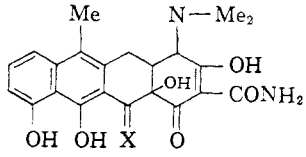
is obtained from oxytetracycline[2] under similar conditions. Structural assignments rest on composition, mode of formation, absorption spectra, dissociation constants and on the striking observation that the 6-deoxy compounds (lacking the C.6 benzyl hydroxyl group) *do not undergo* the very characteristic acid degradation to anhydrotetracycline (IIa) analogs observed with all previously known members of the tetracycline series.[3,4,6,8]

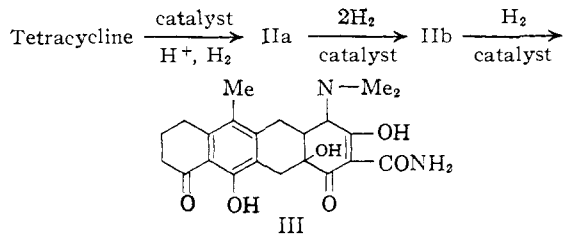
6-Deoxy compound formation also is observed with 6-demethyltetracycline[4] and with desdimethylaminotetracycline analogs.[5]

An acid catalyst apparently is required for 6-deoxygenation. However, in many instances the hydrogenolysis of tetracycline compounds is complicated by a novel effect of noble metal catalysts and hydrogen in promoting acid dehydration at the C.6-C.5a position to form anhydrotetracycline (IIa) analogs, which then, themselves, undergo



IIa, X = O
IIb, X = H_2

hydrogenation. Thus, in the case of tetracycline, an important companion reaction to 6-deoxy compound formation apparently proceeds as shown. Under appropriate conditions compound III (m.p. of the hydrochloride 239–240°, dec., λ_{max} 265 mμ, log ε 4.55, λ_{max} 346 mμ, log ε 3.72 (0.01 *N* HCl in methanol); *pK*'s 4.1, 8.4, ~12.2 (H_2O). *Anal.*



III

Calcd. for $C_{22}H_{27}N_2O_6Cl$: C, 58.60; H, 6.04; N, 6.22; Cl, 7.89. Found: C, 58.59; H, 6.03; N, 5.77; Cl, 7.97) may be obtained in good yield from either tetracycline or anhydrotetracycline. The structural assignment rests on its composition, mode of formation, acidity constants, ultraviolet chromophore (that of a substituted 8-hydroxy-1-tetralone[6]), and on the observation that the hydroxytetralone chromophoric group is unchanged by boiling alkali.

The *in vitro* antimicrobial spectra of 6-deoxytetracycline and 6-deoxyoxytetracycline are comparable to those of the parent substances though some differences are observed.[7] This observation is of particular significance to structure-activity studies since the 6-deoxy compounds complete a series[3,4,5,6,8] of variously substituted tetracyclines—obtained by both chemical and biochemical means—in which every substituent along the "upper periphery" of the basic structure (*cf.* segment A of structure I) has been altered without drastically changing *in vitro* antibacterial activity.

(2) Terramycin is the registered trade-mark of Chas. Pfizer & Co., Inc., for the antibiotic oxytetracycline.

(3) *Cf.* C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **76**, 3568 (1954).

(4) J. R. D. McCormick, N. O. Sjolander, U. Hirsch, E. R. Jensen, and A. P. Doerschuk, *ibid.*, **79**, 4561 (1957).

(5) C. R. Stephens, U. S. Patent 2,786,077, March 19, 1957.

(6) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **75**, 5455 (1953).

(7) A. R. English, private communication.

(8) P. Sensi, G. A. deFerrari, C. G. Gallo and G. Rolland, *Il Farmaco Ed. Sc.*, **10**, (6) 337 (1955).

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BOOK REVIEWS

The Chemistry of Organic Medicinal Products. Fourth Edition. By GLENN L. JENKINS, Professor of Pharmaceutical Chemistry and Dean of the School of Pharmacy, Purdue University; WALTER H. HARTUNG, Professor of Pharmaceutical Chemistry, Medical College of Virginia; KENNETH E. HAMLIN, Jr., Assistant Director of Chemical Research, Abbott Laboratories; and JOHN B. DATA, Associate Professor of Pharmaceutical Chemistry, The School of Pharmacy, Purdue University. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 1957. x + 569 pp. 16.5 × 24 cm. Price, $10.75.

