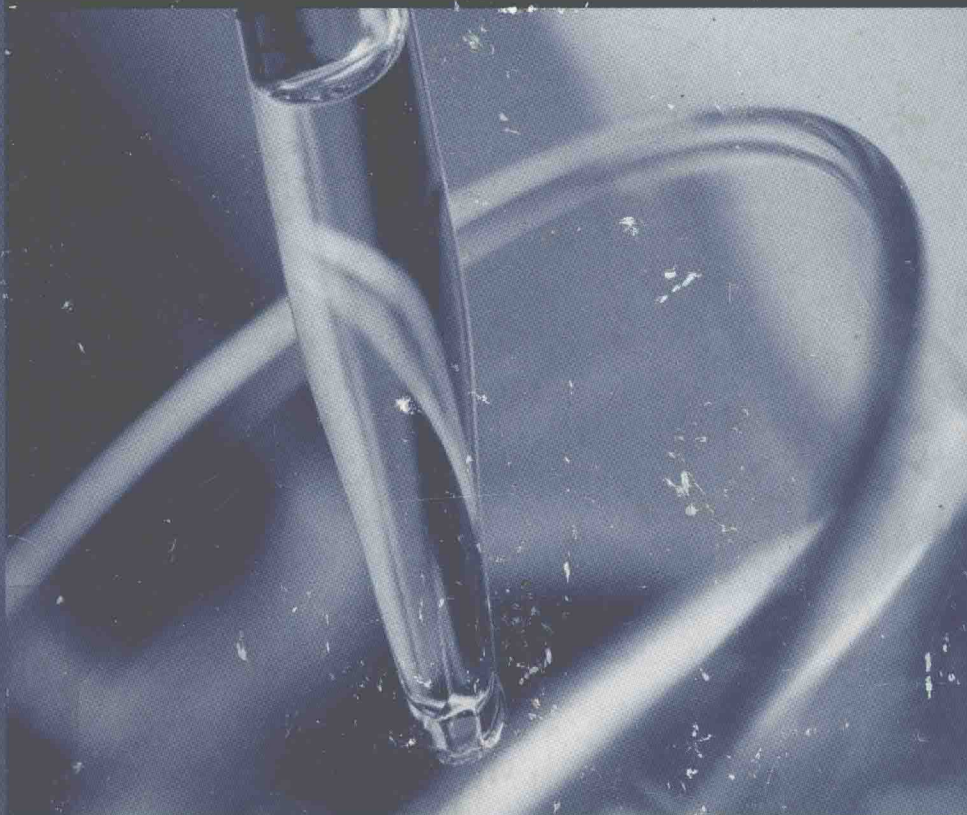


THIRD EDITION

MACROSCALE & MICROSCALE ORGANIC EXPERIMENTS



WILLIAMSON

CUSTOM EDITION FOR THE UNIVERSITY OF MASSACHUSETTS - AMHERST

AND

**Macroscale
Microscale
ORGANIC
EXPERIMENTS**

THIRD EDITION

KENNETH L. WILLIAMSON

Mount Holyoke College

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Macroscale Microscale ORGANIC EXPERIMENTS

Custom Edition for the University of Massachusetts

Preface

Innovation and exploration characterize this Third Edition of *Macroscale and Microscale Organic Experiments*. Building on the strength and success of prior editions, the Third Edition boasts a reorganization that more closely follows organic chemistry textbooks as well as innovative new techniques, features, and experiments. Additionally, throughout this edition one will find experiments and references that tie this course to biochemical and biomedical applications of organic chemistry.

New to This Edition

Techniques

A method has been devised, using the 105° adapter in every Williamson microscale kit, for each student to construct a gas phase IR cell at no cost. Now they can add the third state of matter to traditional solid and liquid phase samples and explore for the first time the gases that are produced in these experiments. In addition, they can explore the myriad gases found in aerosol cans, inhalants, refrigerants, and the like, as well as those from biological sources such as marsh gas and odors ranging from perfumes to putrefaction.

