is collected to give **2d** (0.37 g, 44%). Recrystallization from chloroform–methanol affords dark blue crystals melting at 232–233 °C; NMR ($CDCl_3$–Me_2SO-d_6) δ 11.3 (br t, 1 H), 10.93 (br t, 1 H), 9.01 (m, 1 H), 8.62 (dd, 1 H), 8.20 (s, 2 H), 8.14 (br s, 2 H), 7.75 (m, 1 H), 3.59 (m, 4 H), 3.37 (m, 10 H); MS, *m/e* (relative intensity) 59 (100), 409 (3.0).

Biological Studies. In Vitro Cytotoxicity Evaluation. L1210 murine leukemia cells are routinely maintained as suspension cultures in McCoy's 5A medium supplemented with 10% horse serum, glutamine, penicillin, and streptomycin and grown in an humidified environment of 10% CO_2, 90% air at 37 °C. To assess the in vitro toxicity, each compound was dissolved in dimethyl sulfoxide (Me_2SO) and added to 4 mL of L1210 cells (10^5 cells/tube) to attain final concentrations of 0.01, 0.1, and 10 μg of drug/mL of culture. Each drug concentration was tested in triplicate and in no case was more than 40 μL of Me_2SO added to a given culture. After 96 h of continuous exposure to the drug, the cell concentration was determined with a Coulter counter (Model ZBF, Hialeah, FL). Growth inhibition was calculated for each drug concentration with use of the following formula:

$$\% \text{ growth inhibition} = \left(1 - \frac{\text{cell number treated}}{\text{cell number } Me_2SO \text{ alone}}\right) \times 100$$

The growth inhibition data was then used to calculate the ID_{50} value (the calculated drug concentration required to inhibit cell growth by 50% of control). A compound having an ID_{50} value in excess of 10 μg/mL was considered to be inactive in our system.

In Vivo Efficacy Studies. L1210 murine leukemia cells are maintained in vivo by several intraperitoneal injections of 10^6 cells to BDF_1 mice on a weekly basis. For test purposes, mice were inoculated ip with 10^6 cells and drugs were administered as a single ip injection approximately 24 h later. Prior to injection, the drug suspended in 10% (hydroxypropyl)cellulose solution at a concentration such that 0.1 mL/10 g of body weight delivered the desired dose. Mice were observed daily for signs of toxicity and survival. When all mice had died the mean survival time (MST) for each treatment group (six mice/group) was calculated and the percent T/C determined using the following formula:

$$\% \text{ T/C} = [(\text{MST treated})/(\text{MST control})] \times 100$$

Acknowledgment. This research was supported by Grant CA 24543 from the National Cancer Institute.

Registry No. **2a**, 96706-35-3; **2b**, 96706-34-2; **2c**, 21742-76-7; **2d**, 96706-36-4; **3**, 699-98-9; **4**, 150-78-7; **5**, 3712-11-6; *N,N*-diethylethylenediamine, 100-36-7; *N,N*-dimethylethylenediamine, 108-00-9; 3-(dimethylamino)propylamine, 109-55-7; *N*-acetylethylenediamine, 1001-53-2.

Book Reviews

Biochemical and Clinical Aspects of Pteridines. Volume 3. Cancer, Immunology, Metabolic Diseases. Edited by W. Pfleiderer, H. Wachter, and H. Ch. Curtius. Walter de Gruyter, Berlin and New York. 1984. xii + 541 pp. 17 × 24 cm. ISBN 3-11-010163-7. $100.00.

Pteridines such as tetrahydrobiopterin and neopterin are compounds of great interest and the organizers are to be commended for bringing chemists, biochemists, pharmacologists, and clinicians together yearly in St. Christoph, Arlberg, Austria. Volume 3 is mostly an update of the same areas covered in volumes 1 and 2 (volume 2 is reviewed in *J. Med. Chem.* **1984**, *27*, 1375). Tetrahydrobiopterin is a cofactor for the hydroxylation of phenylalanine, tyrosine, and tryptophan and is thus an essential component in the biosynthesis of catecholamine neurohormones and serotonin. New insight into tetrahydrobiopterin synthesis from GTP is presented by Nichol et al. Sepiapterin can no longer be considered an obligatory intermediate on this pathway which can also be carried out through labile pteridine intermediates. GTP cyclohydrolase, the first enzyme in the conversion of GTP to pteridines, is well reviewed by Blau and Niederwieser and chemical aspects of tetrahydrobiopterin biosynthesis are concisely presented by Ghisla et al. Some of the other topics covered are as follows: (1) tetrahydrobiopterin metabolism in the central nervous system (Blair et al.), (2) photodecomposition of pteridines (Pfleiderer et al.), (3) chemical synthesis of biopterin (Viscontini), (4) the effect of pteridines on (a) the response of the pineal gland to light (Ebels et al.), (b) neurosecretory cells in caterpillars (L'Helias et al.), and (c) aggregation in slime molds (Tatischeff et al.). There are four papers covering HPLC and electrochemical detection of pteridines, four papers on pteridines in immunology, and 19 papers on pteridine excretion in cancer and other diseases. It is reported that T-lymphocytes stimulate macrophages to produce neopterin, a process that can be mediated by γ-interferon (Huber et al.). Although neopterin production is correlated with stimulation of the immune system, a patient lacking GTP cyclohydrolase, and thus unable to synthesize pteridines, has a normal immune response (Blau and Niederwieser). The significance of neopterin production is not clear. Mouse lymphocytes produce biopterin, hydroxymethylpterin, and formylpterin on activation by lectin (Ziegler). Neopterin was not detectable in the mouse system. Urinary neopterin is proposed as a marker for many diseases including rheumatoid arthritis, coeliac disease, ulcerative colitis, gastrointestinal carcinoma, testicle tumors ("testicle" is repeatedly misspelled "testical"), bladder cancer, lung cancer, malaria, leprosy as well as a screening test for potential blood donors. The preface states that the diagnostic value of neopterin may be regarded as a milestone in medical research. The data presented are not convincing. Regrettably, in giving authors freedom to speculate as well as to publish preliminary results, the editors of this volume go beyond acceptable limits. The following quote from the paper of Fuchs et al. titled "Urinary Neopterin Evaluation in Risk Groups for the Acquired Immunodeficiency Syndrome (AIDS)" is scientifically unsound and should be retracted because it deals with a sensitive social issue about which rumors and hysteria abound (J. W. Curran, *N. Engl. J. Med.* **1983**, *309*, 609): "The reason of elevated neopterin in four out of five healthy Haitians is not easily explained, it may be a result of Voodoo-rituals common in population of Haiti. Nevertheless, neopterin elevation seems to be a sign of the special susceptibility of Haitians to develop AIDS." No documentation is given for the suggestion that Haitians have a special susceptibility to develop AIDS and, according to the literature (see J. W. Curran, loc. cit.), there is no such documentation. Errors in spelling and grammar are common throughout this book. Some sections are impossible to follow, for example (p 295), "On the other hand due to the possibility of likewise alterations of biopterin and neopterin the neopterin/biopterin ratios could be misinterpreted if only ratios differing to the normal values are attributed to disorders or malignant conditions respectively." The pteridine field deserves, and good science requires, more thoughtful, thoroughly edited and thoroughly documented work than is found in all too many of the papers included in this workshop.

