Book Reviews

The Peptides: Analysis, Synthesis, Biology. Volume 5. Special Methods in Peptide Synthesis, Part B. Edited by E. Gross and J. Meienhofer. Academic Press, New York. 1983. xxviii + 508 pp. 15 × 23 cm. $179.50.

Peptidologists, serious practitioners as well as the occasional dabbler, will enjoy this fifth volume of the open-ended series on the analysis, synthesis, and biology of peptides. As always, the presentation is beautiful, and the editing meticulous. A distinctive feature of this particular volume is that it is a tribute to the late Erhard Gross, who until his untimely death in 1981 in an automobile accident was one of the two founding editors, along with Johannes Meienhofer. A biographical sketch of Professor Gross and a complete list of his scientific publications is included in the book as a memorial.

Chapter 1 (R. Wetzel and D. V. Goeddel) is a review of the current status of recombinant DNA technology as it applies to polypeptide synthesis. Included are a general introduction to the methodology of gene cloning in *Escherichia coli* and a discussion of how the expression of cloned genes may be maximized so as to make this a practical route to polypeptides such as insulin and human leukocyte interferon. Consideration is also given to the dual problems of product stabilization and peptide secretion once translation has occurred in the producer cell. For those unfamiliar with this remarkable new area of research, a reading of this chapter will be most illuminating. Though it may prompt some peptide chemists to change their stripes and enter the alien world of polynucleotide synthesis in the hope of avoiding technological displacement, most will probably take confort in the thought that, for the moment at least, genetic engineering methods have not been adapted to produce polypeptides containing amino acids other than those coded by DNA. But perhaps this too will happen one day.

Chapter 2 (Yajima and Fujji) presents an up-to-date summary of acidolytic methods in polypeptide synthesis, particularly for the selective removal of a single acid-labile group in the presence of two or more others. Newer blocking groups, such as 4-methoxybenzyl (Mob), 4-methoxybenzyloxycarbonyl (Moz), and mesitylene-2-sulfonyl (Mts), are discussed, as is the use of carbonium ion scavengers in combination with strong acids, such as methanesulfonic acid and trifluoromethanesulfonic acid. Special attention is given to the problems associated with tyrosine, tryptophan, cysteine, methionine, and aspartic acid residues, and a section illustrates in detail the use of selective acidolysis in an elegant new synthesis of ribonuclease A reported by the authors of the chapter in 1980.

Chapter 3 (M. Bodanszky and J. Martinez) offers a facinating collection of peptidic bric-a-brac, lovingly culled from the literature over the years and stored away in anticipation of the day, inevitable in the carrer of every synthetic chemist, when a "foolproof" reaction goes totally astray. The theme of this chapter is the "side reaction", the enemy lurking behind every step of a peptide synthesis. Numerous examples are given of side reactions that can occur during protection and deprotection steps, during coupling, and even during the purification of peptides. Though much of the chemistry is recycled from other chapters in earlier volumes, a useful purpose is nonetheless served by placing the subject in a new and different perspective.

Chapter 4 (N. L. Benoiton) deals with the problem of racemization in peptide synthesis, a topic already addressed twice in earlier volumes, first by Kemp (Volume 1, Chapter 5) and again by Kovacs (Volume 2, Chapter 8). Newer methods of detection and quantitation of racemization are reviewed critically, and there is a very interesting discussion of the rediscovered role of 5-(4*H*)-oxazolones as intermediate species in this process. The multiple factors that affect the extent of racemization, such as temperature, solvent polarity, the type of base used (if any), and the nature of the amino acid and N-protecting group, are analyzed in extenso, and a wealth of data are offered relative to the formation of symmetrical anhydrides, intermediates that have received a less than just share of attention in the past. It is clear from the discussion in this chapter that some of the cherished tenets of peptide chemistry (e.g., that *N*-alkoxycarbonyl amino acids are impervious to racemization) may have to be reconsidered. While the extent of racemization in many of the cited examples is quite small, it clearly can lead to a discrepancy between the biological activity of a natural polypeptide and that of a polypeptide obtained by chemical synthesis, especially via the solid-phase method. One of the advantages of RNA-directed polypeptide synthesis, presumably, is that it occurs with complete stereochemical, as well as sequential, fidelity.

