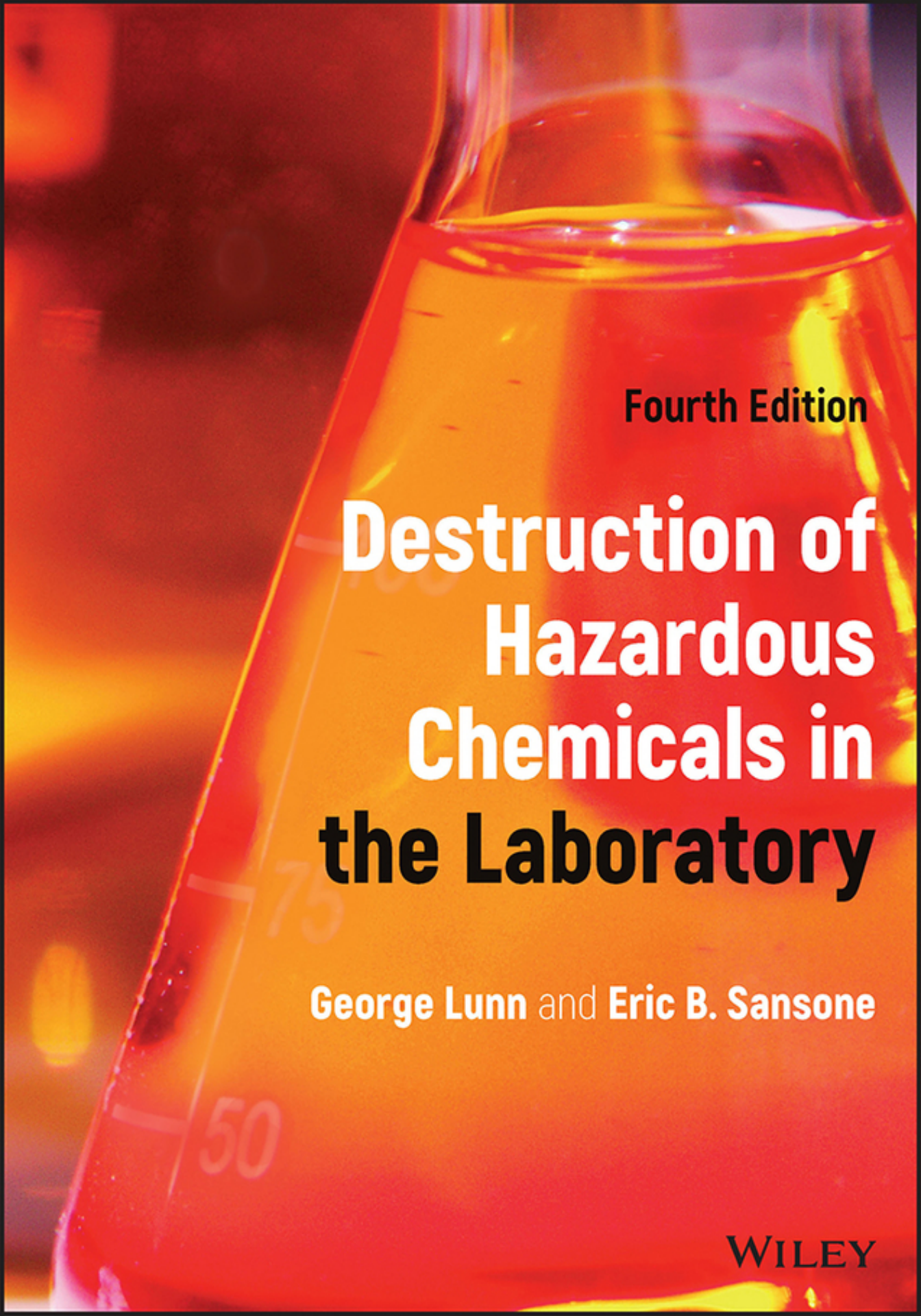
Fourth Edition
Destruction of Hazardous Chemicals in the Laboratory
George Lunn and Eric B. Sansone
WILEY

DESTRUCTION OF HAZARDOUS CHEMICALS IN THE LABORATORY

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Contents

Preface

This is the fourth edition of *Destruction of Hazardous Chemicals in the Laboratory*, originally published in 1990 with a second edition in 1994 and a third in 2012. Many of the monographs from the third edition that deal with specific chemicals have been modified to a greater or lesser extent to take into account recent developments in the literature. Methods for the destruction of pharmaceuticals have been similarly modified and expanded.