Another innovation, the Wilfilter, is a simple polypropylene adapter that converts every reaction tube into a superior Craig tube. This conversion allows the isolation of minute quantities of crystals without transfer losses, free of solvent and almost dry. We are now using this in many experiments; it is a fast and efficient technique.

Features

The opportunities for students to explore organic chemistry in a variety of ways is presented in the new feature entitled “For Further Investigation.” These sections require running reactions and then deducing the nature of the products, usually by IR and NMR spectroscopy. Open-ended investigations include exploring the nature of the gases found in commercial products.

Exploration of another nature is included at the end of many experiments: “Surfing the Web.” I have tried to locate a few relevant sites that add new dimensions to the topic at hand as the unwary student can be overwhelmed by the riches of the Web. “Surfing the Web” leads students to, for example, infrared spectra correlated to vibrations of specific atoms and groups of atoms in a molecule, very clear pictures of melting crystals for the melting point experiment, animations of reactions, and full-color, close-up photographs of many of the experiments presented in this text.

New and Updated Experiments

The “NMR Spectroscopy” chapter has been rewritten to guide students in the use of this powerful technique for structure identification based on the assumption they will be using high-field Fourier transform spectrometers. Most of the NMR spectra have been revised and expanded, and the elements of two-dimensional NMR spectra are also presented.

Similarly, the “Infrared Spectroscopy” chapter has been rewritten so that students can carry out a logical step-by-step analysis of their spectra. Fourier transform IR spectrometers are rapidly coming into general use, because not only do they allow spectra to be obtained in less time, but they also give peak frequencies in digital form. In this edition FTIR spectra have replaced the analog versions of the previous edition. Also new to this chapter is a section on “Gas Phase IR Spectroscopy”; six more gas phase spectra can be found in the *Instructor's Guide*.

New to this edition is an experiment that allows students to prove the stereochemistry of reduction of a diketone to a diol: In Chapter 57, “Synthesis of 2,2-Dimethyl-1,5-dioxolane,” the acetone derivative of hydrobenzoin is prepared and its NMR spectrum analyzed to prove whether the hydrobenzoin is the meso or d,l-compound. Chapter 67, “Isolation of Lycopene and β -Carotene,” has been placed in a more appropriate place in the organization of the manual, giving emphasis to the biochemical nature of the experiment. Chapter 34, “1,2,3,4-Tetraphenylnaphthalene via Benzyne,” is an experiment that has been reinstated from a previous edition.

Throughout the text the scale of the macroscale experiments has been reduced, in most cases to half the former size. This has been done because of the widespread use of 14/20 standard-taper apparatus, the savings in the cost of waste disposal and purchase of chemicals, and for safety reasons. In a few cases microscale experiments have been scaled up, simply to make it easier to isolate products.

The “Searching the Chemical Literature” chapter has been rewritten to reflect not only changes in the references but also the availability of computer databases of this material.

Innovative Techniques from Previous Editions

Innovations from the last edition of this text have proved to be just as valuable as when first introduced. Among the two most important are the use of *t*-butyl methyl ether in place of diethyl ether and the use of anhydrous calcium chloride pellets as a drying agent. *t*-Butyl methyl ether is one of the most common and cheapest solvents being produced because it has replaced tetraethyl lead as an antiknock additive and as an oxygenate, added to reduce pollution, in gasoline. Not only is it cheaper than diethyl ether, it does not easily form peroxides and therefore can be stored more than 30 days after the container is opened; it has a higher boiling point (55°C) than diethyl ether and is therefore somewhat less flammable; and it forms a 4% azeotrope with water, so as it is removed it also removes the last traces of

water from a solution. All in all it should become the solvent of choice, replacing diethyl ether in all applications except the Grignard reaction.

We continue to be very enthusiastic about the use of anhydrous calcium chloride pellets as a drying agent, an innovation introduced in the last edition. These pellets do not fracture and powder and so are ideally suited to drying microscale quantities of solutions where the solvent can simply be drawn off with a Pasteur pipette, making conventional filtration unnecessary.

The unique chapter on computational chemistry and molecular mechanics is an introduction to a tool that, like spectroscopy, can give new insight into the structure of organic molecules. Procedures for the application of this tool are given to no fewer than 20 experiments.

