ORGANIC SYNTHESES

AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

VOLUME 73

1996

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The procedures in this text are intended for use only by persons with prior training in the field of organic chemistry. In the checking and editing of these procedures, every effort has been made to identify potentially hazardous steps and to eliminate as much as possible the handling of potentially dangerous materials; safety precautions have been inserted where appropriate. If performed with the materials and equipment specified, in careful accordance with the instructions and methods in this text, the Editors believe the procedures to be very useful tools. However, these procedures must be conducted at one's own risk. Organic Syntheses, Inc., its Editors, who act as checkers, 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.

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NOTICE

With Volume 62, the Editors of *Organic Syntheses* began a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Divisions of the American and French Chemical Society, The Perkin Division of the Royal Society of Chemistry, and The Society of Synthetic Organic Chemistry, Japan. The soft cover edition is intended as the personal copy of the owner and is not for library use. A hard cover edition is published by John Wiley & Sons Inc. in the traditional format, and differs in content primarily in the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Annual Volumes 65–69 have been incorporated into a new five-year version of the collective volumes of *Organic Syntheses* which have appeared as *Collective Volume Eight* in the traditional hard cover format. It is available for purchase from the publishers. The Editors hope that the new *Collective Volume* series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the 9th and 10th Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendixes. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is preferred.

SUBMISSION OF PREPARATIONS

Organic Syntheses welcomes and encourages submission of experimental procedures which lead to compounds of wide interest or which illustrate important new developments in methodology. The Editoral Board will consider proposals in outline format as shown below, and will request full experimental details for those proposals which are of sufficient interest. Submissions which are longer than three steps from commercial sources or from existing *Organic Syntheses* procedures will be accepted only in unusual circumstances.

Organic Syntheses Proposal Format

1) Authors
2) Title
3) Literature reference or enclose preprint if available
4) Proposed sequence
5) Best current alternative(s)
6) a. Proposed scale, final product:
   b. Overall yield:
   c. Method of isolation and purification:
   d. Purity of product (%):
   e. How determined?
7) Any unusual apparatus or experimental technique?

8) Any hazards?
9) Source of starting material?
10) Utility of method or usefulness of product

Submit to: Dr. Jeremiah P. Freeman, Secretary
Department of Chemistry
University of Notre Dame
Notre Dame, IN 46556

Proposals will be evaluated in outline form, again after submission of full experimental details and discussion, and, finally by checking experimental procedures. A form that details the preparation of a complete procedure (Notice to Submitters) may be obtained from the Secretary.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary. However, checking of such improvements will only be undertaken when new methodology is involved. Substantially improved procedures have been included in the Collective Volumes in place of a previously published procedure.

ACKNOWLEDGMENT

Organic Syntheses wishes to acknowledge the contributions of Hoffmann-La Roche, Inc. and Merck & Co. to the success of this enterprise through their support, in the form of time and expenses, of members of the Boards of Directors and Editors.

HANDLING HAZARDOUS CHEMICALS
A Brief Introduction

General Reference: *Prudent Practices for Handling Hazardous Chemicals in Laboratories,* National Academy Press, Washington, D.C. 1983

Physical Hazards

Fire. Avoid open flames by use of electric heaters. Limit the quantity of flammable liquids stored in the laboratory. Motors should be of the nonsparking induction type.

Explosion. Use shielding when working with explosive classes such as acetylides, azides, ozonides, and peroxides. Peroxidizable substances such as ethers and alkenes, when stored for a long time, should be tested for peroxides before use. Only sparkless "flammable storage" refrigerators should be used in laboratories.

Electric Shock. Use 3-prong grounded electrical equipment if possible.

