lization from ether provided an analytical sample in the form of colorless needles, m.p. 180–181°, $[\alpha]^{24}D$ −41° (*c* 1.3, ethanol).

Anal. Calcd. for $C_{14}H_{15}BrClNO_6$: C, 41.15; H, 3.70; N, 3.43. Found: C, 41.00; H, 3.89; N, 3.45.

5-Bromo-4-chloro-3-indolyl-β-D-galactopyranoside crystallizes as an amorphous solid from methanol, m.p. 237–239° dec., $[\alpha]^{24}D$ −69° (*c* 1.0, 50% DMF).

Anal. Found: C, 41.24; H, 3.78; N, 3.63.

5-Bromo-6-chloro-3-indolyl-β-D-glucopyranoside crystallizes as a mat of colorless needles from methanol, m.p. 196–198°, $[\alpha]^{24}D$ −60° (*c* 1.0, acetone).

Anal. Found: C, 40.81; H, 3.86; N, 3.47.

5-Bromo-4-chloro-3-indolyl-2-deoxy-D-*arabino*-hexapyranoside[9] crystallizes from ethanol as colorless needles, m.p. 211–212°, $[\alpha]^{26}D$ −106° (*c* 1.0, ethanol).

Anal. Calcd. for $C_{14}H_{15}BrClNO_5$: C, 42.83; H, 3.85; N, 3.57. Found: C, 42.54; H, 4.01; N, 3.56.

5-Bromo-4-chloro-3-indolyl-β-D-glucopyranoside (Method B).—To 65 ml. of cold (−5°) dry methanol containing 0.6 g. (0.026 g.-atom) of sodium and under an atmosphere of nitrogen was added, all at once, 7.75 g. (0.026 mole) of 5-bromo-4-chloro-3-indolyl acetate[10] and the stirred mixture was gassed for 0.5 hr. with a stream of dry nitrogen. A solution of 11 g. (0.027 mole) of acetobromoglucose in 65 ml. of methanol was then added dropwise at a rapid rate to the stirred solution while maintaining an external temperature of 0°. After 18 hr., during which time the reaction mixture was allowed to reach room temperature, the solvent was evaporated *in vacuo* at *ca.* 30°. The viscous yellow oil that remained solidified slowly on stirring with water and the dark product was collected and sucked dry. The filter cake was stirred with cold acetone which removed most of the dark material, leaving an off-white solid, 2.6 g. (25% yield), m.p. 240–243° dec. Two recrystallizations from methanol provided an analytical sample, m.p. 240–243° dec., $[\alpha]^{23}D$ −89° (*c* 1.0, 50% DMF).

Anal. Calcd. for $C_{14}H_{15}BrClNO_6$: C, 41.15; H, 3.70; N, 3.43. Found: C, 41.16; H, 3.89; N, 3.39.

1-Acetyl-5-bromo-6-chloroindol-3-ol.—To 45 ml. of 90% sulfuric acid was added, portionwise, with continuous stirring, 9.5 g. (0.029 mole) of 1-acetyl-5-bromo-6-chloro-3-indolyl acetate[10] while maintaining an internal temperature of 20–25°. After 0.75 hr., the reaction mixture was poured on ice, and the yellow solid was collected and washed with generous quantities of a 1% solution of sodium acetate. The vacuum-dried (P_2O_5) product, 7.6 g. (91% yield), m.p. 218–221° dec., afforded analytical material, in the form of pale yellow plates, after first crystallizing from a large volume of ethyl acetate followed by two recrystallizations from ethanol, m.p. 238–239° dec., λ_{max}^{Nujol} 5.82 (amide carbonyl) and 6.0 μ [3-(enolic)carbonyl].

Anal. Calcd. for $C_{10}H_7BrClNO_2$: C, 41.62; H, 2.45; N, 4.85. Found: C, 41.44; H, 2.52; N, 4.97.