Our students are very enthusiastic about the synthesis of a fluorescer using the Wittig reaction and the synthesis of a Cyalume in order to make their own light sticks. Transfer hydrogenation using cyclohexene as the source of hydrogen is another experiment unique to *Macroscale and Microscale Organic Experiments*. Olive oil is thus hydrogenated to a fat that can be converted to soap. The use of Multifiber Fabric in the experiment on dyes and dyeing, Norit decolorizing charcoal in the form of pellets, the microscale cracking of dicyclopentadiene, and the multistep syntheses starting with the benzoin condensation of benzaldehyde, benzyne experiments, and tetraphenylcyclopentadienone are among the innovative experiments that have appeared in previous editions of this text, which dates to 1935 when Louis Fieser was the author. Remember, you saw it first in Williamson.

The “Biomimetic Synthesis of Pseudopellitierene” following the classic work of Robert Robinson is a relatively new experiment, as is the “Conversion of Camphene to Camphor.”

Waste Disposal and Safety

The section at the end of every experiment entitled “Cleaning Up” has been written with the intent of focusing students’ attention on not just the desired product from a reaction but also on all of the other substances produced in a typical organic reaction.

As one of the coauthors of the first edition of *Prudent Practices for the Disposal of Chemicals from Laboratories*, I have continued to follow closely the rapidly evolving regulatory climate and changes in laboratory safety rules and regulations. The safety information in this text is about as current as possible, but this is a rapidly changing area of chemistry; local rules and regulations must be known and adhered to.

Supplements

Instructor’s Guide

The *Instructor’s Guide* is an important adjunct to this text. It contains discussions about the time needed to carry out each experiment and assessment of the rela-

tive difficulty of each experiment, problems that might be encountered, answers to end-of-chapter questions, a list of chemical and apparatus required for each experiment—both per student and per 24-student laboratory—sources of supply for unusual items, and a discussion of hardware and software needed for running calculational chemistry and molecular mechanics experiments.

Desk copies of this *Instructor's Guide* are available by contacting your local Houghton Mifflin sales representative or by contacting:

Houghton Mifflin Co.
222 Berkeley St.
Boston, MA 02116-3764
(800) 733-1717

Web Site

Please visit our Web sites at <http://www.mtholyoke.edu/courses/kwilliam/microscale.shtml> and www.hmco.com for resource information intended to support users of this lab manual.

The Chemistry Tutor Version 2.0 CD-ROM

This CD, authored by Adam Drury of the University of Liverpool, is an interactive introduction to topics in organic chemistry, with a review of topics in general chemistry. It includes a tutorial with text, animations, and interactive problems. It contains 18 content modules of computer-assisted learning material plus four tools, including a periodic table database and chemical calculator.

Acknowledgments

I would like to acknowledge the help of many classes of Chemistry 302 at Mount Holyoke College in developing and refining the experiments in this text, as well as the contributions sent to me by students and faculty at many other institutions. I am also indebted to Rick Danheiser and Scott Virgil at MIT, where I taught in 1996 and 1997.

I also wish to express my thanks to my editor at Houghton Mifflin, Marianne Stepanian, as well as the reviewers of this text, Edward Alexander (San Diego Mesa College), Roger Murray (University of Delaware), George Thyvelikakath (Oral Roberts University), Grace B. Borowitz (Ramapo College of New Jersey), Janet E. Nelson (Middlebury College), Linda A. Jacob (Yale University), Ray Lutgring (University of Evansville), Tracy A. Oriskovich (The Pennsylvania State University), Robert D. Minard (The Pennsylvania State University), J. W. Sam Stevenson (Northeast State Technical Community College), Mark Arant (Northeast Louisiana University), William L. "Hank" Mancini (Paradise Valley Community College), Robert A. Braga (Georgia Institute of Technology), Leslie Gunatilaka (Virginia Polytechnic Institute and State University), and, in particular, Alan Shusterman (Reed) who reviewed the material on computational chemistry.