We have also greatly expanded a section that deals with nonspecific methods for the destruction of hazardous organic chemicals. The methods in this section have been divided into General Procedures and Photolytic Procedures with many subheads (see the Table of Contents). They may be of use when no procedures for destroying a particular compound have been reported. In such cases, the precautions that must be taken when dealing with previously untried procedures are particularly important. These procedures are illustrated with many examples drawn from the literature.

Procedures for the destruction of specific compounds are detailed in the individual monographs, as before. The format for the individual monographs is essentially the same as that used in earlier editions.

As before, this book is a collection of detailed procedures that can be used to degrade and dispose of a wide variety of hazardous materials. The procedures are applicable to the amounts of material typically found in the chemical laboratory. Exotic reagents and special apparatus are not required. The procedures may readily be carried out, often by technicians, in the laboratory where the hazardous materials are used.

Specific funding for research on methods for degrading hazardous chemicals in the laboratory essentially ended in 1993. However, work continues on procedures for the large-scale destruction of hazardous chemicals in connection with the prevention or remediation of environmental pollution, especially in wastewater. This type of research is frequently initially carried out on a laboratory scale, and on occasion, these laboratory scale experiments provide useful information for researchers wishing to dispose of hazardous chemicals in their laboratory.

We have selected reported procedures that appear to us to be adaptable to laboratory use. The procedures described were selected because it appeared that they could be

carried out in the laboratory with readily available reagents and equipment. A number of otherwise excellent procedures were omitted because they appeared to require specialized equipment or biological cultures. Procedures in which a critical reagent must be synthesized were also generally avoided. Because much of the research we cite was aimed at developing a process that could be used on an industrial scale, not all aspects of the process may have been thoroughly explored. Complete destruction of the target compound has not always been demonstrated, and the extent of degradation has frequently been estimated by us, often from a graph. Additionally, the final reaction mixtures were seldom tested for toxicity, although in some cases, major degradation products have been identified.

Any method that is developed from the research cited should be thoroughly tested before being used on a routine basis. Small changes, e.g. reactor geometry or dissolved oxygen, can lead to large changes in the efficiency of the reaction. In some cases, reactions may fail to go to completion because of the accumulation of light-absorbing products.

The safe handling and disposal of hazardous chemicals is an essential requirement for working with these substances. We hope that this book will contribute to and encourage the use of tested and sound practices.

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INTRODUCTION

Most biological agents can be inactivated by treating them with formaldehyde, ethylene oxide, or moist heat, and radioactive materials will decay with the passage of sufficient time, but there are no destruction techniques that are universally applicable to chemical agents. The availability of destruction techniques for specific hazardous chemical agents would be particularly helpful because of the dangers associated with their handling and disposal. In addition, being able to destroy or inactivate the hazardous materials where they are used is advantageous because the user should be familiar with the hazards of these materials and the precautions required in their handling.

Here we present summaries of destruction procedures for a variety of hazardous chemicals, including pharmaceuticals, dyes, and stains, and some chemicals that are derived from biological sources (e.g., ricin and tetrodotoxin). Many of the procedures have been validated, some by international collaborative testing. We have drawn on information available in the literature through 2021 and on our own published and unpublished work. Technological changes have essentially resulted in the closing of many scientific libraries to the general public. Even with the access provided by an institutional affiliation a work such as this becomes more difficult to produce. It is notable that among the journals surveyed in the preparation of this book, the open access movement has made very little progress.[1]

About This Book

This book is a collection of techniques for destroying a variety of hazardous chemicals. It is intended for those whose knowledge of the chemistry of the items covered is rather sophisticated; that is, for those who are aware not only of the obvious dangers, such as the toxic effects of the items themselves and of some of the reagents and other materials used in the methods, but also of the potential hazards represented, for example, by the possible

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formation of diazoalkanes when *N*-nitrosamides are treated with base, nitrosamines generated when nitrosating agents are present or toxic products produced when sodium hypochlorite is used. If you are not thoroughly familiar with the potential hazards and the chemistry of the materials to be destroyed and the reagents to be used, do not proceed.

This book contains a number of monographs that deal with the destruction of hazardous compounds derived from biological sources (e.g., ricin and tetrodotoxin); they are included with other specific destruction procedures. We do not deal with the destruction of biological organisms themselves in detail; however, we have provided a brief listing of destruction techniques applicable to biological organisms in the section entitled Biologicals.

