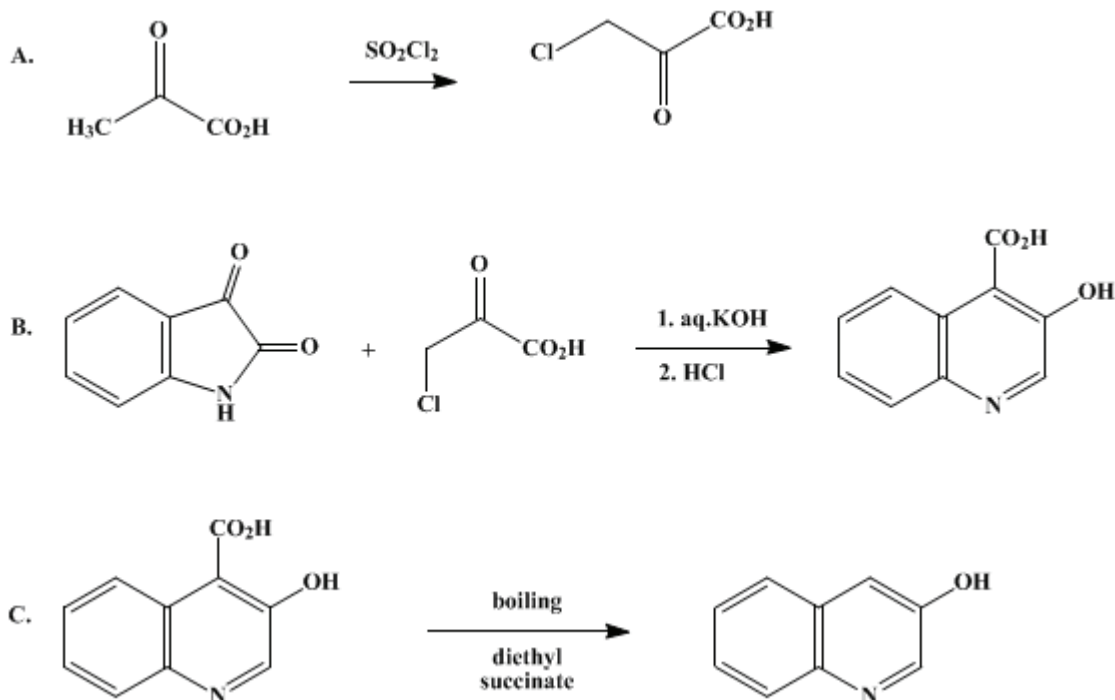


3-HYDROXYQUINOLINE

[3-Quinolinol]



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1. Procedure

Caution! The preparation of chloropyruvic acid should be carried out in a fume hood, as should the purification of 3-hydroxycinchoninic acid and its decarboxylation.

A. *Chloropyruvic acid*. In a 1-l. four-necked flask (Note 1) fitted with a sealed mechanical stirrer, dropping funnel, thermometer, and reflux condenser protected with a calcium chloride tube is placed 249 g. (2.83 moles) of pyruvic acid (Note 2). The stirrer is started and 394 g. (2.92 moles) of sulfonyl chloride (Note 3) is added dropwise over a period of 2 hours. During the addition the temperature is maintained at 25–30° by cooling with a water bath.

The mixture is stirred at room temperature for an additional 60 hours (Note 4), during which time the calcium chloride tube may become spent and need replacement. The viscous, light-yellow liquid product is transferred to a large crystallizing dish and dried in a vacuum desiccator over soda-lime for about 24 hours (Note 5).

The yield of light-yellow chloropyruvic acid is 333–340 g. (96–98%) (Note 6).

B. *3-Hydroxycinchoninic acid*. A 3-l., four-necked flask (Note 1) is equipped with a sealed mechanical stirrer, gas inlet tube, gas outlet consisting of a 1-mm. capillary (Note 7), and thermometer. The flask is charged with a freshly prepared solution containing 448 g. (8 moles) of reagent grade (85% minimum assay) potassium hydroxide and 900 ml. of water. The solution (hot from dissolution of potassium hydroxide) is stirred and 147 g. (1 mole) of isatin (Note 8) is introduced. The solid quickly dissolves to give an orange-yellow solution.

