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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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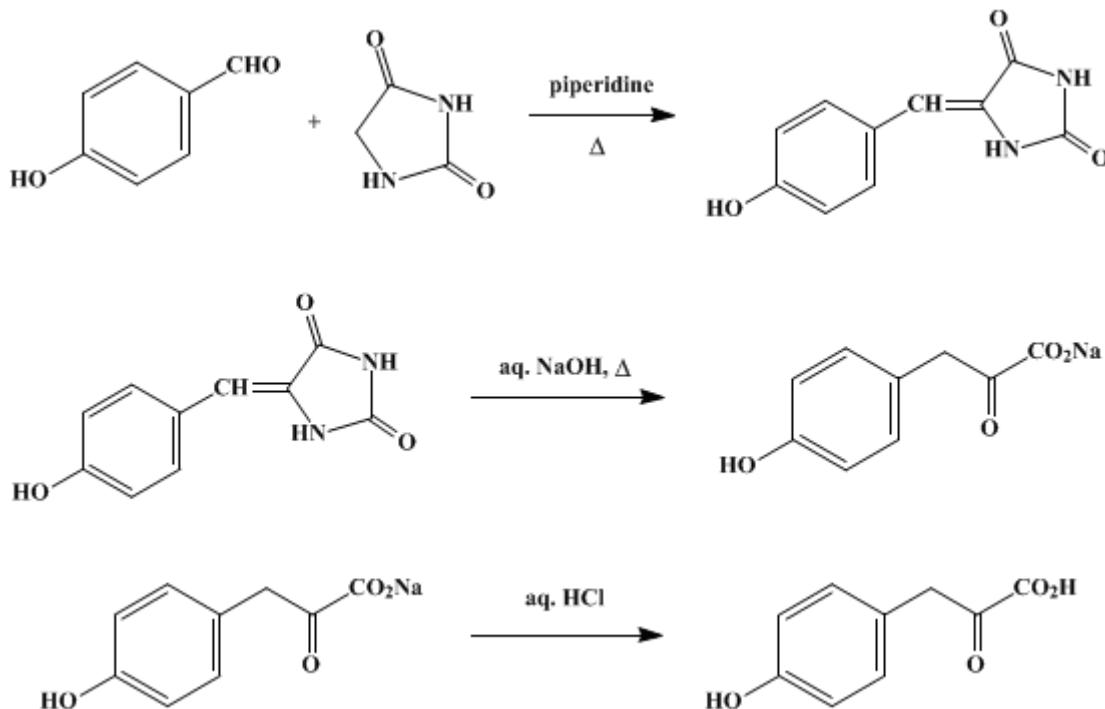
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Organic Syntheses, Coll. Vol. 5, p.627 (1973); Vol. 43, p.49 (1963).

p-HYDROXYPHENYL PYRUVIC ACID

[Pyrvic acid, *p*-hydroxyphenyl-]



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1. Procedure

A. *5-(p-Hydroxybenzal)hydantoin*. An intimate mixture of 6.11 g. (0.050 mole) of *p*-hydroxybenzaldehyde (Note 1) and 5.5 g. (0.055 mole) of hydantoin (Note 2) is placed in a 250-ml. round-bottomed flask. Dry piperidine (10 ml.) is added, a reflux condenser protected by a calcium chloride tube is fitted to the flask, and the flask is immersed in an oil bath so that the level of the reaction mixture is the same as the oil level of the bath. The oil bath is heated slowly to 130° and is held at this temperature for 30 minutes; foaming and gentle boiling occur. The reaction mixture is cooled, and 200 ml. of water at about 60° is added. The contents of the flask are stirred by means of a glass rod until a clear red solution is obtained (Note 3). Any traces of tarry material are removed by filtration. The solution is cooled to room temperature, transferred to an Erlenmeyer flask, and acidified by dropwise addition of 20 ml. of 12*N* hydrochloric acid. The mixture stands at room temperature a few hours, and then the yellow precipitate of *5-(p-hydroxybenzal)hydantoin* is collected on a Büchner funnel and washed thoroughly with cold water (Note 4). After being dried in a vacuum desiccator over potassium hydroxide, the crude hydantoin weighs 8.5–8.8 g. (83–86%). It melts at 310–315° (dec.) and is sufficiently pure for the next step and other preparative purposes (Note 5).