However, it should be noted that guidelines for handling biological materials in the laboratory have been described and specific procedures for their destruction have been published. A survey of the existing literature on this subject is beyond our scope, but overviews of biological safety are available from the Centers for Disease Control and Prevention,[2] the World Health Organization,[3, 4] the National Research Council,[5] and the American Society for Microbiology.[6] Each of these publications deals to a greater or lesser extent with the destruction of biological materials. For a more encyclopedic approach, see McDonnell.[7] Note that steam sterilization, a method of choice for the treatment of much biological waste in laboratories, hospitals, and commercial establishments, does not eliminate all the potential hazards from antineoplastic drug residues.[8] In an interesting study of feather meal, 24 pharmaceuticals or metabolites (mostly antimicrobials) were found in the constituent feathers.[9] In the course of this work, the authors autoclaved (121°C for 30 min) the feather meal. Some compounds were totally degraded by the autoclaving process and some were not degraded at all. Almost three-quarters of the compounds studied were degraded by less than 50%

The destruction methods are organized in what we believe to be rational categories. These categories are listed in the Table of Contents. It is quite likely, however, that others would have categorized these methods differently, so we have provided three indexes. There is a general name index, a cross-reference for the names of dyes and biological stains, and a cross-index linking each pharmaceutical with the type of degradation procedure that has been shown to be appropriate. In each case, the page number given is the first page of the monograph in which the destruction of that compound is discussed. In some cases, the compound itself may not have been studied; it may have been referred to in the Related Compounds section.

Pharmaceuticals are referred to in the monographs and the Name Index only by their United States Adopted Name (USAN). Many dyes and biological stains have multiple names, so in the monograph, we have used a common name for each dye and provided a cross-index for the various other names that are used. We have also included a cross reference of pharmaceuticals and methods for their destruction.

One of the difficulties in preparing a book such as this is deciding what should be included and what should be excluded from the text. We have tried to make the detailed method descriptions and the supporting references complete, but at the same time not include unnecessary details. We also tried to eliminate ambiguity wherever possible,

going so far as to repeat almost verbatim certain procedures for some compounds rather than noting a minor change and referring to another section and so risking a wrong page number or a misinterpretation. It should be noted that some methods are not described in detail because the details in the original papers are sparse. We have gathered many of these techniques in summary tables that provide the essential parameters. In this way, the procedures may be readily compared.

Some general safety precautions are given below. These are not repeated for each group of compounds; in some cases, unusual hazards are noted. For many of the destruction procedures, we use the word "discard" in connection with the final reaction mixture. This *always* means "discard in compliance with all applicable regulations."

Although we have included many validated destruction procedures, we realize that there may be other suitable procedures in the literature. Thus, we would be pleased to hear from readers who have any information or suggestions.

Properties of a Destruction Technique

We have already indicated the advantages of destroying hazardous chemicals at the place where they were generated. It is also useful to consider the desirable properties of a destruction technique for hazardous chemicals.

- Destruction of the hazardous chemical should be complete.
- A substantially complete material accountance should be available, with the detectable products being innocuous materials. (This accountance is often difficult to accomplish. In the absence of a complete material accountance, an assessment of the mutagenic activity or another toxicity measurement of the reaction mixture may provide useful information concerning the potential biological hazards associated with the decomposition products.)
- The effectiveness of the technique should be easy to verify analytically.
- The equipment and reagents required should be readily available, inexpensive, and easy and safe to use. The reagents should have no shelf-life limitations. Preparation of a special reagent or purchase of unusual equipment to accomplish the destruction should not be necessary. We have omitted a number of methods because they required the synthesis of a special reagent or catalyst.
- The destruction technique should require no elaborate operations (such as distillation or extraction) that might be difficult to contain; it must be easy to perform reliably and should require little time.
- The method should be applicable to the real world; that is, it should be capable of destroying the compound itself, solutions in various solvents, and spills.

These properties characterize an ideal destruction technique. Most techniques cannot meet all of these criteria, but they represent a goal toward which one should strive.

Contents of a Detailed Monograph

Each monograph usually contains the following information:

- An introduction describes the various properties of the compound or class of compounds being considered.
- The principles of destruction section details, in general terms, the chemistry of the destruction procedures, the products, and the efficiency of destruction.
- The destruction procedures section may be subdivided into procedures for bulk quantities, solutions in water, organic solvents, and so on if these details are available.
- The analytical procedures section describes one or more procedures that may be used to test the final reaction mixtures to ensure that the compound has been completely degraded. The techniques usually involve packed column gas chromatography (GC) or reverse-phase high-performance liquid chromatography (HPLC), but colorimetric procedures and thin-layer chromatography (TLC) are also used in some cases.
- The mutagenicity assays section describes the data available on the mutagenic activity of the starting materials, possible degradation products, and final reaction mixtures. The data were generally obtained from the plate incorporation technique of the *Salmonella*/mammalian microsome mutagenicity assay (see below).
- The related compounds section describes other compounds to which the destruction procedures should be applicable. The destruction procedures have not usually been validated for these materials, however; they should be fully investigated before adopting them.
- References identify the sources of the information given in the monograph.

