



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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

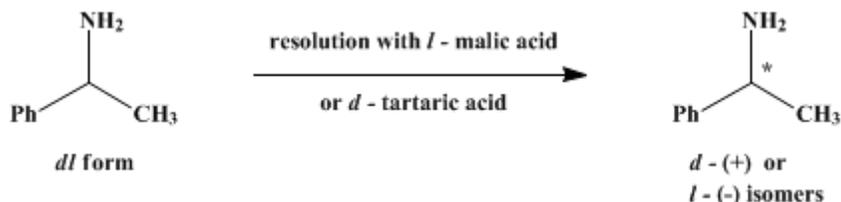
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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.

Organic Syntheses, Coll. Vol. 2, p.506 (1943); Vol. 17, p.80 (1937).

***d*- AND *l*- α -PHENYLETHYLAMINE**

[Benzylamine, α -methyl-, *d*- and *l*-]



Submitted by A. W. Ingersoll

Checked by Reynold C. Fuson and William E. Ross.

1. Procedure

d- α -Phenylethylamine.—A solution of 100 g. (0.75 mole) (Note 1) of *l*-malic acid in 500 cc. of distilled water is mixed with 120 g. (1 mole) of *dl*- α -phenylethylamine (p. 503); the resulting solution is heated for a short time on the steam bath, filtered into a 1-l. beaker, and allowed to cool slowly. After several hours the crude *d*- α -phenylethylamine-*l*-malate which crystallizes is collected by suction filtration and washed on the filter with 25 cc. of ice water. The filtrate and washings are evaporated on a steam bath to a volume about two-thirds that of the original filtrate, and a second crop of crystals is obtained on cooling (Note 2) and (Note 3). By repeating the process it is possible to obtain a third and usually a fourth crop, after which the mother liquor becomes too viscous to permit satisfactory crystallization. The mother liquor is reserved for later use.

The successive crops of crystals are systematically recrystallized as follows, using Norite if necessary. About two-thirds of the first crop is dissolved in about three parts of water and the hot solution allowed to deposit crystals by slow cooling (Note 3). The liquor is filtered or decanted, the remainder of the first crop is dissolved in it, and the process of crystallization is repeated. The remaining crops are then similarly recrystallized in succession from the same liquor, the solution being evaporated to the appropriate volume before each crystallization. The final mother liquor is evaporated in stages, and the viscous residue is united with that from the original crystallization. The various crops are systematically recrystallized from fresh water until pure (Note 4). It is possible to obtain 80–90 g. (63–70 per cent of the theoretical amount) of the pure *d*-base-*l*-acid (anhydrous acid salt).

The pure malate (mol. wt. 255) is decomposed by warming with very slightly more (Note 5) than two equivalents of approximately 2 *N* sodium hydroxide. The amine is extracted, after cooling, with three or four 25-cc. portions of pure benzene, the solution is dried thoroughly with powdered sodium hydroxide, and the pure amine, b.p. 184–185°, $[\alpha]_D^{25}$ + 39.2° to + 39.7° (without solvent), is obtained by distillation (Note 6). A small amount of the amine distils with the benzene. The yield is 35–40 g. (92–94 per cent of the theoretical amount based on the pure malate).

The mother liquors from the original crystallization and recrystallizations are treated in a similar manner, and the sodium malate solutions are united and reserved for the recovery of *l*-malic acid (Note 7). The recovered amine amounts to 75–80 g. and contains 40–50 per cent excess *l*-amine.

l- α -Phenylethylamine.—The recovered amine is converted to the acid tartrate in water solution, using for each gram of amine 1.25 g. of *d*-tartaric acid and 4.0 cc. of water. The solution is boiled with decolorizing carbon, if necessary, filtered, and allowed to cool slowly without disturbance (Note 3). A dense mass of coarse crystals of crude *l*- α -phenylethylamine-*d*-tartrate is deposited. The solution is decanted and evaporated to about two-thirds its original volume, and a second crop of crystals is obtained as before. These operations are repeated once or twice more, after which usually no more coarse crystals, but only a mass of needle-like crystals (mixed salts), can be obtained (Note 8). Meanwhile the first crop is recrystallized from about twice its weight of water. About two-thirds of the

weight of crude salt is thus obtained pure; the mother liquor is used as solvent for the second crop, and so forth. The final mother liquor is united with that from the original crystallization and reserved for the recovery of the partially resolved amine. The yield of pure *l*-base-*d*-acid salt (anhydrous acid salt) is 75–100 g., an amount equivalent to somewhat more than the excess of *l*-amine in the mixture taken. The pure salt has a specific rotation of +13.0 to 13.2° in an 8 per cent solution in water.

