Clinical studies[20] with **5a,b,d** have confirmed the marked diuretic–saluretic and uricosuric activities as well as relative potencies seen in chimpanzees.[21]

The syntheses of **5a** and **5b** have been disclosed;[17] compounds **5c** and **5d** were prepared from **6a** and **6b**[25] which were treated with KO-*t*-Bu and CH_3I in *t*-BuOH–benzene (1:1) to give the analogous compounds where $R^1 = CH_3$. Cleavage of the ether group with pyridine hydrochloride, followed by reaction with $BrCH_2COOEt$ and K_2CO_3 in DMF, then basic hydrolysis, and acidification gave **5c** and **5d**.[25]

Resolution of **5b,c,d** was carried out by recrystallization of appropriate salts of chiral bases as seen in Table IV.

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Book Reviews

Metal Ions in Biological Systems. Volume 1. Simple Complexes. Edited by Helmut Sigel. Marcel Dekker, New York, N.Y. 1974. 267 pp. $21.75.

The editor's objective in this carefully outlined series of six volumes is "to focus attention on the connection between the chemistry of metal ions and their role for life," and "to break down the barriers between the historically independent spheres of chemistry, biochemistry, biology, medicine, and physics." Volumes 2 and 3 of this series were published ahead of Volume 1 and have been reviewed [*J. Med. Chem.*, 17, 910 (1974)].

Volume 1 contains six chapters devoted chiefly to complexes of transition metals with simple ligands such as nucleosides, nucleotides, amino acids, and oligopeptides. Each chapter provides selective rather than exhausting coverage of the literature. The terminology, abbreviations, and symbolisms used throughout are consistent with Volumes 2 and 3, for which the editor should be complimented.

Chapter 1 covers nucleoside and nucleotide complexes. It reviews the several methods used in their study and their limitations, tabulates much stability constant data, and points out that, as expected, hard metal ions bind at the phosphates while soft metals bind at the heterocyclic base. It also stresses that the various methods used to measure binding give results which compare qualitatively but not quantitatively, and possible causes are discussed.

Chapter 2 provides a kinetic and mechanistic background for nucleotide–metal complexation. Chelation of the metal by nucleotide groups is much like any other chelation process, but special factors such as base-stacking introduce new complications only recently appreciated; hence, the discussion is divided into pre- and post-1967 periods. Considerable caution is needed in interpretation of or extrapolation from binding site and complexation studies to more complex systems, however, because the extremes of metal–ligand ratios and concentrations used in the simpler systems may not reflect biological conditions. The fine points of kinetics and mechanism of complexation are reviewed in detail and there is a succinct summary with examples of the biological significance of the results. The latter includes a discussion of the interesting Eigen–Hammes explanation of the often antagonistic effects of calcium and magnesium ions in biological systems involving phosphates.

Chapter 3 covers stereoselectivity in complexation due to ligand–ligand interactions or dissymmetry at the metal center itself. It is a very short chapter and unfortunately does not mention the uses of these phenomena for asymmetric synthesis and reactions of coordinated ligands. Chapter 4 is an effectively organized discussion of the (CD) optical properties of oligopeptide complexes. It is easily read and understood and contains a good development of the structural aspects of peptide complexes. The authors' statement, "All structures appearing in the literature with metal ions coordinated to amide nitrogens that have not undergone deprotonation are incorrect," typifies the clarity with which this chapter is written.

Chapter 5 is a long chapter on the kinetics and mechanism of metal and proton exchange reactions of oligopeptide complexes. It reiterates the structural aspects discussed in Chapter 4, but the duplication is justifiable. Amides and oligopeptides have several unusual features as ligands, one of which is that the stepwise amide pK_a values of coordinated oligopeptides *decrease* rather than increase. The kinetics and mechanism of peptide complexation is itself complex, and this chapter's reader would benefit from prior reading of Chapter 3 in Volume 2 on simple chelate complexes. The section on biological significance discusses copper transport in plasma and the importance of copper–amino acid complexes in plasma, as well as the rare Wilson's disease, which probably has the highest ratio of reviews to clinical cases of any molecular disease known.

