

Additions and Corrections

1970, Volume 13

Manfred E. Wolff, Galal Zanati, G. Shanmugasundaram, Sharad Gupte, and Gunhild Aadahl: Thia Steroids. III. Derivatives of 2-Thia-A-nor-5 α -androstan-17 β -ol as Probes of Steroid-Receptor Interactions.

Page 533. The following lines have been omitted from Table I.

Compd (total dose, mg)	Wt, mg			Body wt, g	
	Ventral prostate	Seminal vesicle	Levator ani	Ini- tial	Final
20 (3.0)	13.3 \pm 0.81	12.4 \pm 0.80	28.8 \pm 1.99	57	91
<i>p</i>	NS	NS	NS		
21	17.4 \pm 0.66	12.4 \pm 0.16	30.0 \pm 2.51	57	91
<i>p</i>	NS	NS	NS		

1973, Volume 16

J. D. Geratz, Alan C. Whitmore, Michael C.-F. Cheng, and Claude Piantadosi: Diamidino- α,ω -diphenoxyalkanes. Structure-Activity Relationships for the Inhibition of Thrombin, Pancreatic Kallikrein, and Trypsin.

Page 971. In Table II, the K_i value for compound 9 with thrombin should read $4.3 \times 10^{-6} M$.

Corwin Hansch, Albert Leo, Stefan H. Unger, Ki Hwan Kim, Donald Nikaitani, and Eric J. Lien: "Aromatic" Substituent Constants for Structure-Activity Correlations.

Page 1208. The σ_m and σ_p in the equation included in Figure 1 are reversed. The correct equation is $\sigma_p = -0.11 (0.03) + 1.23 (0.08) \times \sigma_m$.

Corwin Hansch, Stefan H. Unger, and Alan B. Forsythe: Strategy in Drug Design. Cluster Analysis as an Aid in the Selection of Substituents.

Page 1218. In eq 2, the bar over x'_{jk} should be omitted. The correct equation is

$$d_{ij} = \left[\sum_{k=1}^K (x'_{ik} - x'_{jk})^2 \right]^{1/2} \quad i, j = 1, 2, \dots, N \quad (2)$$

1974, Volume 17

W. Arnold, G. Flouret, R. Morgan, R. Rippel, and W. White: Synthesis and Biological Activity of Some Analogs of the Gonadotropin Releasing Hormone.

Page 314. G. Flouret is at the Department of Physiology, The Medical School, Northwestern University, Chicago, Illinois 60611.

Book Reviews

Annual Review of Pharmacology-1974. Volume 14. Edited by H. W. Elliott, R. Okun, and R. George. Annual Reviews, Palo Alto, Calif. 1974. vii + 594 pp. 16 \times 22.8 cm.

This volume is the fourteenth in the "Annual Review of Pharmacology" series and is another example of the outstanding service which the publishers of the various "Annual Reviews" render to medicinal chemists and to the scientific community at large by reducing the mind-boggling torrent of new literature in the biomedical field to manageable proportions. Most remarkable of all is the way in which this feat is achieved with minimal time lag and at unbelievably low cost to the purchaser.

The prefatory chapter, by E. R. Habermann, is a biography of Rudolf Buchheim (1820-1879), a German scientist who made pioneering contributions to the systematic classification of drugs and was among the first to advocate a rational approach to pharmacological research.

Of the 31 chapters in the book, no fewer than six are devoted in one way or another to the subject of neuromuscular phenomena and the pharmacology of CNS agents. In this category are chapters on the relationship between chemical structure and anticonvulsant activity (J. R. Smythies), the neuropharmacology of drugs affecting movement disorder (A. Barbeau), the regulation of catecholamine and serotonin biosynthesis in the CNS (E. Costa and J. L. Meek), the action of neuropoisons on cholinergic transmission (L. L. Simpson), the effect of lanthanum on smooth muscle (G. B. Weiss), and a review of the status of drug abuse in the U. S. during 1973 (D. E. Smith and D. R. Wesson).

