and by the University of Kansas General Research Fund.

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# *Book Reviews*

**Radiotracer Techniques and Applications. Volume 2.** Edited by E. Anthony Evans and Mitsuo Muramatsu. Marcel Dekker, New York, N.Y., and Basel. 1977. xiii + 524 pp. 16 × 23.5 cm. $49.75.

Volume 2 of this two-volume work is concerned with applications of the radiotracer technique to the life sciences. A diverse field is covered, including biosynthesis, drug distribution and metabolism, pure and applied cytology, enzyme and enzymatic assays, agricultural chemicals, marine biology, competitive binding assays, medical diagnosis, and cancer treatment.

The book is compelling evidence of the power of the radiotracer method in pure and applied biology and of its utility in the solution of biomedical problems. The chapters are generally broad enough in their scope to provide an overview of applications in each of the fields addressed and to make the volume serve also as a reference text.

As in the applications section of the first volume, each chapter is written by a specialist with considerable first-hand laboratory experience, often a major contributor to his field. Thus, the limitations and pitfalls of the methods are as well elaborated as are the uses and advantages.

Except for occasional parochialisms the book is general enough to be used as a text reference for courses in the biological applications of radioactive isotopes. Some chapters taken separately or together will appeal to specialized audiences (e.g., those on biosynthetic studies and drug metabolism); others will give outsiders insight into fields with which they may not be familiar (e.g., the applications to agriculture and marine biology; medical uses as radioimmunoassays, diagnostic procedures, and potential cancer treatments). It should certainly be available to those who use radionuclides regularly in the laboratory.

*Harvard Medical School* **S. James Adelstein**

**Clofibrate and Related Analogs. A Comprehensive Review.** By Donald T. Witiak, Howard A. I. Newman, and Dennis R. Feller. Marcel Dekker, New York, N.Y. 1977. ix + 287 pp. 15.5 × 23.5 cm. $27.50.

This monograph reviews clinical efficacy of the hypolipidemic drug clofibrate, its activity in various animal models, structure–activity relationships of close analogues, and studies to elucidate its mechanism of action. Although comprehensive, one hesitates to call this review authoritative. The efficacy of clofibrate for treatment of heart disease is a matter of controversy and its mechanism of action remains unestablished. The authors do little beyond listing the conflicting pieces of evidence and, for better or worse, make no attempt to present a unifying view as to how clofibrate works.

This book is Volume 7 of the Medicinal Research Series, a new edition in modified format of A. Burger's textbook, "Medicinal Chemistry". While earlier volumes of this series continued more or less in the format of the textbook, the present volume does not. The subject matter is too narrow and too comprehensively treated to lend the book any of the qualities of a textbook. Its usefulness for teaching and learning purposes is therefore limited. Its primary use is as a factual literature survey for biomedical researchers and reviewers. References (774), a good index, and a glossary of selected terms are included. The book is printed by a photocopying process of a double-spaced typewritten manuscript. The 171 pages of text and the 92 pages of references could have been reduced to half or less. At $27.50 this is hardly a bargain.

*Richardson-Merrell, Inc.* **J. Martin Grisar**

**Topics in Antibiotic Chemistry. Volume 1.** Edited by Peter Sammes. Ellis Harwood Limited, Chichester, Sussex, England. 1977. 217 pp. 14.5 × 22.7 cm. $28.50.

This book is the foundation volume for a projected series designed to keep interested workers abreast of antibiotic progress. While seeking a broad disciplinary coverage, the emphasis is to be chemical in describing mechanisms of biosynthesis, the modes of action, and mechanisms of resistance development for the ever-increasing number of antibiotics being characterized today. The achievement of this volume is the review of two families of antibiotics, the aminoglycosides and the ansamycins. It would seem that more classes of compounds could be considered in each volume to assure a reasonable coverage of this large field.

Part A, comprising 99 pages and 214 references, reviews the aminocyclitol antibiotics quite fully from a theoretical viewpoint through the year 1975. It is subdivided on topics of structure, biotransformation, resistance, structure activity, chemistry, and synthesis. Little attention is given to the methodology of recognition, so important for dereplication in the search for new

aminoglycosides. The assay of aminoglycosides is also a by-passed subject in spite of its particular importance in the monitoring of blood levels in clinical applications.