The Fourth Edition has been "completely revised" but the chemical classification of medicinal agents has been retained. The number of chapters remains the same but one, "Natural Mixtures," in the Third Edition appropriately has been replaced by one on "Antibiotics." Primarily, the text is a catalogue of compounds used as medicinal agents and for other purposes (insecticides, flavoring agents). The formula, biological activity, utility (established or merely claimed), toxicity and other properties for each compound are briefly summarized. Statements concerning "activity" and "toxicity" are sometimes indefinite so that the non-expert probably will have to seek clarification elsewhere. He may sometimes wonder whether the claimed activity given for many compounds is true and the expert will question the wisdom of including some of these claims.

The chemical classification employed in the arrangement of the text provides the experienced medicinal chemist with an interesting survey of drugs from his point of view but, to the non-experienced individual or student, this grouping under a given class of a variety of compounds non-related from a drug-action point of view may have only a minimum value. For example, in Chapter 5 on Drugs Containing the Carbonyl Group (aldehydes and ketones) are found formaldehyde (disinfectant and fungicide), hexamethylenetetramine (urinary antiseptic), vanillin (flavor-

ing agent), civetone (used in perfume), 2-methyl-1,4-naphthoquinone (vitamin K_3), glucose (used in manufacturing pharmaceuticals and in foods), cardiac glycosides, steroid hormones, etc. Chapter 11. "Cycles Containing One Hetero Atom," brings together a host of unrelated drugs. It is surprising to find Miracil-D, a thioxanthone derivative used in the treatment of schistosomiasis, following rutin, vitamin E and rotenone.

A further consequence of this arrangement is that the compounds related from a drug-action point of view are scattered throughout the text. Muscle relaxants, such as gallamine triethiodide, decamethonium and curare, are found in three chapters on pages 232, 184 and 384. It is disconcerting not to find analgetics, muscle relaxants, hypotensive agents, diuretics, ganglionic blocking agents, and so forth, listed in the index.

In the preface the authors state: "Medicinal chemistry tends to become more and more the study of chemical reactions between therapeutic agents and living tissue." It is regrettable that they have largely neglected this point of view. A discussion of chemical and physical properties, as they apply to structure–activity relationships in various types of drugs, would have been a valuable and practical contribution. The discussion of "Some Physical and Chemical Properties of Medicinal Agents" in Chapter 16 and "Stereoisomerism" in Chapter 13, of course, has demonstrated the importance of these factors in drug design and *in vivo* activity. Perhaps they will stimulate some readers to seek further to develop medicinal chemistry along these lines.

Contrary to the implication of the title of the text, only a minimum of the chemistry of organic medicinal products is included. The synthesis of drugs, when given, is generally only briefly sketched.

The authors have chosen to provide less reference material in this edition. Much of the text is presumed to be sufficiently well established to require no supporting references and some times trade journals are cited. Supplementary reference material at the end of each chapter has been eliminated. The compounds covered in the text are well indexed.

The binding, paper and printing of the text are satisfactory. There are no major mis-statements of fact although some readers may surmise that certain compounds are more valuable as drugs than they really are. There are a number of minor errors but these are generally quite obviously errors in printing.

Personally I have found this book a valuable and handy reference containing much useful information. It is to be recommended to anyone interested in medicinal chemistry or who is employed in the pharmaceutical field. I surmise it will fulfill a need for many advanced organic chemistry and pharmacy students.

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Advances in Protein Chemistry. Volume XII. Edited by C. B. ANFINSEN, JR., Laboratory of Cellular Physiology, National Heart Institute, Bethesda, Maryland, M. L. ANSON, Cambridge, Massachusetts, KENNETH BAILEY, University of Cambridge, Cambridge, England, and JOHN T. EDSALL, Biological Laboratories, Harvard University, Cambridge, Massachusetts. Academic Press, Inc., 111 Fifth Avenue, New York 3, N. Y. 1957. x + 687 pp. 16 × 23.5 cm. Price, $14.00.

