The three other antihistamines studied, pyrilamine maleate (III)[3], tripelennamine hydrochloride (IV)[4], and methapyrilene hydrochloride (I), are ethylenediamine derivatives. Their salts gave spectra which suggested that $L = 0$. This value is not expected, for it corresponds to equal proportions of all three conformers. Since the departure from $L = 0$ that can be recognized depends in part on the value of M, an attempt was made to estimate this parameter for the NCH_2CH_2N system by studying pyrilamine free base. Its spectrum showed $N = 14.6$ and $L = \pm 3.6$ with $M = \pm 2.0$ Hz.; the electronegativity relationship yields 6.1 Hz. for J_{av}, which is to be compared with the experimental value of 7.9 Hz. ($L > 0$) and 6.7 Hz. ($L < 0$). Thus, L is negative, *i.e.*, n_t is greater than 1/3 so that the *trans*-form is favored in solution and is more stable than the *gauche*-forms.

The N values for the salts, the species present at physiological pH, are 12.1 Hz. (pyrilamine), 12.0 Hz. (tripelennamine), and 11.8 Hz. (methapyrilene). By assuming an upper limit of $M = 2$ Hz. for these molecules, the observed spectra are consistent with L values between -1 and 1 Hz. If only the *trans*-form were present in solution, N and L values of approximately 16 and -6 Hz., respectively, would be expected (13, 14). Although there are experimental and theoretical uncertainties in deducing precise conformer proportions from the coupling constants, it is quite clear that the decreases in N and L, compared with pyrilamine free base, are accompanied by a decrease in the proportion of the *trans*-conformer. Attempts to allow for possible electronegativity effects of a substituent on the proton couplings only reinforce this decrease. Thus, in contrast to methapyrilene in the solid, these three closely related ethylenediamine antihistamines are not exclusively in the *trans*-conformation in solution; in fact, conformationally, they seem very similar to the histamine cation itself.

Although none of the salts studied here is exclusively in the *trans*-form in solution, the ethylenediamine derivatives are among the most active antihistamines. These $NCCN^+$ types have pA_2 values approximately 1 unit higher than the $OCCN^+$ type (15). While it is probably an oversimplification to ascribe all of this difference in activity to conformational preference, the order of decreasing activity is also the order of decreasing N values and, hence, decreasing proportion of the *trans*-conformer. This observation is consistent with the stereospecificity observed in antihistamines of the allylamine type (16), where UV spectra indicate that the more active geometric isomer has the basic N atom and the α-pyridyl ring in a *trans*-arrangement.

(1) G. R. Clark and G. J. Palenik, *J. Amer. Chem. Soc.*, **92**, 1777(1970).

(2) J. Donahue and A. Caron, *Acta Crystallogr.*, **17**, 1178 (1964).

(3) E. J. Ariens, *Advan. Drug Res.*, **3**, 235(1966).

(4) B. Belleau, *ibid.*, **2**, 89(1965).

(5) A. F. Casy, R. R. Ison, and N. S. Ham, *Chem. Commun.*, **1970**, 1343.

(6) M. V. Veidis, G. J. Palenik, R. Schaffrin, and J. Trotter, *J. Chem. Soc. A*, **1969**, 2659.

(7) E. W. Garbisch, Jr., *J. Chem. Ed.* **45**, 480(1968).

(8) R. J. Abraham and K. G. R. Pachler, *Mol. Phys.*, **7**, 165 (1964).

(9) M. Karplus, *J. Chem. Phys.*, **30**, 11(1959).

(10) M. L. Huggins, *J. Amer. Chem. Soc.*, **75**, 4123(1953).

(11) H. O. Schild, *Brit. J. Pharmacol.*, **2**, 189(1947).

(12) C. C. J. Culvenor and N. S. Ham, *Chem. Commun.*, **1966**, 537.

(13) R. J. Abraham, L. Cavelli, and K. G. R. Pachler, *Mol. Phys.*, **11**, 471(1966).

(14) C. C. J. Culvenor and N. S. Ham, *Chem. Commun.*, **1970**, 1242.

(15) R. B. Barlow, "Introduction to Chemical Pharmacology," Methuen, London, England, 1968, p. 357.

(16) *Ibid.*, pp. 368, 371.

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[3] Pyrilamine (III) is 2-[(2-dimethylaminoethyl)(*p*-methoxybenzyl)-amino]pyridine.

