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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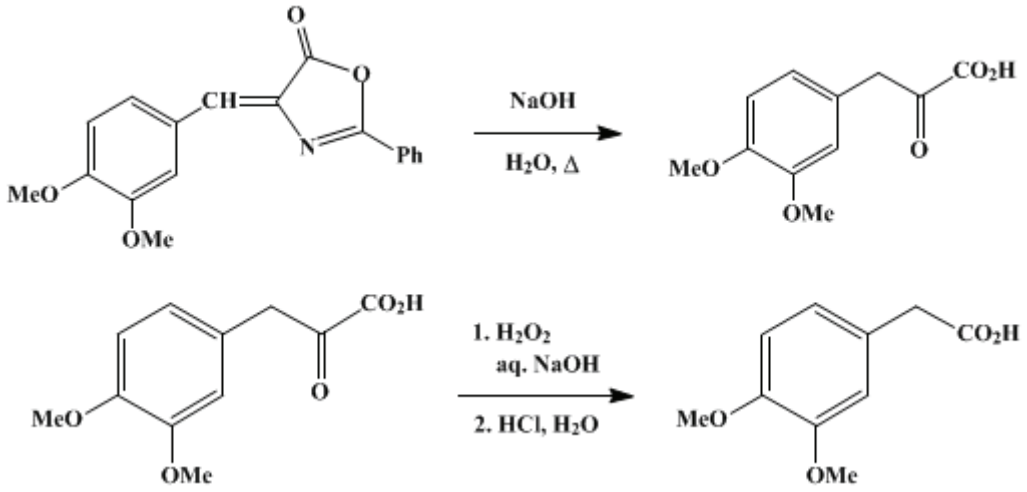
HOMOVERATRIC ACID



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1. Procedure

(*A*) *Methyl Homoveratrate*.—In a 3-l. round-bottomed flask are placed 1 l. of 10 per cent sodium hydroxide solution and 200 g. (0.65 mole) of the azlactone of α-benzoylamino-β-(3,4-dimethoxyphenyl) acrylic acid (m.p. 149–150°) (p. 55). The flask is fitted with a reflux condenser and immersed in an oil bath so that the inner level is lower than the oil level of the bath (Note 1). The mixture is refluxed gently for six to seven hours, until the evolution of ammonia is complete. The resulting solution contains the sodium salts of 3,4-dimethoxyphenylpyruvic acid (Note 2) and benzoic acid.

To the above aqueous solution, contained in a 2-l. wide-mouthed Erlenmeyer flask, is added 85 cc. of 40 per cent sodium hydroxide solution. The flask is equipped with a mechanical stirrer and is cooled in an ice-salt mixture. With stirring, 75 cc. of 30 per cent hydrogen peroxide (Merck's "Superoxol") diluted with 75 cc. of water is added at such a rate that the temperature does not rise above 15°. After standing for about ten hours at room temperature (preferably overnight) the solution is acidified by the cautious addition (Note 3) of 450 cc. of concentrated hydrochloric acid (sp. gr. 1.19). The warm acid solution is extracted with one 400-cc. portion and two 200-cc. portions of warm benzene. The combined benzene extracts are dried over anhydrous magnesium sulfate and filtered through a cotton plug into a 3-l. round-bottomed flask.

The benzene is removed by distillation, 1 l. of methyl alcohol (Note 4) containing 15 cc. of concentrated sulfuric acid is added, and the flask is fitted with an efficient reflux condenser provided with a drying tube. After refluxing gently for five hours the condenser is set downward for distillation and the methyl alcohol is distilled from a steam bath. The residual liquid is cooled and shaken with 500 cc. of cold water. The mixture is transferred to a separatory funnel and extracted with one 400-cc. portion and two 200-cc. portions of benzene. The combined extracts are washed twice with 100-cc. portions of 10 per cent sodium carbonate solution and finally with two 100-cc. portions of water. After the benzene solution has been dried over anhydrous magnesium sulfate, it is transferred to a 2-l. flask and the benzene is distilled, using a steam bath. The residual mixture of methyl benzoate and methyl homoveratrate is transferred to a 250-cc. Claisen flask and distilled under reduced pressure. The first fraction, collected up to 100° at 16 mm., is methyl benzoate (b.p. 87°/16 mm.) and weighs about 75 g. (85 per cent of the theoretical amount). After a small intermediate fraction of 2–3 g., pure methyl homoveratrate is collected at 176–178°/16 mm. or 129–131°/1 mm. The yield is 76–82 g. (56–60 per cent of the theoretical amount based on the azlactone).