And finally I note with sadness the passing of Mary Fieser in 1997. While never a coauthor of Louis Fieser's laboratory manuals, this great chemist and author was a perceptive critic and constant inspiration.

ORGANIC EXPERIMENTS AND WASTE DISPOSAL

An unusual feature of this book is the advice at the end of each experiment on how to dispose of its chemical waste. Waste disposal thus becomes part of the experiment, which is not considered finished until the waste products are appropriately taken care of. This is a valuable addition to the book for several reasons.

Although chemical waste from laboratories is less than 0.1% of that generated in the United States, its disposal is nevertheless subject to many of the same federal, state, and local regulations as is chemical waste from industry. Accordingly, there are both strong ethical and legal reasons for proper disposal of laboratory wastes. These reasons are backed up by a financial concern, because the cost of waste disposal can become a significant part of the cost of operating a laboratory.

There is yet another reason to include instructions for waste disposal in a teaching laboratory. Students will someday be among those conducting and regulating waste disposal operations and voting on appropriations for them. Learning the principles and methods of sound waste disposal early in their careers will benefit them and society later.

The basics of waste disposal are easy to grasp. Some innocuous water-soluble wastes are flushed down the drain with a large proportion of water. Common inorganic acids and bases are neutralized and flushed down the drain. Containers are provided for several classes of solvents, for example, combustible solvents and halogenated solvents. (The containers are subsequently removed for suitable disposal by licensed waste handlers.) Some toxic substances can be oxidized or reduced to innocuous substances that can then be flushed down the drain; for example, hydrazines, mercaptans, and inorganic cyanides can be thus oxidized by sodium hypochlorite solution, widely available as household bleach. Dilute solutions of highly toxic cations are expensive to dispose of because of their bulk; precipitation of the cation by a suitable reagent followed by its separation greatly reduces its bulk and cost. These and many other procedures can be found throughout this book.

One other principle of waste control lies at the heart of this book. Microscale experimentation, by minimizing the scale of chemical operations, also minimizes the volume of waste. Chromatography procedures to separate and purify products, spectroscopy methods to identify and characterize products, and well-designed small-scale equipment enable one to conduct experiments today on a tenth to a thousandth the scale commonly in use a generation ago.

Chemists often provide great detail in their directions for preparing chemicals so that the synthesis can be repeated, but they seldom say much about how to dispose of the hazardous byproducts. Yet the proper disposal of a chemical's byproducts is as important as its proper preparation. Dr. Williamson sets a good example by providing explicit directions for such disposal.

Blaine C. McKusick

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Introduction

Prelab Exercise: Study the glassware diagrams and be prepared to identify the reaction tube, fractionating column, distilling head, addition port, and Hirsch funnel.

Welcome to the organic chemistry laboratory! This laboratory manual presents a unique approach for carrying out organic experiments—they can be conducted on either a microscale or a macroscale. The latter is the traditional way of teaching the principles of experimental organic chemistry and is the basis for all the experiments in this book, a book that traces its history to 1934 when Louis Fieser was its author. Most teaching institutions are equipped to carry out macroscale experiments. Instructors are familiar with these techniques and experiments, and much research in industry and academe is carried out on this scale. These experiments typically involve the use of about 10 g of *starting material*, the chief reagent used in the reaction.

For reasons primarily of safety and cost, there is a growing trend toward carrying out work in the laboratory on a microscale, a scale one-tenth to one-thousandth of that previously used. Using smaller quantities of chemicals exposes the laboratory worker to smaller amounts of toxic, flammable, explosive, carcinogenic, and teratogenic material. Microscale experiments can be carried out much more rapidly than macroscale experiments because of rapid heat transfer, rapid filtration, and rapid drying. Since the apparatus advocated by the author is inexpensive, more than one reaction can be set up at once. The cost of chemicals is, of course, greatly reduced. A principal advantage of microscale experimentation is that the quantity of waste is reduced by one-tenth to one-thousandth of that formerly produced.