A second group of chapters may be classified as dealing with general pharmacodynamic phenomena: the bioavailability of drugs after oral administration (L. F. Chasseaud and T. Taylor), the movement of drugs across fish gills as a model for membrane transport (J. B. Hunn and J. L. Allen), the permeability of the

blood-brain barrier (W. H. Oldendorf), and the relationship between drug distribution and therapeutic effect in man (E. S. Vesell).

The timely area of environmental pharmacology and toxicology is well represented by surveys on the relationship of biotransformation to drug toxicity (J. R. Gillette, J. R. Mitchell, and B. B. Brodie), the variation of carcinogenic effect with age (R. Schoental), the effect of teratogens (J. G. Wilson) and other pharmacologic agents (S. J. Yaffe and M. R. Juchau) on the fetus and newborn child, the toxicology of artificial food colors (J. L. Radomski) and insecticidal chlorinated biphenyls (L. Fishbein), and the action of chemical agents on eggshell formation in birds (W. J. Mueller and R. M. Leach, Jr.).

With respect to chemotherapy, there are useful chapters on antineoplastic agents (S. K. Carter and M. Slavik), antiviral agents (J. G. Tilles), nonsteroidal antiinflammatory drugs (S. H. Ferreira and J. R. Vane), and new semisynthetic penicillins and cephalosporins (L. D. Thrupp).

Generous attention is also given to hormonal and other regulatory mechanisms in chapters dealing with the biochemical role of cyclic AMP and cyclic GMP (T. Posternak), the mode of action of insulin (S. J. Pilkis and C. R. Parks), the effect of drugs on hypothalamus-anterior pituitary function (D. de Wied and W. de Jong), and the pharmacology of contraceptive agents (W. D. Odell and M. E. Molitch).

Renal pharmacology is discussed in two chapters, one dealing specifically with uric acid excretion in the nonhuman primate (G. M. Fanelli, Jr., and K. H. Beyer, Jr.) and the other with more general aspects of kidney function (Yu V. Natchin).

Lastly, in the category of miscellany, there is a chapter on the application of quantum-mechanical calculations to problems of drug-receptor interaction (J. P. Green, C. L. Johnson, and S. Kang), a survey of the current status of pharmacological research

in India (P. C. Dandiya and J. S. Bapna), and the now customary "Review of Reviews" (C. Leake) which concludes the book.

The book is carefully edited and indexed and includes a cumulative author index for volumes 10-14 as well as a useful cumulative subject index for volumes 10-14 arranged according to broad subject categories. As other reviewers have pointed out in connection with previous volumes in this series, high publication speed and low cost are salient attributes of this form of concise literature awareness service. However, certain inherent defects do seem to be an inevitable part of the price. For example, the fact that some chapters deal with very broad topics and others are more narrowly focused is reflected in a disturbing lack of uniformity in depth of coverage. Moreover, it often happens that two or more chapters cover overlapping ground. The chemically oriented reader may find himself somewhat frustrated by the rather infrequent use of structural formulas and other visual aids to complement the text. All in all, however, these matters are easily overlooked in the face of the many other obvious virtues which make this book an indispensable addition to every good biomedical library.

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The Biochemical Basis of Neuropharmacology. 2nd Edition.
By J. R. Cooper, F. E. Bloom, and R. H. Roth. Oxford University Press, London, New York, Toronto. 1974. 272 pp. 14 × 21 cm. \$4.95.

The present edition of this monograph provides a current and fairly comprehensive overview of the biochemical basis of central neurophysiology and neuropharmacology. Although primarily designed for graduate and medical students, it has much to offer to medicinal chemists, and even to those scientists whose specialty lies in some aspect of the function of central nervous system. It is not surprising, in view of the breadth of coverage, that some aspects of brain function are treated in more depth and with greater enthusiasm and erudition than others less closely related to the authors' own research interests. However, from an overall standpoint, the book is well organized and reads easily and well. It provides a wealth of critical insights into current trends in research on functional aspects of brain chemistry. Experts will certainly not always agree with the authors' critiques, but this is to be expected in areas where definitive answers are not as yet available. The authors have clearly not intended to write a reference work and have, therefore, only provided a few selected references to reviews and research publications at the end of each chapter. The lack of referencing of these citations to the relevant sections of the chapters will be considered a significant shortcoming by some readers.