B. *p*-Hydroxyphenylpyruvic acid. Crude *5-(p-hydroxybenzal)hydantoin* (8.5 g., 0.042 mole) and a few chips of porous plate are placed in a 500-ml., three-necked, round-bottomed flask fitted with a reflux condenser, a dropping funnel, and a gas-inlet tube (Note 6). A slow stream of oxygen-free nitrogen (Note 7) is introduced. As soon as the air has been swept out of the apparatus, 240 ml. of 20% aqueous sodium hydroxide solution (w/v) is added through the dropping funnel. The mixture is boiled for 3 hours in an oil bath at 170–180° (Note 8). The *5-(p-hydroxybenzal)hydantoin* dissolves rapidly, and a clear orange solution is obtained that becomes less deeply colored during the reaction. The reaction mixture is cooled by replacing the oil bath by a bath of cold water. Without interrupting the

stream of **nitrogen**, 100 ml. of 12*N* **hydrochloric acid** is added through the dropping funnel at such a rate that foaming and heating of the mixture are not excessive. The flask is disconnected, and 5 g. of **sodium bicarbonate** is dissolved in the mixture (Note 9).

The liquid is transferred to a continuous extractor (Note 10) and extracted with **ether** until the supernatant layer of **ether** remains colorless (about 2 hours). The ethereal extract is discarded (Note 11). The aqueous solution is transferred to a 1-l. beaker and acidified by the cautious addition of 60 ml. of 12*N* **hydrochloric acid** (Note 12). The solution is returned to the extractor, which is attached to a tared round-bottomed flask. The solution is extracted with **ether** until no more *p*-**hydroxyphenylpyruvic acid** is obtained (Note 13). The undried **ether** solution is evaporated to dryness on a boiling water bath to give crude *p*-**hydroxyphenylpyruvic acid** as a pale-yellow crystalline mass. The mass is broken up with a spatula, and the flask is kept over **potassium hydroxide** in a vacuum desiccator until its weight is constant. The yield of crude acid is 6.9–7.2 g. (92–96%). It melts at 210–215° (dec.) (Note 14).

Twelve milliliters of water for each gram of the crude acid (83–86 ml.) is added to the flask, which is then attached to a reflux condenser and immersed in an oil bath at 150°. After 10–20 minutes of boiling, a clear pale-yellow solution is obtained. This is filtered through a fluted filter into an Erlenmeyer flask. After crystallization has started, 8.3–8.6 ml. of 12*N* **hydrochloric acid** (1.2 ml. of acid for each gram of crude acid) is added, and the mixture is allowed to cool slowly to room temperature, during which period it is occasionally agitated. Crystallization is completed by keeping the flask in a refrigerator for at least 10 hours. The product is separated by suction filtration and washed with a small amount of ice water. The purified *p*-**hydroxyphenylpyruvic acid** weighs 4.4–4.7 g. (59–63%) and melts at 216–218° (dec.) (Note 14) and (Note 15).

2. Notes

1. The *p*-**hydroxybenzaldehyde** used was a commercial product (practical grade) melting at 114–117°.
2. **Hydantoin** can be prepared in a variety of ways, notably from **glycine**² or **ethyl aminoacetate**³ and **potassium cyanate**. The checkers used Eastman Kodak "white label" **hydantoin**.
3. Because of the viscous nature of the reaction mixture, which sometimes shows a tendency to crystallize, this is a slow process, but a mechanical stirrer is not required.
4. The checkers found that three or four cold-water washes are sufficient to wash the precipitate to neutral pH.
5. Further purification may be achieved by crystallization from **acetic acid** (50 ml. per g.). A product melting at 315° (dec.) is obtained.
6. The inlet tube, preferably in the center neck, is placed in such a way that it nearly touches the bottom of the flask. Thereby **nitrogen** bubbles effect some agitation of the reaction mixture and prevent bumping of the boiling solution.
7. *p*-**Hydroxyphenylpyruvic acid** is rapidly oxidized in alkaline solution. Commercially available compressed **nitrogen** may be used if the gas is further purified by passage through an alkaline solution of **pyrogallol** (45 g. of **pyrogallol** dissolved in 300 ml. of 50% **sodium hydroxide** solution).
8. This should be done in a hood because **ammonia** is evolved.
9. The purpose of the first extraction is to remove phenolic impurities. Care should be taken to adjust to the proper pH range (6–7). At this pH the solution changes in color from orange to yellow. A small amount of a flocculent precipitate is formed, but, to avoid longer contact of the solution with air, it is not filtered off.
10. A convenient type of extractor is described in *Organic Syntheses*.⁴ The submitter improved the efficiency of the extractor by stirring the aqueous phase with a magnetic stirrer. The inner tube had no filter on the lower end of it and was suspended so that this end was about 1 cm. above the magnetic stirring bar. Tests show that magnetic stirring of the aqueous phase increases the speed of extraction by a factor of 2 to 3. It is convenient to use an extractor of such size that the same apparatus can be used for both extractions. A greater volume of solution must be handled in the second extraction than in the first because of the addition of **hydrochloric acid**.
11. Evaporating the ethereal solution yields not more than 0.3 g. of brown tarry material consisting mostly of impure *p*-**hydroxybenzaldehyde**.
12. **Carbon dioxide** and fumes of **ether** are evolved during the addition of the acid. The solution is stirred by means of a glass rod until the foaming ceases.

