

DRUG DESIGN

edited by E. J. Ariëns

Volume III



DRUG DESIGN

Edited by E. J. Ariëns

DEPARTMENT OF PHARMACOLOGY
UNIVERSITY OF NIJMEGEN
NIJMEGEN, THE NETHERLANDS

VOLUME III

Y074300



ACADEMIC PRESS New York and London 1972

PRINTED IN THE UNITED STATES OF AMERICA



DRUG DESIGN

Edited by E. J. Ariens

DEPARTMENT OF PHARMACOLOGY
UNIVERSITY OF NIMMGEN
NIMMGEN, THE NETHERLANDS

VOLUME III

COPYRIGHT © 1972, BY ACADEMIC PRESS, INC.
ALL RIGHTS RESERVED.

NO PART OF THIS PUBLICATION MAY BE REPRODUCED OR
TRANSMITTED IN ANY FORM OR BY ANY MEANS, ELECTRONIC
OR MECHANICAL, INCLUDING PHOTOCOPY, RECORDING, OR ANY
INFORMATION STORAGE AND RETRIEVAL SYSTEM, WITHOUT
PERMISSION IN WRITING FROM THE PUBLISHER.

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

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

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 72-127678



PRINTED IN THE UNITED STATES OF AMERICA

List of Contributors

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

- ADRIEN ALBERT (229), Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra, Australia
- A. M. BARRETT (205), Department of Pharmacology, School of Medicine, The University of Leeds, England
- R. BEUKERS (1), Royal Netherlands Fermentation Industries, Delft, The Netherlands
- J. BÜCHI (243), Pharmaceutical Institute of ETH, Zurich, Switzerland
- V. CLAASSEN (189), N. V. Philips-Duphar Research Laboratories, Weesp, The Netherlands
- T. KRALT (189), N. V. Philips-Duphar Research Laboratories, Weesp, The Netherlands
- L. LORAND (415), Biochemistry Division, Department of Chemistry, Northwestern University, Evanston, Illinois
- A. F. MARX (1), Royal Netherlands Fermentation Industries, Delft, The Netherlands
- J. L. G. NILSSON (415), Department of Organic Chemistry, University of Uppsala, Stockholm, Sweden
- X. PERLIA (243), Pharmaceutical Institute of ETH, Zurich, Switzerland
- RALPH B. TURNER (393), Department of Botany and Entomology, New Mexico State University, Las Cruces, New Mexico

A. VERLOOP (133), N.V. Philips-Duphar Research Laboratories, Weesp, The Netherlands

M. H. J. ZUIDWEG (1), Royal Netherlands Fermentation Industries, Delft, The Netherlands

List of Contributors

- Numbers in parentheses indicate the pages on which the authors contributed.
- ADRIEN ALBERT (229), Department of Medical Chemistry, Queen's University, Kingston, Ontario, Canada
- A. M. BARRETT (102), Department of Pharmacology, The University of Leeds, England
- R. BARKERS (1), Royal Netherlands Fermentation Industries, Delft, The Netherlands
- J. BOCH (243), Pharmaceutical Institute of ETH, Zurich, Switzerland
- V. CLAASSEN (189), N.V. Philips-Duphar Research Laboratories, Weesp, The Netherlands
- T. KRALJ (189), N.V. Philips-Duphar Research Laboratories, Weesp, The Netherlands
- I. LORAND (415), Biochemistry Division, Department of Chemistry, Northwestern University, Evanston, Illinois
- A. F. MARK (1), Royal Netherlands Fermentation Industries, Delft, The Netherlands
- J. L. G. NILSSON (415), Department of Organic Chemistry, University of Uppsala, Stockholm, Sweden
- X. PERLA (243), Pharmaceutical Institute of ETH, Zurich, Switzerland
- RALPH B. TURNER (393), Department of Botany and Entomology, New Mexico State University, Las Cruces, New Mexico

Preface

Drug design requires cooperation of researchers in fundamental and applied science. Researchers in the drug industry play a most important role in this field. They must convert the requirements for specific bioactive compounds of medicine, agriculture, and of everyday life into workable principles, recognize the potentials arising from basic studies, and integrate them in research and development programs having definite restricted goals. Hopefully the volumes of this treatise will help by presenting surveys of our knowledge on and insight into the pharmacology and medicinal chemistry of various groups of bioactive compounds and by indicating or outlining research programs that have led to or may lead to specific objectives. Volume IV which will be devoted chiefly to the design of drug application forms is in preparation.

