



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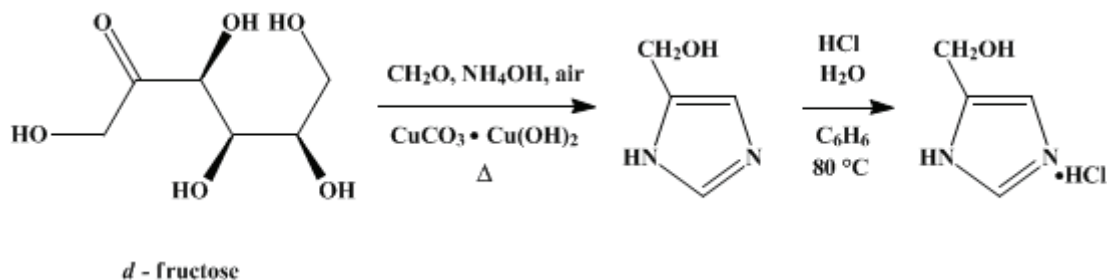
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 3, p.460 (1955); Vol. 24, p.64 (1944).*

## 4(5)-HYDROXYMETHYLIMIDAZOLE HYDROCHLORIDE

### [4-Imidazolemethanol, hydrochloride]



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Checked by H. R. Snyder and R. L. Rowland.

### 1. Procedure

A. *Hydroxymethylimidazole picrate*. To 222 g. (1 mole) of basic cupric carbonate (Note 1) in a 5-l. flask are added 1.5 l. of distilled water and 720 g. (800 ml., 12 moles) of 28% ammonia. The bulk of the copper carbonate is brought into solution by swirling; 112 g. (100 ml., 1.3–1.4 moles) of 37–40% formaldehyde and 90 g. (0.475 mole) of commercial 95% fructose are added. The solution is well mixed and placed on a steam bath under a hood. After 30 minutes of heating with occasional shaking, a moderate current of air is bubbled through the solution (500–600 ml. per minute) (Note 2), with continued heating, for 2 hours longer (Note 3).

The mixture is then chilled in an ice bath for at least 3 hours, and the olive-brown precipitate of the sparingly soluble copper complex of imidazole derivatives is filtered. The product is washed with about 500 ml. of cold water, suspended while moist (Note 4) in 1 l. of water, and rendered just acid to litmus by the addition of concentrated hydrochloric acid (about 40 ml.). Hydrogen sulfide is then passed into the suspension, with frequent shaking, until precipitation of the copper is complete (2–3 hours). The precipitate is filtered and extracted with 500 ml. of hot water in two or three portions. The clear, light-brown to reddish brown filtrate and washings are boiled for 15 minutes, and then 60 g. (0.26 mole) of picric acid is added with stirring; heating is continued until solution is complete.

The greenish yellow plates, which separate as the solution is cooled to room temperature, are filtered, washed 3 times with 150- to 200-ml. portions of water, and air-dried. The filtrate and first washings are combined and heated, 10 g. of picric acid is added, and the mixture is cooled and filtered. This process is repeated, using 10-g. portions of picric acid, until the air-dried picrate fraction so obtained melts below 195° (Note 5).

All fractions melting above 200° (Note 5) are combined and recrystallized from water by adding 700 ml. of water for each 30 g. of crystals, heating the mixture in a covered beaker until solution occurs, treating with charcoal, and filtering through a warm funnel. The crystals deposit upon the slightest cooling. After cooling, the yellow needles (occasionally plates) are filtered, washed, and air-dried; their melting point is 204° or higher, with decomposition (Note 5). The fractions melting at 195–200° (Note 5) are recrystallized in like manner until the melting point is raised to 203°. The yield of crude picrate is 95–100 g. (61–64%); of recrystallized picrate, 84–94 g. (54–60%) (Note 6). The melting point varies slightly with the rate of heating between 203.5° and 206° with decomposition (Note 5).

