following: (a) The electron density of the aromatic ring increases as a result of conjugation between the nonbonding electrons of the methoxyl oxygen and the π cloud of the aromatic ring. Such an increase would result in a stronger drug–receptor complex formation. (b) The 2-methoxyl nonbonding electrons are also directly involved in the interaction with the electron-deficient site at the receptor. This additional interaction enhances the affinity of the drug for the receptor.

The observed increase in psychotomimetic activity associated with the out-of-plane conformation can be explained by invoking steric hindrance from the methoxyl group during the approach of the drug to the receptor site. In the case of compounds with two methoxyl groups perpendicular and on opposite sides of the ring, the approach from either face of the aromatic ring to the receptor site is hindered (Figure 2b). This results in the loss of psychotomimetic activity. However, with the compounds that have one methoxyl group in the out-of-plane conformation, the approach of the drug to the receptor site is hindered only from one face of the ring (Figure 2c,d). This results only in a partial loss of psychotomimetic activity. It should also be pointed out that the methoxyl out-of-plane conformation decreases the electron density of the aromatic ring because the nonbonding oxygen electrons are no longer in conjunction with the π cloud. This should further decrease the affinity of these drugs toward the receptor.

We are currently investigating the electronic and steric implications resulting from the out-of-plane conformation of the aromatic methoxyl groups through the use of electron-deficient model receptor sites.[23]

Experimental Section

Samples for this work were provided by Dr. A. T. Shulgin and the National Institute on Drug Abuse. All chemical shifts and spin–lattice relaxation times were determined on a Bruker WP-60 NMR spectrometer equipped for pulse Fourier transform operation at 15.08 MHz. The system computer allows acquisition of 8K data points, thus yielding 4K data points in the transformed phase corrected spectrum. Samples were 0.75 M solutions of the hydrochloride salts in D_2O at 30 °C. Chemical shifts were determined using 5% dioxane as the internal standard (67.4 ppm downfield from Me_4Si).[24]

Spin–lattice relaxation times for all carbons directly attached to protons were determined simultaneously with complete proton decoupling using the $(180°-\tau-90°-T)_n$ inversion recovery method,[25] where τ is experimentally varied and T is equal to at least 5 times the longest T_1 to be measured. The T_1 calculations were performed on a Nicolet BNC-12 minicomputer using the Bruker T_1 Program/II, which estimates the T_1 values from peak intensities. Each reported T_1 value is the average of at least three determinations.

Heteronuclear nuclear Overhauser enhancement (NOE) measurements were carried out on a degassed sample using the method of Freeman et al.[27] A spectrum was first obtained with continuous broad-band proton decoupling. A second spectrum was then obtained using a pulse-modulated broad-band proton decoupling sequence. In this "gated" experiment, the decoupler is kept on only during data acquisition periods and is turned off during the remainder of the pulse interval. Proton-decoupled ^{13}C spectra are thus obtained without any appreciable NOE. Pulse intervals in both experiments were equal to at least 8 times the longest T_1. Values for the NOE were determined by dividing the individual peak area in the continuously decoupled spectrum with the corresponding peak area in the "gated" spectrum. The NOE sample was identical in every way with the sample used for T_1 measurements.

Acknowledgment. We thank Dr. A. T. Shulgin for the samples he generously provided and for the useful discussions on this work. This study was supported by a grant from the National Institute on Drug Abuse (NIDA-376) and a grant from the University of Connecticut Research Foundation (UCRF-257).

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Book Reviews

Encyclopedia of Chemical Technology. Third Edition. Volume 12. By Kirk-Othmer. Wiley, New York. 1980. xxvi + 1037 pp. 19 × 26 cm. $145.00.

This volume, as in the case of the previous volumes in this third edition, continues to provide chemists with an invaluable source of authoratative information on the many diverse topics of chemical technology. Of particular interest to medicinal chemists in Volume 12 are the excellent and up to date reviews of such topics as histamine and histamine antagonists (11 pages) by R. W. Fleming and J. M. Grisar. The 154-page discussion of hormones includes a survey (8 pages) by C. and J. Rivier, anterior-pituitary hormones (11 pages) by C. H. Li, anterior-pituitary-like hormones (6 pages) by H. Papkoff, posterior-pituitary hormones (11 pages) by A. F. Spatola, adrenal-cortical hormones (28 pages) by V. Petrow, brain oligopeptides (15 pages) by J. and C. Rivier, sex hormones (40 pages) by V. Petrow, and nonsteroidal estrogens (33 pages) by G. C. Crawley. In addition there is a 20-page discussion of hydantoin and derivatives by J. H. Bateman which includes all the medicinally used hydantoins and their physical properties, synthesis, and chemical properties. What makes these volumes particularly useful to chemists wishing to survey current technology is the inclusion of Chemical Abstracts Service registry numbers for all compounds. This is of considerable practical value for the chemist who wishes to further search the literature.