Chapter 5, entitled "α,β-Dehydroamino Acids and Peptides" (K. Noda, Y. Shimohigashi, and N. Izumiya), has special significance in this volume because Professor Gross himself originally planned to be a principal coauthor. His personal contribution to this area, in the form of the structure determination and partial synthesis of the antibiotic nisin, are well-known. There are now a number of recognized dehydro polypeptides in nature, and some of them display antibacterial, antiparasitic, and even antitumor activity. They are, however, highly toxic, and there is speculation as to the possible contribution of the reactive α,β-unsaturated amide group to this toxicity. Since dehydroalanine, in particular, is an excellent Michael acceptor, it is certainly conceivable that polypeptides containing one or more dehydroalanine residues may resemble alkylating agents in reacting with essential thiol groups in enzymes or cell membrane proteins.

Chapter 6 (D. C. Roberts and F. Vellacio) may prove, to some readers at least, to be the most stimulating in the book, as it presents, largely in concise tabular form, an impressive collection of exotic amino acids that can be substituted for the common variety to obtain synthetic polypeptides not accessible by recombinant DNA techniques. Included also in the list are amino acids that contain as part of the side chain a reporter ligand (e.g., a spin-label or ^{19}F-substituted group) or a reactive moiety (e.g., an alkylating group or photoaffinity label). There is a brief, but cogent, discussion of the rationale for including unusual amino acids in synthetic polypeptides, especially where the intent of the work is to delineate the steric and conformational factors that influence the interaction of a natural peptide with its receptor. Although this discussion is couched in fairly classical terms involving the concepts of isosteric and homosteric replacement, many readers will be find it of interest.

In summary, this book continues to uphold the high standards set by its predecessoirs and will be an invaluable addition to the shelves of every library. A minor criticsm is that, until now at least, none of the volumes contains any chapter devoted primarily to the biology of peptides, which after all is advertised in the title as one of the areas to be covered by the series.

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Opioid Peptides. Volumes I–III. By Jőzsef I. Székely and Andrās Z. Rōnai. CRC Press, Boca Raton, FL. Vol. I: 1982. x + 118 pp. 18 × 26 cm. $49.50. Vol. II: 1982. x + 241 pp. 18 × 26 cm. $79.00. Vol. III: 1983. xi + 257 pp. 18 × 26 cm. $83.00.

The writing of these three volumes on opioid peptides was a tremendous undertaking and was written solely by two authors. Although the authors are Hungarians, the English text is well-written. The first volume is devoted to the descriptions of methods used in vitro and in vivo in opioid research. Chapter 1 contains discussions of the receptor binding assay, radioimmunoassay, isolated organ techniques, and biochemical methods. The methods per se are not described; rather, how these methods are used in opioid research is discussed. The reader will need to consult the original references for the actual description of the methods.

Chapter 2 contains a number of in vivo protocols used in this field. In addition to the analgesic effects of opioids and antagonism by naloxone, other opioid effects, such as stimulus properties, behavior, drug interaction, and turnover of neurotransmitters, are included. This chapter contains an enormous amount of pharmacological information. Of particular value to the scientists in opioid research are the many tables in which the findings from the literature of a number of particular opioid effects are summarized. Included in these summaries are the most characteristic pharmacological properties of morphine and its congeners.

In the second volume, the authors discuss the pharmacological properties of opiates and opioid peptides. The chapters in this volume contains discussions on the mode of action of opioids, electrographic analysis of opioid mechanisms, analgesic and behavioral effects of opioids, and the role of endogenous opioids in vegetative regulation and neuroendocrine function. Again, this volume contains very helpful information from the literature in the form of numerous tables.

Opiate receptors and their ligands and the clinical aspects of opioid peptides are the subjects in Volume III. The beginning chapters contain the various aspects of opiate receptors and their endogenous ligands, including their discovery, properties, and distribution. The concept of multiplicity of opiate receptors is introduced, but the historical background is slightly inaccurate. Biosynthesis, release, and degradation of opioid peptides are also discussed.