Chemical Hazards

Because all chemicals are toxic under some conditions, and relatively few have been thoroughly tested, it is good strategy to minimize exposure to all chemicals. In practice this means having a good, properly installed hood; checking its performance periodically; using it properly; carrying out most operations in the hood; protecting the eyes; and, since many chemicals can penetrate the skin, avoiding skin contact by use of gloves and other protective clothing.

a. Acute Effects. These effects occur soon after exposure. The effects include burn, inflammation, allergic responses, damage to the eyes, lungs, or nervous system (e.g., dizziness), and unconsciousness or death (as from overexposure to HCN). The effect and its cause are usually obvious and so are the methods to prevent it. They generally arise from inhalation or skin

contact, so should not be a problem if one follows the admonition "work in a hood and keep chemicals off your hands." Ingestion is a rare route, being generally the result of eating in the laboratory or not washing hands before eating.

b. Chronic Effects. These effects occur after a long period of exposure or after a long latency period and may show up in any of numerous organs. Of the chronic effects of chemicals, cancer has received the most attention lately. Several dozen chemicals have been demonstrated to be carcinogenic in man and hundreds to be carcinogenic to animals. Although there is no direct correlation between carcinogenicity in animals and man, there is little doubt that a significant proportion of the chemicals used in laboratories have some potential for carcinogenicity in man. For this and other reasons, chemists should employ good practices.

The key to safe handling of chemicals is a good, properly installed hood, and the referenced book devotes many pages to hoods and ventilation. It recommends that in a laboratory where people spend much of their time working with chemicals there should be a hood for each two people, and each should have at least 2.5 linear feet (0.75 meter) of working space at it. Hoods are more than just devices to keep undesirable vapors from the laboratory atmosphere. When closed they provide a protective barrier between chemists and chemical operations, and they are a good containment device for spills. Portable shields can be a useful supplement to hoods, or can be an alternative for hazards of limited severity, e.g., for small-scale operations with oxidizing or explosive chemicals.

Specialized equipment can minimize exposure to the hazards of laboratory operations. Impact resistant safety glasses are basic equipment and should be worn at all times. They may be supplemented by face shields or goggles for particular operations, such as pouring corrosive liquids. Because skin contact with chemicals can lead to skin irritation or sensitization or, through absorption, to effects on internal organs, protective gloves are often needed.

Laboratories should have fire extinguishers and safety showers. Respirators should be available for emergencies. Emergency equipment should be kept in a central location and must be inspected periodically.

DISPOSAL OF CHEMICAL WASTE

General Reference: *Prudent Practices for Disposal of Chemicals from Laboratories*, National Academy Press, Washington, D.C. 1983

Effluents from synthetic organic chemistry fall into the following categories:

1. **Gases**

   1a. Gaseous materials either used or generated in an organic reaction.

   1b. Solvent vapors generated in reactions swept with an inert gas and during solvent stripping operations.

   1c. Vapors from volatile reagents, intermediates and products.

2. **Liquids**

   2a. Waste solvents and solvent solutions of organic solids (see item 3b).

   2b. Aqueous layers from reaction work-up containing volatile organic solvents.

   2c. Aqueous waste containing non-volatile organic materials.

   2d. Aqueous waste containing inorganic materials.

3. **Solids**

   3a. Metal salts and other inorganic materials.

   3b. Organic residues (tars) and other unwanted organic materials.

   3c. Used silica gel, charcoal, filter acids, spent catalysts and the like.

The operation of industrial scale synthetic organic chemistry in an environmentally acceptable manner* requires that all these effluent categories be dealt with properly. In small scale operations in a research or academic setting,

*An environmentally acceptable manner may be defined as being both in compliance with all relevant state and federal environmental regulations *and* in accord with the common sense and good judgment of an environmentally aware professional.

provision should be made for dealing with the more environmentally offensive categories.

1a. Gaseous materials that are toxic or noxious, e.g., halogens, hydrogen halides, hydrogen sulfide, ammonia, hydrogen cyanide, phosphine, nitrogen oxides, metal carbonyls, and the like.

1c. Vapors from noxious volatile organic compounds, e.g., mercaptans, sulfides, volatile amines, acrolein, acrylates, and the like.

2a. All waste solvents and solvent solutions of organic waste.

2c. Aqueous waste containing dissolved organic material known to be toxic.

2d. Aqueous waste containing dissolved inorganic material known to be toxic, particularly compounds of metals such as arsenic, beryllium, chromium, lead, manganese, mercury, nickel, and selenium.

3. All types of solid chemical waste.

Statutory procedures for waste and effluent management take precedence over any other methods. However, for operations in which compliance with statutory regulations is exempt or inapplicable because of scale or other circumstances, the following suggestions may be helpful.