Summary Tables

For more recent publications, particularly those derived from papers that discuss methods primarily intended for environmental cleanup, the nature of the material has led us to take a different approach. The organization of these monographs is based on the type of reaction under consideration, e.g., potassium permanganate oxidation and photolysis. In addition, the procedures for pharmaceuticals and all other compounds are separated. Many of these more recent papers provide a limited amount of detail for the procedures of relevance to this book. For example, mutagenicity testing is rare and destruction efficiencies frequently need to be estimated by reference to a graph. Destruction efficiencies taken from a graph are indicated by the term (est), e.g., >95% (est). Frequently tables are used to bring the relevant reaction parameters together.

Mutagenicity Assays

In many cases, particularly the work carried out at the NCI-Frederick Cancer Research and Development Center, the residues produced by the destruction methods were tested

for mutagenicity. Unless otherwise specified, the reaction mixtures from the destruction procedures and some of the starting materials and products were tested for mutagenicity using the plate incorporation technique of the *Salmonella*/mammalian microsome assay essentially as recommended by Ames et al.[10] with the modifications of Andrews et al.[11] Some or all of the tester strains TA98, TA100, TA1530, TA1535, TA1537, and TA1538 of *Salmonella typhimurium* were used with and without S9 rat liver microsomal activation. The reaction mixtures were neutralized before testing. In general, basic reaction mixtures were neutralized by adding acetic acid. Acidic reaction mixtures were neutralized by adding solid sodium bicarbonate. Reaction mixtures containing potassium permanganate were decolorized with sodium ascorbate before neutralization. A 100 μL aliquot of the solution (corresponding to varying amounts of undegraded material) was used per plate. Pure compounds were generally tested at a level of 1 mg per plate in either dimethyl sulfoxide (DMSO) or an aqueous solution. To each plate were added 100 μL of these solutions. The criterion for significant mutagenicity was set at more than twice the level of the control value. The control value was the average of the cells only and cells plus solvent runs. Unless otherwise specified, residues did not exhibit mutagenic activity. The absence of mutagenic activity in the residual solutions, however, does not necessarily imply that they are nontoxic or have no other adverse biological or environmental effects.

Analytical Procedures

For the most part, unless otherwise specified, the analytical equipment used for the work carried out at the NCI-Frederick Cancer Research and Development Center consisted of the following. For HPLC, a dual pump computer-controlled solvent delivery system (Rainin Instrument Co., Woburn, MA) was used with ultraviolet (UV) detection using either a Knauer Model 87 variable wavelength detector (Rainin) or an ABI 1000S diode array detector (Applied Biosystems, Foster City, CA). The injection volume was 20 μL and the flow rate was 1 mL/min. The column was a 250 × 4.6-mm i.d. column of Microsorb 5 μm C8 fitted with a 15 × 4.6-mm guard column of the same material. For GC, a Hewlett Packard HP 5880A instrument was fitted with a 1.8-m × 2-mm i.d. × 0.25-in. o.d. packed silanized glass column. The column was fitted with a guard column packed with the same material. The guard column was changed periodically. The injector temperature was 200°C and the flame ionization detector temperature was 300°C. The carrier gas was nitrogen flowing at 30 mL/min. Injection was by syringe and sample volumes were in the 1–5 μL range. For each instrument, an electronic integrator was used to determine peak areas automatically.

In some cases, we found that injecting unneutralized reaction mixtures onto the hot GC column caused degradation of the material for which we were analyzing. Thus, it might be that degradation was incomplete but the appropriate peak was not observed in the chromatogram because the compound was degraded on the GC column. Spiking experiments can be used to determine if this is a problem. In a spiking experiment, a small amount of the original compound is added to the final reaction mixture and this spiked mixture is analyzed. If an appropriate peak is observed, compound degradation on the GC

column is not a problem. If an appropriate peak is not observed, it may be necessary to neutralize the reaction mixture before analysis and/or use a different GC column. Similar problems may be encountered when using HPLC because of the formation of salts or the influence of the sample solvent; again, spiking experiments should be employed. We have indicated in the monographs some instances where problems such as these were encountered (see, for example, Halogenated Compounds monograph) but spiking experiments should be used routinely to test the efficacy of the analytical techniques.

