crystals. Recrystallization from ethanol gave colorless needles: mp 140–140.5 °C; IR ($CHCl_3$) 2210 cm^{-1}; NMR ($CDCl_3$) δ 2.98–3.72 (m, 4 H), 5.03 (s, 2 H), 7.06–8.20 (m, 6 H). Anal. ($C_{16}H_{12}N_2S$) C, H, N.

Methyl 3,4-Dihydro[1]benzothieno[2,3-*h*]isoquinoline-2(1*H*)-methanimidoate (12). A mixture of 4.6 g (0.018 mol) of 11 and 1.1 g (0.018 mol) of potassium cyanide in 50 mL of methanol was stirred for 4 h at reflux and overnight at ambient temperature. The solvent was distilled off and the residue partitioned between water and ethyl acetate. The organic portion was washed (H_2O) and dried ($MgSO_4$); removal of the solvent yielded 5.0 g (96%) of a tan solid; recrystallization of 100 mg from ethyl acetate/hexane gave 90 mg of pale yellow crystals: mp 128.5–130 °C; IR ($CHCl_3$) 3380, 1633 cm^{-1}; NMR ($CDCl_3$) δ 3.02 (t, J = 5.5 Hz, 2 H), 3.70 (t, J = 5.5 Hz, 2 H), 3.80 (s, 3 H), 4.93 (br, 1 H), 5.14 (s, 2 H), 7.10–8.37 (m, 6 H). Anal. ($C_{17}H_{16}N_2OS$) C, H, N.

1,2,3,4-Tetrahydro[1]benzothieno[2,3-*h*]isoquinoline Hydrochloride (13). A solution of 4.8 g (0.016 mol) of 12 in 50 mL of 80% acetic acid was stirred at reflux overnight. It was poured into 300 mL of water, made basic with 50% sodium hydroxide, and extracted with ether. The ether solution was dried ($MgSO_4$) and concentrated to yield 3.8 g of yellow solid. This solid was dissolved in ethanol and treated with 2-propanolic hydrogen chloride to yield 3.3 g (73%) of pale yellow powder. Recrystallization from glacial acetic acid/water gave white crystals: mp >300 °C; NMR of free amine ($CDCl_3$) δ 1.92 (s, 1 H), 2.71–3.35 (m, 4 H), 4.64 (s, 2 H), 7.06–8.40 (m, 6 H). Anal. ($C_{15}H_{14}ClNS$) C, H, N.

2-Methyl-1,2,3,4-tetrahydro[1]benzothieno[2,3-*h*]isoquinoline Hydrochloride (14). A mixture of 1.7 g (0.007 mol) of 13 (free amine), 0.88 g of 90% formic acid, and 0.65 g of 37% formaldehyde was stirred at ambient temperature overnight and warmed on a steam bath for 5 h. Concentrated hydrochloric acid (0.75 mL) was added and then water, and the mixture was made basic with 50% sodium hydroxide, extracted with ether, washed (H_2O), and dried ($MgSO_4$). Removal of the ether gave 1.7 g (94%) of white solid, which was redissolved in ether and treated with 2-propanolic hydrogen chloride. The white powder was recrystallized from glacial acetic acid to yield 1.7 g (80%) of white crystals: mp 257–262 °C; NMR of free amine ($CDCl_3$) δ 2.59 (s, 3 H), 2.45–3.22 (m, 4 H), 4.17 (s, 2 H), 7.06–8.22 (m, 6 H). Anal. ($C_{16}H_{16}ClNS$) C, H, N.

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Book Reviews

Advances in Biochemical Psychopharmacology. Volume 29. Amino Acid Neurotransmitters. By Francis V. DeFeudis and Paul Mandel. Raven Press, New York. 1981. xxviii + 512 pp. 16 × 24 cm. $59.00.