To allow maximum flexibility in the conduct of organic experiments, this book presents procedures for the vast majority of the experiments on both the microscale and the macroscale. As will be seen, some of the equipment and techniques are different. A careful reading of the two procedures will indicate what changes and precautions must be employed in going from one scale to the other.

Synthesis and structure determination are two major concerns of the organic chemist, and both are dealt with in this book. The rational synthesis of an organic compound, whether it involves the transformation of one functional group into another or a carbon-carbon bond-forming reaction, starts with a *reaction*.

Organic reactions usually take place in the liquid phase and are *homogeneous*, in that the reactants are all in one phase. The reactants can be solids and/or liquids dissolved in an appropriate solvent to mediate the reaction. Some

*Synthesis and structure
determination*

reactions are *heterogeneous*—that is, one of the reactants is in the solid phase—and thus require stirring or shaking to bring the reactants in contact with one another. A few heterogeneous reactions involve the reaction of a gas, such as oxygen, carbon dioxide, or hydrogen, with material in solution. Examples of all of these are found among the experiments in this book.

An *exothermic* organic reaction evolves heat. If it is highly exothermic with a low activation energy, one reactant is added slowly to the other and heat is removed by external cooling. Most organic reactions are, however, mildly *endothermic*, which means the reaction mixture must be heated to overcome the activation barrier and to increase the rate of the reaction. A very useful rule of thumb is that *the rate of an organic reaction doubles with a 10°C rise of temperature*. The late Louis Fieser, an outstanding organic chemist and professor at Harvard University, introduced the idea of changing the traditional solvents of many reactions to high-boiling solvents in order to reduce reaction times. Throughout this book we will use solvents such as triethylene glycol, with a boiling point (bp) of 290°C, to replace ethanol (bp 78°C) and triethylene glycol dimethyl ether (bp 222°C) to replace dimethoxyethane (bp 85°C). The use of these high-boiling solvents can greatly increase the rates of many reactions.

Running an organic reaction is usually the easiest part of a synthesis. The challenge lies in isolating and purifying the product from the reaction because organic reactions seldom give quantitative yields of one pure substance.

In some cases the solvent and concentrations of reactants are chosen so that, after the reaction mixture has been cooled, the product will *crystallize*. It is then collected by *filtration*, and the crystals are washed with an appropriate solvent. If sufficiently pure at that point, the product is dried and collected; otherwise, it is purified by the process of recrystallization or, less commonly, by *sublimation*.

If the product of reaction does not crystallize from the reaction mixture, it is often isolated by the process of *extraction*. This involves adding a solvent to the reaction mixture that dissolves the product and is immiscible with the solvent used in the reaction. Shaking the mixture causes the product to dissolve in the extracting solvent, after which the two layers of liquid are separated and the product isolated from the extraction solvent.

If the product is a liquid, it is isolated by *distillation*, usually after extraction. Occasionally the product can be isolated by the process of *steam distillation* from the reaction mixture.

Organic reactions are usually carried out by dissolving the reactants in a solvent and then heating the mixture to boiling. To keep the solvent from boiling away, the vapor is condensed to a liquid, which is allowed to run back into the boiling solvent.

On a microscale, reactions are carried out in a *reaction tube* (Fig. 1.1a). The mass of the reaction tube is so small that a milliliter of nitrobenzene (bp 210°C) will boil in 10 s and a milliliter of benzene (mp 5°C) will crystallize in the same period of time. Cooling is effected by simply shaking the tube in a small beaker of ice water and heating by immersing the reaction tube to the appropriate depth in an electrically heated sand bath. On a larger scale, heat transfer is not so fast because of the smaller ratio of surface area to volume in a round-bottomed flask.