Spills

Before starting work, have a plan for dealing with spills or accidents; coming up with a good plan on the spur of the moment is difficult. At a minimum have the appropriate decontaminating or neutralizing agents prepared and close at hand. Small spills can probably be cleaned up by the researcher. In the case of larger spills, the area should be evacuated and help sought from those experienced and equipped for dealing with spills, e.g., your institutional safety department.

The initial step in dealing with a spill should be the removal of as much of the spill as possible by using a high-efficiency particulate air (HEPA) filter-equipped vacuum cleaner for solids and absorbents for liquids or solutions. The residue should be decontaminated, as described in the monographs.

While solutions or bulk quantities may be treated with heterogeneous [e.g., nickel–aluminum (Ni–Al) alloy reduction] or homogeneous methods [e.g., potassium permanganate/sulfuric acid ($KMnO_4/H_2SO_4$) oxidation], decontamination of glassware, surfaces, and equipment and the treatment of spills are best accomplished with homogenous methods. These methods allow the reagent, which is in solution, to contact all parts of the surface to be decontaminated. At the end of the cleanup, it is frequently useful to rub the surface with a wipe moistened with a suitable solvent, e.g., water, methanol, or acetone, and analyze the wipe for the spilled compound. See also the introductory Pharmaceuticals monograph and Appendix B – Decontamination and Disinfection of Laboratory Surfaces and Items in Biosafety in Microbiological and Biomedical Laboratories.[2]

Applicability of Procedures

Methods that successfully degrade some compounds may not affect other compounds of the same class or other classes of compounds. This underscores the importance of the thorough testing of any selected procedure. For example, oxidation with $KMnO_4$ in H_2SO_4 solution has been successfully applied to the destruction of several classes of compounds, such as aromatic amines[12] and polycyclic aromatic hydrocarbons.[13] This method gave satisfactory results with some of the antineoplastic agents but not with others, including most of the *N*-nitrosourea drugs.[14] At this point, it is also worth noting that potassium permanganate in sulfuric acid can be used to degrade nitrosamines. As noted in this book, a number of procedures have been found to generate nitrosamine byproducts. It seems likely that potassium permanganate in sulfuric acid will not have

that limitation provided that the reaction is allowed to proceed for a sufficient time and the reaction mixture remains purple indicating that permanganate is still present in the solution.

Nickel–aluminum alloy in dilute base worked well for *N*-nitrosamines,[15] but it was unsatisfactory for the destruction of polycyclic aromatic hydrocarbons.[13]

Chromic acid is an attractive oxidizing agent and has been used successfully to degrade many compounds, but the spent chromium compounds are potentially carcinogenic. These compounds are also environmentally hazardous and may not be discharged into the sewer. For this reason, we have not recommended the use of chromic acid for degrading any of the compounds we have covered. Potassium permanganate/sulfuric acid degradation appears to be as efficient and has fewer hazards.

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SAFETY CONSIDERATIONS

A first step in minimizing risks associated with hazardous chemicals is to prepare a set of guidelines regulating such work. Many organizations have produced such guidelines and many texts have been written on the subject of laboratory safety,[1–9] preventing exposure to hazardous drugs,[10] and the hazardous properties of chemicals.[11–16] Implementing procedures for the safe handling of antineoplastic drugs led to a drop in worker exposure over a 10-year period.[17]

The American Chemical Society provides a list of resources at https://www.acs.org/content/acs/en/about/governance/committees/chemical-safety/publications-resources.html.

Such documents will provide many useful suggestions when preparing guidelines for any laboratory situation. It is important that the guidelines "fit" the management and administrative structure of the institution and that any particular work requirements be taken into account. Obviously, all national and local laws should be obeyed, as well as all institutional regulations. Controlled substances are regulated by the Drug Enforcement Administration. By law, Material Safety Data Sheets must be readily available. All laboratories should have a Chemical Hygiene Plan [29CFR Part 1910.1450] and institutional safety officers should be consulted as to its implementation. The Occupational Health and Safety Administration has made available recommendations for an appropriate Chemical Hygiene Plan based on Reference 1, below. See 29CFR Part 1910.1450 App A. Help is (or should be) available from your institutional Safety Office. Use it.

To ensure the safety of those working with hazardous materials of any kind, policies, responsibilities, and authority must be clearly defined. The responsibilities of the laboratory director, the supervisor, the employee, and the safety committee should be clearly spelled out.

It is important that potentially hazardous materials are handled only by those workers who have received the appropriate training. For that reason, glassware and equipment should be decontaminated in the laboratory before they are transferred to any central washing system.

