

THE BENZODIAZEPINES

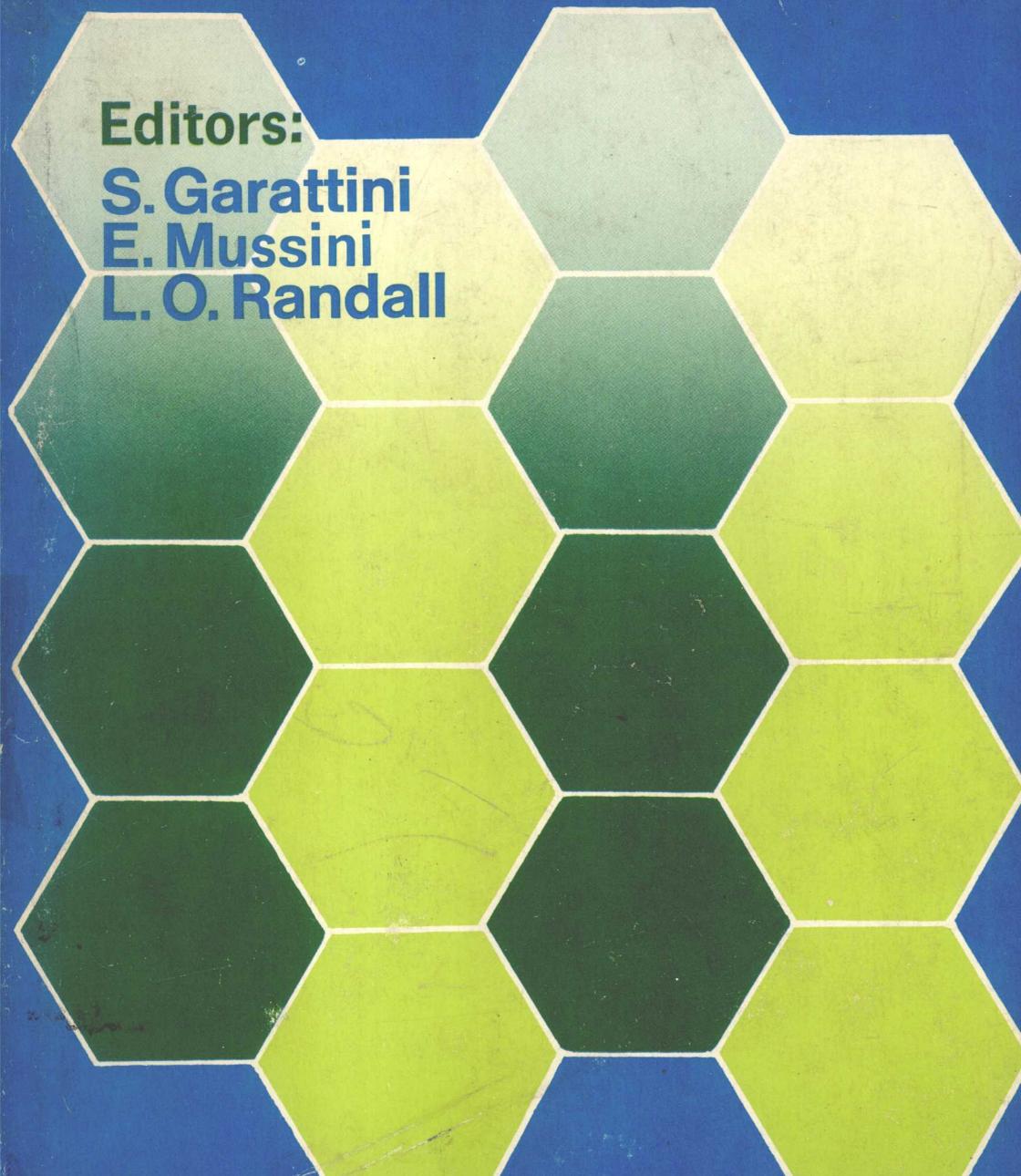
MONOGRAPHS OF THE MARIO NEGRI INSTITUTE
FOR PHARMACOLOGICAL RESEARCH

Editors:

S. Garattini

E. Mussini

L. O. Randall





MONOGRAPHS OF THE MARIO NEGRI INSTITUTE
FOR PHARMACOLOGICAL RESEARCH, MILAN

THE BENZODIAZEPINES

EDITORS:

S. Garattini, M.D.

*Director, Mario Negri Institute
for Pharmacological Research
Milan, Italy*

E. Mussini, M.D.

*Head, Department of Biochemical
Pharmacology
Mario Negri Institute
for Pharmacological Research
Milan, Italy*

L. O. Randall, Ph.D.

*Director, Department of Pharmacology
Research Division
Hoffmann-La Roche, Inc.
Nutley, New Jersey, U.S.A.*

Raven Press • New York

Distributed in the Eastern Hemisphere by

North-Holland Publishing Company • Amsterdam

© 1973 by Raven Press Books, Ltd. All rights reserved. This book is protected by copyright. No part of it may be duplicated or reproduced in any manner without written permission from the publisher.

Made in the United States of America

International Standard Book Number 0-911216-25-1
Library of Congress Catalog Card Number 78-181304

THE BENZODIAZEPINES

MONOGRAPHS OF THE MARIO NEGRI INSTITUTE
FOR PHARMACOLOGICAL RESEARCH, MILAN

Amphetamines and Related Compounds

Edited by E. Costa and S. Garattini

The Benzodiazepines

Edited by S. Garattini, E. Mussini, and L. O. Randall

Chemotherapy of Cancer Dissemination and Metastasis

Edited by S. Garattini and G. Franchi

Isolated Liver Perfusion and Its Applications

Edited by I. Bartošek, A. Guaitani, and L. L. Miller

PREFACE

Since the discovery of chlordiazepoxide hydrochloride in 1957, the benzodiazepines have had a tremendous impact on the treatment of disorders of nervous origin. These drugs have become among the most widely prescribed in medicine. More significant is the widespread scientific investigation that has been generated by this unique class of drugs.

Sufficient material on the benzodiazepines had accumulated in the literature to justify the organization of this symposium. It was the first opportunity to bring together an international group of investigators to attempt the correlation of the chemical, pharmacological, and clinical data. Various authors discussed the structure-activity, general pharmacology, neuropharmacology, psychopharmacology, metabolism, biochemical effects, and clinical activity of the benzodiazepines. In view of the volume of work done in this area, we were compelled to limit the number of topics and the speakers in the program.

The discussions during the symposium revealed many deficiencies in our understanding of the mechanism of action of these centrally active drugs. Their effects in various biological systems should be investigated thoroughly in order to determine with greater precision the particular indications and limitations for each drug in this group. Although there are many benzodiazepine derivatives which appear to exert similar action, they may show differences that could be of fundamental significance if evaluated properly. The discovery of related compounds with different spectra of activity can be predicted.

We hope that the interesting and stimulating character of this symposium has been transmitted to the pages of this volume.

The editors wish to express their appreciation to all the session chairmen, participants, and staff of the "Mario Negri" Institute who contributed to the success of this symposium. We express our gratitude to Zula Melup of the Mario Negri Institute and Virginia B. Martin of Raven Press for their skillful editorial assistance.

THE EDITORS

LIST OF CONTRIBUTORS

BALZAR ALEXANDERSON

Department of Pharmacology, Karolinska Institutet, Stockholm 60, Sweden.

ELLSWORTH L. AMIDON

See D. S. Robinson

*ALLEN BARNETT

Department of Pharmacology, Biological Research, Schering Corporation, Bloomfield, New Jersey 07003.

*G. BARTHOLINI

Research Department, F. Hoffman-La Roche & Co. Ltd., CH-4002 Basel, Switzerland.

DANIEL E. BATES

See L. A. Gottschalk

TRUDY C. M. BEELEN

See E. van der Kleijn

BARRY D. BERGER

See L. Stein

HERMAN BIRCH

See L. A. Gottschalk

*MARIALUISA BOZZA-MARRUBINI

Servizio di Anestesia e Rianimazione "G. Bozza," Reparto di Terapia Intensiva e Rianimazione, Ospedale Maggiore di Milano, Ospedale CA' Granda, 20100 Milan, Italy.