Gases

Noxious gases and vapors from volatile compounds are best dealt with at the point of generation by "scrubbing" the effluent gas. The gas being swept from a reaction set-up is led through tubing to a (large!) trap to prevent suckback and on into a sintered glass gas dispersion tube immersed in the scrubbing fluid. A bleach container can be conveniently used as a vessel for the scrubbing fluid. The nature of the effluent determines which of four common fluids should be used: dilute sulfuric acid, dilute alkali or sodium carbonate solution, laundry bleach when an oxidizing scrubber is needed, and sodium thiosulfate solution or diluted alkaline sodium borohydride when a reducing scrubber is needed. Ice should be added if an exotherm is anticipated.

Larger scale operations may require the use of a pH meter or starch/iodide test paper to ensure that the scrubbing capacity is not being exceeded.

When the operation is complete, the contents of the scrubber can be poured down the laboratory sink with a large excess (10–100 volumes) of water. If the solution is a large volume of dilute acid or base, it should be neutralized before being poured down the sink.

Liquids

Every laboratory should be equipped with a waste solvent container in which *all* waste organic solvents and solutions are collected. The contents of these containers should be periodically transferred to properly labeled waste solvent drums and arrangements made for contracted disposal in a regulated and licensed incineration facility.**

Aqueous waste containing dissolved toxic organic material should be decomposed *in situ*, when feasible, by adding acid, base, oxidant, or reductant. Otherwise, the material should be concentrated to a minimum volume and added to the contents of a waste solvent drum.

Aqueous waste containing dissolved toxic inorganic material should be evaporated to dryness and the residue handled as a solid chemical waste.

Solids

Soluble organic solid waste can usually be transferred into a waste solvent drum, provided near-term incineration of the contents is assured.

Inorganic solid wastes, particularly those containing toxic metals and toxic metal compounds, used Raney nickel, manganese dioxide, etc. should be placed in glass bottles or lined fiber drums, sealed, properly labeled, and arrangements made for disposal in a secure landfill.** Used mercury is particularly pernicious and small amounts should first be amalgamated with zinc or combined with excess sulfur to solidify the material.

Other types of solid laboratory waste including used silica gel and charcoal should also be packed, labeled, and sent for disposal in a secure landfill.

Special Note

Since local ordinances may vary widely from one locale to another, one should always check with appropriate authorities. Also, professional disposal services differ in their requirements for segregating and packaging waste.

**If arrangements for incineration of waste solvent and disposal of solid chemical waste by licensed contract disposal services are not in place, a list of providers of such services should be available from a state or local office of environmental protection.

PREFACE

Annual Volume 73, as is the normal practice for this series, contains a series of 28 checked and edited procedures that describe in detail the preparation of generally useful synthetic reagents, intermediates, or products or exemplify important new synthetic methods of expected broad applicability and significance.

This collection begins with a series of three procedures illustrating important new methods for preparation of enantiomerically pure substances via asymmetric catalysis. The preparation of **3-[(1S)-1,2-DIHYDROXYETHYL]-1,5-DIHYDRO-3H-2,4-BENZODIOXEPINE** describes, in detail, the use of dihydroquinidine 9-O-(9′-phenanthryl) ether as a chiral ligand in the asymmetric dihydroxylation reaction which is broadly applicable for the preparation of chiral diols from monosubstituted olefins. The product, an acetal of (S)-glyceraldehyde, is itself a potentially valuable synthetic intermediate. The assembly of a chiral rhodium catalyst from methyl 2-pyrrolidone 5(R)-carboxylate and its use in the intramolecular asymmetric cyclopropanation of an allyl diazoacetate is illustrated in the preparation of **(1R,5S)-(−)-6,6-DIMETHYL-3-OXABICYCLO[3.1.0]HEXAN-2-ONE.** Another important general method for asymmetric synthesis involves the desymmetrization of bifunctional meso compounds as is described for the enantioselective enzymatic hydrolysis of cis-3,5-diacetoxycyclopentene to **(1R,4S)-(+)-4-HYDROXY-2-CYCLOPENTENYL ACETATE.** This intermediate is especially valuable as a precursor of both antipodes **(4R)-(+)-** and **(4S)-(−)-tert-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE,** important intermediates in the synthesis of enantiomerically pure prostanoid derivatives and other classes of natural substances, whose preparation is detailed in accompanying procedures.