Obviously, it is important to consider the waste disposal aspects of one's work before the work begins. Experiments should always be designed to use the minimum quantities of potentially hazardous materials, and plans should be made in advance to minimize the wastes generated by any experimentation. When purchasing material for the laboratory consideration should be given as to its eventual disposal. Although buying large quantities may result in a lower unit cost, this may be no bargain if you must eventually pay to have large quantities of unused material disposed of. Consideration should also be given to purifying and using existing stocks rather than discarding the old material and buying fresh stock. The purification of laboratory chemicals has been described.[18] As an example, see the Monograph on Butyllithium in this book where methods of retitrating solutions of uncertain concentration are described. In addition, Appendix I describes procedures for drying organic solvents. These procedures may help to reduce the need to discard older material.

Although we concentrate here on laboratory methods for destroying or decontaminating hazardous chemicals, it is valuable to briefly discuss some other approaches to handling chemical wastes. Regardless of the disposal approach selected, only completely decontaminated wastes producing no adverse biological effects should be discarded. Procedures for disposing of hazardous chemicals must comply with all applicable regulations. It is obviously undesirable to deliberately dispose of hazardous chemicals through the sewage system or by evaporation into the atmosphere unless one has solid evidence that their subsequent degradation is extremely rapid, irreversible, complete, and produces safe degradation products.

It is impossible to provide a concise summary of safety practices for handling hazardous chemicals in the laboratory. For a complete discussion, the reader is advised to consult readily available references.[1–16, 19–26] Each institution and facility should tailor its program to meet its needs. It is important that the safety program include procedures for working with chemicals, biological materials, compressed gases, high-voltage power supplies, radioisotopes, and so on.

The following descriptions are designed to give a sufficiently complete guide to the destruction methods available in order to allow one to implement them successfully. The user may wish to consult the sources cited in order to determine the exact reaction conditions, limitations, and hazards that we have not been able to list because of space limitations. In some cases, more than one procedure is listed. In these instances, all the procedures should be regarded as equally valid unless restrictions on applicability are noted. In the course of collaborative testing, we have occasionally found that the efficacy of the same technique varies between laboratories and may also depend on the batch of reagents being used. Thus, we strongly recommend that these methods be periodically validated to ensure that the chemicals are actually being destroyed. These methods have been tested on a limited number of compounds. The efficiency of the destruction techniques must be confirmed when they are applied to a new compound.

The details of analytical techniques are also frequently included. It should be noted that even if 99.5% of a compound is destroyed, the remaining amount may still pose a considerable hazard, particularly if the original reaction was performed on a large scale. The efficiency of degradation is frequently indicated by giving the limit of detection, for example, <0.5% of the original compound remained. This means that **none** of the original compounds could be detected in the final reaction mixture. However, because of the limitations of the analytical techniques used, it is possible that traces of the original compound, which were below the limit of detection, remained. If this is the case, to use the example given above, the quantity that remained was less than 0.5% of the original amount. In cases where the destruction efficiency must be estimated from a graph, it is generally not possible to say with any precision how much remains. Frequently, the best that we can say after looking at the graph is that the destruction efficiency is greater than 95%. How much greater it is not possible to estimate.

The reactions described were generally performed on the scale specified. If the scale is greatly increased unforeseen hazards may be introduced, particularly with respect to the production of large amounts of heat, which may not be apparent in a small-scale reaction. Extra care should, therefore, be exercised when these reactions are performed on a large scale.

In addition to the potential hazards posed by the compounds themselves, many of the reagents used in degradation procedures are hazardous. *Acids and bases are corrosive and should be prepared and used carefully. As noted below, the dilution of concentrated H_2SO_4 is a very exothermic process, which can result in splattering if carried out incorrectly*. All reactions should be carried out in a properly functioning chemical fume hood, which is vented to the outside. Laminar flow cabinets or other recirculating hoods with or without filters are not appropriate. The performance of the hood should be checked by qualified personnel at regular intervals. Hoods should be equipped with an alarm that sounds if the airflow drops below a preset value.

Dissolving concentrated H_2SO_4 in H_2O is a very exothermic process and appropriate protective clothing, including eye protection, should be worn. Concentrated H_2SO_4 should **always** be added to H_2O and **never** the other way around (otherwise splashing of hot concentrated H_2SO_4 may occur). To prepare H_2SO_4 solutions, the appropriate quantity of concentrated H_2SO_4 is slowly and cautiously added to about 500 mL of H_2O, which is stirred in a 1-L flask. When the addition is complete, H_2O is added to bring the volume up to 1 L and the mixture is allowed to cool at room temperature before use. To prepare a 1 M H_2SO_4 solution, use 53 mL of concentrated H_2SO_4, and to prepare a 3 M H_2SO_4 solution, use 160 mL of concentrated H_2SO_4.