*UTE BRAUSCH

Physiologisches Institut der Universität, Humboldtalle 7, 34 Göttingen, Germany.

* The names preceded by an asterisk are those of the first authors.

***A. BRECKENRIDGE**

Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W. 12, England.

CLAIRE G. CABLE

See L. A. Gottschalk

MARY CARSKADON

See W. C. Dement

***G. B. CASSANO**

Istituto di Clinica Psichiatrica, Università di Pisa, 56100 Pisa, Italy.

PAOLO CASTROGIOVANNI

See G. B. Cassano

SILVANA CONSOLO

See H. Ladinsky

L. CONTI

See G. B. Cassano

***LEONARD COOK**

Department of Pharmacology, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

HANS CORRODI

Department of Pharmacology, University of Göteborg, Göteborg, Sweden.

ARNOLD B. DAVIDSON

Pharmacology Department, Smith Kline and French Laboratories, 15th and Sp. Garden, Philadelphia, Pennsylvania.

***JOSÉ M. R. DELGADO**

Department of Psychiatry, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510.

***WILLIAM C. DEMENT**

Department of Psychiatry, Stanford University School of Medicine, Stanford, California 94305.

***ALBERTO DI MASCIO**

Director of Psychopharmacology, Department of Mental Health, Commonwealth of Massachusetts, Boston State Hospital, Boston, Massachusetts 02124.

CONCEZIO DI ROCCO
See G. F. Rossi

*WALTER B. ESSMAN
Department of Psychology, Queens College of the City University of New York, Flushing, New York 11367.

JOHN W. FIORE
See A. Barnett

H. FIRTH
See I. Oswald

EUGENE W. FLEMING
See L. A. Gottschalk

W. FRIIS
See A. D. Rudzik

KJELL FUXE
Department of Histology, Karolinska Institutet, Solnavägen 1, S-104 01 Stockholm 60, Sweden.

D. M. GALLANT
See R. Guerrero-Figueroa

JOYCE GALLANT
See R. Guerrero-Figueroa

*SILVIO GARATTINI
Director, Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea 62, 20157 Milan, Italy.

*K. FRIEDERICH GEY
F. Hoffmann-La Roche & Co. Ltd., Grenzacherstrasse 124, 4002 Basel, Switzerland.

*LOUIS A. GOTTSCHALK
Department of Psychiatry and Human Behavior, California College of Medicine, University of California, Irvine, California 92664.

AMALIA GUAITANI
Laboratory of Isolated Organ Perfusion.
See S. Garattini

PIETER J. M. GUELEN

See E. van der Kleijn

C. GUERRERO-FIGUEROA

See R. Guerrero-Figueroa

*ROBERTO GUERRERO-FIGUEROA

Department of Psychiatry and Neurology, Tulane University School of Medicine, New Orleans, Louisiana.

W. HAEFELY

See M.-A. Monachon

I. HAIDER

See I. Oswald

H.-D. HENATSCH

See U. Brausch

J. B. HESTER

See A. D. Rudzik

ERIC HODDES

See W. C. Dement

*LEO E. HOLLISTER

Stanford University School of Medicine, Stanford, California 94305.

M. JALFRE

See M.-A. Monachon

*SAMUEL C. KAIM

Alcohol and Drug Dependence Service, Veterans Administration Central Office, Washington, D. C. 20420.

*ANTHONY KALES

Department of Psychiatry, College of Medicine, the Pennsylvania State University, the Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033.

H. KELLER

See G. Bartholini

E. K. KILLAM

See K. F. Killam

*KEITH F. KILLAM

Department of Pharmacology, Division of the Sciences Basic to Medicine, School of Medicine, University of California at Davis, Davis, California 95616.

*HERBERT LADINSKY

Laboratory of the Cholinergic System, Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea 62, 20157 Milan, Italy.

R. LAVERTY

Department of Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine, 725 North Wolfe St., Baltimore, Maryland 21205.