B. *Hydroxymethylimidazole hydrochloride*. One hundred and twenty grams (100 ml., 1.2 moles) of 37% hydrochloric acid, 250 ml. of water, and 500 ml. of benzene are placed in a 2-l. round-bottomed flask, which is then immersed in a water bath maintained at 80°. One hundred grams of the pure picrate (0.306 mole) is added to this mixture, and the flask is shaken thoroughly until the picrate dissolves. The benzene layer is decanted. The aqueous layer is then extracted 5 times with 330-ml. portions of benzene,

treated with about 3 g. of [Norit](#), and filtered through a wet filter paper. The clear, pale yellow filtrate is evaporated to dryness at 60–70° under reduced pressure. The resulting pale yellow to slightly brown crystals are taken up in the minimum quantity (30–35 ml.) of hot absolute [ethanol](#). Colorless needles deposit on cooling. Three to four volumes of [ethyl ether](#) are added, and the mixture is kept in the refrigerator overnight. The almost colorless needles are filtered and, after being washed with a small amount of [ether](#), are dried in a vacuum desiccator. The yield amounts to 37–39 g. (90–95%) of a product which melts at 107–109° after sintering a few degrees lower ([Note 6](#)).

## 2. Notes

1. Equally good results are obtained with technical or pure grades of basic copper carbonate,  $\text{CuCO}_3 \cdot \text{Cu}(\text{OH})_2$ . Satisfactory results are obtained also when the reagent is prepared by adding an equivalent amount of a solution of [sodium carbonate](#) to a solution of [copper sulfate](#) and washing the resulting precipitate until it is nearly free of sulfate ion. When the reagent is prepared in this way, 4 moles of [copper sulfate](#) are used for each mole of [fructose](#), and the wet basic [cupric carbonate](#) is used without drying or weighing.
2. If the aeration is omitted, the yield is about 10% lower.
3. No attempt is made to recover [ammonia](#) which escapes during the aeration.
4. The copper precipitate can be dried unchanged but is then difficult to decompose with [hydrogen sulfide](#).
5. One to three such additions usually are necessary. The melting points given are those of the submitters and were observed by immersing the capillary melting-point tubes containing the samples in a bath preheated to a temperature 20° to 50° below the expected melting point and heating rather rapidly. The checkers determined the melting points in the ordinary manner, starting with the bath at room temperature, and observed melting points about 5° lower than those of the submitters. In one of the checkers' preparations the main fraction of crude picrate weighed 86 g. and melted at 193–194°; the second fraction weighed 12 g. and melted at 191–193°; the third fraction, which melted at 186–188°, was rejected. One recrystallization raised the melting point of the first fraction to 199° (75 g. recovered) and that of the second fraction to 197° (9.5 g. recovered). The once-recrystallized products were combined and employed in the preparation of the hydrochloride, which was obtained in the yield described and with a melting point of 107–108°.
6. Equally good yields are obtainable with double the quantities indicated.

## 3. Discussion

4(5)-Hydroxymethylimidazole has been synthesized in a long series of steps from [citric acid](#).<sup>1</sup> Weidenhagen and Herrmann prepared it from [dihydroxyacetone](#).<sup>2</sup> The reaction which provides the basis of the procedure here described<sup>3</sup> was discovered by Parrod<sup>4</sup> and developed by Weidenhagen, Herrmann, and Wegner.<sup>5</sup> The method developed by these last-named investigators, however, provides considerably smaller yields than that described above.

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## References and Notes

1. Pyman, *J. Chem. Soc.*, **99**, 668 (1911); Koessler and Hanke, *J. Am. Chem. Soc.*, **40**, 1716 (1918).
  2. Weidenhagen and Herrmann, *Ber.*, **68**, 1953 (1935).
  3. Darby, Lewis, and Totter, *J. Am. Chem. Soc.*, **64**, 463 (1942).
  4. Parrod, *Bull. soc. chim. France*, (4) **51**, 1424 (1932).
  5. Weidenhagen, Herrmann, and Wegner, *Ber.*, **70**, 570 (1937).
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## Appendix

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

4(5)-Hydroxymethylimidazole hydrochloride

copper complex of imidazole

copper carbonate,  $\text{CuCO}_3 \cdot \text{Cu}(\text{OH})_2$

4(5)-Hydroxymethylimidazole

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether,  
ethyl ether (60-29-7)

citric acid (77-92-9)

formaldehyde (50-00-0)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

copper sulfate (7758-98-7)

Norit (7782-42-5)

picric acid,  
picrate (88-89-1)

dihydroxyacetone

fructose (57-48-7)

4-Imidazolemethanol, hydrochloride (32673-41-9)

cupric carbonate,  
copper carbonate

Hydroxymethylimidazole picrate

Hydroxymethylimidazole hydrochloride