BIOCHEMICAL PHARMACOLOGY AND TOXICOLOGY
A SERIES OF MONOGRAPHS

BIOACTIVATION OF FOREIGN COMPOUNDS

Edited by

M.W. Anders

ACADEMIC PRESS, INC.
(Harcourt Brace Jovanovich, Publishers)

BIOACTIVATION OF FOREIGN COMPOUNDS

Edited by

M. W. Anders

Department of Pharmacology
School of Medicine and Dentistry
University of Rochester
Rochester, New York

1985

ACADEMIC PRESS, INC.
(Harcourt Brace Jovanovich, Publishers)
Orlando San Diego New York London
Toronto Montreal Sydney Tokyo

ACADEMIC PRESS, INC.
Orlando, Florida 32887

United Kingdom Edition published by
ACADEMIC PRESS INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

Library of Congress Cataloging in Publication Data

Main entry under title:

Bioactivation of foreign compounds.

(Biochemical pharmacology and toxicology)
Includes index.
1. Xenobiotics--Metabolism. 2. Xenobiotics--Physiological effect. 3. Xenobiotics--Toxicology. 4. Biotransformation (Metabolism) I. Anders, M. W. II. Series.
[DNLM: 1. Biotransformation. 2. Drugs--Metabolism. 3. Biochemistry. QV 38 B61415]
QP529.B56 1985 612'.015 84-16772
ISBN 0-12-059480-3 (alk. paper)

PRINTED IN THE UNITED STATES OF AMERICA

85 86 87 88 9 8 7 6 5 4 3 2 1

Bioactivation of Foreign Compounds

BIOCHEMICAL PHARMACOLOGY AND TOXICOLOGY

A Series of Monographs

WILLIAM B. JAKOBY, Editor
National Institutes of Health
Bethesda, Maryland

William B. Jakoby (editor). ENZYMATIC BASIS OF DETOXICATION, Volumes I and II, 1980

William B. Jakoby, John R. Bend, and John Caldwell (editors). METABOLIC BASIS OF DETOXICATION: METABOLISM OF FUNCTIONAL GROUPS, 1982

John Caldwell and William B. Jakoby (editors). BIOLOGICAL BASIS OF DETOXICATION, 1983

M. W. Anders (editor). BIOACTIVATION OF FOREIGN COMPOUNDS, 1985

Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

Ahmed E. Ahmed (485), Departments of Pathology, Pharmacology, and Toxicology, University of Texas Medical Branch, Galveston, Texas 77550

M. W. Anders (283), Department of Pharmacology, School of Medicine and Dentistry, University of Rochester, Rochester, New York 14642

Michael C. Archer (403), Department of Medical Biophysics, University of Toronto, Ontario Cancer Institute, Toronto, Ontario, Canada M4X 1K9

R. Bruce Banks (375), Department of Chemistry, University of North Carolina, Greensboro, North Carolina 27412

Michael R. Boyd (243), Laboratory of Experimental Therapeutics and Metabolism, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205

Leo T. Burka[1] (243), Laboratory of Experimental Therapeutics and Metabolism, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205

James S. Bus (111), Department of Biochemical Toxicology, Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina 27709

Allan H. Conney (177), Department of Experimental Carcinogenesis and Metabolism, Hoffman-La Roche Inc., Nutley New Jersey 07110

Mohammed Y. H. Farooqui (485), Departments of Pathology, Pharmacology, and Toxicology, University of Texas Medical Branch, Galveston, Texas 77550

[1]Present address: Systematic Toxicology Branch, Toxicology Research and Testing Program, National Institute of Environmental Health Services, Research Triangle Park, North Carolina 27709.