S. A. LEWIS

See I. Oswald

*PETER LIDBRINK

Department of Histology, Karolinska Institutet, Solnavägen 1, S-104 01 Stockholm 60, Sweden.

ODD LINGJAERDE, JR.

Psykiatrisk Institutet, Universitetet i Oslo, Vinderen, Oslo 3, Norway.

*A. LONGONI

Istituto Carlo Erba per Ricerche Terapeutiche, Via C. Imbonati 24, 20159 Milan, Italy

GIULIO MAIRA

See G. F. Rossi

V. MANDELLI

See A. Longoni

FRANCA MARCUCCI

Laboratory of Biochemical Pharmacology.

See S. Garattini

*ADRIANO MARINO

Istituto di Farmacologia, Università di Bari, 70100 Bari, Italy.

M. MATSUZAKI

See K. F. Killam

MARIO MEGLIO

See G. F. Rossi

M.-A. MONACHON

Department of Experimental Medicine, F. Hoffmann-La Roche & Co. Ltd., CH-4002 Basel, Switzerland.

*PAOLO LUCIO MORSELLI

Laboratory of Clinical Pharmacology, Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea 62, 20157 Milan, Italy.

G. B. MUSCETTOLA

See P. L. Morselli

EMILIO MUSSINI

Department of Biochemical Pharmacology.

See S. Garattini

ERNEST P. NOBLE

Neurochemistry Laboratory, Department of Psychiatry and Human Behavior, California College of Medicine, University of California at Irvine, Irvine, California 92664.

LARS OLSON

See P. Lidbrink

M. ORME

See A. Breckenridge

*IAN OSWALD

Senior Lecturer, University Department of Psychiatry, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH 10 5HF, Scotland.

GIUSEPPE PERI

See H. Ladinsky

I. PESSOTTI

Dpto. Genetica, Facult. Medicina, Ribeirao Preto, Brasil.

L. PIERI

See G. Bartholini

*PAOLO PINELLI

Clinica Neurologica, Via Palestro 3, Università di Pavia, Pavia 27100, Italy.

G. F. PLACIDI

See P. L. Morselli

A. PLETSCHER

Research Department, F. Hoffmann-La Roche & Co. Ltd., CH-4002 Basel, Switzerland.

*LOWELL O. RANDALL

Department of Pharmacology, Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

*G. REGGIANI

Clinical Research, F. Hoffmann-La Roche & Co. Ltd., CH-4002 Basel, Switzerland.

*KARL RICKELS

Psychopharmacology Research Unit, Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

*JÜRIG RIEDER

Department of Experimental Medicine, F. Hoffmann-La Roche & Co. Ltd., CH-4002 Basel, Switzerland.

NICO V. M. RIJNTJES

See E. van der Kleijn

MARCELLA RIZZO

See P. L. Morselli

DONALD S. ROBINSON

Department of Pharmacology, University of Vermont College of Medicine, Given Medical Building, Burlington, Vermont 05401.

*GIAN FRANCO ROSSI

Istituto di Neurochirurgia, Università Cattolica del Sacro Cuore, Via Pineta Sacchetti 526, 00168 Rome, Italy.

*ALLAN D. RUDZIK

CNS Research, The Upjohn Company, Kalamazoo, Michigan 49001.

*RUTH RUSHTON

Department of Pharmacology, University College London, Gower St., London WC1E 6BT, England.

MARTIN B. SCHARF

See A. Kales

*MORTON A. SCHWARTZ

Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

ADRIANA SELENATI

See M.-L. Bozza-Marrubini

FOLKE SJÖQVIST

Department of Clinical Pharmacology, the Medical School, 581 85 Linköping, Sweden.

HARVEY SMYTHE

See W. C. Dement

G. A. SNEED

See R. Guerrero-Figueroa

*LARRY STEIN

Wyeth Laboratories, P.O. Box 8299, Philadelphia, Pennsylvania 19101.

HANNAH STEINBERG

Department of Pharmacology, University College London, Gower St., London WC1E 6BT, England.