[4] Tripelennamine (IV) is 2-[benzyl(2-dimethylaminoethyl)amino]-pyridine.

BOOKS

REVIEWS

Handbook of Experimental Pharmacology, Volume 28, Part 1, Concepts in Biochemical Pharmacology, Edited by B. B. BRODIE and J. R. GILLETTE. Springer-Verlag New York, Inc., 175 Fifth Ave., New York, NY 10010, 1971. xvi + 471 pp., 16.5 × 25 cm. Price $50.40.

This volume continues the high tradition of the Handbook series for breadth of coverage and criticality in the review of specialized aspects of pharmacology.

Part 1 of Volume 28 presents a detailed critique of current information on drug absorption, transport, and disposition in tissues and drug disposition *via* several excretory routes. Part 2 will cover the topics of microsomal and nonmicrosomal biotransformation of drugs as well as bioanalytical methodology for the study of drug metabolism and the isolation and identification of drug metabolites. When complete, this volume will likely become the standard reference work on all aspects of drug absorption, transport, and disposition.

The book is divided into three sections. Section One is entitled Routes of Drug Administration and contains chapters on Absorp-

tion of Drugs from the Gastrointestinal Tract (L. S. Schanker); Buccal Absorption of Drugs (A. H. Beckett and R. D. Hossie); Subcutaneous and Intramuscular Injection of Drugs (J. Schou); Absorption, Distribution and Excretion of Gaseous Anesthetics (H. Rackow); and Absorption of Drugs through the Skin (M. Katz and B. J. Poulsen). Particularly impressive is the fact that the editors have included and encouraged discussion in depth of aspects of drug absorption by routes other than oral administration. The chapters by Katz and Poulsen on drug absorption through the skin, by Greene on aerosols, and by Rackow on gaseous anesthetics are especially timely and well done.

Section Two covers Sites of Drug Transport and Disposition and includes chapters presenting a theoretical description of drug–protein interactions (W. Settle, S. Hegeman, and R. M. Featherstone); Physical Methods for Studying Drug–Protein Binding (C. F. Chignell); Effects of Binding to Plasma Proteins on the Distribution, Activity and Elimination of Drugs (P. Keen); Competition between Drugs and Normal Substrates for Plasma and Tissue Binding Sites (H. M. Solomon); drug entry into the central nervous system (D. P. Rall), bone (H. M. Foreman), adipose tissue (L.C. Mark), and placental transfer of drugs (M. Finster and L. C. Mark). The concluding chapters in this section covering autoradiography in experimental pharmacology (L. J. Roth) and drug accumulation at sympathetic nerve endings (I. J. Kopin) present information which has been extensively reviewed elsewhere and which is, in any case, out-of-place in the context of this volume. Section Two logically leads the reader from a discussion of the underlying physical and chemical forces involved in drug–protein interactions to a description of methodology which can be employed to identify and quantify such interactions and thence to an exposition of their significance to the activity of drugs and to the action of endogenous substances such as hormones.

Section Three: Sites of Drug Excretion surveys the role of the kidney (I. M. Weiner), bile (R. L. Smith), and milk (F. Rasmussen) as systems or vehicles for drug excretion. The book is concluded with a pertinent chapter of toxicological interest on Extracorporeal and Peritoneal Dialysis of Drugs by G. E. Schreiner, J. F. Maher, W. P. Argy, and L. Siegel.

The major strengths of this work are three in number. First, the organization is highly logical and proceeds from the development of the theoretic base for each topic to a discussion of the significance of that topic to drug action in the intact organism. Secondly, each chapter is written by an authority in the field in whose laboratory much of the early work on the development and significance of the subject matter was undertaken. This provides a degree of scope and criticality otherwise unobtainable. Thirdly, the editors have wisely chosen the topics to be covered under the broad heading of "biochemical pharmacology"; their choice leads to a structure which may yet convey some meaning to this frequently misapplied and misunderstood phrase.

"Concepts in Biochemical Pharmacology" should be made available to graduate students in pharmacology, medicinal chemistry, and biopharmaceutics as a reference work and to the research worker in these disciplines looking for an overview of the underlying principles and processes by which drugs are absorbed, translocated in the body, and excreted. The price of this volume should not deter its wide utilization.