Chemoselective and stereoselective general synthetic methods useful for the preparation of a variety of classes of organic molecules are illustrated by the next group of nine procedures. Stereoselective construction of trisubstituted olefins, under investigation since the late 1950's, remains a challenge. Two general, conceptually related, convergent coupling procedures are depicted in the stereodivergent preparation of **(Z)-** and **(E)-6-METHYL-6-DODECENE** via α-dimethylphenylsilyl ketones, and the highly stereoselective preparation of **(E)-2,3-DIMETHYL-3-DODECENE** via thiol esters by way

of thermolysis of the derived β-lactone. A very different approach to olefin synthesis is illustrated by a procedure for preparation of **(Z)-1-ETHOXY-1-PHENYL-1-HEXENE,** which exemplifies a general preparation of trisubstituted enol ethers by alkylidenation of esters. Heteroatom directed *ortho*-metalation is a broadly applicable, highly selective, and efficient method of direct functionalization of aromatic rings. A particularly nice application of this strategy is illustrated in the preparation of **7-INDOLINECARBOXALDEHYDE,** which is not available via traditional aromatic substitution protocols. Development of methods providing acyclic stereocontrol have been of great interest in the past decade. One such method is exemplified by the preparation of **2,3-syn-2-METHOXYMETHOXY-1,3-NONANEDIOL** via intramolecular hydrosilylation. This procedure also details the α-metalation of enol ethers, itself a useful method for the synthesis of a variety of functionalized carbonyl derivatives. The inversion of alcohols is an important and widely employed tactic in organic synthesis. An optimized procedure employing the powerful Mitsunobu protocol is illustrated in the preparation of **(1S,2S,5R)-5-METHYL-2-(1-METHYLETHYL)CYCLOHEXYL 4-NITROBENZOATE.** Hydroboration of olefins affording anti-Markovnikov hydration of olefins is a cornerstone in the arsenal of the modern synthetic organic chemistry. Its use on large scale industrially may be limited by the need to employ hydrogen peroxide to oxidize the intermediate organoborane. The preparation of **(+)-ISOPINOCAMPHEOL** illustrates the use of sodium perborate as a safe, effective, and inexpensive alternative to the use of hydrogen peroxide for oxidation of organoboranes. A simple and effective 1,3-dihydroxylation of silyl enol ethers by oxidation with peracids is illustrated in the preparation of **16α-METHYLCORTEXOLONE** in which the corticoid sidechain is created stereospecifically in one operation. Diazocarbonyl compounds are important, versatile synthetic intermediates. The preparation of **(E)-1-DIAZO-4-PHENYL-3-BUTEN-2-ONE** illustrates a new approach employing diazotransfer to trifluoromethyl β-dicarbonyl compounds that overcomes the limitations of existing methods.

Optimized preparations of important reagents currently not readily available commercially constitute the next group of procedures. The first details an optimized preparation of a mixture of **4-DODECYLBENZENESULFONYL AZIDES,** which can be employed in diazotransfer chemistry such as that illustrated in the preceding procedure. The next procedure illustrates a general preparation of β-ketophosphonates exemplified by the preparation of **BIS(TRIFLUOROETHYL) (CARBOETHOXYMETHYL)PHOSPHONATE,** a widely used reagent for the selective preparation of (Z) electron deficient olefins via the Horner-Emmons protocol. Asymmetric hydroxylation

of enols and enolates has become an increasingly important synthetic method. The last procedure in this group details the preparation of **(+)-(2R,8aS)-[(8,8-DIMETHOXYCAMPHORYL)SULFONYL]OXAZIRIDINE** and the related **(+)-(2R,8aS)-[(8,8-DICHLOROCAMPHORYL)SULFONYL] OXAZIRIDINE,** two reagents which are particularly effective for the asymmetric hydroxylation of 2-tetralones.