After replacement of the gas outlet the flask is flushed with **nitrogen**, and a **nitrogen** atmosphere is maintained during the remaining operations (Note 9). The temperature is maintained at 20–25° by cooling when necessary. The solution is stirred vigorously as 168.5 g. (1.375 moles) of **chloropyruvic acid** (part A) is added gradually over a period of 2 hours (Note 10). After stirring has been continued for an additional hour, the introduction of **nitrogen** and the stirring are terminated, the flask is stoppered, and the mixture is allowed to stand at room temperature for 6 days.

At the end of the standing period the reaction mixture is cooled with stirring and maintained at 15–18°. A solution containing 34 g. of **sodium bisulfite** in 60 ml. of water (Note 11) is added, and the mixture is made acid to Congo red paper by the dropwise addition of reagent grade concentrated **hydrochloric acid** (Note 12) (approximately 480 ml.). The yellow product that precipitates is separated by suction filtration on a large (at least 15-cm.) Büchner (or sintered-glass) funnel and washed with water saturated with **sulfur dioxide**. Drainage of the filter cake, whose consistency is that of putty, is slow. Pressing with a large cork or use of a rubber dam is helpful. The pressed solid is suspended in 1.3 l. of water previously saturated with **sulfur dioxide**, and the mixture is mechanically stirred for 30 minutes.

After the product has been collected as before, the filter cake is pressed well, suspended in 800 ml. of water, and dissolved by stirring and adding the minimum quantity of reagent grade concentrated aqueous **ammonia** (approximately 60 ml.). A small amount of insoluble material is removed by filtration. A saturated solution of 8 g. of **sodium bisulfite** is added to the filtrate. The orange-yellow solution is stirred mechanically and made acid to Congo red paper by the dropwise addition of reagent grade concentrated **hydrochloric acid** (approximately 80 ml.).

The product is again collected by filtration, washed with water, resuspended in 225 ml. of water, collected, and pressed as dry as possible. The filter cake is thoroughly dispersed in 160 ml. of absolute **alcohol**, then filtered, air-dried, and finally dried in a vacuum desiccator over concentrated **sulfuric acid**. The bright-yellow solid is pulverized and redried. The yield is 115–135 g. (60–71%). When this product is inserted in a bath preheated to 210° and the temperature is increased at a rate of 1° per 10 seconds, decomposition with evolution of gas occurs at 219–220° (cor.) (Note 13).

C. *3-Hydroxyquinoline*. A 1-l. beaker is fitted with a thermometer and mechanical stirrer and clamped firmly on an efficient electric heater (Note 14). **Diethyl succinate** (400 ml.) (Note 15) is placed in the beaker and heated to boiling (215–220°) with stirring. **3-Hydroxycinchonic acid** (part B) (94.6 g., 0.5 mole) is added in portions to the boiling solution by means of a metal spoon or Scoopula. Care is taken to prevent too vigorous evolution of **carbon dioxide**. The addition requires 2–3 minutes, during which time a temperature drop is noted unless good heating is maintained.

Stirring and boiling are continued until complete solution is effected. This requires about 6 minutes (Note 16). The stirrer is withdrawn and the beaker is removed from the hot plate for a few minutes. Finally, the solution is stirred and cooled first in a warm water bath and then in an ice bath. After 30 minutes the gray-brown solid is collected by suction filtration and washed with **hexane**. The product is suspended in 250 ml. of **hexane**, filtered, and washed with **hexane**. After drying, the crude gray-colored **3-hydroxyquinoline** weighs 57–63 g. (79–87%), m.p. 175–191° (cor.).

The crude product is suspended in 190 ml. of water and dissolved by the addition of the minimum quantity (31–35 ml.) of concentrated **hydrochloric acid**. The solution is filtered in order to remove a small amount of insoluble material. The filtrate is treated with **decolorizing carbon** (about 3.5 g.), allowed to stand for 30 minutes, and filtered. The filtrate from the charcoal is stirred and treated dropwise with concentrated aqueous **ammonia** (25–29 ml.) until precipitation is complete. The precipitate is removed by filtration, washed with water (two 30-ml. portions), and dried. The yield at this stage is 48–55 g. of material melting at 185–195° (cor.).

