Book Reviews

Bioactive Molecules. Volume 9. Mycotoxins: Chemical, Biological and Environmental Aspects. By Vladimir Betina. Elsevier, New York. 1989. 438 pp, 17.5 × 24.5 cm. ISBN 0-44-9888-8. $155.25.

Volume 1 in this series which was published in 1986 dealt with mycotoxins and phycotoxins. In view of the substantial literature accumulated on this important subject, an updated volume on mycotoxins is very timely indeed. The author has organized this volume through 18 well-written chapters.

Chapters 1–5, introductory in nature, cover mycotoxin-producing fungi and their toxins, the major biosynthetic pathways of mycotoxins, their biological effects, biochemical mode of action, and structure–activity relationships. Chapter 6, dealing with environmental aspects of toxigenic fungi, highlights mycotoxins in agricultural and animal products, their decontamination, and detection in the natural environment. Those engaged in study and control of this growing problem will find it particularly useful.

Chapters 7–18, in expanded coverage, go on to discuss the best known fungal toxin families and individual mycotoxins in some detail with each chapter containing a section on "Environmental Aspects." The author has done an admirable job in presenting a compilation of this magnitude in a clear concise manner. To a beginning researcher, the text provides, through its extensive references, an excellent source of past and ongoing research in the area. In addition to the general index, a separate index of mycotoxin-producing organisms is a very useful feature.

There were a few pages in this reviewer's copy which had faded (but not illegible) printing. From an organic chemist's point of view, some of the structural formulas could have been depicted more clearly. The book should interest not only those working on fungal toxins, but also students and researchers in the fields of microbiology, toxicology, natural products, and environmental sciences. At $155.25 however, some students may find it a bit too expensive.

Chemical Research **Anil K. Saksena**
Infectious Diseases and Tumor Biology
Schering-Plough Research
Bloomfield, New Jersey 07003

Advances in Metal–Organic Chemistry. Volume 1. Edited by L. S. Liebeskind. JAI Press, Inc., London, 1989. xi + 393 pp. 16 × 24 cm. ISBN 0-89232-863-0. $47.10.

This first volume in the series successfully emphasizes the utility of transition-metal reagents in organic synthesis. Editor L. S. Liebeskind encouraged contributors to provide in-depth yet informal discussions of their topics, and this flavor is reflected in the six diverse chapters. The synthetic topics are well distributed with practicing authorities describing their own work in the context of extensive additional references. Slight overlap between molybdenum and iron diene chemistry in two chapters does not detract from the variety of synthetic methods presented.

Some of the standard criticisms common to such volumes apply here. General references through 1985 are common, but more recent references tend to be restricted to those from their own laboratories. In this sense the volume is excellent for providing background information, but significant advances in synthetic applications of transition-metal reagents since 1986 limit this collection of chapters to an introductory role with respect to current activity. The book is well edited and few errors are present. Some schemes are so compact due to reduction that their legibility is questionable. Variation in style, content, and length of the six chapters is substantial.

A. J. Pearson's expertise in diene coordination and elaboration at iron and molybdenum centers is evident in the lead chapter (48 pp, 83 ref). Helpful generalizations, comments on limitations of various methodologies, and occasional experimental procedures are molded into a readable and informative review. I. Ojima provides a thorough coverage of carbonylation reactions of fluorinated substrates (46 pp, 51 ref) with tables of catalytic reaction conditions and product ratios specifying details of interest to practitioners in this area. A. Solladie-Cavallo discusses chiral chromium arene chemistry in an excellent contribution with a succinct introduction to initiate newcomers and guide them through the material (34 pp, 65 ref). J.-E. Backvall deftly surveys the broad range of diene addition reactions mediated by both transition and nontransition metals (40 pp, 91 ref). E. Negishi builds his chapter on a beautiful outline of general approaches to exocyclic alkenes (30 pp, 75 ref). The result is a dense but coherent overview of this area with particular attention given to transition-metal reagents. The final chapter is W. D. Wulff's contribution (184 pp, 190 ref). Applications of heteroatom carbenes have been brought to fruition during the past decade, and this article, which reads somewhat like an extended *Accounts of Chemical Research* manuscript, covers a massive range of chemistry. The benzannulation (3 + 2 + 1) reactions of carbenes receive considerable attention here.

Advances in Metal–Organic Chemistry is an attractive volume that will be a worthwhile addition to private collections for active practitioners in germane areas. It should be found in all technical libraries as a useful reference book.

Department of Chemistry **Joseph L. Templeton**
University of North Carolina
Chapel Hill, North Carolina
27599-3290

Organometallics—A Concise Introduction. By Christoph Elschenbroich and Albrecht Salzer. VCH Publishers, New York. 1989. xi + 479 pp. 17 × 24 cm. ISBN 0-89573-868-6. $38.00.