Staff

Instrumental HPTLC. Edited by W. Bertsch, S. Hara, R. E. Kaiser, and A. Zlatkis. Alfred Hüthig Verlag, Heidelberg and New York. 1980. 390 pp. 15 × 21 cm. $49.00.

This book, describing recent advances in high-performance thin-layer chromatography (HPTLC), is a collection of 16 papers presented at the First International Symposium on Instrumental HPTLC held in May 1980. Essentially two types of papers are included, those that emphasize the basic instrumental methods and chromatographic evaluation in HPTLC and papers detailing applications of HPTLC.

Fundamentals of HPTLC are covered in chapters on sample application, computer evaluation of TLC and HPTLC, quantitation and methods, and instrumentation in HPTLC. Applications described include separations of polycyclic aromatic hydrocarbons in diesel fuel exhaust, trace analysis of selenium in water, steroid hormones, serum amino acids, and drugs in pharmaceutical samples. Unfortunately, the book suffers from a lack of organization. The two chapter types are intermixed with no logical ordering, which results in a confused arrangement of the topics presented.

Another problem with the book is the considerable overlap between several chapters. For example, there are two chapters describing sample application methods and several descriptions of compound-detection techniques (e.g., UV reflectance or fluorescence), and many of the chapters detail the methods and problems of quantitation in HPTLC. This repetition is probably due to the short time between the conference and the book's publication (less than 6 months). Apparently, the editors felt that rapid publication was more important then tight editorial control of content. This does, however, have the significant advantage that all of the work is fresh and up-to-date.

The advantages that HPTLC offers, such as short average analysis time and low cost, are well delineated, but some claims in HPTLC are not well documented. For example, the advantages of an off-line (HPTLC) vs. an on-line (GC or LC) mode of chromatography are clearly overstated. On-line does have some significantly favorable features, such as the ability to interface with a variety of detectors and the ease of preparative separations.

In summary, I do not think this is a book the occasional TLC user or the chromatographer will find essential. Drs. Kaiser and Zlatkis' original book on HPTLC amply fulfills the basic need here. However, for the researcher who finds it necessary to stay current in HPTLC, this volume will be a welcome addition to his library.

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Neuropeptides and Neural Transmission. By Cosimo Ajmone and Wladyslaw Z. Traczyk. Raven Press, New York. 1980. xix + 391 pp. 16 × 24 cm. $40.00.

Research into neuropeptides and related subjects is probably the most intensively investigated of any in biology at this time. The quantity of information being produced in this area is enormous and it is important to be able to sort out rapidly that information which is valuable and that which is not. In addition rapid disemination of data in this field is important. Consequently, the number of research symposia sponsored to discuss research in this area is also very large. Most of these symposia are eventually published as bound volumes. The present volume is the result of such a symposium held in June 1979 under the auspices of the International Brain Research Organization. The volume contains chapters about five neuropeptides: neurotensin, substance P, enkephalin, vasopressin, and oxytocin. The largest number of chapters (16) concerns substance P. There are many faults associated with such volumes. For example, although they are produced rapidly compared to other books, they are slow in appearing compared to journals. Consequently, the information in them is often out of date. Secondly, the contributions are unreviewed. Consequently, such books are often full of data that never see the light of day in a proper journal. The contributions in such books also rarely follow any particular theme and present a jumble of subjects from those that are interesting to those that are on the fringes of the subject.

The present volume cannot escape these criticisms. Those of us who work directly in this field will feel obliged to buy this book, as well as all the other symposia volumes, so that we do not miss some vital piece of data. In fact, this volume is nicely produced, well edited, and, for those who are addicted to this subject, contains some interesting data. However, for somebody in another field who wishes to gain some insights into the topic this book is quite inappropriate. This volume lacks the permanence of a reference text and lacks the immediacy of a journal. I do not know why publishers persist in publishing this type of volume. Presumably there are enough people working in this field who will feel obliged to buy it to salve their conscience that the publisher will turn a tidy profit. For the rest of you, $40.00 can be better spent.

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Syntheses with Stable Isotopes of Carbon, Nitrogen, and Oxygen. By Donald G. Ott. Wiley, New York. 1981. vii + 224 pp. 23.4 × 15.8 cm. $28.50.