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Progress in Tryptophan and Serotonin Research. Edited by H. G. Schlosberger, W. Kochen, B. Linzen, and H. Steinhart. Walter de Gruyter, Berlin and New York. 1984. xix + 889 pp. 17 × 24 cm. ISBN 3-11-009760-5. $73.00.

This book represents the proceedings of an international symposium on tryptophan research that was held in Martinsried,

Federal Republic of Germany in April of 1983. The editors admit that uniformity of nomenclature and of abbreviations was not enforced and that "as in any international meeting, the English was not always flawless" (this is evident from the very first page). The volume also contains several different type styles. None of these problems is particularly bothersome, however, and may be reasonable trade-offs so as not to delay publication. The title of the book seems to be somewhat of a misnomer; a better title may have been "Tryptophan and Its Metabolites". Only about 10% of the book is devoted to serotonin, and several of these chapters reflect the primary interest as being tryptophan (e.g., regulation of serotonin release by tryptophan). To this extent, this tome is of rather limited value (except for those involved with serotonin metabolism) to those whose primary interest is serotonin.

On the other hand, this is an excellent multidisciplinary source (both from a historical perspective as well as for some of the most recent work) on tryptophan research. After several brief introductory chapters on, for example, the pioneering work of Adolf Butenandt (to whom both the symposium and the book were dedicated) and his contributions in the field of tryptophan metabolism, and on a review of tryptophan chemistry, the book is divided into nine logical sections. These cover the analytical, neurobiological, clinical and behavioral, nutritional and metabolic (with separate sections on metabolism in mammals, insects, and plants and microorganisms) aspects of tryptophan; the concluding chapter deals with tryptophan in proteins and peptides. Emphasis is essentially equally divided amongst the various sections, with the clinical sections (behavioral effects and pathology) receiving a double measure of attention.

Because of its multidisciplinary nature, this book will be attractive to those in many areas of tryptophan research, from natural products to analytical chemistry, from nutrition to clinical chemistry. However, it will probably be of most interest to those involved with tryptophan metabolism.

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Asymmetric Synthesis, Volume 4. Edited by James D. Morrison and John W. Scott. Academic Press, Orlando, FL. 1984. xii + 380 pp. 16 × 23.5 cm. ISBN 0-12-507704-1. $85.00.

This latest volume in a continuing series is subtitled "The Chiral Carbon Pool and Chiral Sulfur, Nitrogen, Phosphorus, and Silicon Centers" and contains five contributed reviews.

The first chapter, "Readily Available Chiral Carbon Fragments and Their Use in Synthesis" (226 pages, 560 references), is by John W. Scott and concentrates on the use of readily available chiral carbon fragments for the synthesis of alkaloids, prostaglandins, thromboxanes, leukotrienes, β-lactam antibiotics, macrolides, polyether antibiotics, miscellaneous compounds with chemotherapeutic and pharmacological activity, insect pheromones, sugars, vitamins, and terpenes. Early in the chapter the author lists 375 optically active building blocks. The compounds are arranged in a table on the basis of the length of the carbon chain containing the chiral center, along with their commercial sources, approximate prices, and methods of synthesis with literature citations. The remaining sections of the chapter contain numerous examples of natural product syntheses using chiral starting materials. The Schemes which are employed to illustrate the syntheses are extensively referenced.

The second contribution "Optical Activation and Utilization of Compounds Containing Chiral Sulfur Centers" (36 pages, 128 references) is by Michael R. Barbachyn and Carl R. Johnson. This chapter opens with a section on the optical activation of chiral organosulfur reagents. An extensive review with emphasis placed on the procedures for the preparation of chiral sulfoxides, sulfonium salts, and sulfoximines of high optical purity is presented followed by a section devoted to application of chiral organosulfur reagents to asymmetric synthesis.

