



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.

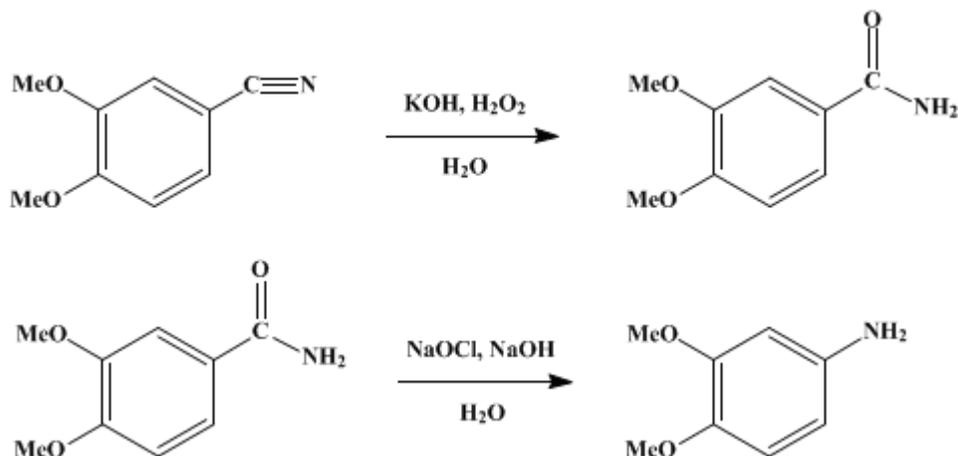
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 2, p.44 (1943); Vol. 16, p.4 (1936).

4-AMINOVERATROLE

[Aniline, 3,4-dimethoxy-]



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1. Procedure

In a 5-l. flask fitted with a mechanical stirrer are placed 1.8 kg. (1.6 moles) of fresh 3 per cent hydrogen peroxide solution, 100 g. of 25 per cent potassium hydroxide solution, and 57 g. (0.35 mole) of veratronic nitrile (p. 622). The mixture is warmed slowly to 45°, with stirring, and the source of heat is then withdrawn. The reaction proceeds with evolution of oxygen, and the temperature continues to rise (Note 1). The amide soon begins to separate; in about fifty minutes the reaction is complete and the temperature begins to fall. The mixture is cooled to 3–5° and allowed to remain in the cooling bath for one and one-half to two hours. The white crystalline product is filtered with suction and dried in the air. The veratric amide melts at 162.5–163.5° and weighs 55–58 g. (87–92 per cent of the theoretical amount).

An alkaline solution of sodium hypochlorite is prepared by passing chlorine (0.412 gram for each gram of the amide) (Note 2) into a mixture of 300 g. of cracked ice and a cold solution of 80 g. of sodium hydroxide in 500 cc. of water, contained in a 2-l. round-bottomed flask. The whole of the veratric amide (55–58 g.) is added in one portion, and the mixture is warmed slowly in a water bath, with mechanical stirring. The material soon darkens in color, and at 50–55° (internal temperature) oily droplets begin to separate. The temperature is raised gradually to 70° and maintained at this point for one hour. A solution of 120 g. of sodium hydroxide in 120 cc. of water is added slowly, and the temperature is increased to 80° for an additional hour.

Upon cooling the mixture, the oily layer of amine solidifies to a red crystalline mass. The crude amine is filtered with suction, washed with two 60-cc. portions of ice-cold water, pressed thoroughly, and transferred to an ordinary 125-cc. Claisen flask. The filtrate is extracted with three 60-cc. portions of benzene, the extracts are transferred separately to the Claisen flask, and the benzene is distilled at atmospheric pressure (Note 3). The residual amine is distilled under reduced pressure and is collected at 172–174°/24 mm. (Note 4). The distillate solidifies quickly to a mass of colorless crystals which melt sharply at 87.5–88° (Note 5). From 58 g. (0.32 mole) of veratric amide there is obtained 39–40 g. (80–82 per cent of the theoretical amount) of 4-aminoveratrole.

2. Notes

1. A large amount of frothing occurs, and the temperature rises to 52–55° during the reaction. The flask

should be removed at intervals and shaken by hand to bring the material carried up by the froth into contact with the solution.

2. The quantity of [chlorine](#) indicated is 5 per cent more than the theoretical amount. The [chlorine](#) may be obtained from a cylinder, but for small amounts it is more accurate to generate [chlorine](#) by treating a weighed amount of [potassium permanganate](#) with an excess of concentrated [hydrochloric acid](#) (0.367 g. $\text{KMnO}_4 \rightleftharpoons 0.412 \text{ g. Cl}_2$). For 55–58 g. of [veratric amide](#) the weight of [permanganate](#) to be used is 20.2–21.3 g.

For generating the [chlorine](#), the requisite weight of [potassium permanganate](#) is placed in a 500-cc. distilling flask fitted with a separatory funnel and suspended so that the flask can be agitated. Concentrated [hydrochloric acid](#) (about 130 cc. is required) is allowed to drop slowly upon the permanganate crystals, and as the reaction progresses the flask is heated. After all the acid has been added the mixture is boiled gently for a few minutes to expel the last portions of [chlorine](#), and the delivery tube is removed rapidly from the alkaline hypochlorite solution to prevent the solution from being sucked back into the generator. A safety bottle should be inserted between the side tube of the generator and the tube which delivers the [chlorine](#) into the alkali.

3. Distillation of the [benzene](#) extracts in this way serves to remove the water, and in the subsequent distillation of the amine no watery fore-run is obtained.

4. Since the [aminoveratrole](#) tends to solidify in the side tube of the distilling flask, it is advisable to distil the material rapidly and to employ a bath temperature about 60° higher than that of the distilling vapor. Care must be taken to avoid contaminating the distillate with a small amount of colored material which comes over if the distillation is carried too far.

5. The melting point of [4-aminoveratrole](#) obtained by reduction of [4-nitroveratrole](#) is reported as $85\text{--}86^\circ$.¹ The amine discolors on exposure to air and light; it should be stored in a sealed, dark container.

3. Discussion

[4-Aminoveratrole](#) has been prepared by the reduction of [4-nitroveratrole](#) with [tin](#),^{1, 2} or [stannous chloride](#),³ and [hydrochloric acid](#). The present procedure is based upon a method used for the preparation of aminopiperole ([3,4-methylenedioxyaniline](#)).⁴

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 2, 619](#)

References and Notes

1. Moureu, Bull. soc. chim. (3) **15**, 647 (1896).
2. Simonsen and Rau, J. Chem. Soc. **113**, 28 (1918); Pollecoff and Robinson, *ibid.* **113**, 645 (footnote) (1918).
3. Heinisch, Monatsh. **15**, 232 (1894).
4. Rupe and Majewski, Ber. **33**, 3401 (1900).

Appendix

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

aminopiperole

[hydrochloric acid](#) (7647-01-0)

[Benzene](#) (71-43-2)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

oxygen (7782-44-7)

tin (7440-31-5)

stannous chloride

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

hydrogen peroxide (7722-84-1)

permanganate

sodium hypochlorite (7681-52-9)

4-Aminoveratrole,
Aniline, 3,4-dimethoxy- (6315-89-5)

Veratronitrile (2024-83-1)

Veratric amide (1521-41-1)

aminoveratrole

4-nitroveratrole (709-09-1)

3,4-methylenedioxyaniline (14268-66-7)