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.*
HYDROXYLAMINE HYDROCHLORIDE and ACETOXIME

1. Procedure

In a 2-gallon (8-l.) wide-mouthed bottle (Note 1) packed in ice-salt mixture are placed 630 g. (8.7 moles) of commercial (95 per cent) sodium nitrite and 5 kg. of chopped ice, and the mixture is well stirred. A cold (0–5°) solution of sodium bisulfite, made by saturating with sulfur dioxide a solution of 495 g. (4.7 moles) of anhydrous sodium carbonate in 1500 cc. of water, is now added slowly with hand stirring. When all is in, a sufficiently large quantity of the ice will have melted to allow a mechanical stirrer to be fitted. A stream of sulfur dioxide is now passed in, with continual stirring, the temperature being kept at 0–2°, until an acid reaction to Congo red paper is obtained and the dark color, which appears just before the reaction is complete, has faded. During the addition of the sulfur dioxide, 500 g. more of ice may be added.

The mixture is now transferred to a 12-l. flask, 495 g. (625 cc., 8.5 moles) of acetone is added, and the solution is heated on the steam bath to 70°. Heating is then discontinued, the flask wrapped in burlap in order to retard loss of heat, and the mixture allowed to stand overnight. The acid is then neutralized with a concentrated (50 per cent) solution of sodium hydroxide (about 720 g. of alkali is required), until a distinctly alkaline reaction to litmus is just obtained.

The resulting acetoxime is now distilled in a current of steam (Note 2), and the distillation is continued until a 5-cc. sample, shaken with 2 cc. of ether, yields no appreciable residue on evaporating the ether. To the distillate (2–2.5 l.) is added 600 cc. of concentrated hydrochloric acid, and the acid solution is distilled at atmospheric pressure until the distillate is free of acetone (Note 3). The residual liquor is then evaporated to dryness on the steam bath, either in an open dish or preferably under reduced pressure. The crude hydroxylamine hydrochloride so obtained, weighing 296–470 g. (49–77 per cent of the theoretical amount), is suitable for many purposes, but is best purified by recrystallization from half its weight of water. By systematic recrystallization of the product from several batches, the yield of pure product, which crystallizes in long flat needles, melting when dry at 150–154°, may be brought as high as 70 per cent of the theoretical amount (Note 4).

In order to prepare pure acetoxime (Note 5), the procedure is modified in the following way: After neutralizing the solution of acetoxime formed after the addition of acetone, the oily layer is separated and the aqueous solution shaken with two or three 150-cc. portions of benzene. The oil and benzene solutions are mixed, the water thereby thrown out is removed, and the oil fractionally distilled with the use of a column, the portion boiling 133–136° being collected as pure acetoxime. This product, which

Submitted by Waldo L. Semon
Checked by H. T. Clarke and Ross Phillips.
weighs 420–480 g. (67–76 per cent of the theoretical amount), solidifies in the receiver to colorless needles melting at 60–61°. The foreruns and aqueous liquors are best distilled with steam and the distillate converted into hydroxylamine hydrochloride as above, whereupon 75–90 g. of pure salt is obtained.

2. Notes

1. The preparation can be run in larger batches than that indicated. Earthenware crocks may suitably replace the glass bottle; but since the external cooling in such vessels is not so efficient, it will be necessary, in case they are used, to add a larger proportion of ice during the reaction in order to maintain the correct temperature. This, however, is no great disadvantage, since the formation of the oxime appears to take place equally well in more dilute solution. Metal cans are entirely satisfactory for the distillation of the faintly alkaline liquids.

2. The acetoxyime may be distilled by direct heating rather than by injection of steam; when the prescribed quantities are taken, however, it will be found that the liquor becomes saturated with sodium sulfate at a point just before the expulsion of the oxime is complete, so that addition of water during the distillation is necessary. More rapid distillation can be obtained by the use of a current of steam, especially if a condensing receiver (p. 479) is employed. The oxime can also, if desired, be isolated for hydrolysis by separation of the oily layer and extraction with benzene; the resulting crude hydroxylamine hydrochloride is, however, apt to be dark in color and to contain inorganic salts.

3. By redistillation of the aqueous acetone with the use of a column, 60 per cent or more of the material taken can readily be recovered and employed in a subsequent batch.

4. The final mother liquors from the recrystallization of the hydroxylamine hydrochloride contain a high proportion of ammonium chloride. The hydroxylamine present therein is best recovered by reconversion into acetoxyime, which is isolated by steam distillation of the faintly alkaline solution.

5. Acetoxyime can be obtained in long needles by allowing the first portions of the steam distillate (which are saturated with oxime) to cool, and filtering off the crystals which separate; unfortunately, this product cannot be obtained in a perfectly dry condition without considerable loss by volatilization.

3. Discussion

Hydroxylamine hydrochloride can be prepared technically by the electrolytic reduction of nitric acid\(^1\) and by the action of sodium bisulfite on sodium nitrite.\(^2\) Raschig, who discovered the latter process, suggested the use of calcium nitrite and bisulfite so that the bulk of the inorganic salts could be removed in the form of calcium sulfate.\(^3\) He also showed that sodium hydroxylamine disulfonate yields acetoxyime on treatment with acetone,\(^4\) and it has long been known that acetoxyime readily yields hydroxylamine hydrochloride on treatment with hydrochloric acid;\(^5\) but apparently these facts in combination were only used advantageously at a later time.\(^6\) Excellent yields have been reported by the reaction of acetone and sodium nitrite with zinc dust.\(^7\)

This preparation is referenced from:


References and Notes

5. Janny, Ber. 16, 170 (1883).
7. Ogata and Hirano, J. Pharm. Soc. Japan 50, 555 (1930) [C. A. 24, 4758 (1930)]

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

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

sodium bisulfite (7631-90-5)

calcium sulfate (7778-18-9)

acetone (67-64-1)

zinc (7440-66-6)

Hydroxylamine hydrochloride (5470-11-1)

ACETOXIME

hydroxylamine (7803-49-8)

calcium nitrite
sodium hydroxylamine disulfonate