The fact that a number of industrial investigators have been willing to contribute to this series of volumes is greatly appreciated.

E. J. ARIËNS

Contents of Other Volumes

VOLUME I

A General Introduction to the Field of Drug Design

E. J. Ariëns

Quantitative Structure–Activity Relationships in Drug Design

Corwin Hansch

Physicochemical Approaches to the Rational Development of New Drugs

J. K. Seydel

A Molecular Orbital Approach to Quantitative Drug Design

A. J. Wohl

Electronic Aspects of Drug Action

Roger L. Schnaare

The Role of Biopharmaceutics in the Design of Drug Products

John G. Wagner

Significance of Pharmacokinetics for Drug Design and the Planning of Dosage Regimens

J. M. van Rossum

Author Index—Subject Index

VOLUME II

Modulation of Pharmacokinetics by Molecular Manipulation

E. J. Ariëns

Factors in the Design of Reversible and Irreversible Enzyme Inhibitors

Howard J. Schaeffer

The Design of Organophosphate and Carbamate Inhibitors of Cholinesterases

R. D. O'Brien

The Design of Reactivators for Irreversibly Blocked Acetylcholinesterase

I. B. Wilson and Harry C. Froede

Inhibition of Protein Biosynthesis: Its Significance in Drug Design

Arthur P. Grollman

Enzymes and Their Synthesis as a Target for Antibiotic Action

M. H. Richmond

The Rational Design of Antiviral Agents

Arthur P. Grollman and Susan B. Horwitz

Design of Penicillins

A. E. Bird and J. H. C. Nayler

The Design of Peptide Hormone Analogs

J. Rudinger

Recent Advances in the Design of Diuretics

George deStevens

Design of Biologically Active Steroids

G. A. Overbeek, J. van der Vies, and J. de Visser

Rational Elements in the Development of Superior Neuromuscular Blocking Agents

M. Martin-Smith

The Design of Tumor-Inhibitory Alkylating Drugs

J. A. Stock

Author Index—Subject Index

VOLUME IV (*Tentative*)

Parenteral Dosage Forms with Prolonged Action

W. A. Ritschel

Peroral Solid Dosage Forms with Prolonged Action

W. A. Ritschel

Design of Topical Drug Products: Biopharmaceutics

Boyd Poulsen

Design of Topical Drug Products: Pharmaceutics

Martin Katz

The Design of Sunscreen Preparations

Goswin W. van Ham and Wolfgang P. Herzog

Litholytic Agents: Preventive and Curative Drugs for Nephrolithiasis

George Kallistratos

The Design of Biologically Active Nucleosides

Alexander Bloch

The Design of Insecticidal Chlorohydrocarbon Derivatives

G. T. Brooks

Author Index—Subject Index

Chapter 4. Anticoagulants Structurally and Functionally Related to Vitamin K

T. Kishi and Y. Goto

I. Introduction	189
II. Mode of Action of Vitamin K	191
III. Biological Activity of Vitamin K Analogs	192
IV. The Structure of Compounds with Vitamin K Activity	193
V. The Structure of Compounds with Anticoagulant Activity	198
References	201

Contents

Chapter 4. Design of β -Blocking Drugs

<i>List of Contributors</i>	ix
<i>Preface</i>	xi
<i>Contents of Other Volumes</i>	xiii

Chapter 1. Microbial Conversion as a Tool in the Preparation of Drugs

R. Beukers, A. F. Marx, and M. H. J. Zuidweg

I. Introduction	3
II. Practical Aspects of Microbial Transformations	5
III. Some Theoretical Aspects of Microbial Transformations	12
IV. Conversions by Microorganisms	34
References	117