The major sections of the book are as follows. First, an introduction to the anatomy of nerves and glia, to the bioelectrical properties of nerves and their relationship to conduction of electrical impulses in axons, and to transmitter release at synapses is provided. Such phenomena are discussed in terms of electrophysiological methods for the study of the ionic processes involved in synaptic function and how effects of drugs on specific functions can be ascertained. This is followed by a discussion of intermediary metabolism in brain, the synthesis of the brain lipids, and a brief survey of compounds such as *N*-acetyl aspartate, glutamate, glutathione, and putative neurotransmitters which would appear likely to be involved in important and unique functions of brain tissue. A tabulation of hereditary disorders associated with aberrations in central function is discussed. The book continues with sections on acetylcholine, catecholamines, and serotonin, in which assay, distribution, enzymes of anabolism and catabolism, and evidence for roles both in synaptic function and integrated central function are presented in depth. The possible sites of interactions of pharmacologically active agents with the synthesis, storage, release, metabolism, and action of each of the neurotransmitters are discussed and convenient summaries provided. The book continues with a similar approach to the amino acids, γ -aminobutyric acid, glycine, and glutamic acid. A rather brief discussion of cyclic AMP in the nervous system follows. This section is concerned exclusively with evidence for a postsynaptic regulatory role of cyclic AMP in catecholamine synapses in cere-

bellar Purkinje cells and peripheral efferent ganglion cells. The book contains brief sections on substance P, histamine, and prostaglandins and a final quite critical chapter on current research concerned with the "cellular mechanisms in memory and learning." For its easy style and broad coverage of the field the book is recommended to both expert and nonexpert.

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Analytical Profiles of Drug Substances. Volume 3. Edited by Klaus Florey with 18 contributors. Academic Press, New York, N.Y. 1974. ix + 581 pp. 15 × 22.5 cm. \$19.50.

A few years ago the Pharmaceutical Analysis and Control Section of the Academy of Pharmaceutical Sciences undertook the enormous task of compiling a series of profiles on widely used drug substances. The purpose of this effort was to provide the scientific community with a reference source containing a wide range of physical, chemical, analytical, and biological data on important chemotherapeutic agents. Such information does not presently exist in any of the official drug compendia or, for that matter, in any one reference source. To this end, Klaus Florey with the assistance of a large number of pharmaceutical scientists (almost exclusively from industry) have to date published three volumes containing profiles on 59 compounds (17 in Volume 3).

The following scheme is utilized for the presentation of data on each substance. 1. General description. This section contains chemical and generic names in addition to a statement on the appearance of the material. 2. Physical properties. Spectra characteristics (infrared, nuclear magnetic resonance, ultraviolet, mass spectra, etc.), solid-state measurements (melting point, polymorphism, thermal analysis, optical characteristics of solid, and X-ray powder diffraction), solubility, and dissociation constants are given in this section. The spectral data are reproduced and the important characteristics pointed out. 3. Chemical synthesis. 4. Stability. The pathways by which the drug will undergo degradation are discussed. 5. Methods of analysis. An extensive survey of analytical procedures, and in certain instances bioassay techniques are presented. 6. There are also short sections on metabolism, pharmacokinetics, and protein binding where appropriate. 7. References. The bibliography at the end of each profile is extensive and up-to-date.

The presentations are in each case concise and lucid. Throughout each of the published volumes one will find data that were derived from company files and thus appear in the literature for the first time.

The profiles are being published at a rate of one volume per year. It would be extremely worthwhile if the process could be accelerated, for this book will serve as a valuable reference source for a wide range of scientists engaged in drug research.

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Principles of Drug Action: The Basis of Pharmacology. Second Edition. By Avram Goldstein, Lewis Aronow, and Sumner M. Kalman. Wiley, New York, N.Y. 1974. 854 pp. \$21.50.

Like its first edition, this book promises "to provide a coherent, rational, and scientifically correct account of the principles underlying every aspect of" drug action. Thus chapters are devoted to molecular mechanisms of drug action; the absorption, distribution, metabolism, excretion, and kinetics of drugs; toxicity, idiosyncrasy, allergy, resistance, tolerance, and physical dependence to drugs; chemical mutagenesis, carcinogenesis, and teratogenesis; and drug development and evaluation in man.