A comprehensive review of the field of organometallic chemistry, the book (previously released in German) includes material on main-group and transition-metal organometallics. The authors have aspired to provide an overview of the massive volume of information in this field, an almost herculean task (particularly, in fewer than 500 pages). The final product is one of only a few books in existence covering both branches of organometallic chemistry. Divided into 18 chapters, the book covers general background (chapters 1–3), main-group organometallics (chapters 4–11), transition-metal organometallics (chapters 12–17), and then provides a comprehensive bibliography for the interested reader (chapter 18).

Chapters 1–3 provide perspective on the historical development of organometallic chemistry and introduce the general concepts of organometallic reactivity. The main-group organometallic material (chapters 4–11) is arranged according to columns in the periodic table, while the chapters discussing transition-metal organometallics (chapters 12–16) relate the chemistry of all transition metals grouped according to ligands and nuclearity. Chapter 17 discusses catalysis and its importance to industrial chemistry. Besides the interesting and comprehensive text, the authors have included useful appendices that provide information on chemical nomenclature and symbols.

Readers are provided with an excellent description of reactivity trends for organometallic molecules, accompanied by examples, and with a comprehensive and well-written discussion of chemical structure, bonding, and spectral characterization for organometallic systems. Special excursion sections highlight interesting concepts in organometallic chemistry, and frequently emphasize the practical applications. The only flaw in this otherwise excellent book is the authors tendency to provide complete references to only major review articles in most cases and failing to cite more than the author and the year for the examples provided. This may frustrate those organic chemists interested in new synthetic

methods, since the book does not discuss in sufficient depth the scope and limitations of individual reactions.

Overall, however, this book enables the reader to gain a basic understanding of organometallic chemistry. It is well-written and provides adequate depth of information for the massive amount of material covered. It is an excellent introductory text for those students interested in gaining a basic understanding of organometallic chemistry and should be quite understandable to the advanced undergraduate or first-year graduate student.

University of Maryland **James W. Herndon**
Department of Chemistry and Biochemistry
College Park, Maryland 20742

Advances in Pain Research and Therapy. Volume 14. Opioid Analgesia. Edited by Constantino Benedetti, C. Richard Chapman, and Giampiero Giron. Raven Press, New York. 1990. xxvii + 466 pp. 16 × 24 cm. ISBN 0-88167-586-586-5. $98.00.

This volume contains symposium papers presented by the International Association for Study of Pain in Venice, Italy, in honor of the 70th birthday of John J. Bonica of the University of Washington, an eminent teacher and researcher in the field of anesthesiology. In the first section, the history of opium in medicine, the basic pharmacology of opioid receptors including tolerance and dependence, and the pharmacodynamics and pharmacokinetics of opioid analgesics are reviewed. The second section deals with clinical problems such as modes of administration and patient-controlled analgesia.

Representatives of the sponsoring organizations were received by Pope John Paul II who commented, in a message reprinted in this volume, on the supernatural nature of human suffering as the means of man's salvation, but he admitted that there is a human component of physical pain "because in it the person discovers himself, his own humanity, his own dignity, his own mission." No mention was made of the pain suffered by women or by animals. The pharmacologists contributing to the symposium wisely concentrated on measurable facets of pain, analgesia, opioid receptors, and ligands, and the advantages, disadvantages, and mechanisms of action of analgesic agents.

In 1847, John Snow, an early anesthesiologist, wrote "it is not easy to reduce a new branch of science to suitable language in the first attempts". This reviewer could not agree with him more. After 65 years in and out of medicinal research on analgesics, I sense that only the approaches and results of the last decade will matter in the long run. This implies that medicinal chemists who have studied analgesics before that decade should go back to school and acquire new basics in pertinent language and methodology. The volume at hand would then complement and bring up-to-date what such a review process might have taught them.

There are 64 contributors. The first chapter starts simply and readably with a history of pain and of opium and its derivatives. It is beautifully illustrated with photographs of many statues, pictures, coins, etc. of antiquity and later periods depicting opium poppies, painful episodes such as Bernini's Rape of Persephone, which, if performed nowadays, would call forth countless lawyers to defend the hapless girl, and many portraits of physicians and chemists up to Friedrich Wilhelm Adam Sertürner (1783–1841), who in 1817 isolated from *Magisterium opii* crystals of what turned out to be morphine, the take-off substance for the chemistry and pharmacology of alkaloids. There is an account of the opium war in which Britain imposed imports of opium upon China in order to weaken the will of the addicted population to resist, a strategy repeated a century later by the Japanese during their occupation of China.