The third chapter, "Preparation of the Enantiomers of Compounds Containing Chiral Phosphorus Centers" (50 pages, 212 references), is by Donald Valentine, Jr. The author points out that his contribution "... is intended to serve as a practical guide to the preparation of new P-chiral compounds by either resolution or asymmetric synthesis". Section I surveys the P-chiral chemistry of P-chiral systems of known absolute configuration. Section II outlines syntheses of P-chiral phosphines. A representative list of P-chiral enantiomers of tertiary phosphines, phosphine oxides, quaternary phosphonium salts, and some related substances has been supplied in tabulation form. The final section discusses the preparation of P-chiral thioacids.

The fourth chapter, "Synthesis and Utilization of Compounds with Chiral Nitrogen Centers" (42 pages, 85 references), is by Franklin A. Davis and Robert H. Jenkins, Jr. and reviews the synthesis, reactions, and properties of nitrogen-containing compounds that derive their optical activity solely from an asymmetric nitrogen atom. Specific attention is devoted to chiral trivalent nitrogen (aziridines, diaziridines, oxaziridines, and alkoxyamines) and chiral tetravalent nitrogen (quaternary ammonium salts and amine oxides).

The last chapter, "Synthesis and Utilization of Compounds with Chiral Silicon Centers" (19 pages, 75 references) is by Cynthia A. and Bruce E. Maryanoff and starts with an introductory discussion of the stereochemistry and mechanism of reactions at silicon centers. What follows is a section devoted to the preparation of optically active organosilanes by classical resolution and asymmetric synthesis and a section concerned with the application of chiral organosilanes in synthesis.

This latest volume of Asymmetric Synthesis, like its predecessors, is well written and well documented. This new volume is invaluable to the practitioner of organic synthesis. The book is excellent.

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Brain Receptor Methodologies: Part A. General Methods and Concepts. Amines and Acetylcholine and Part B. Amino Acids, Peptides, Psychoactive Drugs. Edited by P. J. Marangos, I. C. Campbell, and R. M. Cohen. Academic Press, Orlando, FL. 1984. Part A: xx × 363 pp. 16 × 23.5 cm. $56.00. Part B: 336 pp. $78.20. ISBN 0-12-470350-X.

The technique of radioligand binding has, in the 10 years since its validation, proven to be an invaluable tool in the process of drug discovery and in the elucidation of receptor function at the molecular level. To the medicinal chemist, the technique has become indispensible in allowing for the rapid and reliable determination of structure–activity relationships, free of the problems associated with coupled effector systems. To date, the main source of information on newer developments in the area has been various and sundry symposia volumes which, by their very nature, are ephemeral. To those interested in binding, there has long been a need for a comprehensive, integrated treatment of the technique where questions such as: why is the Scatchard plot out of favor?, what does a Hill coefficient different from unity mean in terms of receptor function?, whatever happened to the D-4 receptor?, and so on are adequately dealt with. A two-volume set entitled "Brain Receptor Methodologies" therefore would be anticipated to fill this gap, providing a comprehensive, topical treatment of receptor binding in terms of theory, technique and, ultimately, receptor characterization.

In the 699 pages of this set, designed by the editors to "provide a treatment of brain receptors that is of broader scope than previously attempted", 33 chapters cover general methods and concepts, methods for studying the receptor molecule and receptor-linked effector systems, plus specific chapters on α- and β-adrenoceptors, dopamine, serotonin, muscarinic cholinergic, GABA, glycine, carnosine, opiate, bombesin, cholecystokinin, TRH, substance P, benzodiazepine, phencyclidine, neuroleptic, tricyclic antidepressant, and adenosine receptors. The intentions of the editors are laudable; however, the result of their endeavours falls far short of a useful reference set. The absence of chapters on calcium entry blocker, excitatory amino acid, and VIP recognition sites is hardly justified by the preface ascribing their omission to "practical realities". In addition, there is a lack of consistency throughout the work, both in the style of presentation and the chapter content.

Instead of one or two concise chapters on receptor theory and the techniques involved in data manipulation, nine of the contributors treat this topic in their individual chapters. These treatments range from excellent as evidenced in the chapters by Burgisser and Lefkowitz, Perry and U'Prichard, Ehlert et al., and Munson to Campbell's historical perspective chapter, which is somewhat superficial. Although the spectrum of data analysis is covered, such fragmentation in its presentation tends to negate the information content. The chapter on ligand synthesis by Wan and Hurt is a valuable first. There is, however, much about this set that is troubling. The inclusion of chapters on little studied recognition sites such as those for carnosine, glycine, and bombesin to the exclusion of histamine, glutamate, NMDA, neurotensin, and other more topical peptides has no rationale and the seven-page chapter by Flockhart and Corbin on the preparation (no more, no less) of the catalytic subunit of cAMP-protein kinase, although competent, reads like filler. One looks in vain for a discussion of 5-HT-1-A receptors and for mention of the μ-1 opiate receptor. Tables comparing the data obtained from different laboratories such as that in Too and Hanley's substance P chapter, while very necessary, are infrequent. The omission of a concise overview of presynaptic receptors, autoreceptors, and receptor modulation of transmitter release is disappointing while the chapter on cyclic nucleotides is predominately an overview of current electrophysiological techniques with the ubiquitous second messenger appearing as an afterthought. The function of cAMP is inadequately dealt with and those interested would ultimately fare far better with the late George Drummond's brief but indispensible monograph on the cyclic nucleotide. In the chapter on adenosine receptors, the faux pas of confusing Londos and Wolff's intracellular P purine recognition site with Burnstock's ATP-sensitive, cell-surface P-2 purinoceptor is lamentable and misleading.