13. This is a slow process, and the extraction time depends on the type of extractor used. With stirring as described in (Note 10), practically quantitative extraction of *p*-hydroxyphenylpyruvic acid can be achieved within 6 hours. Extremely long extraction times may cause decomposition of the product.

14. The checkers observed a decomposition point of 198–202° for the crude acid, 211–214° for the purified acid.

15. A second crystallization from 10 parts of water raises the melting point of the acid to 220°. Any prolonged contact of the hot solution with air will cause some decomposition, notably the formation of traces of *p*-hydroxybenzaldehyde. The checkers preferred crystallization from 10 parts of glacial acetic acid and 10 parts of 12*N* hydrochloric acid,⁵ from which solvent a white product was recovered in 75% yield; m.p. 220° (dec.).

The purity of the *p*-hydroxyphenylpyruvic acid may be checked by paper chromatography. By the ascending method on Schleicher and Schüll paper No. 2043b and *n*-butanol-acetic acid-water (4:1:1) as solvent, the following *R*_f values are obtained: *p*-hydroxyphenylpyruvic acid, 0.71; *p*-hydroxybenzaldehyde, 0.85. Sprays: 2,4-dinitrophenylhydrazine (0.2% in 2*N* hydrochloric acid) and Folin-Denis reagent.⁶

3. Discussion

p-Hydroxyphenylpyruvic acid has been prepared by alkaline hydrolysis of the azlactone of α -benzoylamino-*p*-acetoxy-cinnamic acid⁷ and by a two-step hydrolysis of the azlactone of α -acetamino-*p*-acetoxy-cinnamic acid.⁸ *p*-Hydroxyphenylpyruvic acid has also been prepared by alkaline hydrolysis of 5-(*p*-hydroxybenzal)-3-phenylhydantoin.⁹ The procedure described here is adapted from published directions for the preparation of *p*-hydroxyphenylpyruvic-3-C¹⁴ acid.⁵ 5-(*p*-Hydroxybenzal)hydantoin is prepared according to the method of Boyd and Robson.¹⁰

4. Merits of the Preparation

p-Hydroxyphenylpyruvic acid plays an important role in the biogenesis of compounds with a phenylpropane skeleton, and it has been used as substrate in several enzyme studies. Published procedures for its preparation are unsatisfactory in many ways. The alkaline hydrolysis of the azlactone of α -benzoylamino-*p*-acetoxy-cinnamic acid⁷ makes necessary a tedious separation of the resulting benzoic acid, and the yield is only 34% based on *p*-hydroxybenzaldehyde. The hydrolysis of 5-(*p*-hydroxybenzal)-3-phenylhydantoin⁹ requires a separation of phenylurea. Finally, the two-step cleavage of the azlactone of α -acetamino-*p*-acetoxy-cinnamic acid⁸ does not proceed easily, and impure products are obtained. In applying this procedure to the synthesis of a carboxyl-labeled *p*-hydroxyphenylpyruvic acid, the overall yield was only 9%.¹¹ It must be kept in mind that any prolonged isolation procedure will cause some decomposition of this sensitive compound.

The method of preparing *p*-hydroxyphenylpyruvic acid presented here has the advantage that only volatile by-products, ammonia and carbon dioxide, are formed. Therefore the compound can be obtained in high purity and good yield. There are no difficulties in decreasing the amounts of starting materials to the millimole scale, as shown by the application of this procedure to the preparation of labeled *p*-hydroxyphenylpyruvic acid.⁵

Finally, this method is of general utility, for alkaline cleavage of analogously substituted hydantoins has given a series of substituted phenylpyruvic acids.¹²

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 614
- Org. Syn. Coll. Vol. 6, 78
- Org. Syn. Coll. Vol. 6, 1037

References and Notes

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

oxygen-free nitrogen

p-hydroxyphenylpyruvic-3-C¹⁴ acid

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

piperidine (110-89-4)

2,4-Dinitrophenylhydrazine (119-26-6)

Glycine (513-29-1)

Phenylurea (64-10-8)

potassium cyanate (590-28-3)

phenylpropane (103-65-1)

pyrogallol (87-66-1)

hydantoin (461-72-3)

ethyl aminoacetate (459-73-4)

p-hydroxybenzaldehyde (123-08-0)

p-Hydroxyphenylpyruvic acid,
Pyruvic acid, p-hydroxyphenyl- (156-39-8)

5-(p-Hydroxybenzal)hydantoin (80171-33-1)

α -benzoylamino-p-acetoxyccinamic acid

α -acetamino-p-acetoxyccinamic acid

5-(p-hydroxybenzal)-3-phenylhydantoin

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