The many synthetic enkephalin and other peptide derivatives are introduced in the middle chapters. Especially valuable to the medicinal chemists is the presentation of the structure–activity relationship of the peptide analogues. The activities of the peptide analogues in both in vitro and in vivo assays are given.

The final chapters contain discussions on the clinical aspects of opioid peptides. These topics include the possible relationship of the peptides to acupunture analgesia, opiate tolerance, and dependence and pathogenesis of certain mental disorders.

The literature covered in these volumes is through 1980. Thus, the information may be outdated by 3 years. Nontheless, the compilation of information in the literature for the last decade or so should be a valuable resource for opioid researchers in many disciplines, e.g., pharmacology, medicinal chemistry, biochemistry, endocrinology, anatomy, and physiology. The information in these volumes are certainly more comprehensive than several other books on this subject, which emanated from various symposia. This reviewer recommends these volumes as an excellent starting point for those who are being initiated into this field.

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Studies in Analytical Chemistry. Volume 5. Quantitative Analysis of Steroids. Edited by S. Görög. Elsevier, New York. 1983. 440 pp. 16 × 23.5 cm. ISBN 0-444-99692-2. $95.75.

This is the first book to deal with the quantiative analysis of steroids, which are of great importance in biology and pharmacy. All the important groups of steroids are discussed: sex and adrenocortical hormones, sterols, the D vitamins, bile acids, cardiac glycosides, sapogenins, etc. In the chapters dealing with the analysis of these groups of compounds, all analytical methods that are used for the determination of the compounds are discussed, e.g., classical spectroscopic, chromatographic, electroanalytical, radioanalytical, protein-binding, enzymatic methods, etc.

Detailed description is given of how these methods may be used for the determination of steroids in the pharmaceutical industry and research (purity testing of bulk steroids, the assay of steroid preparations, and the analysis of raw materials and intermediates of steroid syntheses), in biochemistry (the determination of steroids in biological samples and steroid analysis in clinical diagnostics), in the analysis of food products, and so on. The reader can rapidly find required information in terms of either the problem to be solved or the method to be used. Some 2500 references complete the book.

Staff

Advances in Cyclic Nucleotide Research. Volume 15. Edited by P. Greengard and G. A. Robison. Raven Press, New York. 1983. xxii + 500 pp. 16.5 × 24 cm. ISBN 0-89004-881-9. $64.00.

The 15th volume of this successful series contains 10 reviews by well-recognized experts in their own field. A. Ullman and A. Danchin examine the role of cAMP in bacteria, with particular emphasis on the cAMP–catabolite activator protein (CAP) complex and expression of sensitive operons in *Escherichia coli*. P. Devreotes reviews the role of cyclic nucleotides in cell–cell communication in amoebae and suggests new models for chemotactic and secretory transduction mechanisms at work in higher organisms. D. Francko discusses the recent evidence suggesting an important role for cAMP in the regulation of metabolism and ecological interactions in photosynthetic organisms. R. Barber and R. Butcher briefly describe the process of cAMP egress from metazoan cells and speculate on the role of this transport. T. Lincoln and J. Corbin provide a comprehensive update on characterization and function of cGMP-dependent protein kinase and other cGMP-binding proteins. A. Boynton and J. Whitfield exhaustively review the prereplicative events triggered by cAMP and critically assess the role of cyclic nucleotides in the proliferation of normal cells and the deregulation of proliferation by neoplastic transformation. J. Maller reviews data, mostly from microinjection experiments, establishing the role of cyclic nucleotides in the regulation of meiotic cell division in amphibian oocytes. J. Demaille and investigators from the late J.-F. Pechere's group review the control of contractility by protein phosphorylation. The effort to establish unequivocally a link between the cyclic nucleotides and neurotransmitters in synaptic transmission has generated an enormous amount of data; after 2 decades of intensive research activity, however, the biochemical, behavioral, and electrophysiological data do not yet provide any definitive answers. G. Drummond presents an extensive (121 pages and 748 references) review of the information thus far gathered on the role of the cyclic nucleotides in the nervous system. In a brief chapter, W. Miller discusses the physiological effects of cGMP in the vertebrate retinal rod outer segment. This book is well organized with outlined chapters, most of which contain excellent summary statements and hypotheses.