Chapter 6 reviews the sulfide, sulfoxide, and sulfone groups as donor groups in bidentate ligands including sulfur-containing acids and amino acids, vitamins, and antibiotics. The chapter is clearly written and contains a good deal of tabulated equilibrium data for H, Cu, Mn, and Zn complexes of these ligands. All data obtained using a number of classical techniques indicate that -S-, -SO-, and $-SO_2-$, in sharp contrast to -SH, contribute little to the stability of a chelate ring.

This volume, as the others, has a subject and an author index with an adequate number of references. If succeeding volumes maintain the caliber of the first three this will be a very useful collection indeed. However, they are rather expensive considering their size, their simple binding, and the fact that they are not type-set but typewritten and photo reproduced.

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Drug Design. Volume 4. Edited by E. J. Ariens with ten contributors. Academic Press, New York, N.Y. xiv + 489 pp. 15 × 23 cm. $35.00.

The editor explains in the preface that there are three main phases in drug action: (1) pharmaceutical; (2) pharmacokinetic; and (3) pharmacodynamic. The first phase is characterized by disintegration of the dosage form and dissolution of the active substance. The second phase involves absorption, distribution, metabolism, and excretion while the third phase constitutes the drug interaction with its molecular sites of action to produce an effect.

The major part of this volume is devoted to the pharmaceutical phase. It emphasises important aspects in the design of optimally effective pharmaceutical dosage forms.

Chapter 1, "Biopharmaceutics as a Basis for the Design of Drug Products," by Leslie Benet, discusses biopharmaceutics, bioavailability, selection of administration route, getting drugs in solution, gastrointestinal membrane transport, and getting drugs into the small intestine. It also presents five interesting general principles (with appropriate disclaimers) that should be understood by those interested or actively involved in drug design. The reviewer finds principle 3 of major importance. This principle dictates that "before a drug can pass through a biological membrane it must first be solubilized in the fluids bathing that membrane." This excellent 35-page chapter is well documented (92 ref) and well organized.

Chapter 2, "Peroral Solid Dosage Forms with Prolonged Action," by W. A. Ritschel, covers types of peroral prolonged action dosage forms, their evaluation, and pharmacokinetics. It also discusses additives and manufacturing processes unique to prolonged action products. This 36-page chapter with 114 ref gives an adequate analysis of this subject.

Chapter 3, "Parenteral Dosage Forms with Prolonged Action," by W. A. Ritschel, follows the outline of Chapter 2. It is well documented (77 ref) and provides a good coverage of this area.

In Chapters 4 and 5, Martin Katz and Boyd J. Poulsen, respectively, provide a refreshing coverage of "Design of Topical Drug Products: Pharmaceutics and Biopharmaceutics." These two chapters with 275 ref cover the subject well.

Chapter 6, "The Design of Sunscreen Preparations," by Goswin W. van Ham and Wolfgang P. Herzog, is a valuable source of information for those interested in this specialized subject.

The rest of the text is devoted to drug design and evaluation with strong overtones toward the pharmaceutical and pharmacokinetic phases. For example, Alexander Bloch describes acetylated nucleosides (prodrugs) that are more effective than parent nucleosides because they have more lipid solubility and perhaps increased stabilization toward metabolic degradation.

In "The Design of Biologically Active Nucleosides," Alexander Bloch discusses historical perspectives, rationale for design, and synthesis of nucleosides. Their diverse biological effects such as antitumor, antimicrobial, antiprotozoal, antiviral, cytokinin, cardiovascular, immunosuppressive, and learning, are also reviewed. Structural considerations are covered under eleven structure–function headings which include modifications of the heterocycle and the carbohydrate rings, as well as changes of the substituent groups attached to these rings. Depot forms (prodrugs), phosphorylation, and anhydronucleosides are also discussed. Novel approaches toward enhancing biological activity of nucleoside analogs, including concepts "metabolic conditioning" and "metabolic actuation" proposed by Bloch, are presented. In his conclusion, Bloch calls for more extensive design and synthesis efforts and more detailed evaluation of these compounds in many test systems. This well-organized chapter (8) is clearly presented (733 ref).

