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of Organic Compounds

Working with Hazardous Chemicals

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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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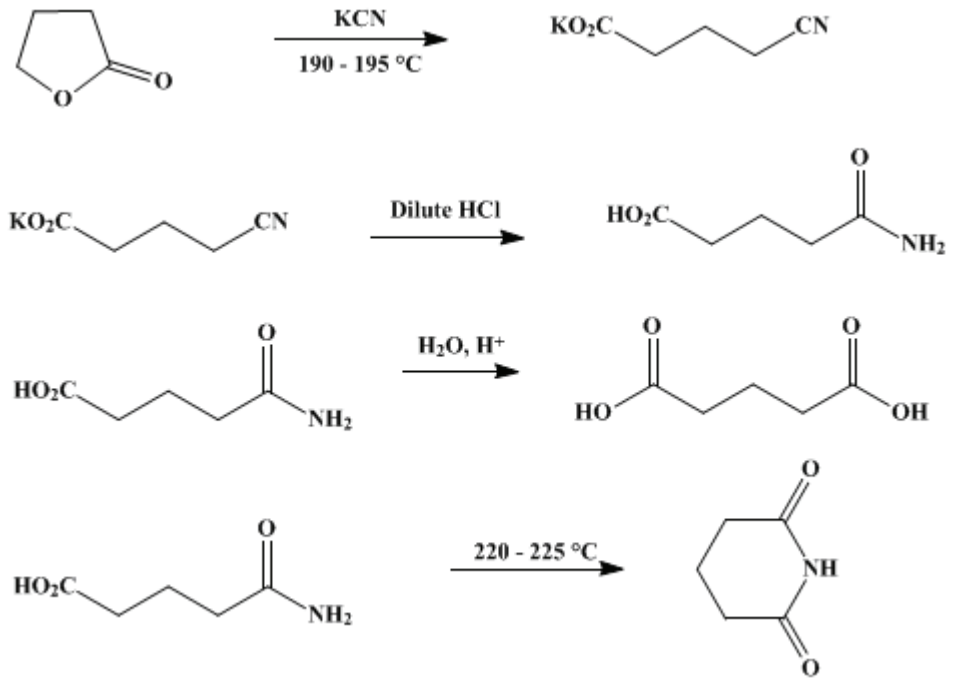
GLUTARIC ACID AND GLUTARIMIDE

[1. FROM γ-BUTYROLACTONE]



Submitted by G. Paris, L. Berlinguet, and R. Gaudry[1].
Checked by James Cason and Edwin R. Harris.

1. Procedure

This preparation should be carried out in a good hood since poisonous hydrogen cyanide may be evolved.

In a 500-ml. three-necked flask fitted with a sealed mechanical stirrer and a reflux condenser are placed 86 g. (1 mole) of γ-butyrolactone (Note 1) and 72 g. (1.1 moles) of potassium cyanide (Note 2). As the contents of the flask are stirred, the mixture is heated in an oil bath for 2 hours at a temperature of 190–195° (Note 3). There is an initial vigorous reaction which soon subsides. After the completion of the heating period the mixture is cooled to about 100°, and the potassium salt of the cyano acid is dissolved in about 200 ml. of hot water. The warm solution is cautiously acidified to Congo red by the addition of about 90 ml. of concentrated hydrochloric acid. The resultant solution, which contains glutaric acid monoamide and potassium chloride, is used to prepare glutaric acid or glutarimide.

A. *Glutaric acid*. To the solution of monoamide is added 200 ml. of concentrated hydrochloric acid, and the mixture is heated under reflux in the hood for 1 hour. The reaction mixture is evaporated to dryness under reduced pressure, and the residue is dried by brief heating on a steam bath at reduced pressure. The residual crystalline solid is broken up, ground in a mortar, and extracted with four 200-ml. portions of boiling chloroform. The combined hot extracts are filtered by gravity through a fluted paper on a heated funnel and then concentrated to about 400 ml. After the solution has been cooled in water to effect crystallization, the glutaric acid is collected by suction filtration, washed with cold chloroform, and dried. The yield of slightly discolored glutaric acid, suitable for many purposes, is 105–110 g. (79.5–83.5%), m.p. 95–97°.