The new sections in the book deal with characterization of drug-receptor interactions (19 pages), receptor isolation (14 pages), environmental toxicity (17 pages), molecular basis of mutation (7 pages), monitoring of drug use (6 pages), and drug interactions (7 pages). This represents somewhat less than 10% of the book. In addition, Chapter 6, "Pharmacogenetic and Drug Idiosyncrasy," and Chapter 11, "Chemical Carcinogenesis," have

been rewritten. On the other hand, Chapters 4 and 13, "The Time Course of Drug Action" and "Drug Development," are essentially unchanged. The discussions on sources of information for selecting drugs in clinical practice and on prescription have been deleted. In balance, this appears to be a minor revision of the first edition.

Since the authors focus upon principles, the book's usefulness will depend upon the reliability of the discussions of accepted principles and the extent to which generalized principles are useful in pharmacology.

The most obvious omission is seen by a consideration of Chapter 4, "The Time Course of Drug Action," 52 pages long. There is no mention of the use of two-compartment models for drug distribution, of the "first-pass" effect of oral administration, of the principles and interpretation of bioavailability studies, nor of the correlation between pharmacokinetics of blood level and pharmacologic response; yet 15 pages are devoted to kinetics of drugs administered by inhalation. Only 4% of the references in this chapter have appeared since the first edition. None of the references would lead the reader to the omitted topics. Thus, the treatment of one of the principles of drug action, pharmacokinetics, is both deficient and misleading.

Two other substantial omissions were noted. First, the only references to quantitative structure-activity relationships (regression analysis) are to articles published in 1965. The authors are apparently unaware of the demonstration of optimum partition coefficients for many processes. This is despite the fact that 21 pages are devoted to structure-activity relationships, and frequent mention of partition coefficients is made in the chapter on absorption, distribution, and elimination of drugs. Second, there is a very detailed analysis (29 pages) of the dose-response curve; yet, the definition of the widely used pA_2 and pD_2 are not given. Probit analysis is considered in a separate chapter altogether and not referenced in the first. Thus two other principles of drug action, quantitative structure-activity relationships and the dose-response curve, are inadequately treated.

In conclusion, the coverage of the topics selected is not uniformly complete, and readers who expect a thorough discussion of principles will not receive such. The danger of this is that the book is written in such an authoritative style that the reader will not be aware of the incomplete treatment of subjects of interest. In spite of these negative comments, this book remains a valuable reference. The clarity of style of the authors makes the topics which they treat easily understood, and a wealth of interesting information is included.

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Toxins of Animal and Plant Origin. Volumes 2 and 3. Edited by A. deVries and E. Kochva. Gordon and Breach, New York, N.Y. Volume 2, with 26 contributions. xiv + 329 pp. 16 × 23.5 cm. 1972. \$22.00. Volume 3, with 22 contributions. xii + 285 pp plus indices. 16 × 23.5 cm. 1973. \$20.00.

The Second International Symposium on Animal and Plant Toxins was held at Tel-Aviv University in February 1970. The proceedings of the symposium have been published in a set of three volumes of approximately equal size, of which these constitute the second and the last members. Volume 2 covers the biochemistry of venoms of species other than snakes and all the pharmacology which was presented. Volume 3 considers the immunology of venoms, with strong emphasis on snake venoms, and the clinical aspects of envenomation. The authors of papers in both volumes are drawn from an international group of authorities.

The individual presentations vary greatly in length and scope, from papers which cover vast amounts of previously published data with a few cursory pages to well thought-out reviews of areas of importance. While the "gadfly" attitude of the former is unfortunate, even these articles are of value to the student who wishes to read an overall view of the field. To the more advanced researcher, however, many of these articles will be a disappointing collection of repeated findings. Those few articles which present new data, or which have the length to present ideas with grace, are quite good. These should prove useful to all, but whether they are worth the price of the two volumes is open to question.