The ansamycins are reviewed in Part B with major emphasis on the clinically important rifamycins. This section does give attention to experimental detail in the areas of fermentation and assay. This reviewer, who has first-hand familiarity with the circumstances of the discovery and development of the streptovaricins has two observations in the interest of accuracy. The streptovaricins were described considerably prior to the rifamycins, 1957 vs. 1959, rather than "concurrently" (p 96). Furthermore, the loss of interest in the streptovaricins was totally unrelated to the successful utilization of the rifamycins as suggested in this volume (p 123). Clinical interest actually declined due to lack of merit in the areas of testing, prior to any announcement of the rifamycins in the literature.

The text is clearly presented, with only a few errors. Structural formulas are well done. The index, however, is a bit sketchy and somewhat inconsistent. This book deserves a place in technical libraries as a reference work for those interested in the antibiotic field.

*The Upjohn Company* **Herman Hoeksema**

**Major Medicinal Plants; Botany, Culture and Uses.** By Julia F. Morton. Charles C Thomas, Springfield, Ill. 1977. xix + 431 pp. 17.5 × 25.5 cm. $49.50.

Any compilation of major medicinal plants will reflect the preferences of the compiler and while few will doubt the modern importance of the opium poppy, Rauvolfia, Cinchona, Digitalis, and the like, it might be difficult to achieve a concensus concerning Storax, Podophyllum, Juniper, and the Marsh Mallow to name but a few of the plants described in this volume. In any case it can be argued that the major modern use of *Erythroxylon coca* is neither medicinal nor legal! In terms of use, there is an apparent emphasis on folk remedies or historical use (e.g., the U.S. Dispensatory of 1960) at the expense of references to the modern status of these drugs as reflected in recent texts on pharmacology, medicinal chemistry, or therapeutics.

The book is beautifully illustrated, partly in color, which no doubt added to its cost. The publishers have set off each chapter with its own front end papers creating an attractive volume which is, however, approximately 20% blank paper. The book will appeal less to the medicinal chemist than to the pharmacognosist or the economic botanist, either of whom may find it a useful reference to the history of some of our natural drugs.

*Northeastern University* **Robert F. Raffauf**

**Spin Labeling Methods in Molecular Biology.** By G. I. Likhtenshtein. Wiley, New York, N.Y. 1976. xiii + 258 pp. 16 × 23.5 cm. $33.00.

Spin labeling methods and their possible applications have been the subject of several recent review-type articles as well as a variety of treatments of a more specialized nature. Likhtenshtein's monograph "Spin Labeling Methods in Molecular Biology", first published in Moscow in 1974, belongs to the category of review-type publications; it is offered here by Wiley-Interscience as a translation of the original text.

Likhenshtein's monograph begins with an introduction into a few elementary principles of EPR spectroscopy—a section which seems too short and incomplete to be of any real value. As the author turns to more specific aspects of spin labels and spin labeling methods the reader finds himself confronted with McConnell's concepts which are, without much preparation, treated in a few lines of text (p 4). Brief sections deal with general topics such as ranges of rotational correlation times, some concepts of anisotropy, and the "search for the mechanism for the elementary motion of the radical".

Subsequent sections are devoted to the "slow motion case" with special consideration given to the work of Kuznetsov and of Goldman et al. and to the "ultraslow region" which includes in some detail the work of Hyde on rapid adiabatic passage phenomena and the Wallach models. The author concludes his introductory chapter with a description of some of the theoretical approaches by Vasserman et al. (p 14) to cases of anisotropic rotation and attempts to provide experimental support for some of the reviewed concepts. All this is familiar reading for the EPR spectroscopist, a well-trained physical chemist or a physicist. The fragmentary treatment of these important topics, however, will not allow a newcomer to the field to follow the presented arguments with a great deal of understanding.

Chapter 2 is dedicated to the synthesis of spin labels and spin labeled compounds. Structural formulas for about 50 derivatives of the familiar five- and six-membered heterocyclic nitroxide free radicals are listed in table format (pp 24–29) with limited additional information and some references. Presentation of synthetic aspects of these compounds—an area where so much important work has been done by Russian chemists—is unfortunately much too brief. Additional tables (pp 35–36) provide essentially only literature references to some spin labeled enzymes and proteins and a few data for spin labeled lysozyme. This chapter contains many useful references. As written, though, it is neither helpful to the newcomer who lacks the necessary background nor is it useful to the experienced researcher who is looking for specific information on spin label compounds.

