



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.

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.

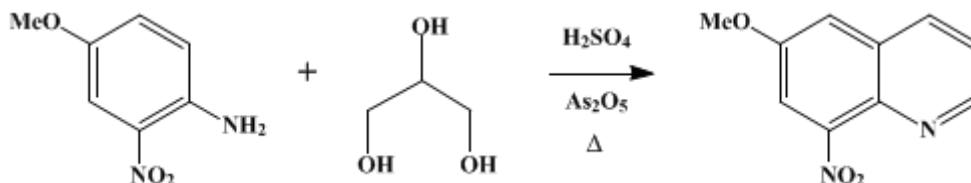
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

*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.568 (1955); Vol. 27, p.48 (1947).*

## 6-METHOXY-8-NITROQUINOLINE

[Quinoline, 6-methoxy-8-nitro-]



Submitted by Harry S. Mosher, William H. Yanko, and Frank C. Whitmore.

Checked by R. L. Shriner, C. E. Kaslow, and Mason Hayek.

### 1. Procedure

*This preparation must be carried out with careful attention to the times and temperatures specified, since Skraup reactions are likely to become violent. The operator should wear goggles, and there should be a safety shower close at hand.*

In a 5-l. three-necked round-bottomed flask, a homogeneous slurry of the following compounds is made by mixing in the order given (Note 1): 588 g. (2.45 moles) of powdered arsenic oxide (Note 2), 588 g. (3.5 moles) of 3-nitro-4-aminoanisole (Note 3), and 1.2 kg. (950 ml., 13 moles) of u.s.p. glycerol. The flask is fitted with an efficient mechanical stirrer and a 500-ml. dropping funnel in which is placed 315 ml. (579 g., 5.9 moles) of concentrated sulfuric acid (sp. gr. 1.84). With good mechanical stirring the sulfuric acid is dropped into the orange reaction mixture over a period of 30–45 minutes. During this addition, the temperature spontaneously rises to 65–70°.

The stirrer and dropping funnel are removed, and a thermometer is inserted in one neck of the flask by means of a stopper so that the bulb is well below the surface of the reaction mixture. A 10-mm. bent glass tube is attached to the second neck by a rubber stopper and attached through a trap to a water aspirator (Note 4). The third neck is closed with a stopper, and the flask and its contents are weighed. The flask, clamped in place in an oil bath which rests on a hot plate (Note 5), is evacuated, and heat is carefully applied at such a rate that the internal temperature slowly rises to 105° (Note 6). The mixture is kept between 105° and 110° until the loss in weight amounts to 235–285 g. (Note 7), which requires approximately 2–3 hours, depending on the efficiency of the aspirator. If the temperature shows any tendency to rise above 110°, the oil bath should be lowered and the mixture cooled.

When the removal of the water is complete, the suction tube is removed and the stirrer and dropping funnel are replaced. The internal temperature is raised with extreme care to 118° and is held rigidly between 117° and 119° during the subsequent addition of 438 g. (236 ml.) of concentrated sulfuric acid (sp. gr. 1.84) from the dropping funnel. The sulfuric acid must be added dropwise over a period of 2.5–3.5 hours, and the temperature *must not* vary from 117–119° (Note 8). After the addition is complete the temperature is maintained at 120° for 4 hours (Note 9) and finally at 123° for 3 hours. The reaction mixture is cooled below 100°, diluted with 1.5 l. of water, and allowed to cool overnight, preferably with stirring (Note 10). The diluted reaction mixture is poured with stirring into a mixture of 1.8 l. (1580 g.) of concentrated ammonium hydroxide (sp. gr. 0.9) and 3.5 kg. of ice in a 12-l. enameled pail. The resultant thick slurry is filtered through a large Büchner funnel (24–30 cm.), and the filtrate is discarded. The earth-colored precipitate is washed with four 700-ml. portions of water and then transferred to a 3-l. beaker and stirred with 1 l. of methanol for 15 minutes. The slurry is filtered and this process repeated (Note 11). The crude product at this point is a light chocolate brown and weighs about 800 g. when dried. It is purified by boiling for 30 minutes with 4.5 l. of chloroform (Note 12) to which has been added 30 g. of decolorizing carbon. The carbon and other humus-like material are removed by filtration from the hot chloroform solution by means of a 24-cm. warm Büchner funnel. The insoluble material is