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ACS Symposium Series. Number 224. Dopamine Receptors. Edited by Carl Kaiser and John W. Kebabian. American Chemical Society, Washington, DC. 1983. 289 + xiv pp. 18 × 27 cm.

This volume is based on two symposia sponsored by the ACS Division of Medicinal Chemistry at the 184th meeting of the American Chemical Society, Kansas City, MO, September 1982. The symposia were entitled "Multiple Categories of Dopamine Receptors" and "Modulation of Dopamine Receptors". The subject matter of the first symposium is obvious, but the interpretation of "modulation" in the second symposium restricts itself primarily to a discussion of dopamine receptor pharmacology and the development of selective therapeutic agents. There is a good deal of controversy in the area of classification of dopamine receptors, and this is nicely emphasized by the present volume. Each chapter is followed by a commentary from another research group that has a somewhat different approach or opinion: for example, Brown and Dawson-Hughes discuss D-1 dopamine receptor mediated activation of adenylate cyclase in the parathyroid, and this chapter is followed by a commentary by Pierre Laduron questioning whether the dopamine-stimulated adenylate cyclase is a receptor site at all. The emphasis of the volume is somewhat different from many that have previously been published—this volume focuses principally on peripheral and pituitary dopamine receptors and the development of selective agonists with therapeutic potential. This focus derives directly from the symposia organizers: Kebabian who has studied the D-1 and D-2 dopamine

sensitive adenylate cyclases in detail for the past decade and Kaiser, from Smith Kline & French Laboratories, who has been involved in the development of selective D-1 agonists for their potent cardiovascular actions.

Leslie Iversen comments in the preface that "little is said in the present volume about radioligand binding assays", but given the emphasis of the volume, this absence does not detract significantly from the volume's focus. Some of the other major chapters include a discussion of D-2 receptors in the intermediate pituitary by Kebabian et al., a description of dopamine receptor binding properties of the anterior pituitary by Caron et al., and dopamine receptors in the periphery and their cardiovascular effects discussed by Goldberg and Kohli, Weinstock et al., and Erhardt. The potential use of dopamine agents in duodenal ulcer disease is highlighted by Szabo and Neumeyer and Arana. Structure–activity relationships in the development of novel dopaminergic agonists and antagonists are covered in a number of chapters by Ginos, Nichols, Horn, Kaiser, McDermed, and Olson et al. CNS systems are covered only from a biochemical and physiological point of view in a single chapter by Stoof. The major lack of this volume given its title is the absence of both receptor binding and electrophysiological studies of CNS dopamine receptors and their potential involvement in psychiatric and neurological disease.

This volume will be very useful to medicinal chemists who are interested in dopamine receptor agonists and antagonists with specific (D-1) receptor specificity and to clinicians with an interest in the periperal actions of dopamine on the cardiovascular and endocrine systems.

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Multiple Dopamine Receptors. Volume 1. By Milton Titeler. Edited by Bernhard Cinader. Marcel Dekker. New York. 1983. x + 173 pp. 15.5 × 23.5 cm. ISBN 0-8247-1735-X. $34.50.

Biochemical approaches to drug and neurotransmitter receptors in the brain by binding techniques have been one of the most active areas in all of molecular neuroscience during the past decade. This work has been of great importance in clarifying mechanisms of synaptic communication and in explaining the actions of drugs of numerous classes. The relationship of a neurotransmitter recognition site to second messengers, such as adenylate cyclase, has been elucidated. The concept that high-affinity drug receptors might in fact represent recognition sites for endogenous neurotransmitters, such as the enkephalins, has emerged from receptor research. The existence of multiple subtypes of neurotransmitter receptors is a product of this field of study. Finally, neurotransmitter receptor binding techniques have provided simple and powerful tools for rapid accurate screening of drugs and for structure–activity analysis.