The use of organic substances labeled with isotopes of C, H, N, and O in the life sciences has steadily increased during the past 40 years. The availability of radioisotopes (especially ^{14}C and ^{3}H) and the existence of simple analytical methods to detect them allowed their exploitation to greatly exceed that of stable isotopes during this period. Recently, however, the improved availability of stable isotopes and rapid advances in spectroscopic methods to detect them have caused a resurgence in their interest.

This text addresses the need of a covenient starting point for the investigator faced with the unfamiliar task of preparing a compound labeled with the stable isotopes of C, H, N, and O. Being a survey of such preparations, it is not an exhaustive compilation of all literature methods. An initial chapter covering general techniques and nomenclature is followed by experimental details to prepare labeled substances arranged in chapters according to functional groups. To accomodate those interested in comparing several labeling strategies for a single compound, the preparation of chemically identical but isotopically different substances is juxtaposed. Each experimental description is followed by useful notes and reference to the primary literature. Handsomely drawn structures clearly indicate the distribution of isotopic labeling even in substances with mixed isotopes. A useful index arranged by compound name locates the preparation of each labeled material. With the expected increase in the use and application of stable isotopes, especially in the life sciences, this book succeeds in its purpose of aiding the novice and stimulating interest in syntheses of compounds labeled with stable isotopes.

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Inorganic Chemistry in Biology and Medicine. ACS Symposium Series. Number 140. Edited by Arthur E. Martell. American Chemical Society, Washington, DC. 1980. viii + 436 pp. 16 × 24 cm. $39.50.

This volume has the strengths (and weaknesses) expected of a topical symposium proceedings. However, it is distinct from the numerous recent texts of "bioinorganic" chemistry in focusing specifically on clinical aspects of inorganic chemistry. Specific symposium topics included "Metals in Nutrition" (B. Pressman, ionophores; F. Nielsen, medical significance of trace metals), "Metals in Disease" (M. Costa, metal carcinogensis; G. Eichorn, alzheimers disease), "Radiopharmaceuticals" (particularly $^{99}Tc_m$), "Anticancer Activity" (including reviews by C. Locke, B. Rosenberg, S. Lippard, and J. Hoeschle on Pt, M. Clarke on Ru, and J. Dabroviak on metal–bleomycins), and an extensive treatment of "Chelation Therapy for Cooley's Anemia and Other Diseases" (J. Nielands, C. Pitt, A. Martell, K. Raymond, M. Jones, C. Shaw, and M. Rubin). These scientists will be familiar to workers in both inorganic and medicinal chemistry.

The general quality of the presented material is high, and the chapters appear well edited. A thorough subject index is included. As a library reference, the book is timely and, due to its unorthodox focus, will likely remain valuable long after most symposia are forgotten. On an individual basis the book can be strongly recommended both to medicinal chemists seeking an overview of current problems in metal-centered clinical chemistry and (bio)inorganic chemists who seek a clearer picture of the clinical

aspects of inorganic chemistry.

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Principles of Medicinal Chemistry. Second Edition. By William O. Foye. Lea & Febiger, Philadelphia. 1981. xiii + 931 pp. 19 × 26.5 cm. $45.50.

The first edition of "Principles of Medicinal Chemistry" was plagued by numerous typographical and structural errors; however, the new addition goes a long way to remedy this situation. While some typographical errors still exist (in one instance, the reader is referred to a nonexistent figure), structural errors are minimal. In comparison with the first edition, the newer edition is quite improved; though it is easier to find words of praise than words of criticism, several bothersome features are still evident. Because of the lag time in preparing this text, the most recent references are several years old (a few 1978's are sprinkled throughout). As a consequence, certain chapters are not as up-to-date as possible. Because the text is multiauthored, it suffers the inconsistencies of various writing styles and fluid format. Furthermore, certain topics (although occasionally because of necessity) are covered in several different chapters. For instance, coverage of biosynthetic pathways (e.g., involving dopamine, serotonin, cyclic AMP, etc.) is redundant. The benzodiazepines, as in the last edition, are discussed in at least three different chapters. Although some attempt has now been made to cross-reference these materials, more cross-referencing would be very helpful. Perhaps it is only natural that some duplication of effort occurs when 47 contributors and 39 chapters are involved, and the differences in writing style and format are irritating only if the text is read in the same manner that one reads a novel.