If a pure grade of glutaric acid is desired, it is decolorized by boiling for about 1 hour with 10 g. of

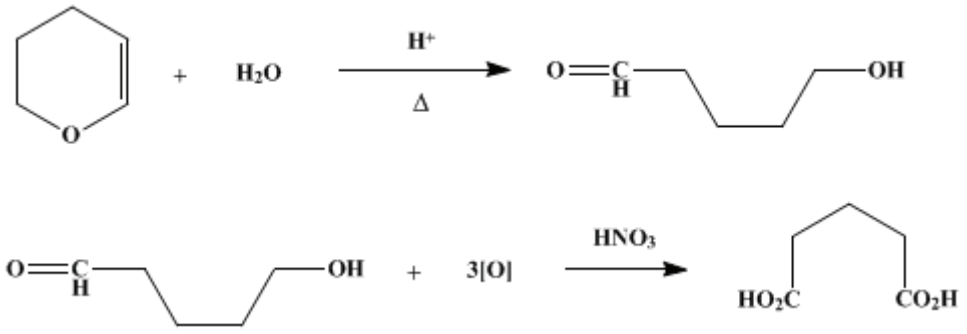
charcoal in water solution. The charcoal is removed by filtration (Note 4), the water is evaporated under reduced pressure, and the dry residue is recrystallized from chloroform. The yield of white glutaric acid, m.p. 98–99°, is 94–99 g. (71–75%).

B. *Glutarimide*. The solution containing the monoamide is extracted with six 50-ml. portions of ether. The ether solution is dried over anhydrous sodium sulfate (or by filtering by gravity through a layer of the drying agent), and then the ether is evaporated by heating on a steam bath; the last portion is removed at reduced pressure. The oily residue of glutaric acid monoamide is placed in a 300-ml. round-bottomed flask which is fitted with a bent tube attached to a short condenser, and the flask is immersed in a bath (Note 5) held at 220–225°. Heating is continued until water no longer distils (3–4 hours). The cooled glutarimide is dissolved in about 200 ml. of water, and the solution is boiled for about 30 minutes with about 2 g. of charcoal. The charcoal is removed by filtration, water is removed by distillation at reduced pressure, and the dry residue is crystallized from about 125 ml. of 95% ethanol, with final cooling in an ice bath. The yield of glittering white crystals of glutarimide, m.p. 152–154°, is 65.5–73.5 g. (58–65%) (Note 6).

2. Notes

1. Butyrolactone from Eastern Chemical Corporation, 34 Spring Street, Newark 2, New Jersey, was used without purification.
2. Satisfactory results were obtained with potassium cyanide, 96–98% purity, from General Chemical Company or with material indicated as of 95% minimum purity, from Merck & Co., Inc. If potassium cyanide pellets are employed, they should be pulverized before use.
3. Since the reaction mixture is acidified after the heating period, it is most convenient to carry out the reaction in a forced-draft hood in order to provide protection against hydrogen cyanide. If higher temperatures than those specified are used, the reaction may get out of control during the initial vigorous reaction.
4. If filtration by gravity through a fluted paper fails to remove the last traces of charcoal, the filtrate should be refiltered by suction through a thin mat of filter aid such as Supercel.
5. The submitters used an oil bath. The checkers used a salt bath consisting of an equimolar mixture of potassium nitrate and sodium nitrite (Heat Transfer Salt). A salt bath should be handled only with proper precautions, which include wearing goggles and gloves and supporting the bath on a stand bolted to the bench.
6. This material is suitable for preparation of N-bromoglutarimide, as follows. In a 1-l. beaker, provided with a mechanical stirrer, 65 g. of potassium hydroxide is dissolved in 200 ml. of water. The vigorously stirred solution is cooled to about −5°, and as the temperature is maintained below 0° there is added gradually 113 g. (1 mole) of glutarimide and cracked ice. To this mixture is added in one portion 160 g. (1 mole) of bromine; then stirring is continued for 1 minute. The mixture is filtered by suction, and the precipitate is dissolved in hot water. On cooling, there crystallizes about 94 g. (49%) of N-bromoglutarimide which melts at about 165°. This product is usually suitable for use as a brominating agent. Pure N-bromoglutarimide, m.p. 180–185°, is obtained only after several recrystallizations from water.

[II. FROM DIHYDROPYRAN]



Submitted by J. English, Jr. and J. E. Dayan[2].

Checked by Arthur C. Cope and Mark R. Kniter.

1. Procedure

In a 1-l. round-bottomed flask equipped with a reflux condenser are placed 400 ml. of 0.2*N* nitric acid (5 ml. of concentrated nitric acid, sp. gr. 1.42, and 395 ml. of water) and 168.3 g. (2 moles) of dihydropyran (Note 1). The mixture is heated on a steam bath or a boiling water bath; the yellowish upper layer dissolves suddenly after 25 to 45 minutes of heating. The flask is swirled to aid the dissolution at this time, and the period of heating is extended for an additional 5 to 10 minutes.

While the hydrolysis of the dihydropyran is taking place, 800 g. (575 ml., 9.25 moles) of concentrated nitric acid (sp. gr. 1.42) is placed in a 2-l. three-necked flask and cooled in an ice-salt bath in a well-ventilated hood. The flask should be equipped with an efficient stirrer, separatory funnel, reflux condenser, and a thermometer. When the temperature of the solution reaches 0°, 5.75 g. of sodium nitrite is added and stirring is continued until most of it has dissolved; the solution becomes yellow.