The number of neurotransmitter or neuromodulator receptors that can be labeled in binding paradigms is constantly escalating. As of this writing, there may be 50 or more distinct receptor subtypes that can be identified in this way. Certain receptors have received the greatest bulk of attention. These include opiate, benzodiazepine, and dopamine receptors. In each of these cases, multiple receptor subtypes exists, therapeutic drug actions can be explained by receptor influences, and receptor binding sites can be linked to second messenger systems by examining the influence of ions or nucleotides upon receptor binding. Milton Titeler has provided an extraordinarily lucid yet rigorous volume reviewing comprehensively what is known about the biochemical properties of dopamine receptors.

This volume is unique in that the author has written it at a level of simplicity, making it valuable for a beginning graduate student as an introduction to the entire field of receptor research. At the same time he has provided direct reproductions of large numbers of tables and figures from virtually all the important publications in the field. Describing the relatively complex area of dopamine receptors at a level of sophistication, which will make the book valuable for the professional who specializes in dopamine research, while keeping the book accessible to students has involved a most skillful, clear writing style on the part of the author. Yet another virtue of this volume is the well-balanced presentation of the work from numerous laboratories. Though the author is himself one of the pioneers in dopamine binding research, he does not slant the presentations toward biases of his own or any other laboratory. Indeed, for every controversial area, he presents each theoretical approach fully.

The book begins with an overview of the role of dopamine in brain function, the nature of receptor binding assays, a brief history of the field, and a review of nomenclature. The second chapter is devoted to fundamental considerations of ligand binding. This is followed by three chapters detailing the properties of three dopamine receptor binding sites. Properties of dopamine receptors in the pituitary are addressed in a single chapter, as are alterations in receptor binding in clinical conditions. The book contains three superb appendixes detailing available ^{3}H-labeled ligands for dopamine receptor binding, descriptions of methodology, and structures of major dopamine agonists and antagonists.

Though there appears to have been a substantial lag between completion of the volume and its appearing in print, the book is surprisingly up-to-date. The only important research not included relates to recent studies from the laboratory of Creese indicating the nature of apparent D_3 dopamine binding, which may, in fact, largely represent a high-affinity state of other types of dopamine receptors, so that there may exist, in fact, only two major receptor subtypes.

One area not covered by the book is autoradiographic visualization of dopamine receptors. Autoradiographic work has provided the basis for the recent ability to visualize dopamine receptors in intact human beings by positron emission tomography (PET scanning). However, one can see how the detailed explication of neuroanatomy needed to present this material might not be feasible for a relatively brief text. Similarly, this volume does not deal with electrophysiological characterization of dopamine actions, which also would require much additional text.

In summary, this is one of the finest single author volumes I have read on neurotransmitter receptors. It is one of the few books that is accessible both to the beginning student and to the advanced researcher. Such a book is highly recommended as well to medicinal chemists interested in an easy to read introduction to the receptor field.

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Handbook of Experimental Pharmacology. Volume 64. Inhibition of Folate Metabolism in Chemotherapy. The Origins and Uses of Co-trimoxazole. Edited by G. H. Hitchings. Springer-Verlag, New York. 1983. XXI + 457 pp. 17 × 25 cm. ISBN 0-387-11782-2. $150.00.

Co-trimoxazole is the generic name for the widely used antibacterial combination of trimethoprim and sulfamethoxazole, introduced in 1968. Both drugs represent inspiring examples of medicinal chemistry in which the basis for their chemotherapeutic action and synergistic interaction is well understood. The 20 reviews included in this volume provide an authoritative, thoroughly documented introduction to co-trimoxazole with emphasis on pharmacological and clinical aspects. Those reviews most likely to be of interest to medicinal chemists are (1) "Selective Inhibitors of Bacterial Dihydrofolate Reductase: Structure–Activity Relationships", by B. Roth; (2) "Dihydrofolate Reductase", by J. J. Burchall; (3) "Sulfonamides: Structure–Activity Relationships and Mechanism of Action", by N. Anand; (4) "Functions of Tetrahydrofolate and the Role of Dihydrofolate Reductase in Cellular Metabolism", by G. H. Hitchings, and (5) "Disposition and Metabolism of Trimethoprim, Tetroxoprim, Sulfamethoxazole, and Sulfadiazine", by C. W. Sigel. The other 15 reviews cover inhibition of bacterial growth, pharmacology, clinical uses, and an overview. With few exceptions, the latest literature citations are to work published in 1980. A useful subject index is included.

