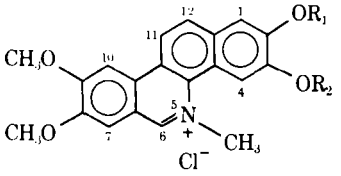

Ia: $R_1 = H$, $R_2 = CH_3$
Ib: $R_1 = CH_3$, $R_2 = H$

ing the presence of a phenolic group in the molecule. The presence of a phenolic hydroxyl group was also indicated by a broad absorption band at 3500–3200 cm.$^{-1}$ in the IR spectrum. A lack of peaks at 1480 and 940 cm.$^{-1}$ in the IR spectrum was suggestive of the absence of the methylenedioxy function in the molecule, which was confirmed by a negative Labat's test and by a lack of absorption in the area of 6 p.p.m. in the NMR spectrum.

An NMR spectrum of fagaronine (I*a*) in dimethyl sulfoxide, with tetramethylsilane as the internal standard, showed peaks for $-N^+-CH_3$ (δ in p.p.m., singlet at 5.11), three $-OCH_3$ (singlets at 4.24, 4.11, and 4.04), 6-position proton (singlet at 9.97), protons at positions 11 and 12 (doublets centered at 8.86, J = 9 Hz., and 8.16, J = 9 Hz.), and protons at positions 1, 4, 7, and 10 (singlets at 7.66, 7.94, 8.13, and 8.36). At this point, Structures I*a* and I*b* were suggested for fagaronine.

A molecular ion, M^+, was observed at *m/e* 350 in the mass spectrum of fagaronine, followed by peaks at *m/e* 349 (M^+-1), 348, 335 (base peak, $M-15$), 334, 320, 306, 292, and a doubly charged species at *m/e* 167.5. The formation of these ions can be explained by the mode of fragmentation proposed for such compounds by Torto and Mensah (3) and Slavik *et al.* (4). Structure I*a* is favored over I*b* for the structure of fagaronine because of the more favorable formulation of the peak at *m/e* 349 ($M^+ - 1$) (9%).

Final proof of the structure of fagaronine by synthesis is in progress.

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BOOKS

REVIEWS

Handbook of Experimental Pharmacology, Volume 28, Part 2, 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. xx + 778 pp. 16.5 × 25 cm. Price $75.00.

This work completes Volume 28. Part 1 [reviewed in *J. Pharm. Sci.*, **60**, 1765(1971)] covered the subjects of absorption, tissue distribution, and excretion of drugs, while Part 2 addresses the topics of analytical techniques for the study of drug metabolism and the significance of microsomal and nonmicrosomal enzymatic metabolism of drugs to pharmacological action. The completed volume is well suited to serve as a single reference work on all aspects of drug disposition. The organization, indexing, and general arrangement will make this volume useful to the nonspecialist with a casual interest in drug disposition as well as to the graduate student and experienced investigator because of the encyclopedic nature of the coverage. Although each of the major topics treated in Part 2 (*e.g.*, analytical methods for drugs and drug metabolites, pathways of drug metabolism, cytochrome P-450, and enzyme induction) has been adequately and extensively reviewed elsewhere, never has this information been brought together in a single work focused upon the specific question of the significance of these topics to drug action.

In any book which is the product of the collaborative efforts of 46 authors, it is to be expected that coverage of each topic will not be uniform with respect to scope and depth. This does not appear to be a serious deficiency of the present volume since the authors have provided extensive referencing (in convenient tabular form in many chapters) to take the reader beyond the material covered in the text. The brevity of some chapters does, however, leave the reader unsated. Regrettably, this is the case with some of the more technically sophisticated and newer methods of analysis such as immunoassay (4-page chapter), enzymatic assays (12 pages), and radioisotope derivative methods (3 pages).

