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.

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.*

QUINOLINE

\[
\text{C}_3\text{H}_5(\text{OH})\text{H}_2 + \text{C}_6\text{H}_5\text{NH}_2 + \text{[O]} \xrightarrow{\text{FeSO}_4, \text{H}_2\text{SO}_4} \text{N} \quad \Delta
\]

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1. Procedure

In a 5-l. round-bottomed flask, fitted with an efficient reflux condenser of wide bore, are placed, in the following order, 80 g. of powdered crystalline ferrous sulfate (Note 1), 865 g. (687 cc., 9.4 moles) of c.p. glycerol (Note 2), 218 g. (213 cc., 2.3 moles) of aniline, 170 g. (141 cc., 1.4 moles) of nitrobenzene, and 400 cc. of concentrated sulfuric acid (sp. gr. 1.84) (Note 3). The contents of the flask are well mixed and the mixture heated gently over a free flame. As soon as the liquid begins to boil, the flame is removed, since the heat evolved by the reaction is sufficient to keep the mixture boiling for one-half to one hour. If the reaction proceeds too violently at the beginning, the reflux condenser may be assisted by placing a wet towel over the upper part of the flask. When the boiling has ceased the heat is again applied and the mixture boiled for five hours. It is then allowed to cool to about 100° and transferred to a 12-l. flask; the 5-l. flask is rinsed out with a small quantity of water.

The 12-l. flask is then connected with the steam-distillation apparatus shown in Fig. 24, a 12-l. flask being used as a receiver (Note 4); steam is passed in (without external heat) until 1500 cc. has distilled (ten to thirty minutes). This removes all the unchanged nitrobenzene (10–20 cc.). The current of steam is then interrupted, the receiver is changed, and 1.5 kg. of 40 per cent sodium hydroxide solution is added cautiously through the steam inlet. The heat of neutralization is sufficient to cause the liquids to boil and thus become thoroughly mixed. Steam is then passed in as rapidly as possible until all the quinoline has distilled. In this process, 6–8 l. of distillate is collected (two and one-half to three and one-half hours are required, unless a very efficient condensing apparatus is used, under which conditions the distillation may be complete in one-half to one and one-half hours). The distillate is allowed to cool, and the crude quinoline separated. The aqueous layer of the distillate is again distilled with steam until all the quinoline has been volatilized and collected in about 3 l. of distillate.

Fig. 24.
This 3 l. of distillate is then mixed with the first yield of quinoline, and 280 g. (150 cc.) of concentrated sulfuric acid is added. The solution is cooled to 0–5°, and a saturated solution of sodium nitrite added until a distinct excess of nitrous acid is present (as shown either by starch-potassium iodide paper or by the odor). This generally requires 50 to 70 g. of sodium nitrite. The mixture is then warmed on a steam bath for one hour, or until active evolution of gas ceases, and is then distilled with steam until all the volatile material has been expelled (4 l. of distillate will result). The receiver is then changed and the mixture in the distillation flask is neutralized, as before, with 700 g. of 40 per cent sodium hydroxide solution. The quinoline is distilled exactly as described above, the aqueous portions of the distillate being distilled with steam until all the quinoline has been isolated. The crude product is then distilled under reduced pressure, and the fraction which boils at 110–114°/14 mm. is collected. The forerun is separated from any water which may be present, dried with a little solid alkali, and redistilled. The total yield is 255–275 g. (84–91 per cent of the theoretical amount based on the aniline taken) (Note
1. In the Skraup synthesis of quinoline the principal difficulty has always been the violence with which
the reaction generally takes place; it occasionally proceeds relatively smoothly, but in the majority of
cases gets beyond control, with consequent loss of material through the condenser. By the addition of
ferrous sulfate, which appears to function as an oxygen carrier, the reaction is extended over a longer
period of time. It is thus possible to work with much larger quantities of material when ferrous sulfate is
employed.
2. In a number of experiments, the glycerol used contained an appreciable amount of water. Under these
conditions, the yield of product is much lower. "Dynamite" glycerol containing less than one-half per
cent of water is best employed; u.s.p. glycerol contains 5 per cent of water and usually gives lower
yields.
3. It is important that the materials should be added in the correct order; should the sulfuric acid be
added before the ferrous sulfate, the reaction may start at once. It is also important to mix the materials
well before applying heat; the aniline sulfate should have dissolved almost completely, and the ferrous
sulfate should be distributed throughout the solution. To avoid danger of overheating, it is well to apply
the flame away from the center of the flask where any solids would be liable to congregate.
4. The apparatus for steam distillation shown in Fig. 24 requires little desk space. In this apparatus the
greater portion of the condensation is effected by the stream of water passing over the receiver. It is,
therefore, necessary that the stream passing through the condenser should be sufficiently rapid to cause
it to form a uniform film over the receiving flask.
Much time can be saved by the use of the steam distillation apparatus described, especially when large
quantities have to be handled. The above directions avoid the use of extraction methods, which not only
consume more time but may lead to appreciable losses of material.
5. Although these directions have been used many times with results exactly as described, in a few cases
the yields have dropped to 60–65 per cent without any apparent reason. At present no explanation can
be given for this.
The percentage yields have been based on the amount of aniline taken. It would probably be more
legitimate to base the calculation on the amounts of aniline taken and of nitrobenzene not recovered,
since undoubtedly the latter is reduced to aniline during the course of the reaction. If this is done, the
yield is found to be only 55 to 60 per cent of the calculated amount.

3. Discussion

Quinoline can be prepared by heating a mixture of aniline, glycerol, and sulfuric acid alone or with
an oxidizing agent like nitrobenzene, arsenic acid, ferric oxide, and vanadic acid. With the use of
nitrobenzene, the reaction, according to the original method, takes place with extreme violence. The
procedure followed here gives higher yields than those obtained with the ferric oxide method and is the
most satisfactory for the preparation of quinoline, but its homologs are preferably prepared by the use of
arsenic acid because of the somewhat greater yields. The violence of the original nitrobenzene method
may also be moderated by the use of acetic or boric acid. Copper sulfate has been used as a catalyst in
the Skraup synthesis, and the iron salt of m-nitrobenzenesulfonic acid has been employed as the
oxidizing agent. Preliminary experiments on the boric acid method showed that the reaction runs
smoothly but gives yields somewhat lower than those reported.

This preparation is referenced from:

References and Notes

1. Konigs, Ber. 13, 911 (1880); Skraup, Monatsh. 1, 316 (1880).
2. Skraup, Monatsh. 2, 139 (1881); Walter, J. prakt. Chem. (2) 49, 549 (1894).
7. Cohn, ibid. 52, 3685 (1930).
9. Mikhailov, Novosti Tekhniki, No. 3–4, 51 (1940) [C. A. 34, 5847 (1940)].

Appendix

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

alkali

sulfuric acid (7664-93-9)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

glycerol (56-81-5)

oxygen (7782-44-7)

copper sulfate (7758-98-7)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

ferrous sulfate (13463-43-9)

arsenic acid (1327-52-2)

Nitrobenzene (98-95-3)

Quinoline (91-22-5)

boric acid (10043-35-3)
aniline sulfate

ferrie oxide (1309-37-1)

vanadic acid

iron salt of m-nitrobenzenesulfonic acid