Overall, therefore, these two volumes do not live up to their promising title nor the stated aims of the editors. Given the distinguished list of contributors, this is difficult to comprehend until one takes into account the fact that the major criticisms made of these volumes concern the editorial input (or lack thereof). Little attempt has been made to ensure an overall consistency or stylistic theme to the contributions while the conscious omission of several important areas of current receptor binding research seriously detracts from the usefulness of these volumes. thus, there is still a need for a well-edited, comprehensive compendium on receptor binding. Until this appears, the reader with an interest in the area of receptor binding that extends to the pecuniary would be far better rewarded by purchasing the second edition of Yamamura, Enna, and Kuhar's seminal volume, "Neurotransmitter Receptor Binding". Unfortunately, the current volumes are not an auspicious debut for Academic Press' Neurobiological Research Series.

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Marihuana in Science and Medicine. Edited by Gabriel G. Nahas, David J. Harvey, Michael Paris, and Henry Brill. Raven Press, New York. 1984. ix + 312 pp. 16 × 24 cm. ISBN 0-88167-014-6. $48.00.

This book is designed to expand on the coverage of pharmacology and toxicology presented in an earlier book, "Marihuana--Deceptive Weed". Coming as it does shortly after the appearance of a book covering a major marihuana symposium in Louisville, KY (Cannabinoids 82, Louisville, KY, Aug 1982) and a soon-to-be published volume resulting from the Satellite Symposium on Marihuana, Oxford, Aug 1984, the reader cannot expect much new information. The book consists of five chapters, one of which Professor Nahas authored and coauthored on three others. The chapters are of uneven length and quality and in some cases lack objectivity; Nahas is strongly opposed to the use of cannabis (as is the reviewer and many other scientists working in this field). Unfortunately, at times this causes some impairment of objectivity in Nahas' treatment of certain areas of marihuana research, which will subsequently be discussed.

The first chapter, prepared by Paris and Nahas, is entitled "Botany: The Unstabilized Species". This is one of the shorter chapters in the book. It deals largely with a description of cannabis botany and of the kinds and types of cannabinoids that can be found in *Cannabis sativa* in various parts of the world. This chapter contains relatively little new information. Probably the most valuable aspect is a considerable treatment of the extensive French literature in this area, which may be unfamiliar to scientists from English-speaking countries. The literature citations, consisting of approximately 125 references, will be of value to individuals wishing to obtain a rapid introduction to the field. In this review and particularly in the summary on page 31, the authors fail to distinguish between the varieties of cannabis that are high in Δ^9-THC and are predominantly found in Mexico, South America, and the United States and those from the Middle East, which are much higher in cannabidiol. Moreover, an important class of cannabinoids with a shorter side chain is not referenced. This type comes from the Far East, particularly Thailand. There are occasional errata; for example, a reference that should be to C. T. Turner, 1980 is ascribed to J. C. Turner, 1980, which is an entirely different paper. On page 23 are given gas chromatographic analyses of various varieties of cannabis. However, no reference is given to the original authors of this method, K. Davis et al., who introduced the use of androstenedione as an internal standard.

The second chapter deals with the chemistry, metabolism, and pharmacokinetics of the cannabinoids and is authored by D. J. Harvey. This is the best chapter in the book. Dr. Harvey, originally trained in chemistry, has been working for many years on the analysis and structure of various cannabinoid metabolites derived from THC, using particularly mass spectrometric techniques. His discussions include treatment of the various naturally occurring cannabinoids, numbering systems, biosynthesis of natural cannabinoids, and some of the physical and chemical properties of these compounds. Harvey presents an excellent account of the disposition, metabolism, and pharmacokinetics. Although most of this material has appeared previously, his chapter presents many of the important elements and brings them together in a clear and unified manner. Harvey gives a good treatment of structure–activity relationships and presents very well the measurement of cannabinoids and their metabolites in body fluids and tissues. Finally, the synthesis of cannabinoids is reviewed, and although again most of this is old work that has been presented in a number of other reviews, it still has its place in an overall review of this nature. Over 300 references are included, and it is conceivable that this chapter alone might be worthwhile for the specialist and libraries to purchase the book.

The third chapter is a long presentation on the toxicology and pharmacology of THC by Gabriel G. Nahas. The discussion includes acute and chronic toxicity of THC and other cannabinoids, cellular toxicity, impairment of cellular growth and macromolecular synthesis, carcinogenicity, pulmonary toxicity, and many other areas. In all of these cases, Nahas stresses data that present unfavorable actions of THC. The problem in this area is that it is gray rather than black and white. Many of the studies have been carried out with enormous doses, particularly those involving cellular toxicity or in isolated cell systems. In no case does Nahas refer to other studies that might indicate that cannabis or THC may not have as great a toxic effect as he believes. This is particularly emphasized in the section dealing with reproductive function and development. Studies in this area involve great controversy and polemical discussions between various groups. The effects, in this reviewer's opinion, are still difficult to determine. In particular, an early report by Kolodny showed that testosterone levels fell after repeated smoking of cigarettes containing Δ^9-THC. On the other hand, Mendelson later reported a similar experiment that failed to indicate any change in testosterone concentration. In some unpublished work, Perez-Reyes and Wall found effects somewhere in between. In other words, there as some lowering of testosterone immediately after the subjects received Δ^9-THC. However, it was not statistically significant, and testosterone levels returned to normal some hours afterward. In his discussion, Nahas accepts Kolodny's unfavorable reports and attempts to explain away (page 144) Mendelson's study that failed to show any significant decrease in testosterone levels.

On the favorable side, Nahas's treatment is thorough and of great topical interest, covering all phases of toxicology and pharmacology. The reviewer must warn the casual reader that a neutral report, however, cannot be expected because of Nahas' conviction that cannabinoids are dangerous drugs. Professor Nahas's coverage of the literature in this field is encyclopedic; over 900 references are cited. These references may be of considerable value to the reader who wishes an introduction to the field.

