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.

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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.

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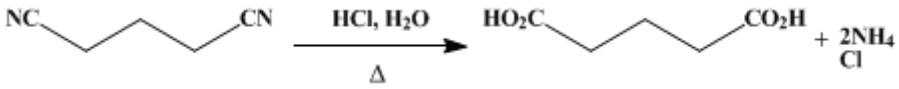
GLUTARIC ACID

[(*A*) (*from Trimethylene Cyanide*)]



Submitted by C. S. Marvel and W. F. Tuley.
Checked by H. T. Clarke and E. E. Dreger.

1. Procedure

In a 2-l. round-bottomed flask are placed 100 g. (1.06 moles) of trimethylene cyanide (p. 536) and 500 g. (424 cc., 4.8 moles) of hydrochloric acid (sp. gr. 1.18). The mixture is refluxed for about four hours and then the solution is evaporated to dryness, preferably under reduced pressure. The dry residue, consisting of glutaric acid and ammonium chloride, is extracted with about 300 cc. of boiling ether. The ether solution is filtered and the residue is further extracted with two 100-cc. portions of boiling ether. The combined ether extracts containing the glutaric acid are evaporated (Note 1) to about 150–200 cc., whereupon the acid begins to crystallize. Then 1 l. of benzene (Note 2) is added, and the mixture is heated until the glutaric acid dissolves. On cooling in an ice-salt bath, the acid crystallizes. The first crop weighs 103–105 g. (Note 3). The filtrate is concentrated to about one-third its original volume and cooled, whereupon a second crop of 13–14 g. of pure glutaric acid is obtained. The total yield is thus 116–119 g. (83–85 per cent of the theoretical amount) of a product melting at 97–98° (Note 4).

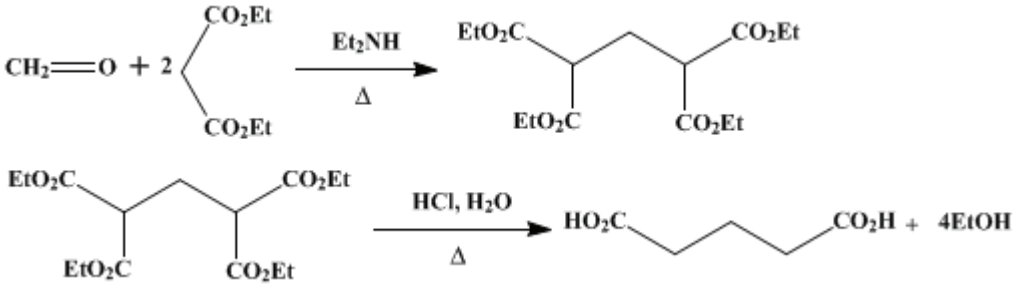
2. Notes

1. Most of the ether can be recovered by concentrating the solution in a flask attached to a condenser set for distillation.
2. The glutaric acid may be directly extracted from the ammonium chloride with benzene, but on a small scale this is less satisfactory than the procedure given.
3. When the benzene solution is chilled to 0° or lower, almost all the glutaric acid separates in the first crop of crystals.
4. It is reported that glutaric acid can be easily and cheaply prepared by the oxidation of cyclopentanone according to the following procedure, which is similar to that for the preparation of adipic acid from cyclohexanone—compare p. 18. The oxidation needs careful control, for if it gets out of hand succinic acid results.

In a 2-l. round-bottomed, three-necked flask fitted with a stirrer and two large-bore condensers are placed 200 cc. of 50 per cent nitric acid and 0.25 g. of vanadium pentoxide. The flask is heated to 65–70° in a water bath (thermometer in the water), and 1 cc. of cyclopentanone is added. Oxidation is indicated by the production of brown fumes. The water bath is removed, and 42 g. (less the 1 cc.) of the cyclic ketone is added from a dropping funnel through the condenser at the rate of a drop every three seconds. The heat of the reaction keeps the flask at about 70°. If the temperature drops, oxidation ceases until the ketone has accumulated, when it may proceed almost explosively. In such a case, or if the temperature is higher, much succinic acid is formed. After addition has been completed, the water bath is replaced and the mixture heated to boiling. The contents of the flask are poured into an evaporating dish (Hood), and the volume reduced one-half. When cold, the acid is filtered and the operation repeated twice; the last time the acid is yellowish, and the color is removed by washing with dilute hydrochloric acid. The crude glutaric acid is white and weighs 50–55 g. (80–85 per cent); m.p. 92–94°. If any succinic acid is present owing to lack of proper control, it separates in the first crop. It is more convenient to allow the mother liquors from several runs to accumulate and work them up separately; from each run 2–3 g. more of glutaric acid may be so obtained. Further purification is accomplished, if desired, by crystallization from benzene. The acid as prepared above always contains traces of nitric acid, but is satisfactory for conversion into the anhydride. If the catalyst is omitted, the yield is less by

10 per cent. (C. F. H. Allen and W. L. Ball, private communication).