Chapter 2. The Use of Linear Free Energy Parameters and Other Experimental Constants in Structure-Activity Studies

A. Verloop

I. Introduction	133
II. Parameters Used in Structure-Activity Studies	139
III. The Multiparameter Approach to Structure-Activity Relationships	160
IV. Interpretation of Regression Equations	167
V. Application of the Hansch Approach	175
References	182

Chapter 3. Anticoagulants Structurally and Functionally Related to Vitamin K

T. Kralt and V. Claassen

I. Introduction	189
II. Mode of Action of Vitamin K	191
III. Biological Activity of Vitamin K Analogs	192
IV. The Structure of Compounds with Vitamin K Activity	193
V. The Structure of Compounds with Anticoagulant Activity	198
References	201

Chapter 4. Design of β -Blocking Drugs

A. M. Barrett

I. Introduction	205
II. Characteristics of β -Adrenoceptor Antagonists	211
III. Structure-Activity Relationships in Arylethanolamines	213
IV. Other Phenylethanolamine Derivatives	215
V. Structure-Activity Relationships in Aryloxypropanolamines	216
VI. Structure-Activity Relationships in Selective β -Adrenoceptor Antagonists	219
VII. Other Properties in Relation to β -Blockade	222
VIII. Summary	226
References	262

Chapter 5. The Design of Biologically Active Acridines

Adrien Albert

I. Introduction: Ionization and Antibacterial Action	229
II. Binding to Nucleic Acids: Intercalation and Chemotherapy	231
III. Prevention of Binding to Nucleic Acids: Pharmacodynamics	240
IV. Conclusion	241
References	241

Chapter 6. The Design of Local Anesthetics

J. Büchi and X. Perliq

I. Introduction	244
II. General Considerations on the Development of New Drugs	245
III. The Classical Procedures for the Development of Local Anesthetics	246
IV. Rational Methods for the Development of Local Anesthetics	306
References	381

Chapter 7. Design of Insect Chemosterilants*Ralph B. Turner*

I. Introduction	393
II. Desirable Characteristics of Chemosterilants	395
III. Methods of Evaluating Chemosterilants	396
IV. Mechanism of Action	398
V. Some Unexplored Areas of Research	411
References	412

Chapter 8. Molecular Approach for Designing Inhibitors to Enzymes Involved in Blood Clotting*L. Lorand and J. L. G. Nilsson*

I. Background Information	415
II. Thrombin	419
III. Fibrinoligase	431
IV. Conclusion	443
References	445

<i>Author Index</i>	449
<i>Subject Index</i>	475

Chapter 1 Microbial Conversion as a Tool in the Preparation of Drugs

R. Beukers, A. F. Marx, and M. H. J. Zuidweg

I. Introduction	3
II. Practical Aspects of Microbial Transformations	5
A. Requirements	5
B. Selection of the Organism	7
1. Random Screening	7
2. Parallel Systems	7
3. Interference with Normal Metabolism	7
4. Enrichment Procedures	8
5. Mixed Cultures	8
C. Large-Scale Conversions	8
1. 11 α -Hydroxylation	8
2. 11 β -Hydroxylation	9
3. 16 α -Hydroxylation	10
4. Introduction of Double Bonds in Some Steroids	10
5. Synthesis of Compound-S 17-Acetate	11
6. Formation of 6-Aminopenicillanic Acid	11
7. Synthesis of Sorbose from Sorbitol	12
III. Some Theoretical Aspects of Microbial Transformations	12
A. Conversion of Uncommon Substrates	12
B. Interference with Metabolic Pathways	13
1. Interference with Biotransformations	13
2. Interference with Biosynthesis	17
3. Interference with Regulation Mechanisms	17
C. Specificity of Enzyme Reactions	18
1. Rate of Conversion Dependent on Structure of the Substrate	20
2. Type of Conversion Dependent on Structure of the Substrate	21
3. Same Substance Converted Differently by Different Organisms	21
D. Conversions by Cell-Free Systems	23
1. Acyl Side Chain Transferase	23