In Chapter 7, "Litholytic Agents: Preventive and Curative Drugs for Nephrolithiasis," George Kallistratos presents a balanced view of this subject. He notes the role of physical, chemical, bacteriological, metabolic, and anatomical factors in the pathogenesis of renal calculi. Possibilities for dissolving the four different types (calcium oxalate, phosphate, uric acid, and L-cystine) of stones are presented, but treatment at present remains largely surgical. This chapter (98 ref) presents an up-to-date overview.

Chapter 9, "The Design of Insecticidal Chlorocarbon Derivatives," by G. T. Brooks, thoroughly describes the status of this subject (105 ref). It provides detailed background discussions on Meyer–Overton hypothesis, physical equilibria, thermodynamic activity, and influence of structure on biological activity. Molecular design from theories of toxic action and means to counteract enzymatic detoxication are detailed. Brooks wisely avoided the politics of chlorocarbon use.

Congratulations to the editor and authors of this instructive text. The reviewer recommends it to those interested in drug design and pharmaceutical product design.

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Drug Metabolism Reviews. Volume 2. Edited by Frederick J. Di Carlo. Marcel Dekker, New York, N.Y. xiii + 308 pp. $25.50.

This volume is divided into ten chapters. The chapters entitled "Intermediates in Drug Metabolism Reactions" and "Automated Assay of Drugs in Body Fluids," and, particularly, the chapter on "The Influence of Stereochemical Factors on Drug Disposition" should be of general interest to everyone engaged in teaching or research in the field of drug metabolism. The latter chapter is a thorough review of an area that should provide an increasing amount of information on drug–enzyme interactions and on the mechanism of drug action. "Intermediates in Drug Metabolism Reactions" is a good review for those interested in oxidative drug activation or detoxification. Two chapters, "Comparative Aspects of Mixed Function Oxidation by Lung and Liver of Rabbits" and "The Nature and Distribution of Enzymes Catalyzing the Conjugation of Glutathione with Foreign Compounds," are concerned with major enzymes involved in drug metabolism, namely mixed function oxidases and glutathione transferases. The five remaining chapters deal with more specialized topics: ascorbic acid in drug metabolism, biological alkylating agents, guanethidine and

related compounds, nitrate esters, and several barbiturates. The chapters are suitably referenced; several are notable in suggesting needed areas for future investigations. The book serves a useful purpose in collecting topics of major interest and provides, along with Volume 1, a helpful compendium of selected topics in the area of drug metabolism.

As is so frequently the case, this review suffers along with many others in the time lag between preparation and publication. Only a few references beyond 1972 appear. Consequently, in certain of the active areas reviewed in this volume much new information has appeared.

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Advances in Drug Research. Volume 7. Edited by N. J. Harper and A. B. Simmonds. Academic Press, London and New York. 232 pp. 15.5 × 23 cm. $15.50.

The current vogue of edited books and review volumes constitutes a distinctly mixed blessing. This form of scientific literature, it is true, does encourage a sizable number of authorities in various fields of scientific endeavor to publish appreciations of trends and accomplishments in their areas of expertise. All too often, however, edited books, particularly the periodical review volumes, consist of loosely connected, often fragmentary articles—in quite discordant styles—dealing with the individual author's pet notions.

It was thus the reviewer's particular pleasure to read the lead chapter in the present volume. The article, "Advances in Penicillin Research" (J. H. C. Nayler), which occupies fully half the book is a truly exemplary review. It enables the nonspecialist, like the undersigned, to gain an appreciation for an unfamiliar field. The article begins with a very basic account of the chemistry of the penicillins and proceeds from there to the rationale for the host of structural modifications which have been made on the parent molecule. The SAR of the semisynthetic penicillins is discussed in detail in pleasingly systematic fashion. Compendious accounts of test methods, mechanism of action studies, development of resistant strains, and clinical usage of the various antibiotics are included. This liberally referenced chapter further contains an unusually thorough discussion of absorption, metabolism, and excretion of the penicillins.

As a change of pace, the second chapter, "Fibrinolysis" (G. R. Fearnley), is a clinician's review. Following a historical introduction to thrombosis and fibrinolysis—which would have profited from inclusion of some reference to the chemistry of these processes—the bulk of the article is devoted to a narrative account of the author's clinical investigations in the area of fibrinolyic drugs. The chapter concludes with a brief discussion of antifibrinolytic drugs.