"Double Paramagnetic Labels" (chapter 3) is perhaps the most informative chapter of the monograph. It presents the underlying principles and selected applications and gives due credit to the accomplishments of the Russian scientists who have put much effort into the use of double labeling techniques.

In chapter 4, the author discusses briefly some aspects of relaxation phenomena in, at best, semiquantitative form and presents some interesting possibilities of the use of paramagnetic ions (using the descriptive but perhaps confusing term "spin probes").

In chapter 5, attention is shifted to possible applications of NMR spectroscopy. It begins with the familiar Solomon–Bloembergen equations, continues with a description of some aspects of relaxation rates, and leads—after the introduction of quite arbitrarily selected values of an apparent correlation time—to a rather useless set of expressions (eq 5.11–5.14, p 94) for the determination of distances. Several actual applications of NMR spectroscopy (e.g., phosphorylase, alcohol dehydrogenase) are then carefully reviewed.

The following two chapters deal with conformational changes in proteins and enzymes and problems related to the local mobility of water. Chapter 6 contains a well-selected review of uses of spin labels to studies of allosteric effects (including the work of McConnell and his colleagues and a concise review of recent Russian work). Why other applications of spin labels in enzymology are not treated here but later on in chapter 9 remains puzzling. Attempts to use measurable parameters of nitroxide labels to monitor the physical state of water and molecular mobilities are outlined in chapter 7, using predominantly material derived from the work of Russian scientists (including the author himself). This is indeed a quite interesting—while perhaps controversial—section but may be difficult for the novice to follow in detail.

Use of fluorescent probes—referred to by the less familiar term "luminescent chromophore groups"—is treated in chapter 8 without much objective information about either theoretical background or typical applications. Why the (well presented) section on Mössbauer spectroscopy and that on the use of heavy atoms in electron microscopy are included in the context of this short monograph is not quite clear.

In chapter 9, the author returns to topics in enzymology. The material selected from literature sources seems more concerned with topics on structure and mode of action of enzymes than with questions related to spin labeling. The final chapter (pp 190–232) of the monograph provides a detailed and informative review of biological and artificial membrane systems. In a brief appended section spin label studies with nucleic acids are reviewed.

Likhtenshtein's book is intended to present "the theoretical and experimental basis for the application of spin labels and spin probes...to a wide range of scientists ranging from undergraduate students to graduate students and experienced researchers". To cover the essentials of the underlying principles of spin labeling methods together with a representative review of applications in the form of a short monograph with roughly 250 pages is definitely

a very ambitious and exceedingly difficult task, especially as one must consider that EPR spectroscopy itself, the method most frequently employed, is far from being a trivial form of spectroscopy. The author has made considerable efforts to cover such an exceptionally wide range in his book. In doing so he frequently chose simple arithmetic expressions which apply only to a limited range of conditions and used these expressions to discuss the important relationships, unfortunately without ever really specifying the particular limitations.

The translation has been executed by someone who knows the two languages of concern quite well but seems not too experienced in handling scientific terminology. The quality of the illustrations and the accompanying captions leaves much to be desired. The figures are often poorly chosen for the particular purpose. The captions are not always clearly expressed and frequently lack the essential information for interpretation of the illustrations (cf. for instance Figure 16, pp 46–47, where excerpts of EPR spectra of liquid and frozen samples are provided side by side in a barely comprehensible way). A minimal amount of technical editing could have eliminated many of these problems in translation and the illustrations and, thus, substantially improved the readability of this book.

The most important contribution which Likhtenshtein's monograph makes to the rapidly expanding literature on spin labels and applications of spin labeling techniques to biological systems rests with its extensive bibliography (583 references). Of special value to most readers will be the review-type material on much of the Russian work which is not too well known and may not be readily accessible. It is on these grounds that I recommend the book to the experienced scientist as a useful addition to his working library. For this group of readers, the monograph also does contain sufficiently new and unusual ideas which can stimulate much creative and investigative thinking.