(9) The bromo sugar component in this case was the stable 3,4,6-tetra-*O*-(*p*-nitrobenzoyl)-α-D-*arabino*-hexopyranosyl bromide which was recently reported by W. W. Zorbach and G. Pietsch [*Ann.*, **655**, 26 (1962)]. It is assumed, though it is in no way certain, that the product is the β-anomer.

(10) S. J. Holt and P. W. Sadler, *Proc. Roy. Soc.* (London), **B148**, 492 (1958); S. J. Holt in "General Cytochemical Methods," J. F. Danielli, Ed., Academic Press, New York, N. Y., 1958, p. 375.

Book Reviews

Handbuch der Experimentellen Pharmakologie. Volume 15. **Cholinesterases and Anticholinesterase Agents.** Sub-Editor, GEORGE B. KOELLE. Contributors: K. B. Augustinsson, L. E. Chadwick, J. A. Cohen, H. Cullumbine, D. R. Davies, K. P. DuBois, D. Grob, C. O. Hebb, F. Hobbiger, Bo Holmstedt, A. G. Karczmar, G. B. Koelle, N. Krishna, A. S. Kuperman, I. H. Leopold, J. P. Long, X. Machne, L. A. Mounter, D. Nachmansohn, R. A. Oosterbaan, K. R. W. Unna, G. Werner, V. P. Whittaker, J. H. Wills, and E. Zaimis. 1220 pp. Springer-Verlag, Berlin–Gottingen–Heidelberg. 1963. $74.50.

Since the publication of the first paper on cholinesterases (CHE) in 1914, considerable progress has been made on the specificity and the physiological role of these enzymes and their inhibitors, especially in the last 30 years. It is pointed out by one of the contributors that about 200–300 papers have been published each year since 1950 on CHE and antiCHE compounds. The rapid progress made, and the voluminous information published in this area make it very difficult for an individual scientist to keep up with all the developments. Perspective in such a vast subject is gained best by broad reviews written by experts or teams of experts on various aspects related to the area. The fifteenth volume in the series "Handbuch der Experimentellen Pharmakologie" offers an admirable attempt to cover the broad area of CHE and antiCHE compounds.

This volume is divided into four major sections. Each section is subdivided into four to seven chapters, and the whole text contains 24 chapters. Most of the chapters are very comprehensive, and within their chosen or allocated chapters, the authors had clear scope to develop their themes as seemed best to them. The book has adequate author and subject indexes.

Section I.—Components of cholinergic systems: acetylcholine (ACH), choline acetylase (CHAC), and acetylcholinesterase (ACHE). This section contains six chapters. The chapter by Whittaker is an extensive discussion on the analytical methods for the identification, detection, and estimation of cholinesters. The biochemical aspects of CHAC is discussed by Nachmansohn. The formation, storage and liberation of ACH is presented by Hebb. Augustinsson's chapter is a comprehensive review of the classification and the comparative enzymology of the types of CHE and the methods for their determination. The significance of ontogenetic appearance of CHE, and relationships between CHE, neurogenesis, and function is discussed by Karczmar. The chapter by Koelle includes much detail on the methods available for the cytological localization of ACHE and non-specific CHE. This chapter also contains an excellent discussion of the physiological functions of ACH and ACHE.

Section II.—Chemical classification and biochemical reactions of the anticholinesterase agents. This section contains four chapters. Cohen and Oosterbaan have given a lucid account of the interaction of ACHE with substrates and inhibitors, and the chemical analysis of the active sites of esterases related to ACHE. Long has provided an enormous amount of information on the relationships between the chemical structure and the reversible antiCHE properties of many classes of chemical compounds, making use of classification and tabular presentation. This author has clearly pointed out the requirements for making valid structure-activity relationship (SAR) comparisons and the limitations of such studies. Holmstedt's chapter is devoted to the SAR of the organophosphorus antiCHE agents. This chapter includes, unexpectedly but appropriately, a historical account of the development of the organophosphorus inhibitors in industries, universities, and military research institutes. The various chemical reactions in the metabolism of organophosphorus antiCHE agents by mammals and microorganisms are discussed by Mounter.