The reprecipitated product is pulverized, dissolved in a boiling mixture of **methanol** (about 420 ml.) and water (about 360 ml.), and treated with decolorizing charcoal for about 10 minutes. The boiling mixture is filtered through a fluted filter paper placed on a large Pyrex funnel resting on a wide-mouthed Erlenmeyer flask containing a little boiling solvent of the same composition. The filtrate is concentrated to incipient precipitation (about 600 ml. volume) and allowed to cool. After drying, the yield of tan-

colored crystalline 3-hydroxyquinoline is 44–47 g. (61–65%), m.p. 199–200° (cor.) (Note 17).

2. Notes

1. If suitable dual outlets are used, a three-necked flask is satisfactory.
2. Pyruvic acid from Matheson, Coleman and Bell was distilled just before use. Material boiling at 46–47° at 4 mm. was employed.
3. Technical grade sulfuryl chloride from Matheson, Coleman and Bell was found satisfactory.
4. The stirring prevents foaming and promotes the evolution of the gases.
5. It is advisable to change the desiccant at least once during the drying period.
6. The chloropyruvic acid prepared in this manner is satisfactory for use in the next reaction without purification. It often crystallizes to form a waxy solid or semisolid which is quite hygroscopic. The pure anhydrous material is reported² to melt at 45°, while the monohydrate obtained by other methods^{3,4,5} melts at 57–58°. The chloropyruvic acid is normally used immediately, but it has been stored successfully in a desiccator at room temperature for a few days or for longer periods in an airtight container in the refrigerator. Material which has been stored for long periods gives poorer yields in the Pfitzinger reaction (part B) than that which has been freshly prepared.
7. When solids are added to the flask, the gas outlet is replaced by a powder funnel and nitrogen flow is increased slightly. If a separatory funnel is used (cf. (Note 10)), a dual outlet is needed.
8. Commercial isatin from Eastman Kodak or Matheson, Coleman and Bell has been used, but poorer yields are obtained (about 10% less) than when purified material is employed. Purification by reprecipitation⁶ or by recrystallization from glacial acetic acid⁶ is equally satisfactory.
9. Maintaining an atmosphere of nitrogen minimizes the darkening of the reaction mixture due to air oxidation.
10. If the chloropyruvic acid remains essentially as a viscous liquid, it may be introduced via a dropping funnel containing a large-bore stopcock. If the material has set up to a waxy solid, it must be introduced in portions through a powder funnel.
11. If no precautions are observed, the reaction mixture rapidly darkens after acidification when exposed to air. The sulfur dioxide generated upon acidification of the sodium bisulfite largely prevents this discoloration; however, the precipitated product should be collected *without delay* of more than a few hours. The sulfur dioxide used in the wash water also protects the product.
12. At about the midpoint in the addition of acid, frothing tends to raise the precipitate out of the flask. Addition of a 1-ml. portion of ether controls the frothing. A second portion of ether may be required later, but the frothing subsides as the addition proceeds.
13. 3-Hydroxycinchoninic acid of this purity is adequate for decarboxylation. A sample recrystallized from dimethylformamide or 5*N* hydrochloric acid decomposes at 224° when observed as described before.
14. It is advantageous to use a mechanical stirrer, but successful reactions have been carried out using manual stirring. A run in which no stirring was employed gave acceptable results.
15. Commercial diethyl succinate from Carbide and Carbon Chemicals Co. or from Eastman Organic Chemicals was found satisfactory. Nitrobenzene has been used successfully a number of times; however, it is considered a less desirable solvent to handle.
16. The heating time is kept to a minimum in order to reduce the darkening of the solution, which increases as the heating time is extended.
17. Once recrystallized, 3-hydroxyquinoline is pure enough for most purposes. One or two more recrystallizations are required to produce white crystals, m.p. 201–202° (cor.).