I must hesitate, on the other hand, to recommend this book unreservedly to a newcomer in the field of spin labeling. He might at best consider it as a possible addition to a highly specialized collection of advanced level books, which cannot realistically be used without other fundamental reference works and without the necessary background knowledge for critical assessment and independent work in this field.

*University of Pennsylvania* **Heinz Schleyer**

**The Total Synthesis of Natural Products. Volume 3.** Edited by John ApSimon. Wiley-Interscience, New York, N.Y. 1977. ix + 566 pp. 15.5 × 23.5 cm. $35.00.

I have an allergy toward multi-authored books, an affliction which does not dissipate itself with the present text. Consider the dilemma faced by its conscientious editor, Professor John ApSimon of Carleton University. This book was originally planned as a four chapter work; unfortunately, only three chapters materialized on schedule. Three years later, and one can imagine the frustration on all sides of just waiting, it was decided to go to press with only three chapters and to add at the end of each of these a list of references to cover developments for the past 3 years. The result, in spite of the valiant efforts of its editor and authors, is that the book is dated even before it appears. Maybe the solution is to publicize the names of would be authors that promise to contribute chapters, and then do not come through, so that they can be properly ostracized!

The first chapter, written by Professor Kametani, covers the synthesis of isoquinoline alkaloids. The subject matter is arranged in terms of synthetic methods: Bischler–Napieralski, Mannich, phenolic coupling, photochemistry, etc. This is not the usual way of discussing this topic which is commonly handled by alkaloidal groups: simple isoquinolines, benzylisoquinolines, aporphines, protoberberines, etc. Nevertheless, this chapter is a fresh and worthwhile presentation, but one which will be much more easily read, enjoyed, and understood by the specialist in the field than by the novice or uninitiated.

One point needs to be clarified at this stage. On p 129 it is stated: "In 1957, Barton and Cohen proposed the theory of phenolic oxidation in the biogenesis of aporphine alkaloids". This is a somewhat misleading statement since back in 1932 Robinson and Schöpf independently attempted the oxidation of *N*-methyllaudanosoline in an effort to prepare an aporphine. In justice to Professor Kametani, however, he does bring up this contribution of Robinson and Schöpf on pp 143–145.

Professor Kutney is the author of the second chapter, which covers the synthesis of indole alkaloids. Although the book has few typographical errors, it is Professor Kutney's misfortune that every page from 287 to 385 is headlined: "Total Synthesis of Alklaoid [sic] Families". This is only a very minor and somewhat amusing irritant. One should bring up here another characteristic of multi-authored books, namely, that each author will use the approach he deems best to cover his material. In lieu of the Kametani "methods" approach, the presentation this time is in terms of alkaloidal groups: yohimbine, oxindole, strychnine, etc. The discussion of the material is generally readable and lucid, and Professor Kutney has done an admirable job of covering a complex subject.

In the third chapter, Professor Stevens deals with the synthesis of the Mesembrine, Amaryllidaceae, Lycopodium, and Erythrina alkaloids, even though the topic of the Amaryllidaceae and Erythrina alkaloids was covered to some extent in the first chapter. Nonetheless, Professor Stevens has written an intelligent and well thought-out analysis of the subject matter, which made the chapter a pleasure to read.

The jacket to the book puts forth the claim that: "This three-volume set has been compiled to provide the first definitive reference for...synthetic approaches...of natural products". In view of the 3-year delay in publication, one can question whether indeed it is "definitive". The book will, however, find utilization as a useful source of references and as a mechanism for a general review of synthetic approaches to alkaloid synthesis. Short compounds and reactions indexes have been appended, but no author index is available. The price of $35 is reasonable by present standards for a book which is 566 pages long.

*The Pennsylvania State University* **Maurice Shamma**

**Anticonvulsants. Volume 15. Medicinal Chemistry.** Edited by Julius A. Vida. Academic Press, New York, San Francisco, London. 1977. ix + 638 pp. 15.5 × 23.5 cm. $59.00.

This text is directed especially to medicinal chemists who are or may become interested in the research and development of new anticonvulsant agents, but it should be useful to others interested in the therapeutics of epilepsy. The first comprehensive review of its kind, prepared by W. J. Close and M. A. Spielman, covered the literature through 1958 and was published as a chapter in "Medicinal Chemistry", Vol. V (W. H. Hartung, Ed., Wiley, New York, N.Y., 1961). This review covers the literature from 1959 through 1975. The format followed is, to a marked degree, that used by Close and Spielman with modifications to suit the purpose of the authors of the various chapters.