Section III.—Systematic pharmacology of antiCHE agents. This section contains seven chapters. The actions of antiCHE compounds on the secretory glands, smooth muscle, and the cardiovascular system are summarized by Cullumbine. The chapter by Zaimis deals with the actions of antiCHE compounds at autonomic ganglia and the theories regarding the release of ACH at ganglia. Werner and Kuperman have reviewed the actions of antiCHE compounds at the neuromuscular junction of amphibian, avian, and mammalian muscle. In their discussion, these authors have included information on the nature of the types of CHE at the neuromuscular junction, potentiation of contractile response by antiCHE compounds, and the antidromic activity in the motor nerves. The chapter by Machne and Unna is devoted to the actions of antiCHE compounds in certain functional areas of the brain, including midbrain reticular formation and spinal cord. Nachmansohn has discussed the evidence for the role of ACH in axonal conduction of nerve impulse. The actions of antiCHE compounds on insects and other invertebrates is summarized by Chadwick. Karczmar has reviewed the morphogenetic, toxic, and the melanophore effects of antiCHE agents during ontogenesis. He has included in his discussion the actions of antiCHE agents on function during development.

Section IV.—Toxicology and therapeutic applications of the anticholinesterases. This section contains seven chapters. The

acute and subacute toxicity of the various types of antiCHE compounds is discussed by DuBois. The neurotoxicity of organophosphorus compounds (in poultry and man) is summarized by Davies. The chapter by Wills is a critical survey of the various types of pharmacological antagonists of the antiCHE agents and their modes of action. The review by Hobbiger on the activation of phosphorylated ACHE contains considerable information on the metabolism, toxicity, and therapeutic applications of PAM-2 and related compounds. The two chapters by Grob deal with (1) antiCHE intoxication in man and its treatment, and (2) the usefulness of antiCHE agents in the treatment of myasthenia gravis. Leopold and Krishna have compiled a review on the local use of antiCHE agents in ocular therapy.

There is considerable overlapping of subject material from one chapter to another. For example, the therapeutic applications of PAM-2 in organophosphorus (antiCHE) poisoning in man is covered in Chapters 21 and 22 in different degrees of detail. Sometimes the same references are repeated and listed. A certain degree of overlapping is both useful and unavoidable because the subject material in different chapters is closely related. Different or contrary opinions on the same subject are evaluated critically by the different authors. For example, the role of ACH in axonal conduction of nerve impulse is discussed by three contributors—Nachmansohn, Hebb, and Koelle. The three authors arrive at different conclusions and, thus, a certain degree of overlapping has served a useful purpose.

This volume should be of great interest not only to research pharmacologists and to research workers in related disciplines, but also to entomologists and environmental health scientists. However, it should be pointed out that, although the book deals mainly with antiCHE compounds, many of which are used as insecticides, very little space is allotted to a discussion of the insect's nervous system, the role of ACH–CHE–CHAC system in the insects, and the mechanisms of insecticidal action. Only one chapter (16) is allotted for the action of antiCHE compounds on insects. Brief discussions on this subject are included in the chapters by Hebb (3) and Karczmar (5 and 17).

The literature seems to be thoroughly covered through 1961. The price of the volume may not be too high to pay for this convenience.

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Diuretics. Chemistry and Pharmacology. By GEORGE DESTEVENS. Volume I of **Medicinal Chemistry, a Series of Monographs.** Edited by GEORGE DESTEVENS. xiii + 186 pp. Academic Press, Inc., New York, N. Y. 1963. $7.00.

This book is the first of a series of monographs on medicinal chemistry and, since it was written by the editor of the series, presumably should set the pattern for the rest of the volumes.

The first chapter sums up in eleven pages the "general physiological and pharmacological considerations" for renal function and the pharmacological evaluation of diuretics. After this are presented separate chapters on the various classes of diuretics—xanthines, triazines, organomercurials, sulfonamides, thiazides, aldosterone antagonists, and a miscellaneous group. The book concludes with an eleven-page chapter on the therapeutic use of diuretics in the treatment of hypertension.