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AMA Drug Evaluations 1971. Evaluated by the AMA Council on Drugs. American Medical Association, Chicago, IL 60610, xxviii + 1040 pp. 28 × 21 cm. Price $15.00.

One of the most frequently encountered problems in the area of drugs is to find a reliable, complete, and reasonably up-to-date source for drug information. The publication of "AMA Drug Evaluations 1971" is a significant effort toward filling that void. The AMA has attempted to bring together in a single source essential therapeutic information about the most commonly used drugs.

The 1040-page guide includes more than 1200 single entity drugs and mixtures, describing effectiveness, safety, reactions, and dosage. Evaluative statements based on opinions of the AMA Council on Drugs are also included. Whenever possible, statements comparing relative effectiveness and safety are given. The following information is given for each drug: appraisal, action and uses, limitations and precautions, adverse reactions, dosage, route of administration, preparations, available sizes and strengths, known sources of supply, and commercial name or names by which the drug is sold in the United States.

The book is divided into two major sections. The first of these is subdivided into 90 therapeutic classifications. Each chapter contains an introductory statement that discusses the overall therapeutic category, followed by descriptions and evaluations of all drugs in the class—old or new, single entity or combination.

Drugs marketed in the last ten years make up the second section, the New Drugs Section. In this section, drugs are listed alphabetically by generic name; more detailed information is provided for these newer drugs.

A somewhat unusual, but most helpful, feature of the book is the inclusion of three indexes. The Indications Index uses diseases, symptoms, and other indications as the main headings. The second index uses various adverse reactions as the main headings, and the third index utilizes nonproprietary (generic) and trade names of drugs as the entry terms.

This book should prove to be an indispensable reference source for those in need of reliable and concise drug information. Although this book was four years in the works, it was well worth the wait.

Staff Review ■

NOTICES

The Pineal Gland. A Ciba Foundation Symposium. Edited by G. E. W. WOLSTENHOLME and J. KNIGHT. Churchill Livingstone, London, England, 1971. xi + 401 pp. 16 × 24 cm.

The Family and Its Future. A Ciba Foundation Symposium. Edited by K. ELLIOTT. J. & A. Churchill, 104 Gloucester Place, London, England, 1970. x + 230 pp. 15.5 × 23.5 cm.

Hormones and the Immune Response. Ciba Foundation Group No. 36. Edited by G. E. W. WOLSTENHOLME and J. KNIGHT. J. & A. Churchill, 104 Gloucester Place, London, England, 1970. ix + 172 pp. 12.5 × 18.5 cm.

Hypertrophic Obstructive Cardiomyopathy. Ciba Foundation Study Group No. 37. Edited by G. E. W. WOLSTENHOLME and M. O'CONNOR. J. & A. CHURCHILL, 104 Gloucester Place, London, England, 1971. ix + 220 pp. 13 × 19 cm.

Handbook of Drug Interactions. By GERALD SWIDLER. Wiley-Interscience, New York, NY 10016, 1971. vi + 384 pp. 15.5 × 23.5 cm. Price $15.

Pyrogens and Fever. A Ciba Foundation Symposium. Edited by G. E. W. WOLSTENHOLME and J. BIRCH. Churchill Livingstone, London, England, 1971. xi + 232 pp. 16 × 24 cm.

Teamwork for World Health. A Ciba Foundation Symposium. Edited by G. WOLSTENHOLME and M. O'CONNOR. J. & A. Churchill, 104 Gloucester Place, London, England, 1971. xiii + 242 pp. 16 × 24 cm.

Identifizierung Von Arzneistoffen. By H. AUTERHOFF and K.-A. KOVAR. Wissenschaftliche, Verlagsgesellschaft mbH, 7000 Stuttgart 1, Postfach 40, Germany, 1971. 143 pp. 21 × 29 cm. Price DM 27.50. (*German*)

Encyclopedia of Industrial Chemical Analysis, Vol. 12: Dyes to Flour. Edited by F. D. SNELL and L. S. ETTRE. Wiley, New York, NY 10016, 1971. xiv + 618 pp. 18.5 × 26 cm.

Energy Metabolism in Trauma. A Ciba Foundation Symposium. Edited by R. PORTER and J. KNIGHT. J. & A. Churchill, 104 Gloucester Place, London, England, 1970. x + 202 pp. 15.5 × 23.5 cm.