The final article of the book, "Psychotomimetic Drugs Biochemistry and Pharmacology" (R. W. Brimblecombe), is an absorbing and highly readable account of the state of knowledge in this intriguing area of psychopharmacology. The discussion of the SAR of these agents almost reads like a street guide to drugs, being studded with initials like LSD, THC, and STP (according to a teenage son: Serenity, Tranquility, Peace). The pharmacology, and where available the clinical results, of the three main classes of drugs, the sympathomimetic amines (indoleamines, phenylalkylamines, LSD), antiacetylcholine drugs (*e.g.*, piperidyl glycolates), and the cannabinoids are described in some detail. A critical account of accumulated knowledge and current research in biochemical pharmacology aimed at elucidating the mechanism of action of the various psychotomimetic agents completes the review.

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Biochemistry of the Developing Brain. Edited by W. Himwich. Marcel Dekker, New York, N.Y. Volume 1, 338 pp. 16 × 24 cm. $24.50. Volume 2, 325 pp. 16 × 24 cm. $24.50.

This two volume set provides the reader with 13 chapters by different authors on subjects related to biochemical changes which occur during the development of the brain. Unfortunately, such a multi-author approach to a general subject has certain inherent disadvantages. Thus, although the volumes are a rich source of data and information through the year 1972 on this broad area of research, the reader will find many instances of redundancy between chapters. The approach of different authors varies considerably. Certain chapters treat a rather narrow research problem in great detail, while others attempt a comprehensive review of a broad area. The difficulties in relating the classical biochemical alterations to functional changes in the brain during development are apparent whenever the authors have attempted to make such correlations. The nonexpert in this field will regret the lack of a unifying chapter to sum up the many detailed chapter presentations.

The first chapter by H. E. Himwich presents studies on weight, water content, and chemical composition (proteins, phospholipids, cholesterol, inorganic ions) of the developing rat and human brain and attempts to relate these data to cell growth, axon development, and myelination. Data which indicate that developmental changes occur first in evolutionary older regions of the brain and then proceed to the younger regions are presented. J. M. Davis and W. A. Himwich present studies on the changes in concentrations of amino acids, phosphoethanolamine, urea, and proteins which occur during development. Emphasis is on amino acids, such as glutamate, GABA, glycine, etc., which appear to have functions other than as precursors of protein. B. Huber and H. Kuriyama present data on GABA and associated synthetic and degradative enzymes during development and discuss evidence indicating a correlation between development of the GABA-generating system and synaptogenesis in cerebellum. H. C. Agrawal and A. N. Davison treat developmental alterations in proteins, phospholipids, and cholesterol and their relationship to morphogenesis, particularly myelination, in the brain. The effects of thyroid function, nutritional states, and metabolic and genetic disorders on development of myelin sheaths are discussed. G. Levi deals primarily with his studies on developmental aspects of amino acid transport in brain slices from the chick. S. Berl deals with developmental aspects of metabolic compartmentalization with particular emphasis on glutamate metabolism. R. Balazs and D. Richter treat the effects of thyroid and corticosteroid hormones on morphogenesis and certain biochemical parameters in cerebrum and cerebellum. E. Howard treats the effects of hormones on cell growth with emphasis on the measurement of the DNA content of brain tissue. J. O'Neill presents a detailed discussion of carbohydrate metabolism (Embden-Meyerhof pathway, pentose monophosphate pathway, glycoproteins) with particular reference to the brain. A. J. Trevor, D. Y. Shirachi, and V. C. Sutherland discuss developmental aspects of the intermediary metabolism of carbohydrates, the Krebs cycle, aerobic and anaerobic mechanisms, metabolic enzymes, the effect of electrical stimulation, etc. Most of the data is from studies with brain slices. C. J. Van de Berg presents a comprehensive survey of developmental changes in levels and distribution of enzymes of intermediary metabolism and of enzymes concerned with putative neurotransmitters. Alterations in nucleic acids and proteins are also discussed. Hormone effects and genetic and metabolic disorders are treated. M. Winick treats developmental aspects of cell growth (DNA content) and the effect of nutritional state and corticosterone. The final chapter by Z. I. Barboshoua and L. N. Simouskii treats differences in the ability of the central nervous system of young and old animals to adapt to hypoxia and hypokinesia.

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