This volume represents the proceedings of a symposium that was held on July 10 and 11, 1980, in Colmar, France, as a satellite to the 28th International Congress of Physiological Sciences. This volume presents approaches to the understanding of amino acid actions from many biological disciplines, including physiology, morphology, pharmacology, and biochemistry. Particular emphasis is placed on the roles of amino acids in integrated central nervous system functions and behavior, receptor pharmacology at both in vivo (electrophysiological) and in vitro (ligand binding) levels, amino acid uptake and release, enzymology, metabolism, and autoradiographic studies.

This volume should facilitate further research in this area and would improve our understanding and therapeutic management of many human neuropsychiatric disorders, including epilepsy and parkinsonism. It will be of interest primarily to biological scientists, clinicians, and to those medicinal chemists who wish to increase their knowledge on amino acid neurotransmitters.

Staff

Marijuana. The First Twelve Thousand Years. By Earnest L. Abel. Plenum Press, New York. 1980. xi + 289 pp. 16 × 23.5 cm. $17.95.

LSD. My Problem Child. By Albert Hofmann. Translated by Jonathan Ott. McGraw-Hill, New York. 1980. xiii + 210 pp. 14 × 21.5 cm. $9.95.

Here are two small, very well written books on the histories of two of our most interesting psychoactive drugs, one ancient, one modern; one natural, the other synthetic; and both controversial.

In recent years, much of what has been written in the scientific and lay press about the social, political, legal, chemical, pharmacological, and medicinal concerns connected with the use and abuse of *Cannabis* has done little more than confirm that "Those who cannot remember the past are condemned to repeat it." Our age is certainly not the first to attempt to deal with these problems. Abel's book is a balanced, well-documented review of the facts, the myths, and the legends surrounding the religious, economic, and medicinal history of one of Man's ancient and most useful cultivated plants. It contains but a smattering of chemistry and pharmacology as well as a brief reference to the modern medicinal potential of THC and its derivatives; yet no one with even a peripheral interest in the impact of *Cannabis* on our society—scientists, parents, teachers, social workers, and the legal profession—should miss this very readable account of all that has gone before.

Hofmann's "problem child", not yet 50 years of age—closer to 40 for all practical purposes and a test-tube baby at that—brought fame to its parent and honor to his house, yet terror and trouble to much of the rest of the neighborhood once it learned to get around. Will it ever grow up? If father does know best, there is hope. With considerable soul searching, the author analyzes his own experiences with LSD and psilocybin, those of his colleagues, friends, and acquaintances, as well as Man's historical search for the mystical experience, in an attempt to answer the question, to find the proper place for these potent psychoactive agents in contemporary society. They are not, he concludes, for everybody: Crossing the line between reality and Reality (if one be permitted to put it that way) carries risks along with its potential rewards and the risks are not yet all that well-known. The translator is to be congratulated in capturing the sense of awe and wonder with which Hofmann regards his child, problem or not.

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Isotopes: Essential Chemistry and Applications. By J. A. Elvidge and J. R. Jones. Royal Society of Chemistry, London. 1980. xii + 400 pp. 20.8 × 14.7 cm. $32.50.

Today the safe and informative exploitation of the stable and radioactive isotopes of C, H, N, O, P, and S is widespread, especially in the life sciences. This text dealing with the chemistry

and applications of such isotopes is the product of a lecture series delivered at the University of Surrey, England, in 1979 by leading international experts.

Divided into ten chapters, each contributed by a noted authority, this volume addresses such topics as the purity and stability of radiochemicals, ^{13}C NMR in medicinal chemistry, ^{2}H and ^{3}H NMR, and the application of isotopes in drug metabolism, biosynthesis, and organic reaction mechanisms. The book does not pretend to completely cover each topic but reviews them in a critical, clearly written, and up-to-date and well-referenced style. Carefully drawn diagrams and figures add much to the clarity of the text. It is inevitable and accepted that a greater emphasis be placed on the isotopes of C and H because of their pivotal importance in organic chemistry. Especially interesting and informative for this reviewer were the chapters dealing with ^{3}H and ^{13}C NMR. Although ^{3}H NMR can now be routinely performed in only a few laboratories in the world, it provides a wealth of information on the extent and position of radiolabeling in ^{3}H compounds. At a time when many of us are beginning to take the acquisition and interpretation of ^{13}C NMR for granted, the text reviews a number of recent advances in the field, including ^{1}H–^{13}C two-dimensional NMR.