Effect of temperature

“Working up the reaction”

Chapter 3: Crystallization

Chapter 7: Vacuum Distillation and Sublimation

Chapter 8: Extraction of Acids and Bases

Chapter 5: Distillation

Chapter 6: Steam Distillation

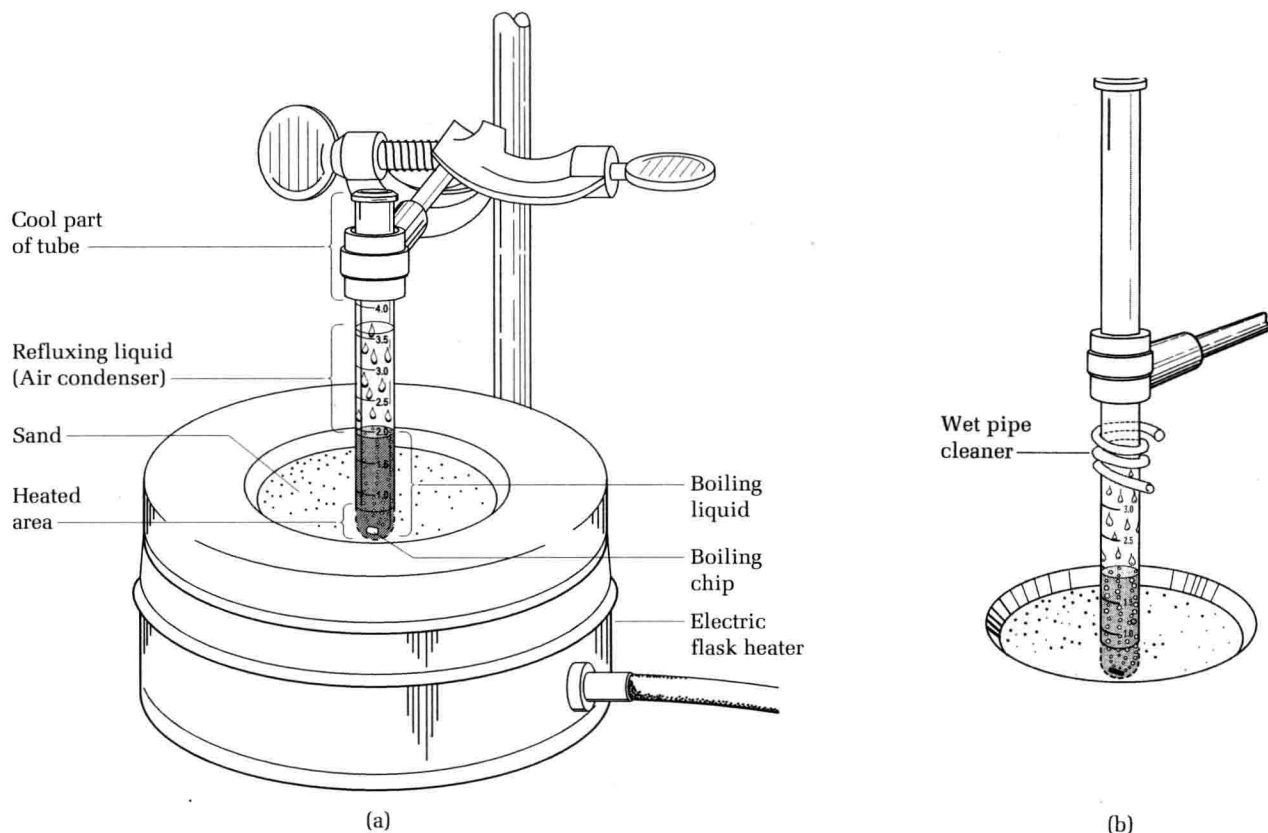


FIG. 1.1: (a) Reaction tube being heated on a hot sand bath in a flask heater. The area of the tube exposed to heat is small. The liquid boils and condenses on the cool upper portion of the tube, which functions as an air condenser. (b) The condensing area can be increased by adding the distilling column as an air condenser.

Cooling is again conducted using an ice bath, but heating is sometimes done on a steam bath for low-boiling liquids. Higher temperatures require electric *heating mantles* or *flask heaters*.