The next five procedures of the final set illustrate the important process of preparation of enantiomerically pure materials beginning with readily available enantiomerically pure natural substances. Use of commercially available enantiomerically pure pyrrolobenzodiazepine-5,11-diones to prepare **(1S,2S)-(+)-2-(N-TOSYLAMINO)CYCLOHEXANECARBOXYLIC ACID** is described in the first procedure. The next preparation illustrates an optimized preparation of **DIETHYL (2S,3R)-2-(N-tert-BUTOXYCARBONYL)-AMINO-3-HYDROXYSUCCINATE** from diethyl (+)-tartrate employing neighboring group participation to control substitution stereochemistry. Illustrating a method conceptually related to the Seebach methodology, the next procedure describes an optimized preparation of **(R)-(−)-3-AMINO-3-(p-METHOXYPHENYL)PROPIONIC ACID** from (S)-(+)-asparagine. The first of the final two procedures in this group details a general method for the preparation of γ-keto acids through metalation and alkylation of dihydrofuran followed by hydrolysis as illustrated by the procedure for preparation of **4-KETOUNDECANOIC ACID.** This material serves as the starting point for an accompanying procedure which employs S-(+)-2-phenylglycinol as the chiral template for the preparation of a chiral bicyclic lactam from which **S-(−)-5-HEPTYL-2-PYRROLIDINONE** is derived via a series of reductions including a key stereoselective silane reduction of an acyliminium ion.

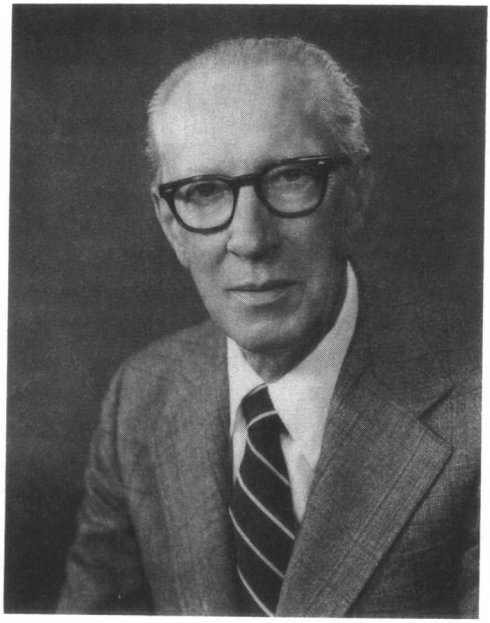
The final series of five procedures presents optimized preparations of a variety of useful organic compounds. The first procedure in this group describes the preparation of **3-BROMO-2(H)-PYRAN-2-ONE,** a heterodiene useful for [4+2] cycloaddition reactions. An optimized large scale preparation of **1,3,5-CYCLOOCTATRIENE,** another diene useful for [4+2] cycloaddition, is detailed from the readily available 1,5-cyclooctadiene. Previously, the availability of this material has depended on the commercial availability of cyclooctatetraene at reasonable cost. A simple large scale procedure for the preparation of **3-PYRROLINE** is then presented via initial alkylation of hexamethylenetetramine with (Z)-1,4-dichloro-2-butene. This material serves as an intermediate for the preparation of 2,5-disubstituted pyrroles and pyrrolidines via heteroatom-directed metalation and alkylation of suitable derivatives. The preparation of extremely acid- and base-sensitive materials by use of the retro Diels-Alder reaction is illustrated in the prepa-

ration of **2-CYCLOHEXENE-1,4-DIONE,** a useful reactive dienophile and substrate for photochemical [2+2] cycloadditions. Functionalized ferrocene derivatives have found utility in a number of contexts, including as chiral ligands in chiral metal complexes employed in asymmetric catalysis. The next procedure details a highly optimized preparation of **ETHYNYLFERROCENE,** a useful intermediate for this purpose, which illustrates a general method for the transformation of aldehydes to the homologous terminal alkyne. The final procedure in this group details a fully optimized, safer method for the large scale preparation of **4,5-DIBENZOYL-1,3-DITHIOLE-1-THIONE,** an important component in the synthesis of bis(ethylenedithio)tetrathiofulvalene (BEDT-TTF), a material which forms a variety of conducting and superconducting charge-transfer salts.