*LEO H. STERNBACH

Director of Medicinal Chemistry, Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

GORDON E. STOLZOFF

See L. A. Gottschalk

R. N. STRAW

See A. D. Rudzik

BENGT STRINDBERG

See J. Vessman

C. STUDENT

See U. Brausch

ANDERS SUNDWALL

See J. Vessman

J. TAGNEY

See I. Oswald

KOHSI TAKANO

See U. Brausch

A. H. TANG

See A. D. Rudzik

*KENNETH M. TAYLOR

Department of Pharmacology, University of Otago Medical School, Dunedin, New Zealand.

M. TOMKIEWICZ

See R. Rushton

REGINA L. ULIANA

See L. A. Gottschalk

*LUIGI VALZELLI

Department of Neuropsychopharmacology, Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea 62, 20157 Milan, Italy.

*EPO VAN DER KLEIJN

Department of Clinical Pharmacy, Sint Radboud Ziekenhuis, Katholieke Universiteit, Heyendaal, Nijmegen, The Netherlands.

*JÖRGEN VESSMAN

Department of Clinical Pharmacology, the Medical School, 581 85 Linköping, Sweden.

GERNOT WENDT

See J. Rieder

*H. WESSELING

Instituut voor Klinische Farmacologie der Rijksuniversiteit, Bloemsingel 1, Groningen, The Netherlands.

C. DAVID WISE

See L. Stein

VINCENT P. ZARCONE

See W. C. Dement

TON L. B. ZUIDGEEST

See E. van der Kleijn

CONTENTS

xiii List of Contributors

CHEMISTRY AND PHARMACOLOGY

Chemistry

- 1 Chemistry of 1,4-benzodiazepines and some aspects of the structure-activity relationship.
LEO H. STERNBACH

General Pharmacology: Structure-Activity Relationships

- 27 Pharmacological activity of some benzodiazepines and their metabolites.
LOWELL O. RANDALL and BERYL KAPPELL

BIOCHEMISTRY

Pharmacokinetics and Metabolism

- 53 Pathways of metabolism of the benzodiazepines.
MORTON A. SCHWARTZ
- 75 Metabolic studies on benzodiazepines in various animal species.
SILVIO GARATTINI, EMILIO MUSSINI, FRANCA MARCUCCI,
and AMALIA GUAITANI
- 99 Pharmacokinetics and metabolism of the hypnotic nitrazepam.
JÜRIG RIEDER and GERNOT WENDT
- 129 Kinetics of the distribution of ^{14}C -diazepam and its metabolites in various areas of cat brain.
P. L. MORSELLI, G. B. CASSANO, G. F. PLACIDI,
G. B. MUSCETTOLA, and M. RIZZO

- 145 Kinetics of general and regional brain distribution of closely related 7-chloro-1,4-benzodiazepines.
EPPO VAN DER KLEIJN, PIETER J. M. GUELEN, TRUDY C. M. BEELEN, NICO V. M. RIJNTJES, and TON L. B. ZUIDGEEST
- 165 Comparative pharmacokinetics of oxazepam and nortriptyline after single oral doses in man.
JÖRGEN VESSMAN, BALZAR ALEXANDERSON, FOLKE SJÖQVIST, BENGT STRINDBERG, and ANDERS SUNDWALL
- 175 Discussion Summary
A. BRECKENRIDGE
- Neurobiochemistry**
- 177 Subcellular actions of benzodiazepines.
WALTER B. ESSMAN
- 191 The interaction of chlordiazepoxide, diazepam, and nitrazepam with catecholamines and histamine in regions of the rat brain.
K. M. TAYLOR and R. LAVERTY
- 203 The effects of benzodiazepines, meprobamate, and barbiturates on central monoamine neurons.
PETER LIDBRINK, HANS CORRODI, KJELL FUXE, and LARS OLSON
- 225 Effect of benzodiazepines on uptake and efflux of serotonin in human blood platelets *in vitro*.
O. LINGJÆRDE, JR.
- 235 The effect of diazepam on the turnover of cerebral dopamine.
G. BARTHOLINI, H. H. KELLER, L. PIERI, and A. PLETSCHER
- 241 Increase in mouse and rat brain acetylcholine levels by diazepam.
H. LADINSKY, S. CONSOLO, G. PERI, and S. GARATTINI