For microscale heating, a *sand bath* in an electric 100-mL flask heater filled with sand is a versatile heat source (Fig. 1.1a). The relatively poor heat conduction of sand results in a very large temperature difference between the top of the sand and the bottom. Thus, depending on the immersion depth in the sand, a similarly wide temperature range will be found in the reaction tube. Because the area of the tube exposed to heat is fairly small, it is difficult to transfer enough heat to the contents of the tube to cause solvents to boil away. The reaction tube is 100 mm long so that the upper part of the tube can function as an efficient *air condenser* (Fig. 1.1a), since the area of glass is large and the volume of vapor is comparatively small. The air condenser can be made even longer by attaching the empty *distilling column* to the reaction tube using the *connector with support rod*

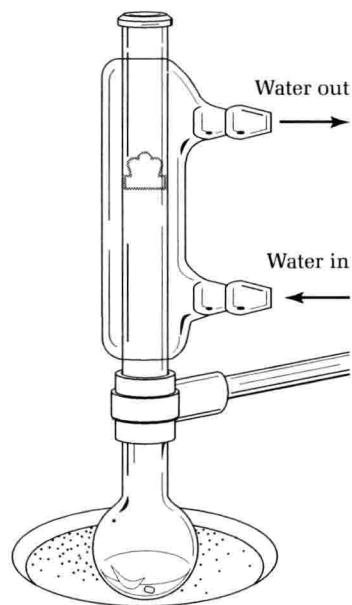


FIG. 1.2: Refluxing solvent in a 5-mL round-bottomed flask fitted with a water-cooled condenser.

(Fig. 1.1b). The black connector is made of Viton, which is resistant to high-boiling aromatic solvents. The cream-colored connector is made of Santoprene, which is resistant to all but high-boiling aromatic solvents. Solvents such as water and ethanol are boiled, and as the hot vapor ascends to the upper part of the tube, they condense and run back down the tube. This process is called *refluxing* and is the most common method for conducting a reaction at a constant temperature, the boiling point of the solvent. For very low-boiling solvents such as diethyl ether (bp 35°C), a pipe cleaner dampened with water makes an efficient cooling device. A water-cooled condenser is also available (Fig. 1.2) but is seldom needed.

On a larger scale, the same electric flask heater or a sand bath on a hot plate can be used to heat a flask that is connected via a *standard-taper ground glass joint* to a water-cooled *reflux condenser*, where the water flows in a jacket around the central tube. The high heat capacity of water makes it possible to remove the large amount of heat put into the larger volume of refluxing vapor (Fig. 1.3).

It is worth noting that the reaction tube (Fig. 1.1a) functions as both flask

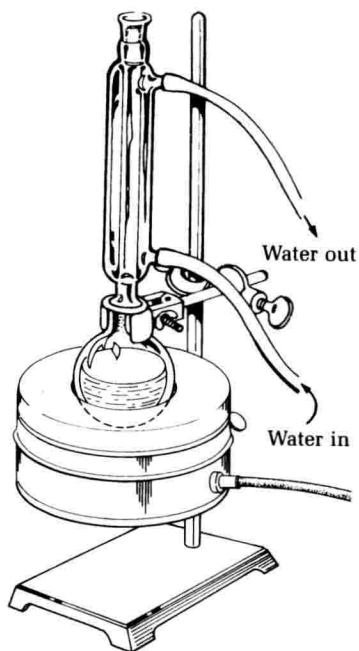


FIG. 1.3: Reflux apparatus for larger reactions. Liquid boils in the flask and condenses on the cold inner surface of the water-cooled condenser.

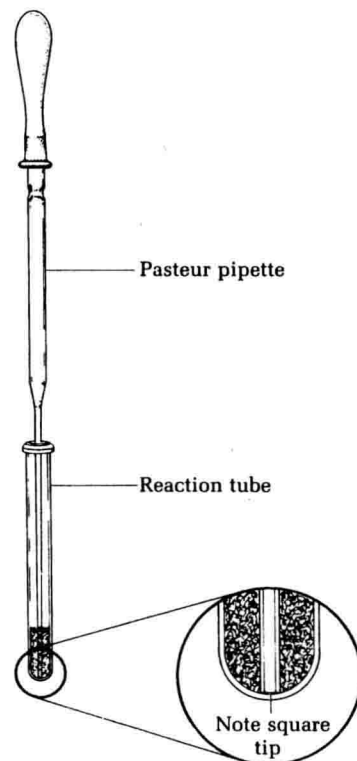


FIG. 1.4: Filtration using the Pasteur pipette and reaction tube.