The fourth and shortest chapter is the "Medical Use of Cannabis" by Gabriel G. Nahas. Nahas's treatment of this subject is superficial and again relates to his strong opposition to the use of cannabinoids, either for social or therapeutic uses. Because this chapter is so short in a field that has extensive literature, it might have been preferable to omit it.

The fifth chapter deals with cannabis intoxication and mental illness, authored by Henry Brill and Gabriel G. Nahas. This chapter is interesting and undoubtedly will be controversial in a field that is already extraordinarily filled with controversy. About one-third of this chapter reviews the work of Moreau, a French scientist who published extensively on hashish intoxication in the 1840s. The authors of this chapter present an excellent review of Moreau's work. It was indeed of interest to learn of the extraordinarily accurate perceptions that this scientist had in this field almost 150 years ago. As with other chapters in which Nahas is involved, the emphasis is strongly on the harmful effects of cannabis intoxication, particularly in adolescence. Over 150 references are cited in this section. This chapter is interesting reading, particularly to one such as the reviewer who is trained in medicinal chemistry. Again, the reader is warned that a completely objective presentation will not be found and controversial views presented.

In summary, "Marihuana in Science and Medicine" presents an interesting discussion of a number of fields of topical interest in cannabinoid chemistry, toxicology, and pharmacology. It contains an outstanding treatment on the chemistry and metabolism of the cannabinoids as well as an in depth review of the toxicology and pharmacology. Undoubtedly it should be in every library of scientists working in the field and in general libraries of medicinal chemistry, toxicology, and pharmacology.

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1,3-Dipolar Cycloaddition Chemistry. Volumes 1 and 2. Edited by Albert Padwa. Wiley, New York. 1984. Volume 1: xiii + 817 pp. Volume 2: xiii + 704 pp. 18.5 × 26 cm. ISBN 0-471-08364-X (set). $295.00 (set).

Cycloaddition reactions have and will continue to play a prominent role in synthetic-organic and physical-organic chemistry with important or useful applications in closely aligned disciplines including medicinal chemistry. Of the cycloaddition reactions available, the 1,3-dipolar cycloaddition process, which has been investigated principally during the course of the last 20 years, has proven to be nearly unmatched in its capabilities for providing simple or complex heterocycles with predictable regio-, stereo-, and most recently enantiocontrol. Further developments in the area as well as the practical applications of 1,3-dipolar cycloadditions depend on the assimilation of the information into a single source for consultation by those less familiar with the details of the studies to date. This two-volume set on 1,3-dipolar cycloadditions succeeds in this purpose. Fifteen chapters contributed by 21 authors cover extensively, but not exhaustively, the topics of 1,3-dipolar cycloaddition reactions. In addition to a general and superb introduction by Professor R. Huisgen (Chapter 1), the major classes of 1,3-dipolar cycloadditions are treated in detail independently: nitrile ylides (Chapter 2), nitrile oxides and imines (Chapter 3), diazoalkanes (Chapter 4), azides and nitrous oxide (Chapter 5), azomethine ylides (Chapter 6), azomethine imines (Chapter 7), mesoionic ring systems (Chapter 8), nitrones (Chapter 9), azimines and related compounds (Chapter 10), and ozone and carbonyl oxides (Chapter 11). An independent treatment of the intramolecular 1,3-dipolar cycloaddition (Chapter 12), theory of 1,3-dipolar cycloaddition (Chapter 13), 1,3-dipolar cycloreversions (Chapter 14), and higher order dipolar cycloadditions are provided. The material in each chapter is well referenced and an additional, cumulative author and subject index is included. Thus the series easily accommodates the interested student, those teaching specialized topics including the 1,3-dipolar cycloaddition, as well as the active participants in the field of 1,3-dipolar cycloadditions.

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Theoretical Drug Design Methods. By Rainer Franke. Elsevier, Amsterdam and New York. 1984. 412 pp. 17 × 24.5 cm. ISBN 0-444-99634-6. $75.00.

This book, which appears as Volume 7 of the Pharmacochemistry Library series, is a revised, updated, and expanded English version of the author's book "Optimierungsmethoden in der Wirkstofforschung" originally published by Akademie Verlag, Berlin, DDR, in 1980.

The subject of theoretical drug design methods is covered by the author in comprehensive fashion in 15 chapters. There is an extensive treatment of the extrathermodynamic approach (Hansch analysis) in which physicochemical properties of compounds and substituents are related to biological properties and also a thorough discussion of many other methods that have come into use in recent years.

The subject matter is arranged logically in an appropriate sequence. An introductory chapter includes a discussion of the formulation of problems in drug design and the second chapter deals with measures of biological activity. The following five chapters cover the extrathermodynamic approach to quantitative structure–activity analysis, the main physicochemical parameters, hydrophobic, electronic, and steric, associated with that approach, and the problem of collinearities between these parameters. Next comes a chapter on the practical aspects of Hansch analysis with some illustrative examples.

Chapter 9 covers other approaches to quantitative structure–activity analysis with extrathermodynamic molecular parameters, which includes a description of principal component analysis, classification methods, and linear discriminant analysis. Chapter 10 discusses non-computer-assisted methods based on the extrathermodynamic approach.

A description of the Free–Wilson model and its relationship with the extrathermodynamic approach and an account of substructural, topological, and pattern recognition methods is provided in Chapter 11. Chapters 12 and 13 deal with receptor mapping and pharmacophores, and biological response profiles, respectively.

Concluding remarks, the subject of Chapter 14, nicely summarizes the current state of development and the place of QSAR in drug design and contains an interesting table of examples of current predictions from QSAR's. The final chapter is a useful appendix covering some principles of linear regression analysis, the most widely employed method in QSAR analysis.