One minor inconvenience in the text was the lack of a subject index. Aside from this, the book provides a convenient starting point for those wishing to known more about the chemistry and applications of stable and radioisotopes.

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Terpenoids and Steroids. Volume 10. Specialist Periodical Reports. By J. R. Hanson, Senior Reporter. The Chemical Society, Burlington House, London. 1981. xi + 284 pp. 14.5 × 22.5 cm. $115.00.

This volume continues a remarkable series which has put all natural products chemists and those working in the areas on the frontier between chemistry and biology in its debt. It covers the new chemistry of sesquiterpenoids, diterpenoids, triterpenoids, carotenoids and polyterpenoids, and steroids reported between September 1978 and August 1979. The Senior Reporter, Dr. J. R. Hanson, of the University of Sussex, comments that unfortunately it was not possible to include the customary chapter on the monoterpenoids. This chapter has always been welcomed by the present reviewer as providing a critical, wide-ranging, and individual view of chemistry in its field which serves as admirable reading both in itself and also for the chapters which have followed. However, this omission, in this reviewer's opinion, simply illustrates the pressures of space in this burgeoning field and, I understand, will be remedied in future volumes.

I do not see how it is presently possible for any active researcher in the field of terpenoid and steroid chemistry to manage without access to these admirable volumes. In a time of escalating inflation and increasing financial stringency, these volumes are among the few which I can confidently say are indispensable. Long may they flourish!

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Introduction to Biological Membranes. By Mahendra Kumar Jain and Roger C. Wagner. Wiley, New York. 1980. xiii + 382 pp. 15 × 23 cm. $29.90.

Although the study of membranes has become generally recognized as a discipline in its own right, the workers in this field can have very different backgrounds and divergent perspectives. For this reason, any attempt to bring the different aspects of membrane structure and function together in a coherent study is welcome. This introductory text attempts to do that and is to a large extent successful. The two authors, a chemist and a biologist, have taken turns in writing individual chapters. On the whole, however, the book is weighted more toward chemistry, emphasizing in terms of physiocochemical concepts the fundamentals of membrane structure and function.

Of the 15 chapters, two deal with the structure and surface chemistry of lipids and the conformations of phospholipids and their organization in lipid bilayers and in biological membranes. The physicochemical properties of membrane proteins, their interactions with the lipid component, and their topography in the membrane are discussed in another chapter, while membrane carbohydrates comprise a fourth chapter. A considerable part of the book is dedicated to the various types of transport across membranes and bilayers. One chapter deals with solubility-diffusion across the bilayer. Another discusses transport through channels, carriers, and ionophores. Passive facilitated transport, active transport, and bulk transport make up three additional chapters. Other functional aspects of membranes discussed in this book include a chapter on receptor function with a general description of transmitter and hormone induced changes and a short chapter dealing with bioelectric phenomena where the permeability changes induced by electrical potential are outlined. The rest of the book covers diverse but important topics. There is a brief introductory chapter followed by a chapter on the use of electron microscopy to study membrane structure. Another chapter describes the chemistry of the basic membrane components and their isolation, composition, and metabolism, with special emphasis given to lipids. Finally a chapter on membrane biogenesis briefly discusses the biosynthesis of lipids, proteins, and carbohydrates and then outlines the mechanism with which the individual components are assembled into a membrane structure capable of growth and differentiation.

The book is written lucidly and its contents are well balanced. There are adequate illustrations and tables from the literature that provide a fair amount of quantitative information. Referencing is good with citations running up to 1979. Throughout the book the discussion is maintained at a sophisticated enough level so that the researcher can use it as a fair overview of the subject. It is regrettable that this attempt at a well-written and concise text on membranes is saddled with a serious flaw. Interspersed in the text the reader will encounter numerous errors extending from simple typographical ones or errors in the structural formulas to descriptive errors (e.g., with sp^3 carbons, a dihedral angle of 120° represents an eclipsed not a gauche conformation). Such a flaw unavoidably casts some doubt on the quality of the product. In spite of this shortcoming, this reviewer gives the book a good overall evaluation and recommends it as a graduate level text for medicinal chemists or biochemists, as well as good reading material for any newcomer in the field of membranes.

