Organic Syntheses

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.

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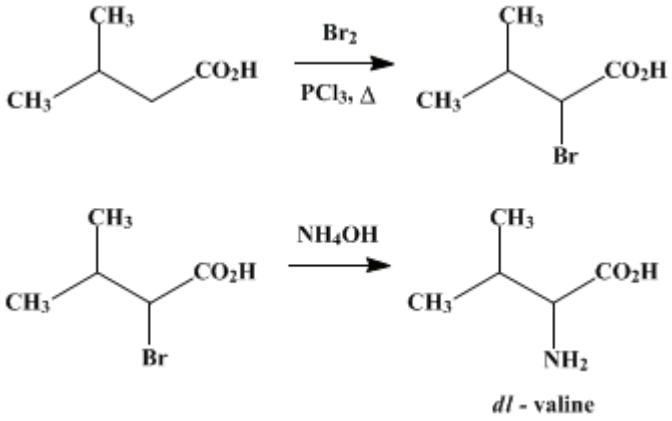
dl-VALINE

[Isovaleric acid, α-amino]



dl - valine

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1. Procedure

A. α-*Bromoisovaleric acid*. One kilogram of commercial isovaleric acid monohydrate is placed in a 3-l. round-bottomed flask together with 500 ml. of benzene. The water and benzene are distilled, using a short column, until the temperature of the vapor reaches 100°. The temperature rises rapidly when the benzene is removed. The residue is cooled, and 878 g. (934 ml., 8.6 moles) of it is placed in a 3-l. round-bottomed flask fitted with a long reflux condenser. The top of the condenser is connected by glass tubing to an empty 500-ml. Erlenmeyer flask which acts as a safety trap. A second outlet on the Erlenmeyer flask connects to a gas-absorption trap (Note 1). One and five-tenths kilograms (480 ml.) of dry bromine (Note 2) is added to the acid, and then 15 ml. of phosphorus trichloride is added through the top of the condenser.

The mixture is heated on an oil bath at 70–80° for 10–20 hours or until the condenser no longer shows the deep red color of bromine. Another 25-ml. portion of bromine is added and the flask heated as before. When the color has again disappeared, the temperature of the bath is slowly raised to 100–105° and maintained there for 1.5–2 hours.

The crude bromo acid is placed in a 2-l. modified Claisen flask and distilled under reduced pressure. The low-boiling fraction is mainly unbrominated acid (Note 3). The fraction boiling at 110–125°/15 mm. is collected. The yield is 1364–1380 g. (87.5–88.6%).

B. *dl-Valine.* To 2 l. of technical ammonium hydroxide (sp. gr. 0.90) in a 3-l. round-bottomed flask is added 330 g. (1.82 moles) of α-bromoisovaleric acid. A stopper is wired in and the flask allowed to stand at room temperature for a week. The contents from three such amination flasks are combined in a 12-l. flask, and the ammonia is removed by heating on the steam cone overnight. The solution is then concentrated to a thin paste (about 800 ml.) by means of a water pump (Note 4). The solid material is collected on a filter and, when dry, amounts to 470 g. This is recrystallized by dissolving in 2.4 l. of water heated to 95° on a steam cone, treating with 10 g. of Norit for 30 minutes, filtering hot, adding an equal volume of 95% ethanol, and cooling overnight in the icebox. The valine is collected on a filter and washed with 150 ml. of cold absolute ethanol. The yield is 200–235 g. A second crop is obtained by evaporating the filtrate from the recrystallization on the water pump until crystals form, adding an equal volume of 95% ethanol, and cooling as before. The amino acid obtained in this way amounts to 34 g.

The second filtrate from the recrystallization together with the filtrate from the original concentration is evaporated to dryness and extracted with 500 ml. of glacial acetic acid on a steam cone.