The discovery of the endogenous opioid peptides and the peptides from which these are fragmented biosynthetically led to the recognition of their Greek-letter receptor sites, μ, δ, and κ. This in turn produced a redefinition of analgesics which should be distinguished from antinociceptives. Analgesic antagonists are also receptor-oriented and these activities can be confirmed both in vitro and in vivo. Norbinaltorphimine is selective as a κ-antagonist, so far only in vitro. The most startling discovery has been that morphine is present in low concentrations in normal animal tissues, where it can be biosynthesized from its nonmorphinan precursor, reticulin. Enkephalin analogues with μ and δ specificity, both linear and dimeric, have been synthesized, while cyclic enkephalin analogues with greater rigidity can decrease their adaptability to the binding requirements of different receptors. In the series of enkephalins as well as of synthetic morphine analogues (ethylketazocin) and benzodiazepines (trifluadom) SAR studies are still of great importance, but the pharmacological profile of these compounds can be more clearly defined with sources of one or another of opioid receptors, e.g. the mouse was deferens and dopamine neurons. Even so, none of the many peptides tested has attained more than limited utility as a drug.

Other chapters examine opiate transmission with biogenic amines and the social problems posed by tolerance and dependence. This particular report should be required reading for those who work on these urgent contemporary problems.

This is an important collection of studies in pain research. Together with the amply referenced clinical observations, they should be on the shelves of antinociceptive pharmacologists and anesthesiologists.

510 Wiley Drive **Alfred Burger**
Charlottesville, Virginia 22901

Chirality and Biological Activity. Edited by Bo Holmstedt, Hartmut Frank, and Bernard Testa. Alan R. Liss, Inc., New York. 1990. xvi + 283 pp. 15 × 23.5 cm. ISBN 0-471-56225-2. $120.00.

This is the Proceedings of an International Symposium held at Tübingen, Federal Republic of Germany, April 5–8, 1988. Although the significance of molecular chirality to the chemistry of life has long been recognized, detailed examination of the principles and mechanisms has become possible only recently by utilizing modern technology. Previous symposia on biological stereoselectivity have focused mainly on its role in drug action and metabolism. The objective of the present symposium was to foster interactions of scientists from different areas, i.e. those interested in development of stereoanalytical methods, others concerned with the molecular principles of chiral recognition and biological stereoselectivity, as well as those concerned with a focus on the more practical significance of chirality in pharmacology and toxicology.

The organizers were successful in achieving their objectives as amply evidenced by the breadth of coverage provided in this book, which is comprised of four parts, each consisting of two to nine presentations by experts in the field. The introductory part (A) gives a historical review of the use of enantiomers in biological studies and the basic definitions and concepts of biochirality. Part B is devoted to various analytical and bioanalytical techniques for studying chirality. Biological and metabolic aspects of biological stereoisomers are the subject of part C. In part D selected topics relating to pharmacokinetic and pharmacodynamic aspects of biochirality are addressed. Each section is followed by a list of pertinent references. A comprehensive subject index is also included.

All medicinal chemists are likely to find one or more topics of interest in this well organized and carefully edited volume; however, only few will be concerned with the entire book. *Chirality and Biological Activity* is clearly recommended for all institutional libraries.

Staff

Bioactive Molecules. Volume 19. Leukotrienes and Lipoxygenases. Chemical, Biological and Clinical Aspects. Edited by Joshua Rokach. Elsevier Science Publishers B.V., Amsterdam. 1989. xxxii + 518 pp. 17 × 24.5 cm. ISBN 0-444-87464-x. $189.50.

This volume is a multidisciplinary overview of leukotriene research and is organized into the following chapters: 1. Chemistry of the leukotrienes and other lipoxygenase products; 2. Biochemistry of the lipoxygenase pathways; 3. Assay methods for various lipoxygenase products; 4. Pharmacology and pathophysiology of leukotrienes; 5. Evidence for the involvement of

leukotrienes and other lipoxygenase products in disease states; and 6. Enzyme inhibitors and leukotriene receptor antagonists. Twelve of the sixteen contributors are from Merck, including the editor. The subject index and, in particular, the table of contents are highly itemized and helpful.

This book is unique in that it is a very detailed compilation from *both* a chemistry and a biology point of view, and thus is quite useful to both the synthetic organic chemist as well as the pharmacologist. The first chapter is an exhaustive survey of the synthetic efforts around leukotrienes and their analogues, including details about reaction conditions and SAR data. The next chapter discusses the biosynthetic pathways of the leukotrienes, the characterization of the enzymes, and the lipoxygenase product distribution from various cell types. The different assay methods are compared in the third chapter with brief experimental details. The next two chapters deal with the biological activity of the leukotrienes in various in vitro assays and in vivo models. The evidence for the role of leukotrienes as mediators in various disease states and, hence, the implications for drug intervention are discussed at length and these chapters are thorough literature reviews. The last chapter is also an excellent review of all the known (up to about early 1988) lipoxygenase inhibitors and leukotriene receptor antagonists with extensive comparative analyses. This is not only useful from an informational point of view but also from a historical perspective of drug development in this field.