A good review article is a source of satisfaction to both the reader and the author. Chemists are deeply indebted to their colleagues who are undertaking and delivering such reviews. Moreover, the time that an author now needs to devote to such a task is frequently much greater than it was some years ago.

For the current volume of "Advances in Protein Chemistry," Francis Crick and John Kendrew have written a timely and lucid chapter on X-Ray Analysis and Protein Structure. After an informal introduction to the nature of X-ray diffraction, a thorough summary is given of the knowledge which the technique has provided on the physical structures of specific proteins. The results are weighed thoughtfully in relation to the information on the chemistry of the same molecules. The final section is a brief discussion of the structure of viruses.

Henry Isliker has succeeded in summarizing nearly five hundred papers on the Chemical Nature of Antibodies within the compass of a relatively brief review, which is in essence a short textbook on the subject. Students and researchers will find the article valuable. The volume contains a detailed review by Harold Scheraga and Michael Laskowski, Jr., in which they discuss both what is known and what is not yet known of the Fibrinogen–Fibrin Conversion. In an article on Human Hemoglobins: Their Properties and Genetic Control, Harvey Itano focuses attention mainly on the genetic aspects of the subject.

A review of Hans Neurath on the Activation of Zymogens covers data on trypsinogen, chymotrypsinogen, pepsinogen and procarboxypeptidase. The findings already available in the literature are supplemented by references to recent results (in press) from the laboratory of the author and his associates. C. H. Li's review on the Melanocyte-Stimulating and Lactogenic Hormones forms Part II of a pair of articles on the Hormones of the Anterior Pituitary Gland, the first part having been published last year. The present report brings up to date the information on MSH and prolactin.

The final article, by Murray Goodman and George Kenner, is a compendium on the Synthesis of Peptides. A review of methods of synthesis is followed by nearly a hundred pages of tables, which provide an index to the literature on synthetic peptides prepared since Joseph Fruton's review on the subject in 1949. Much work has gone into the compilation of the information, and the article will be very useful. The review would have profited, however, from more attention to accepted English usage. In addition, the abbreviations employed in the tables present some problems, and the authors of the review solicit comments from the readers on this point. Some of the abbreviations may be too brief to be clear, and, in general, a closer adherence to chemical nomenclature might be helpful.

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Chemotherapy and the Central Nervous System. By HENRY MCILWAIN, Ph.D., D.Sc., Professor of Biochemistry in the University of London at the Institute of Psychiatry (British Postgraduate Medical Federation); Honorary Biochemist, the Bethlem Royal Hospital and the Maudsley Hospital; Formerly member of scientific staff, Medical Research Council, and of the Council's Department of Bacterial Chemistry, and Unit for Cell Metabolism. Little, Brown and Company, Boston 6, Mass. 1957. viii + 328 pp. 16 × 24 cm. Price, $10.00.

This small volume by a highly competent neurochemist does not pretend to be an exhaustive or encyclopedic treatment of the rapidly moving field of chemical pharmacology as related to the central nervous system. It represents, rather, a selection of some of those topics which are of interest because they represent new advances in the field or are fundamental to it. The volume is written in an interesting manner with special and appropriate attention to the historical aspects of the field and to the development of its important concepts. Among the selected topics of interest are the mode of action of anesthetics from biochemical and physiological points of view, the pharmacology of the barbiturates and antipyretics, an excellent chapter on the general principles of neuropharmacology, including the distribution of drugs, the blood–brain barrier, and general principles of drug metabolism. The two chapters on infection and anti-infective substances are important and frequently overlooked in current interest in neuropharmacology. The special pharmacology of agents of neuropsychiatric usefulness is treated in sections on epilepsy and anticonvulsant drugs, pain and analgetics, tolerance and habituation, as well as a consideration of the relationship between drugs and mental state, model psychoses, and a discussion of some of the phenothiazine derivatives and reserpine. The book should be of value to those who wish to find a very readable review of many important aspects of this subject.

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