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Problems of Antiviral Therapy. The Beecham Colloquia. Edited by Sir Charles H. Stuart-Harris and John Oxford. Academic Press, London. 290 pp. 16 × 23.5 cm. $30.00.

The fifth Beecham colloquium on infections was held to discuss the relatively slow progress in the development of antiviral compounds and to find ways to accelerate progress in this area. Twenty-seven participants, 19 from Great Britain, 4 from Europe, and 4 from the U.S.A., gathered to discuss various areas of clinical virology and therapeutics. Among the subjects reviewed in the Proceedings of this colloquium and clinical target illnesses worthy of study, presently available antivirals, and potentially promising new approaches. Long and free discussion follow each formal presentation to maximize the exchange of information and the generation of new ideas.

To a large extent the volume succeeds in its goals of identifying problem areas and suggesting directions for further research. Some presentations are outstanding, particularly those by Choppin et al. on "Analogues of Viral Polypeptides Which Specifically Inhibit Viral Replication", by Oberg on "Inhibitors of Virus-Specific Enzymes", by Field on the "Problem of Drug-Induced Resistance in Viruses", and by Scott on "Interferon: Perspectives for Clinical Problems". The discussions provide for an informal give and take among the participants, helping to illuminate problem areas and topics of controversy.

The free-wheeling discussions also illustrate the major weakness of the volume, a certain lack of organization and careful editing. Open discussions often lead to misquotes and misinterpretation of others' data, since references are not readily at hand when the discussions are held. If misstatements are made, they should be corrected by the editors or individual speakers prior to publication. Unfortunately, several factual errors are left uncorrected, and there are occasional internal contradictions between statements made by individual participants. In addition, the individual contributions could have been organized in a more orderly sequence. For example, a presentation of acyclovir resistance should not have preceded one on acyclovir, and chapters on approaches to clinical problems shouldn't precede chapters on the problems themselves.

Several books address individual topics reviewed in this volume, but few attempt to cover the entire area of viral therapy and problem diseases. Perhaps the most successful is "Antiviral Agents and Viral Diseases of Man" edited by Galasso, Merigan, and Buchanan. "Problems of Antiviral Therapy" updates many topics covered by Galasso et al. but is less cohesive and thorough in its approach. It may well be useful to specialists in antivirals who want current information on specific topics and sophisticated opinions on where research efforts should be directed. It will be less satisfactory, and is not recommended, for those wishing an organized and comprehensive review of antiviral therapy.

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Monograph Series of the European Organization for Research on Treatment of Cancer. Volume 12. New Anticancer Drugs: Mitoxantrone and Bisantrene. Edited by Marcel Rozencweig, Daniel D. Von Hoff, and Maurice J. Staquet. Raven Press, New York. 1983. 210 pp. 16 × 24 cm. ISBN 0-89004-888-6. $25.00.

Volume 12 of the EORTC monograph series examines new experimental and clinical applications of mitoxanthrone and bisantrene. A roster of eminent contributing authors report on experimental therapeutic and biochemical studies of anthracenedione derivatives, activity of mitoxanthrone and bisantrene in a human tumor cloning system, and preclinical toxicology studies on the two drugs. Mitoxantrone in children with advanced malignant disease is investigated, as is its use in hematologic malignancies. Clinical trials of both drugs are presented as well.

Staff

Books of Interest

Kirk-Othmer Encyclopedia of Chemical Technology. Third Edition. Volume 23. Thyroid and Antithyroid Preparations to Vinyl Polymers. Edited by Martin Grayson. Wiley, New York. 1983. xxvi + 979 pp. 18.5 × 26.5 cm. ISBN 0471-02076-1. $180.00.