A major problem in reviewing (and writing) a book of this type is to decide what constitutes proper coverage of the topics discussed, and even what topics to include. This reviewer feels that medicinal chemistry should be defined as the design and synthesis of potential therapeutic agents. In order to be effective, the practitioner must be thoroughly familiar with the methods of evaluation and the mode of action (if known) of his agents, and the limitations of the clinically useful compounds, as well as with the structure–activity relationships and methods of synthesis. In general, the success of a medicinal chemistry project in developing a lead depends on how keenly the biological aspects are brought to bear on the synthetic aspects of the problem. The more precisely a new compound can be evaluated, the more useful will it be in influencing the choice of new compounds to be prepared.

The present volume is an excellent, comprehensive, and up-to-date treatment of the synthesis and structure–function aspects of the various types of diuretic agents. However, the detailed discussion of the known or probable reasons for these structure–function relations seems to be rare. Thus on page 116, there is a table of a dozen thiazides which shows a thousandfold potency difference between chlorothiazide and cyclopenthiazide. Certainly, some of the factors contributing to this, such as a comparison of protein binding, distribution, relative sites of action in the tubule, blood levels, and rates of excretion are known for at least some of these compounds. Such considerations might explain some of these potency differences and indicate which areas might be more profitably explored.

The section on renal physiology, according to the preface, was "written in a relatively uncomplicated and concise manner so that all those not well versed in the field could readily understand the dynamics of renal function." Unfortunately, the level of understanding that could be gained by reading this section would also be uncomplicated. The type of testing described in the section on pharmacological evaluation does not reflect the methods used by a modern reasonably sophisticated renal laboratory. Surely, today no one would consider that much is known about the character of the activity of a diuretic until the results of several types of renal clearances obtained in several different physiological states are available. Only clearance studies reveal the effect of the agent on tubular electrolyte transport and filtration rate, and thus indicate those drugs with useful natriuretic properties.

The section on the use of diuretics in hypertension also seems to be written in a relatively uncomplicated manner. There is no clear agreement, contrary to the statement on page 161, that thiazides lower blood pressure as a direct consequence of their diuretic and natriuretic activity. The hypotensive activity of the salt-retaining thiazide diazoxide as well as other data at least suggest a direct hypotensive effect. For instance, changes in peripheral resistance independent of changes in extracellular fluid volume have been proposed as a major factor in the hypotensive effect of the thiazides. Also in the discussion of the clinical utility of the thiazides as diuretics, their potassium losing properties are mentioned, but today medicinal chemists should also be concerned with their uric acid retention properties and possible diabetogenic liability.

The present book is a valuable contribution to the literature, and has met very well the author's goal of "surveying the field in its entirety, with particular emphasis on the chemistry of diuretically active compounds and their structure–activity relationships." If the coming volumes in this series are up to the standards set by this one, then indeed the series "will act as a catalyst for further developments" as hoped by the author in his preface.

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International Pharmaceutical Abstracts. Volume 1. Edited by D. E. FRANCKE. 20.2 × 26.6 cm. Published by the American Society of Hospital Pharmacists, 2215 Constitution Ave., N. W., Washington, D. C. 20037. 1964. $15.00 (individual subscription).

This new abstract journal will appear biweekly, and offer abstract articles from all major and standard journals, 450 journals so far, in the following areas: biopharmaceutics, physical pharmacy, pharmaceutical technology, pharmaceutical chemistry, pharmacology, investigational drugs, drug evaluations, adverse drug reactions, drug laws and regulations, and the history, ethics, sociology, and literature of drugs. There will be at least 6000 abstracts annually, each abstract averaging 200 words, except for shorter abstracts of legal, trade, and professional articles.

While there will be some overlapping with *Chemical Abstracts*, the collection of abstracts of medicinal and pharmaceutical interest under one cover, and the promised rapid appearance of abstracts after publication of the journal articles should persuade any scientist in the field, and all professional pharmacists, to read this welcome new organ.

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