Chapter 10: Thin-Layer Chromatography

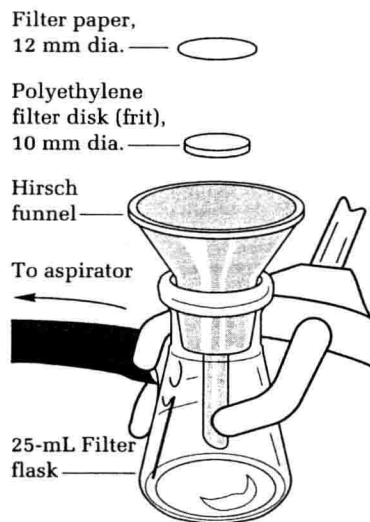


FIG. 1.5: Hirsch funnel with an integral adapter, polyethylene frit, and 25-mL filter flask.

Chapter 11: Column Chromatography

Chapter 8: Extraction

and reflux condenser and is completely equivalent in function to the macroscale standard-taper flask and reflux condenser of Fig. 1.3 but costs about 1/40th as much.

The progress of a reaction can be followed by withdrawing tiny samples at intervals and analyzing them by *thin-layer chromatography*. If the product of a reaction crystallizes from the reaction mixture on cooling, it is isolated by *filtration*. On a microscale, this can be done in several ways. If the crystals are large enough and in the reaction tube, this is accomplished by inserting a *Pasteur pipette* to the bottom of the tube while expelling the air and withdrawing the solvent (Fig. 1.4). Very effective filtration occurs between the square tip of the pipette and the bottom of the tube. This method of filtration has several advantages over the alternatives. The mixture of crystals and solvent can be kept on ice during the entire process. This minimizes the solubility of the crystals in the solvent. There are no transfer losses of material because an external filtration device is not used. This technique allows several recrystallizations to be carried out in the same tube with final drying of the product under vacuum. Knowing the *tare* of the tube (the weight of the empty tube) allows the weight of the product to be determined without removing it from the tube. In this manner a compound can be synthesized, purified by crystallization, and dried without ever leaving the reaction tube. After removal of material for analysis, the compound in the tube can then be used for the next reaction. This technique is used in many of the microscale experiments in this book. When the crystals are dry, they are easily removed from the reaction tube. When they are wet, it is difficult to scrape them out. If the crystals are in more than about 2 mL of solvent, they can be isolated by filtration on the *Hirsch funnel*. The one that is in the microscale kit of apparatus is particularly easy to use because the funnel fits into the *filter flask* with no adapter, and it is equipped with a *polyethylene frit* for removal of the crystals (Fig. 1.5). The *Wilfilter* is especially good for collecting small quantities of crystals (Fig. 1.6).

Macroscale quantities of material are crystallized in *Erlenmeyer flasks*; the crystals are collected in porcelain or plastic *Büchner funnels* fitted with pieces of filter paper in the bottom of the funnel. A *filter adapter* (*Filtovac*) is used to form a vacuum-tight seal between the flask and funnel (Fig. 1.7).

Many solids can be purified by the process of *sublimation*. The solid is heated, and the vapor of the solid condenses on a cold surface to form crystals in an apparatus constructed from a *centrifuge tube* fitted with a rubber adapter (a *Pluro stopper*) and pushed into a *filter flask* (Fig. 1.8). Caffeine can be purified in this manner. This is primarily a microscale technique, although sublimers holding several grams of solid are available.

Mixtures of solids and, occasionally, of liquids can be separated and purified by *column chromatography*. The *chromatography column* for both microscale and macroscale work is very similar (Fig. 1.9).

Often the product of a reaction will not crystallize. It may be a liquid, it may be a mixture of compounds, or it may be too soluble in the solvent being used. In this case, an immiscible solvent is added, the two layers are shaken to effect *extraction*, and after the layers separate, one layer is removed. On a microscale, this can be done with a *Pasteur pipette*, and the process is repeated if necessary.