The pure salt (mol. wt. 271) is dissolved in four parts of water; the amine is liberated with an excess of 20–25 per cent sodium hydroxide solution, extracted with benzene, and purified as described for the *d*-amine. The constants agree closely with those given for the *d*-amine, and the yield is 32–42 g. (94–96 per cent of the theoretical amount based on the pure tartrate, or 53–70 per cent based on the total *l*-amine originally present).

The amine recovered in the same way from the mother liquors amounts to 40–50 g. and contains a slight excess of *d*-amine. It may be used conveniently in the next run in place of the *dl*-amine.

2. Notes

1. The amount of malic acid theoretically is sufficient to convert half of the amine to the acid salt and the remaining half to the neutral salt.
2. Small amounts of the volatile amine are lost by hydrolysis during the evaporation and recrystallization of the salt.
3. Fractional crystallization is facilitated by inoculating the warm solution with a crystal of the species expected to separate and allowing crystallization to proceed slowly without disturbance.
4. The purity of *d*- α -phenylethylamine-*l*-malate is not readily determined by its melting point or specific rotation, but rather by its massive crystalline form and solubility. The acid and neutral *l*-base-*l*-acid salts are much more soluble, and usually do not crystallize at all.
5. Excess alkali must be avoided if the malic acid is to be recovered, since it is slowly racemized by heating with concentrated alkali.
6. When the amine is to be used in water solution a weighed amount of the pure salt may be decomposed with alkali, the base distilled quantitatively with steam, and the entire distillate used.
7. The solution containing sodium malate is neutralized with acetic acid, diluted to contain about 5 per cent of sodium malate, and treated at the boiling point with 10 per cent lead acetate solution until lead malate no longer precipitates. The lead malate is collected after cooling and washed by trituration with boiling water. The salt is made into a thin paste with distilled water and decomposed with hydrogen sulfide (two days). The lead sulfide is filtered and the malic acid solution evaporated to a convenient volume. After titration of an aliquot, the solution may be used instead of pure acid in another run. The recovery is 70–80 per cent.
8. The *l*-base-*d*-acid salt no longer can be obtained pure when the solution contains about equal proportions of the salts of *d*- and *l*-amines. For this reason, also, an initial resolution of the *dl*-amine with *d*-tartaric acid is not feasible.

3. Discussion

The present method is adapted from that of Lovén.¹ The resolution has been carried out with *d*- α -bromocamphor- π -sulfonic acid (*l*-form);^{2, 3} with *l*- and *dl*-malic acids (*d*- and *l*-forms);⁴ with *l*-quinic acid and *d*-tartaric acid (*d*- and *l*-forms),⁵ and with *d*- and *l*-6, 6'-dinitrodiphenic acids (*d*- and *l*-forms).⁶ Methods employing *d*-benzylmethylacetyl chloride,⁷ *d*-oxymethylenecamphor,⁸ *l*-quinic acid,⁹ and *d*-camphoric anhydride¹⁰ are of theoretical interest only. The *dl*-amine is not resolved by the active camphor-10-sulfonic acids¹¹ or mandelic acids.¹²

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 717
- Org. Syn. Coll. Vol. 5, 932

1. Lovén, J. prakt. Chem. **72**, (2) 307 (1905). See also Lovén, Ber. **29**, 2313 (1896).
 2. Hunter and Kipping, J. Chem. Soc. **83**, 1147 (1903).
 3. Ingold and Wilson, *ibid.* **1933**, 1502.
 4. Ingersoll, J. Am. Chem. Soc. **47**, 1168 (1925).
 5. André and Vernier, Compt. rend. **193**, 1192 (1931).
 6. Ingersoll and Little, J. Am. Chem. Soc. **56**, 2123 (1934).
 7. Kipping and Salway, J. Chem. Soc. **85**, 444 (1904).
 8. Pope and Read, *ibid.* **95**, 171 (1909).
 9. Marckwald and Meth, Ber. **38**, 801 (1905).
 10. Freylon, Ann. chim. phys. (8) **15**, 140 (1908).
 11. Pope and Harvey, J. Chem. Soc. **75**, 1110 (1899).
 12. Ingersoll, Babcock, and Burns, J. Am. Chem. Soc. **55**, 411 (1933).
-

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

camphor-10-sulfonic acids

mandelic acids

D- and L- α -Phenylethylamine

Benzylamine, α -methyl-, d- and l-

acetic acid (64-19-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

hydrogen sulfide (7783-06-4)

lead sulfide

decolorizing carbon,
Norite (7782-42-5)

lead acetate

malic acid,
l-malic acid (617-48-1)

dl- α -phenylethylamine (3886-69-9)

Phenylethylamine (64-04-0)

sodium malate

D-tartaric acid (147-71-7)

lead malate

d- α -phenylethylamine-l-malate

l- α -phenylethylamine-d-tartrate

d-benzylmethylacetyl chloride

d-oxymethylenecamphor

d-camphoric anhydride