Following the organization begun in Part 1, the present volume opens with Section Four: Methods of Studying the Metabolism of Drugs. Subsection A: Assay of Drugs and Their Metabolites is introduced with a chapter on Basic Principles in Development of Methods for Drug Assay written appropriately by B. B. Brodie whose efforts spanning 30 years in methodology development have been crucial in enabling the study of drug action and disposition to proceed at a rational level. Other chapters in the subsection cover Absorption Spectrophotometry (R. P. Maickel and T. R. Bosin), Fluorometry (H. S. Ackerman and S. Udenfriend), The Use of Labeled Drugs (R. P. Maickel, W. R. Snodgrass, and R. Kuntzman), Radioactive Isotope Derivatives of Nonlabeled Drugs (R. Kuntzman, R. H. Cox, and R. P. Maickel), Gas Chromatography (M. W. Anders), Enzymatic Assays in Pharmacology (A. K. Cho), an eloquent defense of Bioassay (M. Vogt), and the subsection closes with a glimpse of the applicability of immunoassay methods for drugs presented by S. Spector. The approach used in this portion of the book is briefly to identify the theoretical principles underlying the methods presented and immediately to launch into examples of their application to the measurement of drugs, drug metabolites, and some endogenous compounds in tissues, body fluids, excreta, and *in vitro* assay systems. Liberal referencing and the setting forth of many examples appraise the reader of the scope of each method. I highly recommend the chapter by B. B. Brodie on principles in the development of assay methods to young investigators and beginning graduate students, since it gives an excellent overview of variables which must be taken into consideration in any investigation in which a drug or group of drugs must be quantitatively measured in a biological matrix. The pitfalls in such analyses are well detailed. Throughout the subsection the methods chosen for discussion were judiciously selected for their application to the determination of weak organic electrolytes, a classification which covers the vast majority of drugs and other chemicals of broad biological significance. Particularly impressive are the short chapters on enzymatic assays in pharmacology and immunoassay in that these procedures offer the ultimate in both sensitivity and specificity, a marriage of virtues usually not inherent in a single analytical approach.

Subsection B: Isolation and Identification of Drug Metabolites treats techniques useful in the preliminary separation of related compounds and their identification. Paper, Column, and Thin Layer Chromatography; Countercurrent Distribution; and Electrophoresis procedures are covered by E. O. Titus, with emphasis upon such practical considerations as choice of solvents for countercurrent distribution, extraction of metabolites from tissues, and properties of adsorbents for column chromatography. This approach enables the reader quickly to develop a "feel" for the practical applicability of the methods as well as to point out the important variables to be considered. Isotope Dilution Analysis (V. T. Oliverio and A. M. Guarino) is exemplified as a technique useful for the determination of drugs such as tolbutamide, thalidomide, and warfarin. A general survey of the utility of spectroscopic methods for the identification of drug metabolites is given by P. Bommer and F. M. Vane. In this chapter, attention is directed to mass spectrometry, NMR, UV, and IR spectroscopy, optical rotatory dispersion, and circular dichroism. Examples are given of the application of NMR and mass spectrometry to the study of diazepam and triprolidine metabolism. While valuable, this chapter repeats much information presented by C. F. Chignell in Part 1 on methods for studying drug–protein interactions. The combined use of gas chromatography and mass spectrometry as an approach to the separation and subsequent identification of closely related compounds is presented by A. M. Guarino and H. M. Fales. The power of the approach is well detailed and the tabular lists of examples of applications useful. One's enthusiasm for the methodology is tempered, however, by the price of a complete system including a computer which effectively puts this technique out of the range of all but a few laboratories and research centers.

The major strengths of Section Four are that the methods presented are highly relevant to their stated purpose, namely, the isolation, identification, and determination of drugs and derived metabolites in biological materials. Exposition of the methods is clearly directed to practical problems associated with their use, in contrast to many textbooks and reviews of analytical methods which frequently leave the biologist in a state of frustrated exasperation. Most significantly, each chapter is written by a biologist having wide experience in the application of the methods discussed.