Chapter 1 presents a short review of currently available anticonvulsant agents, trade and generic names and dates for those marketed in the United States, and brief comments on the utility of these drugs for treatment of various types of epilepsy.

Chapter 2 is a relatively short discussion of the neuropharmacology and treatment of epilepsy; yet, it is sufficiently detailed to provide some understanding of the nature and diversity of epileptic seizures, possible causes, and the pharmacological and clinical aspects of the use of current drugs for treatment of specific types of seizures. Medicinal chemists will appreciate this overview as background to a search for new and better anticonvulsant agents.

Chapter 3 is a discussion of methods various investigators have used in attempts to assess anticonvulsant activity in animals, only a few of which are widely used regularly. Factors such as route of administration, time of peak effect, importance of animal species and strain, type of convulsion-inducing agent, and manner of reporting data are noted. Data for most types of known clinically effective anticonvulsants are presented.

Chapter 4 is a discussion of the physiological disposition of major types of anticonvulsant agents, including factors that influence absorption, distribution, metabolism, and excretion. The importance of such information for the design of more effective drugs as well as in developing the most effective regimen for a useful drug is noted.

Chapter 5, "Cyclicureides", covers barbiturates, hydantoins, oxazolidinediones, succinimides, and a few closely related compounds. The author has recapitulated some aspects of what Close and Spielman reviewed, summarized new information that has been published in the last nearly two decades on these agents, and developed some new perspectives. The many new analogues which have been reported are tabulated with indications of anticonvulsant activity in animal models.

Chapter 6, "Benzopyrans", is a review of work that has been reported on the investigation of cannabinoids and related synthetic analogues as potentially useful anticonvulsant agents. Approximately 110 compounds (natural and synthetic) are listed in tabular form with animal experimental data. Activity in this type of compound appears to be most readily detected by the audiogenic seizure test but a few derivitized cannabinoids showed potent activity in the maximal electroshock test.

Chapter 7 covers the reported literature on heterocyclic compounds except those reported in Chapters 5 and 6. Compounds with rings of three to seven or more atoms and with one or more heteroatoms as well as mono-, di-, and polycyclic compounds are included. This very large and diverse group of compounds is recorded in 95 tables. Animal data are included when possible but are often of limited significance. Benzodiazepines are discussed in a separate section and table. Acetazolamide, several diazepines, sulthiamine, and carbamazepine have been shown to be clinically effective. Animal test data suggest that some of the many other reported compounds may deserve further study.

Chapter 8 is concerned with "noncyclic anticonvulsants" but only in the sense that what is viewed as the pharmacophoric group is noncyclic. Ureas, carbamates, carboxylic acids and amides, sulfonamides, and hydrazones with noncyclic and cyclic moieties are discussed. Among these compounds, the sodium salt of *n*-dipropylacetic acid is remarkable for its simplicity and effectiveness in several types of epilepsy. The authors discussed the possibility that valproic acid exerts its effect by influencing levels of GABA in cerebral tissues.

The text is well written and contains only a very few typographical or formula errors. It is replete with references. The index appears adequate. Indexing each of the many individual compounds reported would have been impractical. The reader seeking the presence or absence of a specific compound must search the tables. Anyone interested in therapy for epilepsy will find it a useful reference, especially for the medicinal chemist.

*The Franklin Institute* **Glenn E. Ullyot**

**Design of Biopharmaceutical Properties through Prodrugs and Analogs.** Edited by Edward B. Roche. American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D.C. 1977. viii + 455 pp. 15 × 23 cm. $20.00 (APhA Member $13.00).

This book contains papers delivered at a symposium organized by the Medicinal Chemistry Section of the Academy of Pharmaceutical Sciences in Nov 1976. The objective of the volume is to present broad coverage of the development of both prodrugs and analogues which change the absorption, distribution, metabolism, and excretion of drug prototypes. One of these objectives, namely, the design of prodrugs for improved absorption, is well met. The other purposes are only partially fulfilled.

