (+)-amine sulfate. The combined crops of (+)-amine sulfate are dissolved in a minimum volume (about 45 ml. of hot water), and the resulting hot solution is diluted with acetone until it is just saturated at the boiling point. After the solution has been allowed to cool to room temperature, the pure (+)-amine sulfate which separates as white needles, m.p. 240–265° dec. (5.0–6.1 g.) is collected on a filter and washed with cold 95% ethanol. The combined mother liquors and washings are concentrated to dryness, and the residual solid is recrystallized from aqueous acetone to separate additional crops (2.6–2.8 g.) of the pure (+)-amine sulfate. The total yield of the pure amine sulfate is 7.8–8.9 g. (45–51% on the basis of the starting α -phenylethylamine).

A mixture of the pure (+)-amine sulfate (7.8–8.9 g.) and 40 ml. of water is treated with 6.0 ml. of aqueous 50% sodium hydroxide and the resulting mixture is shaken with four 75-ml. portions of ether. The combined ether extracts are washed with 50 ml. of saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated by distillation of the ether through a 30-cm. Vigreux column. The residual liquid is distilled under reduced pressure to separate 5.1–5.5 g. (41–44%) of the (+)-amine as a colorless liquid, b.p. 85–86° (21 mm.), n_D^{25} 1.5243–1.5248, $[\alpha]_D^{29}$ +39.7° (neat) (Note 7).

2. Notes

1. A practical grade of racemic α -phenylethylamine supplied by Eastman Organic Chemicals is satisfactory. However, if the racemic amine is highly discolored, distillation before use is recommended.

2. Sometimes a salt separates in the form of white needles. The (-)-amine recovered from these needlelike crystals is not optically pure; $[\alpha]_D^{25}$ –19° to –21° (neat). If the product separates either partially or completely as needlelike crystals during the crystallization, the mixture should be warmed until all the needlelike crystals have dissolved, and then the solution should be allowed to cool slowly. If possible, the solution should be seeded with the prismatic crystals. Separation of the prismatic and needlelike crystals can also be effected by taking advantage of the fact that the needles dissolve more rapidly than the prisms in warm methanol.

3. Because of the low rate of solution of the amine salt, the desired solution is obtained most rapidly by dissolving the salt in excess solvent and then concentrating the solution.

4. The literature value (d_4^{25} 0.9528)² for the density of α -phenylethylamine was used to calculate the specific rotation.

5. From the reported specific rotation value, $[\alpha]_D^{25}$ –40.14° (neat),³ $[\alpha]_D^{22}$ –40.3° (neat),⁴ the optical purity of this preparation is estimated to be 98%. The boiling point of this amine at atmospheric pressure is 186–187°.

6. For example, a 14.1-g. (0.116 mole) sample of amine, $[\alpha]_D^{28}$ +23.8° (neat), was estimated to contain 0.0676 mole of excess (+)-amine. Therefore 3.52 g. (0.0345 mole) of concentrated sulfuric acid was added.

7. From the reported specific rotation value, $[\alpha]_D^{25}$ +40.6° (neat),² the optical purity of this preparation is estimated to be 98%. The boiling point of this amine at atmospheric pressure is 186–187°.

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3. Discussion

The method presented is based on the procedure of Theilaker and Winkler.⁴ It makes use of (+)-tartaric acid, an inexpensive and readily available material, as the resolving agent and provides optically pure samples of α -phenylethylamine.

Some other methods of resolution include the use of *l*-malic acid [(+)-form],⁵ *l*- and *dl*-malic acids [(+)- and (-)-forms],⁶ *l*-malic acid and *d*-tartaric acids [(+)- and (-)-forms],⁷ *d*- α -bromocamphor-*n*-sulfonic acid [(-)-form],⁸ *l*-quinic and *d*-tartaric acids [(+)- and (-)-forms],⁹ 2,3,4,6-tetraacetyl-D-glucose [(+)-form],¹⁰ and barium (-)-bornyl sulfate [(+)- and (-)-forms].¹¹

The enantiomers of this amine are useful resolving agents. Some of the compounds which have been resolved with one of the optically active forms of α -phenylethylamine are: mandelic acid,¹² α -methylmandelic acid,¹³ α -ethylmandelic acid,¹⁴ 2-phenylpropionic acid,¹⁵ 2-(*p*-nitrophenyl) propionic acid,¹⁶ 2,3-dichloro-2-methylpropionic acid,¹⁷ 2-phenylbutyric acid,¹⁵ 2-phenylvaleric acid,¹⁸ 2-phenylcaproic acid,¹⁸ α -methylhydrocinnamic acid,¹⁹ β -methylhydrocinnamic acid,²⁰ benzylsuccinic acid,²¹ *N*-formylphenylalanine,²² *N*-acetyl-3,5-dibromotyrosine,²³ *N*-acetyltryptophan,²⁴ 6,6'-dinitrodiphenic acid,²⁵ and 3-methylcyclohexanone and β -methylcinnamaldehyde, via the amine bisulfite complexes.²⁶

References and Notes

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

R(+)- AND S(-)- α -PHENYLETHYLAMINE

racemic α -phenylethylamine

d- α -bromocamphor-*n*-sulfonic acid

barium (-)-bornyl sulfate

6,6'-dinitrodiphenic acid

(S)-(-)- α -Phenylethylamine

ethanol (64-17-5)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Mandelic acid (90-64-2)

sodium chloride (7647-14-5)

acetone (67-64-1)

(+)-tartaric acid (87-69-4)

magnesium sulfate (7487-88-9)

l-malic acid (617-48-1)

α -Phenylethylamine,
Benzylamine, α -methyl (3886-69-9)
 α -methylmandelic acid (515-30-0)
2-Phenylpropionic acid (492-37-5)
2,3,4,6-tetraacetyl-D-glucose
 α -ethylmandelic acid
2,3-dichloro-2-methylpropionic acid (10411-52-6)
2-phenylbutyric acid (90-27-7)
2-phenylvaleric acid
2-phenylcaproic acid
 α -methylhydrocinnamic acid (1009-67-2)
 β -methylhydrocinnamic acid (4593-90-2)
benzylsuccinic acid (36092-42-9)
N-formylphenylalanine
N-acetyl-3,5-dibromotyrosine
N-acetyltryptophan (1218-34-4)
3-methylcyclohexanone (591-24-2)
 β -methylcinnamaldehyde
2-(p-nitrophenyl) propionic acid (19910-33-9)
(R)-(+)- α -Phenylethylamine (2627-86-3)

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