The author, Professor Rainer Franke, has been for many years a leading researcher in the field of theoretical drug design methods and this background has provided him with the necessary knowledge and overall perspective for writing this excellent, comprehensive book. Particularly noteworthy for their depth and value are Chapters 5, 8, and 9 dealing with electronic effects, practical aspects of Hansch analysis, and other approaches to QSAR with extrathermodynamic molecular parameters, respectively. The textual material throughout the book is carefully developed and explained, fully referenced, and well illustrated with many informative examples. There is a good subject index but no author index. The references are up to date.

There are impressively few errors both factual and grammatical and the writing style is impeccable for a translated work. The odd trace of its non-English origin remain as in the spellings Electronik p 80 and Funktion on pp 30, 80. The book would have benefited from a greater use of subtitling; for example, Chapter 6 has none. In places the text is a bit too heavy in general mathematical formalism, which reduces readability for the average reader. However, these minor flaws have no material impact on the overall quality of the work.

Professor Franke's book is highly recommended for reading and reference purposes to all scientists and students interested in the theory and practice of QSAR. The author is to be congratulated on his success in producing such a high quality and useful volume.

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Handbook of Stereoisomers: Drugs in Psychopharmacology. Edited by Donald F. Smith. CRC Press, Boca Raton, FL. 1984. 488 pp. 18.5 × 26 cm. ISBN 0-8493-2940-X. $125.00 U.S./ $145.00 Foreign.

This is a book of high importance.

The pharmacist in the year 2000 may justifiably look upon our present-day practice with disdain. Our drug references listing generic and trade names generally omit (*RS*) or (±) prefixes for chiral agents marketed as racemates. Nor do our pharmacopoeia give the essential information on therepeutic potencies of the enantiomers of a racemic drug. As a consequence, the practising physician has no idea whether the drug prescribed by him contains a *single* (nonchiral agent), or *two* (a racemate with cumulative action of enantiomers), or *three* (a racemate with nonadditive action of enantiomers), or *even more* (mixture of two racemates with cumulative actions, etc.) distinct pharmacological entities. Since nearly one drug out of every four is of racemic composition, our negligence is enormous. Basic information on enantioselective pharmacological properties of chiral structures, if available at all, is scattered around in the literature. The source of collected data that helps clarify the situation is welcome, hence the primary merit of the book.

Stereoisomer is, of course, a term broader than optical isomer and the book considers geometrical isomers and diastereomers as well. Yet, the dominant part of the volume deals with chirality. The title is felt a bit unfortunate; its first part implies lexical pretensions that do not match with style and scope. "Stereoisomer Drugs in Psychopharmacology" might have been a better choice.

The first (Basic Terms in Stereochemistry by A. S. Horn) and last (Glossary by D. F. Smith and P. A. Lehmann F.) chapters intended to help the uninitiated are necessary for an interdisciplinary work of this kind. The aim is not completely achieved, however. Although Emil Fischer's proposition is still in current use for sugars and amino acids, the absolute configuration today does not refer to a "relationship to D- or L-glyceraldehyde as reference compounds". The statement: "Any structural feature of a molecule which gives rise to optical activity may be called a chiral center" overlooks structures possessing a chiral axis or helicity without containing any center of asymmetry. The formulae chosen to represent *Z,E* isomerism are wrong and the sequence rule as applied to them is false. This failure may in part be the consequence of an undesirable layout of the chapters disintegrated into condensed text and separate passages of structural formulae and tables. The discussion on relations between stereo structures of drugs and drug effects loses its most lively context if the text is deprived of both the formulae of compounds and data on their pharmacological effect. Being annoyed by the necessity of turning 10–30 pages every now and again, the reader probably will soon fail to consult data or structures to which reference is made; hence, even the best written pages can become dry and boring. The authors of only a few chapters managed to camouflage some of their structural formulae in figures allowed to appear within the text.

A well-written introduction to the subject is given by the editor himself presenting a survey of pitfalls and shortcomings in recent practice. Included is a table on selected *racemic* psychotherapeutic drugs which might be of interest unless it would not list indiscriminately mianserin (marketed as racemate of stable enantiomers), nalorphine (marketed as the active (−)-enantiomer), oxazepam (subject to spontaneous racemization in aqueous solution), flurazepam (lacking an asymmetric center though chiral by virtue of its nonplanar diazepine ring, i.e., unresolvable conformational racemate) and chloral hydrate (achiral).

The discussion on muscarinic cholinergic drugs by D. J. Triggle is a high-level comprehensive account of stereochemical aspects for both agonists and antagonists. While much information is given on structure–activity relations, the author does not yield to current hypotheses on receptor subclassification and on the distinct character of agonist and antagonist binding sites but treats them critically. The structural formulae are not devoid of a few misprints.

Receptors for nicotine exist in brain, but their nature is still a matter of debate. Such basic questions as to whether all nicotinic receptors are cholinergic remain to be answered. A concise account on nicotine enantiomers with reference to their pharmacological and biochemical effects by M. D. Aceto, B. R. Martin, and E. L. May is interesting reading; the potency ratios of (+)-nicotine/(−)-nicotine in the tables should be understood reciprocally.

C. O. Rutledge, D. E. Walters, and G. L. Grunewald report on conformational preferences in uptake mechanisms of noradrenergic drugs. The authors review the neuronal uptake transport system and critically evaluate various methods (X-ray, NMR, MO calculations) used to determine the conformation of flexible molecules. By applying a large number of conformationally restricted analogues, this chapter beautifully represents how much care had to be taken before the antiperiplanar conformer of amphetamine could be assigned as the active form.