The book includes chapters with the following titles: (1) Perspective on Prodrugs and Analogs in Drug Design; (2) Receptor Site Consideration in Structural Modification; (3) Structural Aspects of Selective Distribution; (4) Structural Effects of Partitioning Behavior of Drugs; (5) Correlation Analysis in the Design of Pharmacodynamic Properties of Drugs; (6) Alteration of Pharmacokinetics through Structural Modification; (7) Novel Approaches for the Design of Membrane Transport Properties of Drugs; (8) Physical Model Approach to the Design of Drugs with Improved Intestinal Absorption; (9) The Prediction of Chemical Lability through Substituent Effects; (10) Design of Prodrugs through Consideration of Enzyme–Substrate Specificities; (11) Alteration of Drug Metabolism through Structural Modification; (12) Application of Physical Organic Principles to Prodrug Design; (13) Solubility and Melting Point Considerations in Drug Design; (14) Prodrug, Molecular Structure and Percutaneous Delivery; (15) Design of Improved Taste Properties through Structural Modification. Most of the chapters are well written and adequately referenced. The reviewers were particularly impressed with chapters 6 (Robert E. Notari), 7 (N. Bodor), 8 (N. F. Ho, J. V. Park, W. Morozowich, and W. I. Higuchi), 9 (M. Charton), 10 (G. L. Amidon, R. S. Pearlman, and G. D. Leesman), 11 (S. D. Nelson), and 12 (W. Morozowich, M. J. Cho, and F. J. Kezdy). These, more than the remaining presentations, exemplify one of the very strong points of the volume. That is, a wealth of ideas are presented for the researcher interested in prodrug design, synthesis, and biopharmaceutical evaluation. For this reason alone, the reviewers can heartily recommend the book.

Several authors in the text point out the difficulty inherent in preparing analogues to modify pharmacokinetic features of a drug. Perhaps this is why few examples of this type of endeavor are presented despite the mention in the book's title. Furthermore, the reviewers found little description of the design of prodrugs for desired distribution or excretory patterns. However, this may again reflect the state of the art. One other shortcoming of the volume is its somewhat incomplete index. For example, at least two chapters provide information of apomorphine; yet, only one is indexed.

Overall, the book presents modern concepts in a scholarly manner, is fairly priced, and is generally free of typographical and substantive errors. Additionally, material is presented that is likely to become of increasing importance to medicinal chemists. For these reasons, the authors recommend its availability to all students and researchers in medicinal chemistry and allied drug sciences.

*University of Texas at Austin* **William H. Soine**
**Robert V. Smith**

**The Antigens. Volume 4.** Edited by Michael Sela. Academic Press, New York, N.Y. 1977. xiv + 582 pp. 23.5 × 15 cm. $41.00.

The antigens discussed in this volume, each as a chapter, are lipids, antibiotics, protective antigens of bacteria, and pathogenic fungi. The remaining three chapters cover antigenic competition, adjuvants, and lectins. Obviously, lipids as antigens play a significant role in the story of cellular antigens. For example, Forssman antigen is a lipid. Thus, the chapter on lipids is particularly timely and important. The chapter on antibiotics is concerned with the ability of these agents to act as immunogens, antigens, and allergens. The immunology of the bacterial and fungal antigens is important for an understanding of both their infectious and structural properties. The chapter on in vivo antigenic competition examines models involving interacting cells. The great variety of both adjuvants and lectins makes the last two chapters particularly enjoyable to read. Thus, this series continues to feature selected, important topics and cover a broad variety of immune phenomena. It is also to be commended for consistently drawing upon authoritative contributors.

**Staff Review**

## Books of Interest

**R Factor (Drug Resistance Plasmid).** By Susumu Mitsuhashi. University Park Press, Baltimore, Md. 1977. vii + 315 pp. 16 × 23.5 cm. $29.50.

**Neurotoxicology. Volume 1.** By Leon Roizin, Hirotsugu Shiraki, and Nenad Grčević. Raven Press, New York, N.Y. 1978. xxxviii + 658 pp. 18.5 × 26.5 cm. $55.00.

**Drug Discrimination and State Dependent Learning.** By Beng T. Ho, Daniel W. Richards III, and Douglas L. Chute. Academic Press, New York, N.Y. 1978. xiv + 392 pp. 16 × 23.5 cm. $23.00.