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Progress in Drug Metabolism. Volume 5. Edited by J. W. Bridges and L. F. Chasseaud. Wiley, New York. 1980. ix + 358 pp. 15 × 23 cm. $85.00.

With Volume 5 of *Progress in Drug Metabolism* the editors continue the format established in earlier volumes by presenting five chapters that cover a variety of timely subjects. The first chapter, titled "The Distribution and Role of Cytochrome P-450 in Extrahepatic Organs", consists of a lengthy (111 pages) and thorough coverage of a topic that has received only a relatively modest amount of attention in the drug metabolism literature. The roles played by cytochrome P-450 in mitochondrial and microsomal steroid metabolism in the adrenal gland are rather extensively reviewed, and the limited information available regarding mammary gland cytochrome P-450 is discussed. The metabolism of xenobiotics by adrenal, placental, ovary, testis, and mammary gland tissues is a complex topic of potential toxicological significance, but it is difficult to conclude whether cytochrome P-450 is involved to a significant extent in detoxification and/or toxification processes in these tissues. The ability of the diuretic spironolactone to cause a decrease in the hepatic and extrahepatic cytochrome P-450 levels of several animal species is reviewed. Studies on the mechanism of this phenomenon indicate that metabolism of spironolactone to deacetylspironolactone precedes the decrease of cytochrome P-450 activity and that the presence of the sulfur atom of spironolactone is essential in the destruction of cytochrome P-450.

Hydroxylation of fatty acids and vitamin D_3 metabolism by renal tissues are covered in this chapter, as is the metabolism of xenobiotics by the kidney. Although this organ contains relatively high levels of cytochrome P-450, its xenobiotic metabolizing capacity appears to be rather low. Thus, renal P-450 may be more important in the metabolism of endogenous compounds than foreign substances. Other topics emphasized in the first chapter are brain and splenic cytochrome P-450 and prostaglandin synthesis and metabolism.

There are wide gaps in our knowledge and understanding of the normal physiological roles of cytochrome P-450 in extrahepatic tissues. Little is known about the multiplicity of these enzyme systems, their interactions with inducers and inhibitors, or their importance in xenobiotic metabolism.

The second chapter, "Species Variations in Some Hepatic Microsomal Enzymes that Metabolize Xenobiotics", focuses upon microsomal monooxygenase, epoxide hydratase, and glucuronyltransferase. A considerable amount of comparative data is tabulated for mammals, birds, and fish. Trends in the comparative data for each of the three enzyme systems are discussed, and the chapter is concluded with an interesting consideration of the evolution of the enzyme systems to meet the demands of changing habitat and diet.

The chapter titled "Pharmacokinetics and Metabolism of Non-Steroidal Anti-Inflammatory Agents" provides comprehensive coverage of the recent literature regarding the pharmacokinetics and metabolism of salicylates, arylacetic acids, 2-arylpropionic acids, higher arylcarboxylic acids, and heterocyclic agents such as phenylbutazone. The chapter is well organized and well written. It contains a wealth of information that makes it profitable reading for anyone interested in drug metabolism, regardless of whether they are involved in antiinflammatory drug research. For those actively pursuing the development of new antiinflammatory agents, it is a unique and valuable compilation.

A variety of bioanalytical methodologies have been reviewed in previous volumes of these series, and that useful practice is continued in the present volume with the chapter titled "Monitoring of Drug Disposition by Immunoassay". Various aspects of radioimmunoassay, nonisotopic immunoassays (e.g., spin immunoassay), enzyme immunoassays, and luminescent immunoassays are discussed. Also included is a review of the clinical application of immunoassays to the measurement of drugs such as the cardiac glycosides, tricyclic antidepressants, anticonvulsants and theophylline.