Of necessity a great emphasis is placed on dopaminergic mechanisms when psychopharmacological effects are concerned. J. G. Cannon discusses structural features of dopaminergic agonists including derivatives of aporphine, 2-aminotetralin, and ergot alkaloids. This chapter again deals with stereochemistry on a high level supported by well-drawn structural formulae among which the appearance of an extraneous structure is puzzling.

The contribution of J. Hyttel, J. Arnt, and K. P. Bøgesø on configurational stereoisomers of antipsychotic drugs is a voluminous item living up to most of the promise of the title as to be a handbook. It discusses many drugs belonging to diverse classes of compounds and presents biochemical and pharmacological data (in 50 tables) and calls attention to cases where information on enantiomers is not available. The "flagpole–bowsprit type of interaction" between hydrogen atoms of butaclamol may not be an easily understandable jargon for those unfamiliar with sailing ships.

Antidepressant drugs are divided among the next three chapters according to their chemical structure. Chiral stereoisomers are reviewed by V. J. Nickolson and R. M. Pinder, *Z* and *E* isomers are dealt with by S. B. Ross, and finally, conformationally restricted stereoisomers are discussed by A. R. Martin. The large number of drugs as well as biochemical, pharmacological, and behavioral data used to illustrate the varying degrees of stereoselectivity show that the mechanism of action for these drugs are very complex. The structures themselves defy a good deal the above classification. The major metabolite of nortriptyline (a structure with *Z,E* isomerism) is not only chiral (10-hydroxynortriptyline) but also optically active; the conformationally restricted class includes both *Z,E* isomers and chiral structures (atropisomers and compounds with asymmetric centers).

Monoamine oxidase enzymes and their inhibitors are necessarily treated by the preceding chapters on antidepressant drugs. A brief account by M. Tenne and M. B. H. Youdim discusses additional stereochemical aspects including the rate-determining stereospecific abstraction of an α-hydrogen from alkylamines in the enzymatic oxidation process.

Although literature on racemic amphetamine is quite extensive (39 separate diseases were treated by amphetamine before 1946), the available information on the psychopharmacological effects of amphetamine enantiomers is excellently surveyed in a few pages by D. P. van Kammen, P. T. Ninan, and D. Hommer. Of special interest is their notion that the enantiomeric effects depend on experimental variables and the mechanism of action is still open to debate.

The pharmacology of the constituents of marijuana (cannabinoid stereoisomers) is dealt with by W. L. Dewey, B. R. Martin, and E. L. May, who point out that natural isomers have 5–100 times higher potency than unnatural ones depending upon the species and on the individual test concerned. Though some of the effects suggest the existence of a specific receptor in the central nervous system, the lack of a specific antagonist and of any in

vitro system for investigation has not allowed so far this hypothesis to be established.

The hallucinogenic property of phenylisopropylamines is also affected by stereochemical factors. R. A. Glennon presents a clear-cut survey extending to several drugs subjected to human and animal studies and critically evaluates theories concerning the favorable fit of molecules to neurotransmitter receptors; an impressive span from preparative organic chemistry to behavior.

The finding that different conformations of the flexible 4-aminobutyric acid (GABA) are active at receptor and uptake sites prompted both configurational and conformational aspects to be included into the discussion on GABA-ergic drugs. The competent review also covers inhibitors of GABA metabolism. P. Krogsgaard-Larsen, P. Lenicque, and P. Jacobsen offer many examples to illustrate the effects of stereostructure on GABA-ergic activity.

The remaining two chapters deal with opiate stereoisomers with considerable overlap. H. N. Bhargava lays emphasis on pharmacological effects and assay procedures while E. F. Hahn and G. W. Pasternak discuss receptor mechanisms and opiate receptor heterogeneity. Neither of the two chapters mentions picenadol, the enantiomers of which were reported in 1982 to antagonize each other.

The last remark applies more or less to the volume as a whole. References extend to 1981 with later ones appearing exceptionally, which renders the book a little outdated. The subject index is very detailed and could be even more useful if pages of structural formulae were also given to compound names. Since the table of contents lists only title of chapters without authors' names (why does it?), it takes quite a time to find out which chapter is associated with a certain contributor.

It is certainly a merit of the editor that he was able to persuade so many experts to such a collective effort. The book is a very useful reference work, most probably the only available of its kind. Moreover, several chapters are examples of expert treatment of structure–activity relations and convey real pleasure to the reader. University lecturers can use it in education, medicinal chemists and pharmacologists in research, pharmacists for compiling and refreshing basic information in drug references. Without the shortcomings this book could have been a masterpiece. With them still a milestone.

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Methods in Molecular Biology. Volume 1. Proteins. Edited by John M. Walker. Humana Press, Clifton, NJ. 1984. xii + 365 pp. 16 × 24 cm. ISBN 0-89603-062-8. $45.00.

"Methods in Molecular Biology. Proteins" is the first volume of a series on modern methodology of protein chemistry practiced by molecular biologists. Step-by-step procedures, reagents, and special notes on the methods are concisely presented in many short chapters. A particular procedure is easy to find from the chapter headings. The methods range from standard techniques of protein determination and characterization, immunoaffinity purification and SDS polyacrylamide gel electrophoresis separation, and analysis of proteins to various mapping and sequencing procedures. Computer analysis of gel scanning is also presented. Curiously, protein purification and characterization methods are limited to analytical scale since preparative purification of proteins is not considered necessary for hybridoma production. Current reliable methods of N-terminal and C-terminal sequence analysis methods are described. Such a description of *manual* methods is welcome as most biochemists are not in high-budget labortories that can afford the latest automatic instrumentation or may want to perform these techniques occasionally. The book leads up to hybridoma technology and related immunochemical techniques including enzyme-linked immunosorbant assay. The methods seem very complete for the polyacrylamide gel analytical work; however, the radioimmunoassay description is sketchy. Nevertheless, since this is such a specialized field in itself more detail is probably not necessary for the purposes of this book. The main value is rather the description of hybridoma methods. One term that caught my attention is "biro", which I assume to be an Anglo colloquialism for a ball point pen.