3. Discussion

The method of synthesis described for chloropyruvic acid is essentially that reported.² This procedure affords the product in excellent yields from readily available materials by a short, convenient route. Other less acceptable methods involve chlorination of pyruvic acid with sulfur dichloride⁷ or hypochlorous acid⁸ and the treatment of ethyl chloro(1-hydroxyheptyl)- or (α -hydroxybenzyl) oxalacetate γ -lactone with 50% hydrochloric acid.^{3,4,5}

The procedure described for the preparation of 3-hydroxycinchoninic acid is adapted from that reported.⁹ This synthesis is successful when bromopyruvic acid or its ethyl ester is substituted for

chloropyruvic acid.⁹ The reaction of isatin with chloropyruvic acid to produce 3-hydroxycinchoninic acid has been reported;¹⁰ however, no details or physical properties were given. This method offers a decided advantage over the method involving diazotization of the difficultly accessible 3-aminocinchoninic acid.¹¹

Until recent years the only syntheses of 3-hydroxyquinoline involved multistep processes, the last step of which consisted of the conversion of 3-aminoquinoline to 3-hydroxyquinoline via the diazonium salt.^{12,13,14} Small quantities of quinoline have been oxidized to 3-hydroxyquinoline in low yields by using oxygen in the presence of ascorbic acid, ethylenediaminetetraacetic acid, ferrous sulfate, and phosphate buffer.¹⁵ The decarboxylation of 3-hydroxycinchoninic acid in boiling nitrobenzene has been reported.^{9,11} The procedure described involves a simplified modification of this method.

References and Notes

1. Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania.
2. M. Garino and I. Muzio, *Gazz. Chim. Ital.*, **52 II**, 226 (1922).
3. H. Gault, J. Suprin, and R. Ritter, *Compt. Rend.*, **226**, 2079 (1948).
4. H. Gault, J. Suprin, and R. Ritter, *Compt. Rend.*, **230**, 1408 (1950).
5. R. Ritter, *Ann. Chim.*, **6** (12), 247 (1951).
6. C. S. Marvel and G. S. Hiers, *Org. Syntheses*, Coll. Vol. **1**, 327 (1951).
7. J. Parrod and M. Rahier, *Bull. Soc. Chim. France*, **1947**, 109.
8. E. A. Shilov and A. A. Yasnikov, *Ukrain. Khim. Zhur.*, **18**, 611 (1952).
9. E. J. Cragoe, Jr., C. M. Robb, and M. D. Bealor, *J. Org. Chem.*, **18**, 552 (1953).
10. Kracker, Luce, and Fitzky, Office of the Publication Board, Department of Commerce, P. B. Report 58,847, frames 782–786 (July 25, 1947).
11. K. C. Blanchard, E. A. Dearborn, and E. K. Marshall, Jr., *Bull. Johns Hopkins Hosp.*, **88**, 181 (1951).
12. W. H. Mills and W. H. Watson, *J. Chem. Soc.*, **97**, 753 (1910).
13. G. Bargellini and M. Settimj, *Gazz. Chim. Ital.*, **53**, 601 (1923).
14. R. Kuhn and O. Westphal, *Ber.*, **73B**, 1105 (1940).
15. B. B. Brodie, J. Axelrod, P. A. Shore, and S. Udenfriend, *J. Biol. Chem.*, **208**, 741 (1954).

Appendix

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

soda-lime

ethyl chloro(1-hydroxyheptyl)- or (α -hydroxybenzyl)oxalacetate γ -lactone

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

sulfur dioxide (7446-09-5)

oxygen (7782-44-7)

nitrogen (7727-37-9)

ferrous sulfate (13463-43-9)

sodium bisulfite (7631-90-5)

carbon dioxide (124-38-9)

decolorizing carbon (7782-42-5)

sulfuryl chloride (7791-25-5)

potassium hydroxide (1310-58-3)

Nitrobenzene (98-95-3)

hypochlorous acid (7790-92-3)

Quinoline (91-22-5)

Isatin (91-56-5)

Pyruvic acid (127-17-3)

sulfur dichloride (10545-99-0)

dimethylformamide (68-12-2)

hexane (110-54-3)

Diethyl succinate (123-25-1)

phosphate

3-Hydroxyquinoline,
3-Quinolinol (580-18-7)

Chloropyruvic acid (3681-17-2)

3-Hydroxycinchoninic acid (118-13-8)

bromopyruvic acid (1113-59-3)

3-aminocinchoninic acid

3-aminoquinoline (580-17-6)

ethylenediaminetetraacetic acid (60-00-4)

ascorbic acid