Section Five: Sites of Drug Metabolism is divided into Subsection A: Microsomal Enzymes and Subsection B: Nonmicrosomal Enzymes. The introductory chapter, Pathways of Drug Metabolism (R. T. Williams) is a clear exposition of the major metabolic reactions undergone by drugs and other foreign compounds, and prepares the reader for the in-depth discussions of individual pathways of metabolism which follow. Chapters on Morphological Characteristics of Hepatocyte Endoplasmic Reticulum (J. R. Fouts), Cytochrome P-450 (R. W. Estabrook), Mechanisms of Induction of Drug Metabolizing Enzymes (H. V. Gelboin), and Inhibition of Drug Metabolism (G. J. Mannering) present broad considerations applicable to several pathways of metabolism. Estabrook's treatment of cytochrome P-450 takes the historical perspective and traces well the attempts at resolution of important questions surrounding the functioning and significance of this species. Functioning of the microsomal enzymes in the metabolism of endogenous constituents such as steroids, fatty acids, and cholesterol is discussed by A. H. Conney and R. Kuntzman. Other chapters in this subsection cover Model Systems in Studies of the Chemistry and Enzymatic Activation of Oxygen (V. Ullrich and H. Staudinger), Enzymatic Oxidation at Carbon (J. Daly), *N*-Oxidation Enzymes (J. H. Weisburger and E. K. Weisburger), Enzymatic *N*-, *O*-, and *S*-Dealkylation (T. E. Gram), Reductive Enzymes (J. R. Gillette), Oxidative Desulfuration and Dearylation of Selected Organophosphate Insecticides (P. A. Dahm), Metabolism of Halogenated Compounds (E. A. Smuckler), Glucuronide-Forming Enzymes (G. J. Dutton), and Tissue Distribution Studies of Polycyclic Hydrocarbon Hydroxylase Activity (L. W. Wattenberg and J. L. Leong). Although some chapters are extremely abbreviated, each is a pithy account of the respective topics by an individual closely identified with the development of each research area. If the subsection has a deficiency, it may be that each of the enzymatic pathways discussed is not covered uniformly in depth and scope. As an example, one finds information on the influence of age, diet, drugs, and environmental factors upon glucuronide-forming enzymes, but not with respect to several other pathways. Species differences in enzyme activity are treated by some authors and not by others. On the whole this problem is offset by the liberal use of references.

Subsection B of Section Five treats nonmicrosomal enzymes of importance both in the metabolism of drugs and normal constituents of the body. Such pathways as sulfate conjugation (A. B. Roy); acetylation, deacetylation, and amino acid conjugation (W. W. Weber); mercapturic acid formation (E. Boyland); and methyltransferase enzymes (J. Axelrod) are surveyed but not covered in great depth. The chapter on Amine Oxidases (E. A. Zeller) identifies important questions regarding monoamine oxidase(s) such as the existence of multiple molecular forms of the enzyme, and speculation on the biological significance of its presence in tissues. A particularly valuable chapter is that on Enzymes that Inactivate Vasoactive Peptides (E. G. Erdos), with emphasis upon kininases and angiotensinases. Esterases are surveyed by B. N. LaDu and H. Snady. The volume closes with a provocative chapter by H. G. Mandel on The Metabolism of Analogs of Endogenous Substrates. The emphasis here is upon the pharmacological and therapeutic significance of the metabolic conversion of drugs which are analogs of purines and pyrimidines, and describes the potential clinical importance of the modification of the metabolism of such agents in the treatment of neoplastic diseases. The examples chosen illustrate well the necessity of understanding the biological disposition of drugs for the design of a rational therapeutic regimen.

"Concepts in Biochemical Pharmacology" will be of wide utility to graduate students, investigators, and clinicians. As a reference source, it should be available to departments of medicinal chemistry, biochemistry, biopharmaceutics, and pharmacology. The volume will find a place as a classic work in the field of drug disposition.

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