2. Halogen Peroxidase	23
3. Transpeptidase	24
4. β -Tyrosinase	24
E. Biochemical Studies	25
1. Introduction	25
2. Reactions Involving Oxygen	26
3. Reactions Involving Hydrogen	32
IV. Conversions by Microorganisms	34
A. Oxidation	34
1. Hydroxylation	34
2. Epoxidation	58
3. Oxidation of Alcohols to Aldehydes or Ketones	60
4. Oxidation to Carboxylic Acids	62
5. Oxidation of Ketones to Esters and Lactones	66
6. Oxidation of Amino Groups	68
7. Oxidation of Sulfides	69
8. Oxidative Degradation	70
9. Formation of Double Bonds by Dehydrogenation	72
B. Reduction	75
1. Reduction of Aldehydes, Ketones, or Acids to Alcohols	75
2. Formation of Amines by Reduction	81
3. Reduction of Hydroxyl Groups	83
4. Reduction of Halogens	85
5. Reduction of Double Bonds	86
6. Reduction of Hydroperoxides	89
C. Esterification	90
1. Carboxylation	90
2. N-Acetylation	91
3. Phosphorylation	92
D. Glycosylation	94
E. Hydrolysis	95
1. Esters	95
2. Amides	96
3. Lactones	97
4. Glycosides	98
5. Epoxides	98
6. Sulfoxides	99
7. Chlorinated Acids	99
F. Addition	101
G. Formation of Peptide Bonds	102
H. Amination	104
I. Deamination	105
J. Decarboxylation	106
K. Dehydration	107
L. Demethylation	108
1. O-Demethylation	108
2. N-Demethylation	110
M. Isomerization	111

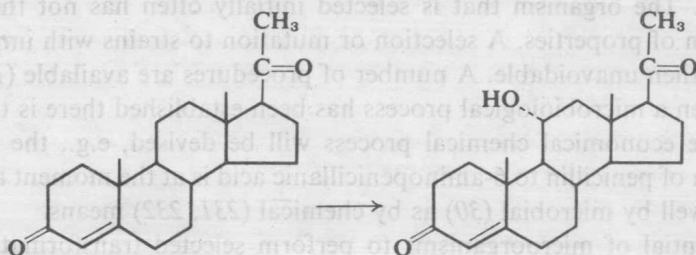
N. Miscellaneous Transformations	113
1. Wagner-Meerwein Rearrangement	113
2. D-Homoannulation	114
3. Cyclization of Unsaturated Fatty Acids	114
4. Condensation	115
5. Some Complex Transformations	115
References	117

I. Introduction

In the course of a program designed to study microbial transformations of steroids and sterols, it was discovered that the triterpenoid acid, eburicoic acid, was converted by the fungus *Glomerella fusarioides* to 3,4-seco- $\Delta^{8,24(28)}$ -eburicadien-4-ol-3,21-dioic acid, a new compound with antibacterial properties (251).

In the course of a routine screening procedure several microorganisms were found to oxidize the 4-methyl group of Miracil D. A preferred microorganism is *Aspergillus sclerotiorum*. Conversion products were the 4-hydroxymethyl analog (Hycanthone), the 4-carboxaldehyde and the corresponding carboxylic acid (359).*

The quotations above are from only two of a large number of reports that illustrate the use of microorganisms in the preparation of new compounds with biological activity. Such publications have appeared since 1952, when Peterson and Murray discovered that a strain of the fungus *Rhizopus arrhizus* could be used to convert progesterone into 11α -hydroxyprogesterone in a 50% yield (336). From the latter substance cortisone may be synthesized in



good yield. The introduction of an 11α -hydroxyl group is chemically very difficult. The synthesis of cortisone used at that time started with substances with a 12-oxygen function, cholic acid or hecogenine (113), and required many reaction steps with a moderate overall yield.

The discovery of Peterson and Murray has initiated an extensive screening

* Copyright (1966) by the American Chemical Society. Reprinted by permission of the copyright owner.

for other microorganisms with similar activity. At the moment the mold *Rhizopus nigricans* is used for this hydroxylation with a yield of over 90%.