With respect to the chapters themselves, most have been updated or rewritten, some remain more or less unchanged from the first edition, and a few new chapters have been added. Some of the major changes are as follows: "Molecular Orbital Theory in Drug Design" has given way to a more generalized treatment of the topic under "Theoretical Aspects of Drug Design". The chapter on "Neuroleptic and Anxiolytic Agents" has been rewritten and more emphasis has been placed on proposed mechanisms of action. (Unfortunately, the current work on benzodiazepine receptors was too recent to receive more than a brief comment.) A companion chapter on "Drugs Used to Treat Neuromuscular Disorders" makes an easy transition from neuroleptics to antiparkinsonism agents and central muscle relaxants. Analgesics has also been completely rewritten. Although coverage of the topic approaches graduate level, it is, nonetheless, well done. The chapters on "Cholinergics and Adrenergics" have been updated; while the agonistic aspects are thoroughly covered, ganglionic, neuromuscular, and α-adrenergic blockers receive comparatively little attention. The section on "Antiallergenic Agents" has also been updated to include an introductory discussion of inhibitors of mediator release, as well as 100 additional references.

A much needed chapter on "Cancer Chemotherapy", conspicuously absent from the first edition, has now been added. The prime shortcoming of this section is that there is very little detail or discussion on proposed mechanisms of action. Two other new chapters are "Organ-Imaging Radiopharmaceuticals" (which replaces "Diagnostic Agents") and, as an appendix, a section on pK_a.

The second edition of "Principles of Medicinal Chemistry" is a text which should have broad appeal. The basic emphasis is not on synthetic chemistry but, rather, on mechanism of drug action, structure–activity relationships, metabolism, and drug–receptor interactions. Thus, the text should be useful to pharmacy students, as well as to undergraduate students in other related disciplines, including students in the basic sciences. The text contains sufficient reference citations (and, for several chapters, sufficient depth) to be valuable for beginning graduate students in pharmaceutical and medicinal chemistry, as well as for graduate students and professionals in pharmaceutics, pharmacology, and related fields. Finally, although perhaps uppermost in the minds of most undergraduate students at least, is cost. Even with the inflationary trend being what it is, the price tag on this text may detract somewhat from its usefulness as a general undergraduate text.

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Enzymatic Basis of Detoxication. Volumes I and II. Edited by William J. Jakoby. Academic Press, New York. 1980. Volume I: xi + 415 pp. 16 × 23.5 cm. $43.00. Volume II: ix + 369 pp. 16 × 23.5 cm. $38.50.

Toxicology's recent growth has, among other things, emphasized the interdisciplinary nature of current scientific investigations. The intention of these volumes as stated by the editor is to relate to pharmacologists, toxicologists, and biochemists, and the authors, for the most part, succeed admirably in their tasks. As pointed out by Jakoby, a great deal of information has been accumulated over the past decade concerning the enzymes of detoxication. Many of the proteins have been purified to homogeneity and, in addition, the existence of a variety of isoenzymes and their substrate specificities have been established. The volumes, as the editor states, "presents the current state of our knowledge of foreign compound metabolism at the level of what specific enzymes can do". The concise summary which these two books entail fill a void which all investigators and students in the related fields will very much appreciate. Personally, having just completed teaching a graduate-level course in xenobiotic biochemistry, I would have enthusiastically welcomed the appearance of these books in the fall.

Volume I opens with a short philosophical discussion of detoxication enzymes and then proceeds to Part 1 entitled "Physiological Aspects". This section includes chapters on pharmacokinetics, human genetic variation, enzyme induction, and comparative detoxication. Part II, "Mixed Function Oxygenase Systems", follows and this section has an excellent summary (3 chapters) on the current state of affairs with respect to the cytochrome P-450 system and a chapter on the flavin-containing monooxygenase. Part III, "Other Oxidation–Reduction Systems", closes out volume I and contains chapters on aldehyde and ketone processing enzymes, xanthine oxidase, superoxide dismutase, glutathione peroxidase, and monoamine oxidase.

Volume II, Part I, "Conjugation Reactions and Related Systems", focuses on the usual reactions associated with that generic title. It is a real pleasure to find in many of the chapters a succinct summary of various viewpoints currently being actively investigated. Multiplicity of glucuronyl transferases, glutathione transferases, and the sulfotransferases are particular cases in point. Part II, "Hydrolytic Systems", contains two chapters, one on the epoxide hydrolase and one on amidases and carboxyl esterases.

The individual chapters, for the most part, are not repetitious and flow together reasonably well. There is a cumulative index for volumes I and II at the end of each book which is very adequate. In short, an experienced or beginning investigator in this field can look up a chapter and quickly learn the salient features of a particular enzyme (i.e., molecular weight, tissue and subcellular distribution, etc.) and have ready access by the extensive references to specifics regarding purification, substrate specificity, and many other relevant topics. All investigators whose research impinges on this area can not afford to not have these two volumes more than an arm's length away.