James R. Gillette (29), Laboratory of Chemical Pharmacology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20205

Patrick E. Hanna (375), Departments of Medicinal Chemistry and Pharmacology, University of Minnesota, Minneapolis, Minnesota 55455

Dietrich Henschler (317), Institut für Pharmakologie und Toxikologie, Universität Würzburg, D-8700 Würzburg, Federal Republic of Germany

Richard D. Irons (259), Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina 27709

Donald M. Jerina (177), Laboratory of Bioorganic Chemistry, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205

P. David Josephy[2] (451), Laboratory of Pulmonary Function and Toxicology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709

Laurence S. Kaminsky (157), Laboratory of Biochemical and Genetic Toxicology, New York State Department of Health, Albany, New York 12201

George E. Labuc (403), Department of Medical Biophysics, University of Toronto, Ontario Cancer Institute, Toronto, Ontario, Canada M4X 1K9

Wayne Levin (177), Department of Experimental Carcinogenesis and Metabolism, Hoffman-La Roche Inc., Nutley, New Jersey 07110

Ronald P. Mason (451), Laboratory of Molecular Biophysics, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709

Elizabeth C. Miller (3), McArdle Laboratory for Cancer Research, University of Wisconsin School of Medicine, Madison, Wisconsin 53706

James A. Miller (3), McArdle Laboratory for Cancer Research, University of Wisconsin School of Medicine, Madison, Wisconsin 53706

S.J. Moloney[3] (433), Department of Biochemistry, The University of Texas Health Science Center, Dallas, Texas 75235

Robert A. Neal (519), Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina 27709

Sidney D. Nelson (349), Department of Medicinal Chemistry, University of Washington, Seattle, Washington 98195

Paul R. Ortiz de Montellano (121), Department of Pharmaceutical Chemistry, University of California, San Francisco, California 94143

[2]Present address: Department of Chemistry and Biochemistry, University of Guelph, Guelph, N1G 2W1 Ontario, Canada.

[3]Present address: Avon Products, Inc., Toxicology Department, Suffern, New York 10901.

Lance R. Pohl (283), Laboratory of Chemical Pharmacology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20205

R.A. Prough (433), Department of Biochemistry, The University of Texas Health Science Center, Dallas, Texas 75235

Donald J. Reed (71), Department of Biochemistry and Biophysics, Oregon State University, Corvallis, Oregon 97331

Tadashi Sawahata (259), Toxicology Laboratory, Toray Industries, Inc., Sonoyama, Otsu 520, Japan

Dhiren R. Thakker[4] (177), Laboratory of Bioorganic Chemistry, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205

Norman M. Trieff (485), Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, Texas 77550

Alexander W. Wood (177), Department of Experimental Carcinogenesis and Metabolism, Hoffman-La Roche Inc., Nutley, New Jersey 07110

Haruhiko Yagi (177), Laboratory of Bioorganic Chemistry, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205

[4]Present address: Center for Drugs and Biologics, Food and Drug Administration, Bethesda, Maryland 20205.

Preface

The elucidation of the understanding of the mechanisms by which chemicals produce toxic effects is a challenge to pharmacologists, toxicologists, and biochemists. Although significant gaps in our knowledge remain, work in many laboratories over the past two decades has shown that the metabolic alteration, or bioactivation, of chemicals—either to stable, but toxic, metabolites or to reactive electrophiles—is necessary for the elicitation of a toxic response.

This volume in the Biochemical Pharmacology and Toxicology series aims to summarize the body of knowledge on chemical bioactivation. The introductory chapters deal with historical developments and with factors that affect all chemicals. The emphasis of the remainder of the volume is on the mechanisms of bioactivation of chemical classes. These chapters provide information on biochemical reaction mechanisms and the fate of toxic metabolites. The enzymology of bioactivation enzymes has been treated briefly because this was the subject of earlier volumes in this series (*Enzymatic Basis of Detoxication,* Volumes I and II, edited by W. B. Jakoby, Academic Press, 1980).

The biochemical view presented in this work should enhance our ability to predict bioactivation mechanisms for new compounds and to make better judgments on the hazards posed by exposure to chemicals.

M. W. Anders

Contents

14. Nitrosamines

Michael C. Archer and George E. Labuc

15. Hydrazines

R. A. Prough and S. J. Moloney

16. Nitroimidazoles

P. David Josephy and Ronald P. Mason

Introduction