The continuing success of this series derives from the dedicated efforts of many people in the Organic Syntheses family, all of whom are committed to the belief that the reliable, general procedures made available through this series serve an important function in disseminating the important new technology for modern organic synthesis not only among their professional colleagues in industry and academia around the world, but also, most importantly, to the new generation of organic chemists in training at all levels. I thank my colleagues on the Board of Editors for their assistance and dedication in the selection, checking, and in some cases, modification and improvement of the procedures presented herein. Indeed, the benefits of these efforts to our science of organic chemistry accrue in unexpected ways, as was the case when an unanticipated outcome during checking led to new insights and exciting avenues for further investigation. I am especially indebted to Professor Jeremiah P. Freeman, Secretary to the Board, and our Assistant Editor, Dr. Theodora W. Greene, whose invaluable and untiring efforts made my task and that of the entire Board of Editors most enjoyable and interesting. Dr. Greene is especially to be acknowledged for the assembly of the index.

ROBERT K. BOECKMAN, JR.

Rochester, New York
December 1994



THEODORE L. CAIRNS
July 20, 1914–September 16, 1994

Theodore L. Cairns, as a research scientist in the DuPont Company, made important contributions to the science of chemistry, applications of chemistry, and U.S. scientific policy.

Ted was born in Edmonton, Canada, in 1914. After a bachelor's degree from the University of Alberta in 1936, he earned a Ph.D. under Roger Adams at the University of Illinois in 1939. He served as an instructor in organic chemistry at the University of Rochester until 1941, when he joined the Central Research Department of DuPont in Wilmington, Delaware. There he spent the next thirty-eight years, the last eight as the Director of that department.

As a leader in the research of a major chemical company with a high reputation for innovation, his expertise and advice were sought by both scientific and governmental organizations. On the scientific side, he was a member of the National Academy of Sciences. He had an important role on several of its committees, such as those that produced the influential report "Prudent Practices for Handling Hazardous Chemicals in the Laboratory" and a useful survey of basic research in chemistry in the United States. He was active in the

American Chemical Society; for example, he served a term as chairman of the Division of Organic Chemistry.

Cairns was an editor of *Organic Syntheses* from 1949 to 1956, where he gained a reputation as an exceptionally diligent checker of preparations. He was an editor of its sister publication, *Organic Reactions*, from 1959 to 1969.

Cairns served on President Nixon's Scientific Advisory Committee (1970–1973) and on the Delaware Governor's Council on Science and Technology (1969–1972).

Ted's contributions to science and technology were recognized by several awards: The American Chemical Society award for creative work in synthetic organic chemistry (1968); the Perkin medal of the British Society of Chemical Industry (1973); and the Cresson Medal of the Franklin Institute (1974).

I worked directly under Ted for most of my career with the DuPont Company. Like many other DuPont chemists, I found him an encouraging and inspiring leader who took bad breaks, and even foolish blunders, in stride. These qualities served him well not only as a research director, but as an *Organic Syntheses* editor.

BLAINE C. MCKUSICK

October 21, 1994

EVAN C. HORNING
June 6, 1916–May 14, 1993

Evan C. Horning, Secretary of the Board of *Organic Syntheses* (1940–1949) and Editor-in-Chief of Collective Volume III (1995), died on May 14, 1993. After a number of years as an organic chemist, his interests changed to analytical biochemistry where he and his wife, Marjorie, made outstanding contributions to the fields of gas chromatography, mass spectrometry, and gas and liquid-mass spectrometric analysis of biological materials.

Dr. Horning was born in Philadelphia, PA, received a B.S. degree from the University of Pennsylvania (1937) and a Ph.D. from the University of Illinois (1940), doing his thesis work with Professor R. C. Fuson. He was an instructor at Bryn Mawr College during 1940–1941 and became an instructor of chemistry at the University of Michigan (1941). Here he met his wife, Marjorie, who became his co-worker and co-author of numerous publications for over 50 years.

At Michigan, he and his associates studied alkyl-substituted 2-cyclohexen-1-ones and their isomerization to aromatic compounds. Related studies were continued at the University of Pennsylvania where he became an assistant professor (1944) and an associate professor (1945–1947). His interests shifted gradually to the furans, coumarins, and morphine-type compounds. He accepted the position of Chief of the Laboratory of Chemistry at the National Institutes of Health in 1950.