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Anticancer Agents Based on Natural Product Models. Edited by John M. Cassady and John D. Douros. Academic Press, New York. 1980. xiv + 500 pp. 15 × 23.5 cm. $49.50.

This book gives a comprehensive and up-to-date review of several natural products and their congeners used as anticancer drugs, both for laboratory research and for clinical treatment of patients.

Chapter 1, on the development of new antitumor anthracyclines, by F. Arcamone, is an excellent review of the recent knowledge

of daunomycin and doxorubicin, both of which are well-established in the treatment of solid human tumors. Chapters 2 and 3 deal with trichothecanes and nucleosides, respectively. Chapters 4, 5, and 6 are excellent summaries on mitomycin, bleomycin, and streptozocin, respectively, all of which are streptomyces-derived antibiotics which are used routinely in the clinic. Most recent knowledge of clinical and biological activity and modes of action of these agents is covered in reasonable depth. Chapter 7 is a comprehensive compilation of the several terpenoids, including a large number whose promising antitumor activity was discovered during NCI screening of natural products. This chapter, by J. M. Cassady and M. Suffness, is replete with references to the work of the late Professor S. Morris Kupchan, who pioneered this program. Chapters 8, 9, and 10 review the present-day knowledge of dimeric catharanthus alkaloids (e.g., vincristine and vinblastine), podophyllotoxins, and maytansinoids, whose use have been established clinically or are in the process of becoming so. Chapter 11 deals with Harringtonine and Chapter 12 deals with camptothecin and analogues, which are effective experimental antitumor agents. Synthesis of chemical analogues and study of their mechanism of action in vitro, which have been of great interest to chemists, are encapsulated in this chapter. Chapter 13 deals with the subject of microbial transformations as an approach to analogue development. This topic is certainly of current interest. Finally, Chapter 14 is a comprehensive review of a number of natural products with antitumor activity isolated from plant and microbial sources. Some of these are of most recent origin. Their inclusion in this chapter brings the reader to the very frontier of knowledge of anticancer agents of great promise.

An important feature of the book is the extensive compilation of data on the biological activity of the compounds. The large body of this work done under NCI auspices affords a uniform basis for comparison.

Each of the chapters is well-written and provides an up-to-date compilation of investigations in specialized research areas. The literature is covered in most cases through 1978 and into 1979.

Despite these many positive features, the text is marred by careless proofreading. A disconcerting number of errors remain, ranging from easily amended typographical lapses (ehtyl for ethyl) to the more serious misnumbering of compounds in the text. Although the structural formulas are, for the most part, well and clearly drawn, a few have been reduced beyond the point of legibility. Several others are incorrect. The structure of thalicarpine is given in two chapters. On its first appearance a methylene group is omitted, and on its second appearance an incorrect aromatic substitution pattern is drawn.

Anyone interested in the subject of cancer chemotherapy will most certainly enjoy reading this book. Many will find it a valuable acquisition.

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Progress in Pharmacology. Volume 4. Number 1. Cyclic Nucleotides and Calcium as Mediators of Cellular Functions. Edited by H. Vapaatalo and T. Metsä-Ketela. Gustav Fischer Verlag, Stuttgart and New York. 1980. ix + 183 pp. $58.50.

The series "Progress in Pharmacology" is a source of review-type papers by either one or several authors. This edition contains 21 papers which were presented at the Fifth Scandinavian Symposium on Cyclic Nucleotide Research held at Ikaalinen/Tampere, Finland, in June of 1979. With one exception, all papers are of Scandinavian authorship.

The theme of cyclic nucleotides and calcium is well-adhered to. Although only a third or less of the papers deal with Ca^{2+}, all deal with cyclic nucleotides. Topics addressed include the role of these second messenger substances in myocardial, skeletal, and smooth muscle responses, the inflammatory process, endocrine hormone responses, histamine receptor-coupled events, cell growth and malignancy and neurotransmission. In some instances, new findings are incorporated into the review-type format, but by and large what these articles provide is an overview of how diverse cellular functions are regulated by these second messengers which, in turn, affect each other. Thus, calcium ions regulate adenylate and guanylate cyclase activities, as well as phosphodiesterase activity, while cAMP and/or cGMP alter the cytoplasmic calcium ion level, as well as the responsiveness of calcium-dependent processes. The variety of events which are covered in this volume attests to the importance of this relationship in nature.

In summary, this issue of "Progress in Pharmacology" provides a broad view of the involvement of cyclic nucleotides and calcium in regulatory cellular function. It is not intended to provide an exhaustive resource but rather gives a relatively up-to-date synopsis of discrete topics. The price of this paperbacked volume seems high and will certainly restrict its acquisition to well-funded investigators in the research area of this symposium.

Staff