The final chapter considers "Pharmacokinetics and Metabolism of Industrial Chemicals". The chapter opens with a brief review of basic pharmacokinetic principles and theoretical kinetic models describing chemical interaction with macromolecules. The use of pharmacokinetics in toxicological evaluation is illustrated with data derived from studies with styrene, 2,4,5-trichlorophenoxyacetic acid, and 1,4-dioxane. The discussion is then extended to the evaluation of macromolecular interaction data (covalent binding) in conjunction with pharmacokinetic and metabolism studies on vinylidene chloride and tetrachloroethylene. The chapter concludes with a discussion of genotoxic and epigenetic (cytotoxic) mechanisms involved in the tumorigenic effects of vinylidene chloride and tetrachloroethylene. Overall, a lucid and interesting analysis of the data is presented.

Volume 5 is similar to previous volumes in this series in that it is a useful resource for those scientists who are interested in a multidisciplinary approach to the field of drug metabolism.

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Fieser and Fieser's "Reagents for Organic Synthesis". Volume 8. By Mary Fieser. Wiley Interscience: New York. 1980. 602 pp. 16 × 23.5 cm. $36.00.

As a continuing series, Volume 8 presents up-to-date information on the advances and developments in the use of reagents in organic synthesis. The detailed scope of this series meets the needs of chemists in obtaining a roundup of developments on the use of a variety of reagents. The forthcoming Volumes 9 and 10 of this series will be eagerly anticipated.

Staff

Progress in Pharmacology. Volume 3. Number 3. Clinical Pharmacokinetics of Benzodiazepines. By U. Klotz, L. Kangas, and J. Kanto. Gustav Fischer Verlag, Stuttgart and New York. 1980. 72 pp. 17 × 24 cm. $32.50.

"Progress in Pharmacology" publishes comprehensive reviews of specific topics in pharmacology, toxicology, and related fields. Each issue consists of one extensive review, generally between 50 and 100 pages in length. Publication of individual issues is unscheduled and depends upon the receipt of suitable manuscripts. Since the series was instituted several years ago, some 13 issues have appeared, dealing with a variety of topics in clinical and basic pharmacology.

The third number of Volume 3 is devoted to a comprehensive review of the clinical pharmacokinetics of benzodiazepine derivatives. Dr. Klotz of the Bosch Institute of Clinical Pharmacology in Stuttgart is the first author. His collaborators are Drs. Kangas and Kanto of Turku, Finland. These three scientists clearly are among the world's authorities on benzodiazepines. Their research groups have made many major contributions to our understanding of the pharmacokinetic properties of the numerous benzodiazepines currently in use and of the implications of these properties for clinical therapeutics.

In careful and exhaustive fashion, the authors take up the pharmacokinetic properties of individual benzodiazepines. Specific drugs that are covered are chlordiazepoxide, diazepam, desmethyldiazepam, oxazepam, lorazepam, medazepam, clonazepam, flunitrazepam, flurazepam, and nitrazepam. The outline-type organizational style makes it easy to locate particular topics in the mass of information that is available. Typical topic headings for each drug include absorption, protein binding, tissue distribution, routes of biotransformation, rate of elimination, multiple doses kinetics, effect of disease states on kinetics, and relation between pharmacokinetics and clinical effects. An additional chapter is devoted to the subject of benzodiazepine kinetics during pregnancy and labor, which is a particular research interest of Drs. Kangas and Kanto.

The bibliography is exhaustive and consists of 471 citations. The literature review appears to be very complete; I cannot find any notable omissions. Unfortunately, citations of articles appearing later than 1978 are unusual, suggesting that timeliness of the review suffers somewhat by the inevitable delays in typesetting and publication.

On balance, this is an extremely valuable and complete review of benzodiazepine pharmacokinetics. The monograph should be in the hands of all clinical and basic scientists involved in benzodiazepine research, as well as those who have an interest in following this rapidly expanding field. This review is current only through 1978 but still is the most comprehensive and readable single source on benzodiazepine pharmacokinetics.

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