boiled with 500 ml. of [chloroform](#), the resultant mixture filtered, and the combined filtrates concentrated by distillation from a steam bath to a volume of 1.5–2.5 l., at which point crystals of the [6-methoxy-8-nitroquinoline](#) separate. The solution is then cooled to 5°, and the first crop of crystals is obtained by collection on a 24-cm. Büchner funnel. The crystals are transferred to a 1-l. beaker, stirred with 400 ml. of [methanol](#) for 15 minutes, and again collected on a Büchner funnel and washed with 200 ml. of [methanol](#). The product consists of light-tan crystals which weigh 435–500 g. and melt at 158–160° ([Note 13](#)). By concentrating the filtrate to 400–500 ml., a second crop of crystals weighing 25–65 g. is obtained which, after washing with [methanol](#) in the same way as above, melts at 158–159°. The total yield is 460–540 g. (65–76%) ([Note 14](#)), ([Note 15](#)).

## 2. Notes

1. It is desirable to carry out the reaction without interruption. In order to do this, it is best to set up the apparatus and mix the [arsenic oxide](#), [3-nitro-4-aminoanisole](#), and [glycerol](#) on one day and start the [sulfuric acid](#) addition the first thing in the morning of the following day. If the reaction must be interrupted, the mixture can be allowed to cool after it has been heated under reduced pressure. The yield is not affected, but great care must be exercised in reheating the reaction mixture since it sets to a glass, and it is very easy to superheat the outer portions while the center is still cold. If this happens, vigorous decomposition is very likely to occur.
2. Although powdered [arsenic oxide](#) was used, probably an equivalent amount of any form of the oxide, such as syrupy [arsenic acid](#), would be suitable since the excess water would be removed when heated under reduced pressure.
3. The [3-nitro-4-aminoanisole](#) was the technical commercial product, m.p. 124–126°, obtained from E. I. du Pont de Nemours and Company.
4. It is desirable to have a manometer in the system. The pressure should drop to approximately 30 mm. as the temperature approaches 105°. If, during the initial evacuation, foaming occurs, it will be necessary to loosen the stopper on the reaction flask or trap and let in air until foaming subsides and steady bubbling commences.
5. The oil bath can be heated by a hot plate which is connected in series to a variable resistance for temperature control. It may be heated with a Bunsen burner, but the temperature of the reaction must then be watched continually. The flask should be clamped in place in such a manner that the source of heat can be removed quickly if necessary.
6. The external temperature may be kept at about 110–115° but should not be raised above this, particularly after the internal temperature has reached 105°. If the temperature rises uncontrolled at this point, complete decomposition of the reaction mixture will result.
7. The loss in weight is dependent upon the quality of the [arsenic oxide](#) and [glycerol](#) used. If these are dry, the weight loss should be as indicated. The lower figure is equivalent to 1 mole of water for each mole of [glycerol](#).
8. The success of the reaction depends upon the temperature control at this and subsequent points. Since the temperature is dependent upon at least four variables—the rate of addition of [sulfuric acid](#), the rate of stirring, the heat of reaction which decreases as the reaction proceeds, and the heat applied—the temperature must be watched very closely. Too rapid addition of the [sulfuric acid](#) during the initial stages of the addition will result in an uncontrolled rise in temperature, terminating in the complete oxidation of the reaction mixture by the [sulfuric acid](#). A large volume of [sulfur dioxide](#) is evolved, and the reaction mixture is converted into a voluminous, porous, [carbon](#) mass. *The progress of the reaction must be watched throughout its complete course and cannot be left unattended.*
9. The reaction is complete when a drop of the mixture on a piece of wet filter paper does not give an orange ring due to the presence of unreacted [3-nitro-4-aminoanisole](#). If the test is still positive at the end of the heating period, the temperature should be cautiously raised to 125° and heating continued until the test is negative. If the reaction does not go to completion, it is very difficult to remove this unused starting material from the product and it must be repeatedly decolorized and recrystallized.
10. On cooling, the sulfate salt of the 6-methoxy-8-nitroquinoline partially crystallizes from the reaction mixture. By stirring the mixture, the product comes down as a fine tan, microcrystalline precipitate. This can be isolated and crystallized, but it is more convenient to work it up in the form of the base.
11. These [methanol](#) washings remove much of the impurities, especially small amounts of unreacted [nitroanisidine](#), with a minimum loss of product. The solubility of [6-methoxy-8-nitroquinoline](#) in [methanol](#) at room temperature is 0.8 g. per 100 g. of solvent and at the boiling point is 4.1 g. per 100 g.

of solvent. The solubility in [chloroform](#), on the other hand, is 3.9 g. per 100 g. of solvent at room temperature and 14.2 g. at the boiling point. It is possible to obtain about 12 g. of product by working up these washings, but it is usually not worth the trouble.