(*B*) *Homoveratric Acid*.—In a 500-cc. round-bottomed flask are placed 250 cc. of 10 per cent sodium hydroxide solution and 76 g. (0.36 mole) of methyl homoveratrate. The flask is fitted with a reflux condenser and the mixture is boiled gently. The saponification proceeds rapidly, and the ester layer disappears after about ten minutes. The mixture is refluxed gently for twenty minutes longer, after which the solution is cooled in an ice bath and then poured slowly, with stirring, into a mixture of 125 cc. of concentrated hydrochloric acid and 350 g. of ice. Crystals of the hydrate of homoveratric acid separate at once. After standing for about thirty minutes the crystalline product is filtered with suction and washed on the filter with two 25-cc. portions of ice water. The crystals are pressed thoroughly on the filter, pulverized, and allowed to stand overnight in a vacuum desiccator containing soda lime (to remove residual hydrochloric acid) and calcium chloride. The yield in the saponification is almost quantitative and amounts to 70 g. (55 per cent of the theoretical amount based on the original azlactone). This product melts at 96–97° and contains traces of sodium chloride. For purification it is dissolved in 350 cc. of hot benzene and the solution is filtered. To the hot filtrate is added 150 cc. of hot ligroin (b.p. 70–80°), and the solution is covered with a watch glass and allowed to cool slowly. After standing for several hours (preferably overnight) in a cool place, the crystals are filtered with suction and washed with a cold solution of 35 cc. of benzene and 15 cc. of ligroin, followed by 50 cc. of cold petroleum ether. The solvent is removed as completely as possible by pressing on the filter and finally by allowing the product to stand in a vacuum desiccator (Note 5). The purified homoveratric acid weighs 65 g. (51 per cent of the theoretical amount based on the original azlactone) and melts sharply at 98°.

2. Notes

1. The inner level is kept below that of the oil in order to avoid the otherwise uncontrollable bumping of the solution.
2. 3,4-Dimethoxyphenylpyruvic acid can be isolated from this solution in the following way (J. S. Buck and W. S. Ide). The aqueous solution of the sodium salts is saturated with sulfur dioxide, while the temperature is maintained below 40°. The benzoic acid precipitates and is filtered with suction and washed with a small quantity of water. The filtrate and washings are placed in a 3-l. round-bottomed flask provided with a mechanical stirrer and heated to boiling. Concentrated hydrochloric acid is added cautiously, with stirring, until present in excess. The acid must be added carefully since the solution tends to become supersaturated with sulfur dioxide, which is subsequently liberated with violence. A heavy precipitate of 3,4-dimethoxyphenylpyruvic acid separates; after the reaction mixture has cooled, this is filtered with suction, dried, and washed with two 50-cc. portions of ether. The yield of 3,4-dimethoxyphenylpyruvic acid is 110–116 g. (76–80 per cent of the theoretical amount), and the product melts at 181–184°. It can be purified by crystallization from glacial acetic acid.
An alternative procedure for the preparation of homoveratric acid (J. S. Buck and W. S. Ide) consists in isolating the pyruvic acid and subjecting it to the oxidation given in the second paragraph of part (*A*). This variation obviates the esterification but in the hands of the checkers did not prove so satisfactory as the one described.
3. Large quantities of carbon dioxide are evolved during the addition of the acid.
4. It is unnecessary to use especially dried methyl alcohol. High-grade commercial methanol is quite satisfactory.
5. Since the acid forms a hydrate it is advisable to minimize the exposure of the acid to atmospheric moisture.

3. Discussion

Homoveratric acid has been prepared by the methylation of homoprotocatechuic acid[1] or homovanillic acid[2] with methyl iodide, and from veratric aldehyde through the azlactone and 3,4-dimethoxyphenylpyruvic acid.[3] Homoveratric acid has also been prepared by hydrolysis of its amide or nitrile: the amide was obtained from veratroyl chloride through the diazoketone,[4] or from veratric aldehyde cyanohydrin through α-chlorohomoveratramide;[5] the nitrile was obtained by catalytic reduction of acyl derivatives of veratric aldehyde cyanohydrin.[6]

The procedure given above is adapted from published directions for the preparation of homoveratric acid[3] and *p*-methoxyphenylacetic acid.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 471

References and Notes

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2. Tiemann and Matsmoto, ibid. **11**, 143 (1878).
3. Haworth, Perkin, and Rankin, J. Chem. Soc. **125**, 1693 (1924).
4. Arndt and Eistert, Ber. **68**, 205 (1935).
5. Hahn and Schulz, ibid. **72**, 1302 (1939).
6. Kindler and Peschke, Arch. Pharm. **271**, 432 (1933); Kindler and Gehlhaar, ibid. **274**, 377 (1936).
7. Cain, Simonsen, and Smith, J. Chem. Soc. **103**, 1036 (1913).

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

ligroin

petroleum ether

azlactone of α-benzoylamino-β-(3,4-dimethoxyphenyl) acrylic acid

sodium salts of 3,4-dimethoxyphenylpyruvic acid

hydrate of homoveratric acid

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

methyl alcohol,
methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

Benzoic acid (65-85-0)

carbon dioxide (124-38-9)

hydrogen peroxide (7722-84-1)

Methyl iodide (74-88-4)

methyl benzoate (93-58-3)

Pyruvic acid (127-17-3)

magnesium sulfate (7487-88-9)

veratric aldehyde (120-14-9)

Homoveratric acid (93-40-3)

Methyl homoveratrate (15964-79-1)

3,4-Dimethoxyphenylpyruvic acid (2460-33-5)

homoprotocatechuic acid (102-32-9)

homovanillic acid (306-08-1)

veratroyl chloride (3535-37-3)

veratric aldehyde cyanohydrin

α-chlorohomoveratramide

p-methoxyphenylacetic acid (104-01-8)