The inorganic salts are filtered and the acetic acid is removed by distillation under reduced pressure. One liter of water is added, and it, too, is removed by distillation under reduced pressure. This operation is repeated. These three distillations require 1 day. The residue is dissolved in the minimum amount of hot water (about 300 ml.). The solution is then treated with Norit as before and filtered hot, and an equal volume of 95% ethanol is added. The yield on cooling overnight in the icebox is 34 g. An additional 8 g. can be obtained from the mother liquor by concentration and addition of ethanol as was done with the original mother liquor. The total yield of valine is 300–311 g. (47–48%), which decomposes at 280–282° in a sealed capillary (Note 5) and (Note 6).

2. Notes

1. The hydrogen bromide may be absorbed in water and constant-boiling hydrobromic acid formed (*Org. Syntheses* Coll. Vol. **1**, 26 (1941).
2. The bromine is dried by shaking with 1 l. of concentrated sulfuric acid.
3. The low-boiling fraction (56–80 g.) may be combined with the next portion of acid to be brominated, or several such fractions are collected and brominated together. In this latter case, only three-fifths as much bromine is used as in the original run.
4. This condition is attained when 1850–1950 ml. of distillate has been collected (5 hours).
5. The quantities stated for each fraction are approximate. If separations are incomplete, the melting point will be 275–280°.
6. Valine prepared in this manner has the calculated amino nitrogen content.

3. Discussion

Valine has been prepared by the action of ethanolic ammonia on α-chloroisovaleric acid;[2] by the action of aqueous ammonia on α-bromoisovaleric acid;[3] through the reaction of hexamethylenetetramine with α-bromoisovaleric acid in dioxane or dioxane-xylene (91% yield);[4] by the action of ammonia and ammonium carbonate,[5] or ammonium carbonate alone on α-bromoisovaleric acid;[6] by heating isopropylmalonazidic acid[7] or isopropylcyanoacetazide[8] in ethanol and subsequent hydrolysis; by the action of ammonia and hydrogen cyanide[9] or ammonium chloride and potassium cyanide[10] on isobutyraldehyde, followed by hydrolysis; by reaction of α-hydroxyisovaleronitrile with ammonia under pressure, followed by hydrolysis;[11] by reaction of isopropyl bromide with the sodium salt of acetamidomalonic ester or acetamidocyanoacetic ester,[12] and subsequent hydrolysis; by reduction of dimethylpyruvic acid phenylhydrazone;[13] by hydrolysis of α-carbomethoxy-α-phenylacetamidoisovaleronitrile;[14] and by the reaction of isobutyraldehyde with ammonium carbonate and sodium cyanide in aqueous methanol followed by hydrolysis.[15]

α-Bromoisovaleric acid has been prepared in several ways as described in an earlier volume.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 93

References and Notes

1. These directions are the result of the efforts of a large number of men who have worked on the preparation of valine at the University of Illinois.
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16. *Org. Syntheses* Coll. Vol. **2**, 95 (1943).

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

isopropylcyanoacetazide

sodium salt of acetamidomalonic ester or acetamidocyanoacetic ester

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ammonium carbonate (506-87-6)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ammonium chloride (12125-02-9)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

α-Bromoisovaleric acid (565-74-2)

HYDROBROMIC ACID,
hydrogen bromide (10035-10-6)

bromine (7726-95-6)

Isopropyl bromide (75-26-3)

potassium cyanide (151-50-8)

Norit (7782-42-5)

phosphorus trichloride (7719-12-2)

ammonium hydroxide (1336-21-6)

xylene (106-42-3)

hexamethylenetetramine (100-97-0)

dioxane (123-91-1)

isobutyraldehyde (78-84-2)

Isovaleric acid, α-amino,

DL-Valine (516-06-3)

valine (72-18-4)

isovaleric acid monohydrate

α-chloroisovaleric acid

isopropylmalonazidic acid

α-hydroxyisovaleronitrile

dimethylpyruvic acid phenylhydrazone

α-carbomethoxy-α-phenylacetamidoisovaleronitrile