Screening programs have since been extended to obtain other valuable microbial conversions leading to products already known or to new compounds with useful biological activity. A series of papers dealing with the conversion of 19-nortestosterone may serve as an illustration of a study to discover new drugs (43, 116-120, 257).

The utilization of microorganisms to carry out a certain transformation may have decisive advantages when compared with the chemical methods.

Microbial transformations, which are essentially enzyme reactions, are very selective in nature, often specific and well suited to obtain special conformations. A microbial process, if available, can be superior to a chemical one when a modification of only one of several similar substituents is required or when a stereospecific conversion is wanted. The number of reaction steps may be much smaller and in some cases a combination of two or more reactions can be performed by the same organism. The conversion takes place under very mild conditions and may have a high yield.

Chemical processes, on the other hand, are as a rule easier to handle and require less complicated equipment. The fermentation technique is quite expensive, implying the necessity of a high yield of conversion and a minimal production of side products. The concentration of the substrate, for the same reason, is bound to a certain minimal limit.

The way from the discovery of an organism suitable to carry out the desired transformation to an industrial process can be very long and tedious. Most cases never even reach the pilot plant, mainly because the process is not economical. The organism that is selected initially often has not the right combination of properties. A selection or mutation to strains with improved qualities is then unavoidable. A number of procedures are available (153).

Even when a microbiological process has been established there is the risk that a more economical chemical process will be devised, e.g., the partial degradation of penicillin to 6-aminopenicillanic acid is at the moment accomplished as well by microbial (30) as by chemical (231, 232) means.

The potential of microorganisms to perform selected transformations is almost unlimited. No wonder the use of microbial systems to achieve desired changes has a very long history. Records dating from 3,000 B.C. are available to show that ancient civilizations, unknowingly, made use of yeasts to convert the sugar moiety of certain plant materials into ethanol in the production of intoxicating liquors. The scientific explanation of these processes had to wait till 1857, when Pasteur published his famous paper on the nature of fermentations (330).

Following this discovery, attempts to obtain desirable changes in substrate molecules have been made by many investigators.

Boutroux in 1880 succeeded in a conversion of glucose into gluconic acid (46), Brown obtained propionic acid from *n*-propanol, and fructose from mannitol (52). In 1896 Bertrand discovered the important conversion of sorbitol into sorbose (37) and in 1898 the formation of dihydroxyacetone from glycerol (38, 39). Most of these conversions are still being applied on an industrial scale. Numerous microbial transformations have since been described (464).

The discovery of the antibiotics initiated a rapid development of the fermentation industry. When it was then found that in certain cases microorganisms could be used to accomplish valuable transformations the application on large scale proved feasible.

This chapter will deal with those microbial transformations that have been used in the preparation of drugs or closely related substances. It will be impossible to give a complete compilation. The most important or interesting conversions will be mentioned, arranged according to the chemical type of the reaction (464), and illustrated by some examples and recent publications. Only those reactions will be considered that represent a relatively small change in the substrate molecule. The product of the conversion must have been isolated and identified. This implies that hypothetical intermediates in degradative or biosynthetic pathways will not be mentioned.

A number of reviews on microbial conversions have been included in the list of references (9, 71, 74, 145, 197, 222, 223, 298, 349, 420, 425, 459, 500, 501, 505).

II. Practical Aspects of Microbial Transformations

A. REQUIREMENTS

A microbial transformation proceeds as a result of the catalytic action of the biocatalysts, i.e., the enzymes. In many cases the combined enzyme activities of a microorganism lead to a complete breakdown of the substrate. An organism is suited to yield a particular product if two requirements are fulfilled: (a) the presence of the enzyme or enzymes catalyzing the desired transformation and, (b) the absence or suppression of the activity of enzymes catalyzing further conversion of the product. Various possibilities exist to prevent the unwanted reactions: inhibition of certain enzymes by special agents, chemical modification of the substrate or mutation of the organism. Examples of each possibility will be given in Section III, B.

The majority of enzymes catalyzing transformations are found inside the cell or bound to the outer membrane. This applies in particular for those enzymes that possess a requirement for a cofactor, i.e., enzymes catalyzing