The major drawback of the book is that the book is already somewhat dated. There is only the occasional 1988 reference; most of references being pre-1987. This is particularly a drawback in this field of research where there have been so many recent developments, especially with respect to emerging clinical data. These data are discussed briefly in the Conclusion; however, this section contains no references.

Overall, I found the book to be an extensive review of the leukotriene/lipoxygenase area up to 1988, and I don't believe that any other review as complete as this one exists. It is an excellent reference source, particularly for those new to this area of research.

Pfizer Central Research **Hiroko Masamune**
Groton, Connecticut 06340

Progress in Medicinal Chemistry. Volume 26. Edited by G. P. Ellis and G. B. West. Elsevier Science Publishers B.V., Amsterdam. 1989. vii + 586 pp. 15 × 21.5 cm. ISBN G-444-81038-2. $197.25.

This volume provides a compendium of six reviews, three relating to cancer therapy. These include a very comprehensive treatise on antifolates, and two timely contributions on aromatase inhibition in breast cancer and endocrine treatment of prostate cancer. The remaining three chapters span diverse topics, including the use of microcomputers in biomedical education, a broad treatise on the use of high field NMR spectroscopy in medicinal chemistry, and finally a stimulating review of the pharmacology of copper complexes and their possible role in the treatment of chronic diseases.

The chapter on the antifolates provides a wonderfully detailed review of the medicinal chemistry surrounding methotrexate (MTX). While summarizing the wealth of synthetic chemistry developed in the course of 40 years that followed the discovery of MTX, the author also details the pharmacological insights provided by the availability of numerous close analogues. The chapter is dissected along structural grounds, on the basis of the site of modification of the parent MTX. In the current era, where study of the molecular biology of clinical and experimental disease is gaining emphasis, this chapter reinforces the value of small-molecule pharmacology (and dedicated medicinal chemistry) in the elucidation and manipulation of metabolic and biochemical pathways in normal and pathologic states.

The hormonal approach to the therapy of estrogen-dependent breast cancer begins with frontline use of antiestrogens and follows with second-line treatment with aromatase inhibitors, in an attempt to suppress circulating estrogen levels after direct antagonism fails. The chapter describing this approach details the development of increasingly potent and selective steroidal and nonsteroidal inhibitors of aromatase, and concentrates on a number of chemical strategies for the development of steroidal enzyme-activated irreversible inhibitors. The clinical data supporting this therapeutic strategy is not extensively discussed, particularly the rationale for upstream inhibition (estrogen-biosynthesis inhibition) in a setting where direct antagonism (estrogen-binding inhibition) fails. In contrast, the chapter on the endocrine treatment of prostate cancer concentrates almost exclusively on the clinical experience with various therapeutic strategies (castration, estrogen and progesterone suppression of pituitary gonadotropin release), and provides a detailed biological rationale for those approaches. The bulk of the chapter deals with the preclinical and clinical pharmacology of the lutenizing hormone releasing hormone analogue goserlin. Little detail of the medicinal chemistry or general pharmacology of this class of agents is described, but the chapter does provide a nice description of a successful drug discovery and development program.

Computer-assisted learning (CAL) is addressed in a basic fashion in a chapter providing general background on microcomputer features and structural organization. This is followed by a description of the advantages and pitfalls of interactive strategies for the use of microcomputers as an educational aid in biomedical education. The very basic nature of this chapter allows it to be a useful primer for CAL in disciplines outside those described. The chapter dealing with high field NMR spectroscopy in medicinal chemistry provides a terse, but very useful guide to practical applications (supported by well-chosen examples) of the spectroscopic techniques that have emerged over the past decade. The reader is walked through studies of complex structure and conformational assignments, as well as studies of intermolecular interactions, using 2-dimensional correlation spectroscopy, heteronuclear methods, classic and transfer NOE techniques, and solid-state NMR. The section conveys a clear sense of the power of modern NMR spectroscopic methods to characterize solution phase (and now even solid phase) structures.

The final chapter in this text deals with a survey of copper complexes and their possible role either directly in the etiology of various disease states or as possible physiologic modulators of the pathology in diseases as diverse as epilepsy, infectious diseases, and cancer. Starting with a summary of copper's role in various enzyme systems and the metabolism of various copper complexes, the section rapidly moves into repeated calls for the study of copper complexes in the therapy of numerous disease states. The most extensive case is made for the use of copper in the treatment of a wide number of inflammatory diseases, although frequently the clinical data cited by the author is either anecdotal or from uncontrolled, small studies.

Once again, the timeliness and quality of the chapters in this compendium are of high quality, providing useful overviews for both those with a general interest and also for researchers in the areas covered by the reviews.

Department of Medicinal Chemistry **Eric R. Larson**
Central Research Division
Pfizer Inc.
Groton, Connecticut 06340