



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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

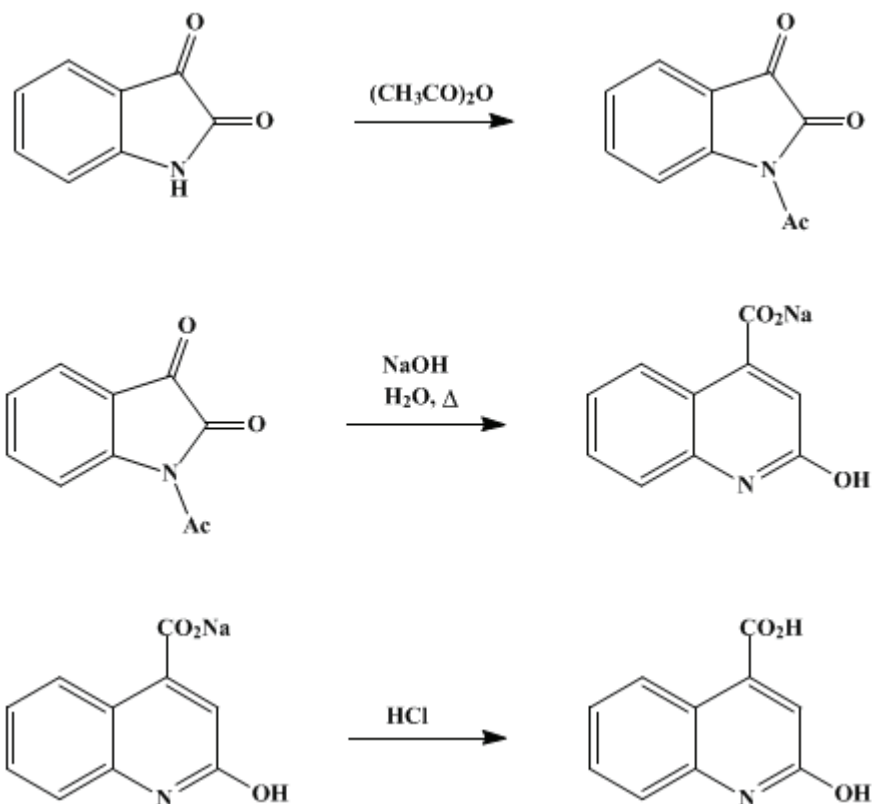
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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2-HYDROXYCINCHONINIC ACID

[Cinchoninic acid, 2-hydroxy-]



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1. Procedure

A. *N-Acetylisatin*. In a 3-l. three-necked flask equipped with a mercury-sealed stirrer and reflux condenser are placed 600 g. (4.1 moles) of *isatin* (Note 1) and 1390 ml. (14.7 moles) of *acetic anhydride* (Note 2). This mixture is refluxed for 4 hours over a free flame with constant stirring. The solution is allowed to cool slowly to room temperature with stirring and is then cooled to about 10° (Note 3). The slurry of crystals is collected on a 12-in. Büchner funnel and washed with five 175-ml. portions of *ether* or until the washings are light red. The yield of crude air-dried *N-acetylisatin*, m.p. 141–142° (cor.), is 635 to 643 g. (82–83%) (Note 4).

B. *2-Hydroxycinchoninic acid*. To a solution of 160 g. (about 3.8 moles) of U.S.P. *sodium hydroxide* in 9.6 l. of water in a 12-l. flask is added 310 g. (1.64 moles) of crude *N-acetylisatin*. The mixture is stirred mechanically and heated to boiling; the flame is adjusted to maintain gentle boiling. After the mixture has boiled 1 hour (Note 5) the flame is removed, 50 g. of *decolorizing carbon* is added cautiously (vigorous boiling and frothing may occur if the solution is too hot), and the suspension is stirred for 30 minutes. The charcoal is allowed to settle for a few minutes, and the solution is siphoned into a filter funnel containing a layer of Supercel. The filtrate is allowed to cool overnight in a 5-gal. crock. The solution is stirred with a hook-type stirrer driven by a powerful motor (Note 6), and 6 *N hydrochloric acid* is added until the mixture is neutral to Congo red. The suspension is filtered immediately (Note 7) through a 12-in. Büchner funnel, and the solid is washed with 2 l. of water. The filtrate is made distinctly acid to Congo red and set aside for a few hours. The solid acid is dried at 90°

for 2 days; the anhydrous acid, m.p. 346–347° (cor.), so obtained has the correct neutral equivalent (Note 8) and weighs 200 to 205 g. (70–73% over-all yield, based on isatin consumed). From the acidified filtrate, after precipitation is complete, about 60 g. of isatin is recovered.

2. Notes

1. Commercial isatin, m.p. 199.0–200.5° (cor.), was obtained from the National Aniline and Chemical Company.
2. Acetic anhydride obtained from the Carbide and Carbon Chemicals Corporation was employed. Redistillation of this reagent did not increase the yield.
3. If the solution is not stirred during the cooling, the product crystallizes as a solid cake which is difficult to remove from the flask.
4. Recrystallization from benzene, unnecessary for the present purpose, gives a yellow crystalline product of m.p. 142.0–143.5° (cor.).
5. It is convenient to make two of these runs simultaneously. A reflux condenser is unnecessary, but if none is used the stopper holding the stirrer must be provided with a vent to permit steam to escape.
6. The ordinary small laboratory stirring motor is insufficiently powerful to maintain rapid agitation after most of the cinchoninic acid has precipitated.
7. If the mixture is not filtered immediately after acidification, or if the first end point is overrun, isatin is precipitated along with the cinchoninic acid and the product has a deep red color. Such material can be freed of isatin by dissolving it in sodium bicarbonate solution, filtering, and reprecipitating.
8. This crude acid, which is satisfactory for most purposes, can be recrystallized from glacial acetic acid to yield a product melting at 352–353° (cor.).

3. Discussion

2-Hydroxycinchoninic acid has been prepared by the rearrangement of N-acetylisatin in alkali,^{2,3,4} by the treatment of isatin with malonic acid in glacial acetic acid,⁵ by heating cinchoninic acid with concentrated potassium hydroxide,⁶ and by the treatment of ethyl 2-chlorocinchoninate with 30% sodium hydroxide.⁷

References and Notes

1. Work done under contract with the Office of Scientific Research and Development.
2. Camps, *Arch. Pharm.*, **237**, 659 (1899).
3. Ainley and King, *Proc. Roy. Soc. London*, **125B**, 60 (1938).
4. Campbell and Kerwin, *J. Am. Chem. Soc.*, **68**, 1837 (1946).
5. Borsche and Jacobs, *Ber.*, **47**, 354 (1914).
6. Koenigs and Koerner, *Ber.*, **16**, 2152 (1883).
7. Thielpape, *Ber.*, **71B**, 387 (1938); Ger. pat 670,582 [*C. A.*, **33**, 6348 (1939)].

Appendix

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

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

Isatin (91-56-5)

Malonic acid (141-82-2)

2-Hydroxycinchoninic acid,
Cinchoninic acid, 2-hydroxy- (15733-89-8)

N-Acetylisatin (574-17-4)

cinchoninic acid (486-74-8)

ethyl 2-chlorocinchoninate