This volume is a very useful collection of methods that will serve well as a laboratory reference. A minor point is that the information presented here in the style of technical reports would have been clearer if presented in a textbook style with photos and more diagrams of procedures and assemblies.

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Strategies and Tactics in Organic Synthesis. Edited by Thomas Lindberg. Academic Press, Inc. New York. 1984. xiv + 370 pp. 16 × 23.5 cm. ISBN 0-12450280-6. $57.00.

This timely book provides the reader with a fascinating account of problems related to total synthesis in organic chemistry. Thirteen chapters are written by a number of outstanding synthetic chemists and their associates. Written in their own personalized style, each contributor has provided an in-depth analysis of the synthetic objective and has also given a behind-the-scene, as-it-happened account of the strategies, philosophy, and events leading to the conquest of their targets. In this period of rapid communication of results, the space limitations in journals, the conceptual and tactical aspects of a problem are often left out and, in many cases, never divulged. This is ever so important whether the reader is a seasoned practioner of the art of synthesis or a young graduate student. Both could benefit enormously from the genesis of an idea, its evolution, and eventual execution in the laboratory.

The following titles and authors can be found in this book: "Theme and Variations: A Synthesis of Superphane", Virgil Boekelheide; "The Total Synthesis of Gibberellic Acid", Rick L. Danheiser; "A Prostaglandin Synthesis", Josef Fried; "Synthesis of Indole Alkaloids", Philip Magnus; "Synthesis of Tylonolide, the Aglycone of Tylosin", William P. Jackson, Linda D.-L. Lu Chang, Barbara Imperiali, William Choy, Hiromi Tobita, and Satoru Masamune; "Pericyclic Reactions in Organic Synthesis and Biosynthesis: Synthetic Adventures with Endiandric Acids A-G", K. C. Nicolaou and N. A. Petasis; "Plato's Solid in a Retort: the Dodecahedrane Story", Leo A. Paquette; "The Synthesis of Fomannosin and Illudol", M. F. Semmelhack; "Evolution of a Synthetic Strategy: Total Synthesis of Jatrophone", Amos B. Smith III; "On the Stereochemistry of Nucleophilic Additions to Tetrahydropyridinium Salts: A Powerful Heuristic Principle for the Stereorationale Design of Alkaloid Syntheses", Robert V. Stevens; "A Nonbiomimetic Approach to the Total Synthesis of Steroids; The Transition Metal-Catalyzed Cyclization of Alkenes and Alkynes", K. Peter C. Vollhardt; "Evolution of a Strategy for Total Synthesis of Streptonigrin", Steven M. Weinreb; "Methynolide and the Prelog–Djerassi Lactonic Acid: an Exercise in Stereocontrolled Synthesis", James D. White.

The selection of topics is representative of a wide enough cross-section of activities in modern organic synthesis and literature coverage within each chapter is excellent. Obviously many other topics (and authors) come to mind, but the intention of the monograph is well served by the coverage provided. It does indeed focus on the tactical and strategic aspects of synthetic design. I recommend this book to be used in a special topics course on natural product synthesis and synthetic strategy in general. It will also stand well alongside other books on the organic chemist's shelf. By today's standards and considering the quality of the print and schemes, it is affordable at $57.00 to most professionals but somewhat out of reach for a student. The editor, Dr. Thomas Lindberg, should be congratulated on assembling some "great works of art" in organic synthesis in one volume.

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Books of Interest

Glass Capillary Chromatography in Clinical Medicine and Pharmacology. Edited by Halvor Jaeger. Marcel Dekker, New York. 1985. 19 × 26 cm. xi + 640 pp. ISBN 0-8247-7103-6. $99.75/U.S. and Canada; $119.50/all other countries.

Methods in Molecular Biology. Volume 2. Edited by John

M. Walker. Humana Press, Clifton, NJ. 1984. 16 × 23.5 cm. xiv + 375 pp. ISBN 0-89603-064-4. $45.00.

Safety Testing of New Drugs. Laboratory Predictions and Clinical Performance. Edited by D. R. Laurence, A. E. M. Mclean, and M. Weatherall. Academic Press, Orlando, FL. 1984. 16 × 23.5 cm. viii + 174 pp. ISBN 0-12-438350-5. $28.00.

The Methylxanthine Beverages and Foods: Chemistry, Consumption, and Health Effects. Progress in Clinical and Biological Research. Volume 158. Edited by Gene A. Spiller. Alan R. Liss, New York. 1984. 16 × 23.5 cm. xii + 413 pp. ISBN 0-8451-5008-1. $78.00.

Drugs and Pregnancy. Maternal Drug Handling—Fetal Drug Exposure. Edited by B. Krauer, F. Krauer, F. E. Hytten, and E. del Pozo. Academic Press, Orlando, FL. 1984. 16 × 23.5 cm. xi + 281 pp. ISBN 0-12-425960-x. $22.00.

Biochemical Pharmacology and Toxicology. A Series of Monographs. Biological Basis of Detoxication. Edited by John Caldwell and William B. Jakoby. Academic Press, Orlando, FL. 1984. 16 × 23.5 cm. xiii + 429 pp. ISBN 0-12-155060-5. $54.00.