12. The 4.5 l. of [chloroform](#) used is more than is necessary to dissolve the product, but this amount prevents the difficulties arising from crystallization in the Büchner funnel during filtration.

13. If, during the reaction, the temperature has not been properly regulated, the crystals may require another treatment with [decolorizing carbon](#) and crystallization from [chloroform](#).

14. The product may also be recrystallized from hot [ethylene dichloride](#) using 300 ml. of solvent for each 100 g. The recovery is 80–90% of [6-methoxy-8-nitroquinoline](#) melting at 160–161°.

15. By the same procedure the submitters have prepared [6-ethoxy-8-nitroquinoline](#) in 70% yield, [8-methoxy-6-nitroquinoline](#) in 68% yield, [6-chloro-8-nitroquinoline](#) in 75% yield, and [6-methoxy-5-bromo-8-nitroquinoline](#) in 69% yield from the properly substituted aromatic amines.

### 3. Discussion

[6-Methoxy-8-nitroquinoline](#) was first obtained by Schulemann and coworkers<sup>1</sup> by a modification of the Skraup reaction. Various other modifications of this reaction have been used.<sup>2,3,4,5,6,7,8,9</sup> The modification given here was the best of several tried and is taken from the procedure of Strukov.<sup>10</sup> It has been reported that 85% [phosphoric acid](#) may be used in place of [sulfuric acid](#) in certain Skraup reactions; thus with [3-nitro-4-aminoanisole](#), [acrolein](#), and [arsenic trioxide](#), with 85% [phosphoric acid](#), a 60% yield of [6-methoxy-8-nitroquinoline](#) was obtained.<sup>11</sup> A preparation from [α-bromoacrolein](#) has been reported.<sup>12</sup>

---

### References and Notes

1. Schulemann, Schuenhöfer, and Winger, Ger. pat. 486,079 [*C. A.*, **24**, 1937 (1930)]; F. Bayer and Co., Brit. pat. 267,457 [*C. A.*, **22**, 1216 (1928)].
2. Magidson and Strukov, *Arch. Pharm.*, **271**, 359 (1933).
3. Fourneau, Trefouel, Bovet, and Benoit, *Ann. inst. Pasteur*, **46**, 514 (1931).
4. Altman, *Rec. trav. chim.*, **57**, 941 (1938).
5. Brahmachari and Bhattacharyee, *J. Indian Chem. Soc.*, **8**, 571 (1931).
6. Misani and Bogert, *J. Org. Chem.*, **10**, 347 (1945).
7. Morgan and Tipson, *J. Am. Chem. Soc.*, **68**, 1569 (1946).
8. Yale, *J. Am. Chem. Soc.*, **69**, 1230 (1947).
9. Haskelberg, *J. Org. Chem.*, **12**, 434 (1947).
10. Strukov, *Org. Chem. Ind. U.S.S.R.*, **4**, 523 (1937) [*C. A.*, **32**, 4987 (1938)].
11. Yale and Bernstein, *J. Am. Chem. Soc.*, **70**, 254 (1948).
12. Baker, Tinsley, Butler, and Riegel, *J. Am. Chem. Soc.*, **72**, 393 (1950).

---

### Appendix

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

sulfate salt of the 6-methoxy-8-nitroquinoline

[sulfuric acid](#) (7664-93-9)

[methanol](#) (67-56-1)

[chloroform](#) (67-66-3)

Acrolein (107-02-8)

glycerol (56-81-5)

sulfur dioxide (7446-09-5)

ethylene dichloride (107-06-2)

arsenic acid (1327-52-2)

decolorizing carbon,  
carbon (7782-42-5)

phosphoric acid (7664-38-2)

ammonium hydroxide (1336-21-6)

6-Methoxy-8-nitroquinoline,  
Quinoline, 6-methoxy-8-nitro- (85-81-4)

arsenic oxide

3-nitro-4-aminoanisole (96-96-8)

nitroanisidine

6-ethoxy-8-nitroquinoline

8-methoxy-6-nitroquinoline

6-chloro-8-nitroquinoline

6-methoxy-5-bromo-8-nitroquinoline

arsenic trioxide

$\alpha$ -bromoacrolein