Appropriate protective clothing should be worn.[20, 21] This clothing includes, but is not limited to, eye protection (safety glasses or face shield), lab coat, and gloves. Rubber gloves generally allow the passage of organic liquids and solutions in organic solvents; they should not be allowed to routinely come into contact with them. Permeation of

gloves by chemicals has recently been comprehensively reviewed.[27, 28] Nelson and Phalen have reviewed the art and science of selecting the right glove.[29] Protective clothing should be regarded as the last line of defense and should be changed immediately if it becomes contaminated.

Wastes should be segregated into solid, aqueous, nonchlorinated organic, and chlorinated organic material and disposed of in accordance with local regulations.

In the introductions to the monographs, we did not try to give an exhaustive listing of the toxicity data [e.g., LD_{50} (the dose that is lethal for 50% of the animals tested) or threshold limit values (TLVs) data] or other hazards associated with the compounds under consideration. Instead, we attempted to give some indication of the main hazards associated with each compound or class of compounds. Extensive listings of all the *known* hazards associated with these compounds can be found elsewhere.[11, 14, 15]

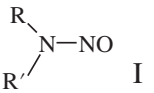
All organic compounds discussed in this book should be regarded as flammable and all volatile compounds should be regarded as having the capacity of forming explosive mixtures in confined spaces. In many cases, the toxic properties of many of these compounds have simply not been adequately investigated. Prudence dictates that, unless there is good reason for believing otherwise, all of the compounds discussed in this book should be regarded as volatile, highly toxic, flammable, human carcinogens, and should be handled with great care.

Other hazards are introduced by the reagents needed to perform the destruction procedures. Examples are the inadvertent formation of nitrosamines and the use of sodium hypochlorite, Ni–Al alloy, and $KMnO_4$.

Nitrosamine Formation

This chapter describes some of the problems with nitrosamine formation that have become all too apparent in recent years. A full discussion would require a book of its own so this monograph will confine itself to a few general aspects of the issue. The FDA has issued Guidance on the subject[30] and there has been a recent comprehensive review.[31] However, this is a fast-evolving area and it is impossible to predict future developments. All we can say is that when planning any destruction procedure, the generation of nitrosamines should be carefully considered.

Nitrosamines are compounds of the general form (**I**), where R and R′ are usually aryl or alkyl, although other variants where R or R′ are heteroatoms (e.g., oxygen) are known. See the Nitrosamine monograph later in this book for the physical nature and hazardous properties of these compounds.



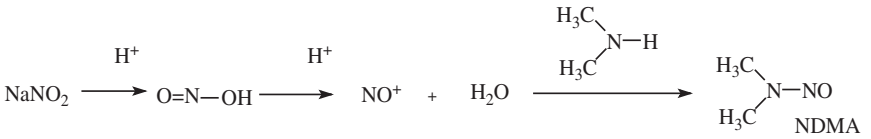
I

Many nitrosamines are carcinogenic and mutagenic (see the Nitrosamine monograph). An alkyldiazonium ion is thought to be the proximate mutagen.[31] Note that

not all nitrosamines are mutagenic. Some may not be mutagenic because metabolic activation is significantly impaired by steric hindrance.[31]

As Elder et al. state "It is now abundantly clear that the N-nitrosation reaction can occur between nitrous acid (or residual nitrites in an acidic environment) and any small chain alkyl secondary or tertiary amine."[31] These need not be major components of the system. For example, the nitrosating agent could come from naturally occurring ammonia and the secondary amine could be a minor impurity or degradation product from an otherwise innocuous compound. Because nitrosamines are such potent carcinogens even very inefficient reactions can readily generate nitrosamine levels of concern.