The solution obtained by the hydrolysis of dihydropyran is placed in the separatory funnel, and about 10 ml. is added to the nitric acid solution at a temperature below 0°. After the evolution of brown nitrogen dioxide fumes begins (in about 10 minutes), the addition is continued at a rate that allows the temperature to be held below 10° (Note 2). The addition requires about 3 hours (Note 3) and (Note 4). When the addition is completed, the blue-green solution is stirred for an additional 1.5 hours as brown fumes continue to be evolved. The cooling bath then is removed and stirring is continued as the temperature is allowed to rise slowly to 25–30° (Note 5). As the reaction nears completion, the color changes from blue-green to green to light yellow. Appearance of the light yellow color indicates the end of the reaction and normally requires 2 to 3 hours after the addition is completed. The volume of the solution then is reduced either by evaporation on a steam bath or by distillation under reduced pressure.

In the latter method, after removal of all the water, an additional 100 ml. of water is added and the distillation is repeated to remove the remaining nitric acid. The solid residue remaining from either method of removing water from the reaction mixture is recrystallized from a mixture of 100 ml. of ether and 1 l. of benzene. Insoluble sodium nitrate and succinic acid are removed by filtration of the hot solution. Upon cooling, 185–198 g. (70–75%) of glutaric acid is obtained in the first crop, m.p. 89.5–91.5° (Note 6). On concentrating the benzene solution to 200 ml. and cooling, an additional 18–23 g. of crude glutaric acid can be obtained (Note 7).

2. Notes

1. Dihydropyran is available from the Electrochemicals Department, E. I. du Pont de Nemours and Company, or can be prepared by the dehydration of tetrahydrofurfuryl alcohol.[3]
2. More efficient cooling may shorten the time required for the addition.
3. As the hydrolyzed dihydropyran solution cools, it may become cloudy and δ-hydroxyvaleraldehyde may separate as a red liquid. The separation can be avoided by continuing to heat most of the solution while a small part is left in the separatory funnel, but it is not essential, for the yield is not affected by the separation of phases at this point. Oxidation of the pure aldehyde in a similar manner is stated to give a 90% yield of glutaric acid.[4]
4. The separatory funnel is removed after the addition is completed to facilitate the removal of nitrogen oxides.
5. Care should be taken that the temperature does not rise above room temperature; if this occurs much succinic acid is produced. If the temperature rises too high the cooling bath should be replaced again until the temperature does not exceed 25–30° on its removal.
6. The glutaric acid obtained has a neutralization equivalent of 66.3 (theory 66.1) and is suitable for most synthetic work.
7. This material melts at 80–82° and can be purified by recrystallization. In a series of preparations it is advantageous to save these residues and combine them for recrystallization.

3. Discussion

Methods of preparation of glutaric acid are given in an earlier procedure.[5] In addition to these, glutaric acid has been obtained by the oxidation of glutaraldehyde in the presence of catalysts,[6] by the ozonization of cyclopentene followed by permanganate cleavage of the ozonide,[7] by the nitric acid oxidation of 2-cyanocy-clopentanone,[8] by the oxidation of pentamethylene glycol with nitrogen tetroxide,[9] and by the condensation of acrylonitrile with ethyl malonate, followed by acid hydrolysis of the mono- and di-adduct.[10]

Glutarimide has been prepared from glutaric acid and sulfamide[11] or formamide,[12] by distillation of ammonium glutarate,[13] by hydrolysis of pentanedinitrile with acetic acid,[14] and by oxidation of piperidine with hydrogen peroxide.[15]

Method I, based on a published procedure,[16] offers a more convenient synthesis of glutaric acid and its imide and may be readily adapted to a large scale.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 824

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

nitrogen oxides

2-cyanocy-clopentanone

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

formamide (75-12-7)

chloroform (67-66-3)

nitric acid (7697-37-2)

hydrogen cyanide (74-90-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

potassium cyanide,
potassium cyanide pellets (151-50-8)

sodium nitrite (7632-00-0)

Succinic acid (110-15-6)

potassium hydroxide (1310-58-3)

piperidine (110-89-4)

hydrogen peroxide (7722-84-1)

nitrogen dioxide (10102-44-0)

pentanedinitrile (544-13-8)

ethyl malonate (1071-46-1)

nitrogen tetroxide

Glutaric acid (110-94-1)

γ-butyrolactone,
Butyrolactone (96-48-0)

pentamethylene glycol (111-29-5)

tetrahydrofurfuryl alcohol (97-99-4)

sodium nitrate

potassium chloride (7447-40-7)

Cyclopentene (142-29-0)

acrylonitrile (107-13-1)

dihydropyran

δ-hydroxyvaleraldehyde (4221-03-8)

Glutarimide (1121-89-7)

glutaric acid monoamide

N-bromoglutarimide (3699-18-1)

glutaraldehyde (111-30-8)

sulfamide (7803-58-9)

ammonium glutarate