[(*B*) (*from Ethyl Malonate*)]



Submitted by T. J. Otterbacher
Checked by F. C. Whitmore and F. L. Carnahan.

1. Procedure

Ethyl Propane-1,1,3,3-tetracarboxylate.—To a mixture of 1600 g. (1510 cc., 10 moles) of ethyl malonate (Note 1) and 400 g. of 40 percent formalin (5.3 moles) in a 5-l. round-bottomed flask, cooled to 5° by immersion in ice, is added 25 g. (35 cc.) of diethylamine. The mixture is then allowed to come to room temperature and remain for fifteen hours, after which the flask is heated under a reflux condenser on a boiling water bath for six hours. The aqueous layer is then separated, and the residue is distilled under reduced pressure (Note 2) from a 3-l. special Claisen flask (p. 130). The ester distils at 190–200°/12 mm. (210–215° /20 mm.). The yield (Note 3) is 1000 g. (61 per cent of the theoretical amount).

Glutaric Acid.—A mixture of 125 g. (0.37 mole) of the above product, 125 cc. of concentrated hydrochloric acid, and 125 cc. of water is heated (Note 4) in a 1-l. flask under a reflux condenser until it becomes homogeneous (six to eight hours). The contents of the flask are then evaporated to dryness, and the residual glutaric acid is transferred to a 100-cc. Claisen flask and distilled under diminished pressure. The fraction boiling at 185–195° /10 mm. is collected. It is moistened with water (Note 5) and heated gently, after which it is dried at 30°. On recrystallization from benzene, it separates in colorless needles, m.p. 96–97°. The yield is 38–40 g. (76–80 per cent of the theoretical amount).

2. Notes

1. The ethyl malonate used was a fraction of the technical grade boiling over a 3° range under diminished pressure.
2. The ester is distilled slowly at first in order to vaporize the water at a temperature below 50°.
3. The high-boiling residue (500 g.) is stated[1] to contain considerable amounts of ethyl pentanehexacarboxylate.
Directions are also available for the preparation of ethyl propane-1,1,3,3-tetracarboxylate in high yield from ethyl malonate, paraformaldehyde, and alcoholic potassium hydroxide.[2] Prior to distillation of the ester a little hydrochloric acid is added to destroy the catalyst.
4. In order to prevent loss of material through the condenser by bumping, the flask should be heated in an oil bath at 115° or its contents stirred vigorously.
5. The product is moistened to convert any anhydride, formed at the high temperature of distillation, into the acid.

3. Discussion

Glutaric acid can be prepared by the hydrolysis of trimethylene cyanide with acids or alkalies;[3] the hydrolysis of methylene dimalonic ester[4] or methylene dicyanoacetic ester;[5] and the oxidation of cyclopentanone with nitric acid[6] or catalytically.[7] Glutaric acid can also be prepared from methylcyclohexane by catalytic oxidation,[8] and from pentamethylene glycol by oxidation with

permanganate.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 496

References and Notes

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3. Reboul, Compt. rend. **82**, 1197 (1876); Ann. chim. phys. (5) **14**, 501 (1878); Markownikov, Ann. **182**, 342 (1876).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ester

cyclic ketone

methylene dimalonic ester

methylene dicyanoacetic ester

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

formalin (50-00-0)

Adipic acid (124-04-9)

nitric acid (7697-37-2)

Cyclohexanone (108-94-1)

vanadium pentoxide

Succinic acid (110-15-6)

potassium hydroxide (1310-58-3)

Trimethylene cyanide (544-13-8)

Cyclopentanone (120-92-3)

ethyl malonate (1071-46-1)

Glutaric acid (110-94-1)

Ethyl propane-1,1,3,3-tetracarboxylate

diethylamine (109-89-7)

ethyl pentanehexacarboxylate

methylcyclohexane (108-87-2)

pentamethylene glycol (111-29-5)

paraformaldehyde (30525-89-4)