Starting in 2018, reports have surfaced that various blood pressure medications, e.g., valsartan, have been contaminated with nitrosamines.[32, 33] The formation of *N*-nitrosodimethylamine (NDMA) in valsartan was attributed to a manufacturing process that used sodium azide to form a tetrazole ring.[31] Sodium nitrite was used to remove excess azide (see the Azide monograph). Excess nitrite then reacted with small amounts of dimethylamine, present as an impurity in the dimethylformamide (DMF) solvent, to form NDMA. This finding has triggered waves of recalls and drug shortages. The following mechanism has been proposed.[34]

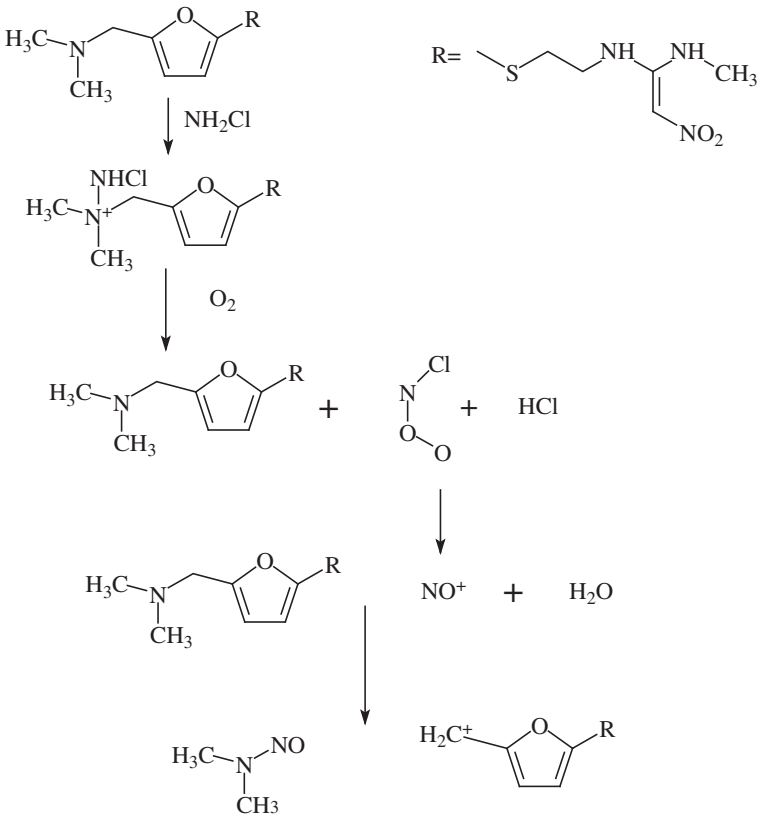


Note that in this case, neither of the species thought to be responsible for the formation of NDMA, i.e., sodium nitrite and dimethylamine, were principal components of the synthetic scheme. Sodium nitrite was used to remove excess azide and dimethylamine was an impurity in the DMF.

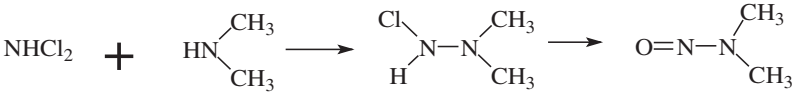
The increasing amounts of pharmaceuticals that are found in water and wastewater can provide a ready source of secondary amines. Shen and Andrews[35] studied the ability of numerous pharmaceuticals to yield dimethylamine and then NDMA when they were allowed to react with chloramine. They studied 20 pharmaceuticals with dimethylamino or diethylamino groups, all of which produced some amount of NDMA or *N*-nitrosodiethylamine (NDEA). Ranitidine produced the highest amount of NDMA. The highest nitrosamine yield was at pH 7–8.[36] Other authors have investigated the formation of nitrosamines from ranitidine,[37–39] metformin,[40] DMF[41] nizatidine,[37] chlorpheniramine,[37] and doxylamine.[37]

It should be noted that ranitidine alone generates NDMA under stress conditions (40°C and 75% relative humidity).[42] The presence of sulfite suppresses the generation of NDMA to some extent.[43]

A possible mechanism for the generation of NDMA from ranitidine in the environment has been proposed as follows.[44]



Researchers in the field of water and wastewater have been interested in the problem of nitrosamine contamination for many years.[45–48] NDMA is a particular threat but other nitrosamines have been found. Chloramine (NH_2-Cl) is widely used for water disinfection, lasting longer in the pipes and producing fewer disinfection by-products.[49] However, chloramine can react with secondary amines, such as dimethylamine, to form nitrosamines, such as NDMA. A possible mechanism is shown below.[47]



There are many other routes to the formation of nitrosamines, for example chlorination or ozonation, or the presence of nitrosating agents. The dimethylamine may be naturally occurring or may arise from the degradation of compounds having a dimethylamino group. Other secondary amino groups may give rise to other nitrosamines. Nitrosation can occur in nitrate-rich wastewater under UV-C illumination.[50] NDMA is formed when metformin is degraded with ozone[51] and also when tetracycline and oxytetracycline react with sodium hypochlorite.[52]