Most of the papers have introductory material which will allow the nonexpert to follow the presentations. Documentation in most cases is quite adequate. The text is produced from print, thereby avoiding the often distracting look of books reproduced directly from manuscript; no doubt this also contributed to the rather long time before publication. In most cases figures and tables are legible, although some tables are reduced virtually to the point of vanishing. It is unfortunate that many of the figures were not more carefully drawn, for they are very difficult to decipher as they now stand. In summary, this set of volumes should present a useful, although often superficial, survey of much of the research currently being conducted on venoms.

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Interferons and Interferon Inducers. Edited by N. B. Finter with 11 other contributors. American Elsevier, New York, N.Y., and North-Holland Publishing Co., Amsterdam and London. 598 pp. 17 × 24 cm. \$31.00.

Despite the large number of reviews published on interferons and interferon inducers, this volume represents a welcome addition to the interferon literature, covering subjects in a breadth and depth often not possible in a shorter wide-ranging treatise. Originally published under the title "Interferons" in 1966 (as volume 2 of "Frontiers of Biology" under the general editorship of A. Neuberger and E. L. Tatum), this edition is totally revised and substantially expanded to include such areas of recent vintage as interferon induction by synthetic polynucleotides and the effect of interferon (and inducers) on tumors and tumor viruses. Contributors to this book are all acknowledged experts in the field, each writing in an area of his special interest. Most appropriately, a brief, but eminently readable, historical perspective is provided in the opening chapter by K. Cantell.

Interferon has been likened to the grin of Lewis Carroll's Cheshire cat, and it may surprise some to learn that so much research has been based on a substance which has not yet been chemically characterized. R. Z. Lockart deals with the criteria involved in ascribing the designation interferon to a viral inhibitor and secondly with the general biological properties of interferon. The closely allied topic of the assay of interferons and their inducers is discussed by N. B. Finter, and K. H. Fantes summarizes the agonizing problems of the purification and physicochemical properties of interferons, both representing undertakings of immense theoretical and practical value. The clinical use of interferon as well as its purification depends upon an understanding of the factors governing interferon production, and these subjects as well as the phenomenon of tolerance (or hyporeactivity) are reviewed by M. Ho.

To circumvent the formidable problems associated with the large-scale production of human interferon (either from cultured cells or chemical synthesis), substantial effort has focused on nonviral interferon inducers. T. C. Merigan summarizes the wide variety of materials which have been shown to elicit an interferon response, and D. C. Burke treats the related subject of the mechanism of interferon production by viruses, nucleic acids, endotoxin, and polyanions.

Two chapters by N. B. Finter deal with the antiviral effects of interferons and interferon inducers in experimental animals and in monkeys and man. The exciting topic of the effect of interferon and its inducers on tumors and tumor viruses is dealt with at length by M. N. Oxman. S. Baron places the interferon system in perspective with the other natural defense systems called upon during the course of viral infections.

A variety of circumstantial evidence has been accumulated suggesting that interferons may have a wider role than simply an antiviral defense mechanism. At any rate, it is clear that studies on the mechanism of interferon action (J. A. Sonnabend and R. M. Friedman) are of interest not only because of practical aspects related to interferon, but because they will continue to divulge important information on the molecular biology of both viruses and the vertebrate cell.

Other chapters include the pharmacokinetics of interferon (M. Ho), noninterferon viral interference (R. A. Bucknall), interferon-like substances in plants and bacteria (K. H. Fantes), the action

of interferons (and inducers) on nonviral infections (T. C. Merigan), and the phenomenon of varied interferon response dependent on animal virus, cell type, and other factors (M. Ho).

In general, this reviewer finds this volume has a pleasant format and is coherent and well written, representing more than just a literature survey. The editor has prepared a good subject index and the references are all under a common listing with referral back to the text for the paper's salient features. Unfortunately, the most recent references are to 1971 articles and not all contributions are equivalent in this respect. The nonspecialist reader should thus be aware that apparently unavoidable deletions of more recent findings occur.

There is little doubt that this work will find itself in most laboratories engaged in active interferon research; however, the interdisciplinary nature of the interferon field coupled with the book's inherent readability commends it to the shelves of all who share an interest in the chemotherapy of viral and neoplastic diseases and the molecular biology of animal viruses and cells.

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