

THE ALKALOIDS

Chemistry and Pharmacology

Edited by
Arnold Brossi

Founding Editor
R. H. F. Manske

VOLUME XXI

THE ALKALOIDS

Chemistry and Pharmacology

Edited by
Arnold Brossi
National Institutes of Health
Bethesda, Maryland

Founding Editor
R. H. F. Manske

VOLUME XXI

1983



ACADEMIC PRESS

A Subsidiary of Harcourt Brace Jovanovich, Publishers

New York • London

Paris • San Diego • San Francisco • São Paulo • Sydney • Tokyo • Toronto

COPYRIGHT © 1983, 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 7DX

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 50-5522

ISBN 0-12-469521-3

PRINTED IN THE UNITED STATES OF AMERICA

83 84 85 86 9 8 7 6 5 4 3 2 1

LIST OF CONTRIBUTORS

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

- TADASHI ARAI (55), Department of Antibiotics, Research Institute for Chemobiodynamics, Chiba University, Chiba, Japan
- JAN BERGMAN (29), Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden
- JUN-CHAO CAI* (101), School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706
- *MICHAEL A. COLLINS (329), Department of Biochemistry and Biophysics, Loyola University of Chicago, Stritch School of Medicine, Maywood, Illinois 60153
- EDDA GÖSSINGER (139), Institut für Organische Chemie, Universität Wien, Vienna, Austria
- KOERT GERZON (1), Department of Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana 46223
- C. RICHARD HUTCHINSON (101), School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706
- AKINORI KUBO (55), Department of Organic Chemistry, Meiji College of Pharmacy, Tokyo, Japan
- JAN LUNDSTRÖM (255), Astra Pharmaceuticals, Södertälje, Sweden and Department of Pharmacognosy, Faculty of Pharmacy, Uppsala University, Uppsala, Sweden
- GORDON H. SVOBODA (1), Indianapolis, Indiana 46226
- BERNHARD WITKOP (139), National Institutes of Health, Bethesda, Maryland 20205

*Present address: Department of Medicinal Chemistry, Shanghai Institute of Materia Medica, Academia Sinica, Shanghai, 200031, People's Republic of China.

PREFACE

Twenty volumes of *The Alkaloids* have appeared, sixteen of which were edited by its founder, the late R. H. F. Manske, and four by R. G. A. Rodrigo. Devoted to reviews of nitrogen-containing plant constituents, *The Alkaloids* has been received with great interest by scientists investigating the botany, chemistry, pharmacology, characterization, biosynthesis, taxonomy, and medical uses of plant alkaloids. This editor does not intend to alter the policy or appearance of a periodical of high scientific quality that is indispensable to experts in the field.

The chapters devoted to simple isoquinoline alkaloids and quinazolinocarboline alkaloids, organized in the traditional manner, represent updated reviews on two important groups of plant alkaloids. The chapters on camptothecines and acridone alkaloids focus on two groups of plant alkaloids that have attracted attention in recent years as antitumor agents. To broaden its scope, however, future contributions will focus not only on plant alkaloids, but on chemically related, nitrogen-containing substances originating from such other sources as mammals, amphibians, fish, insects, microorganisms, and oceanic plants. This is illustrated here with reviews on amphibious alkaloids, mammalian alkaloids, and isoquinolinequinones from actinomycetes and sponges. In addition to covering all aspects of the recent chemistry of this group of substances, the chapter on amphibious alkaloids presents in detail the biochemical and pharmacological properties of these interesting toxins. It is expected that the broadened scope of *The Alkaloids* will not adversely affect its objectives, but will rather enhance its quality through contributions of interest to a wider scientific audience. The positive response of the scientific community at large to the planned changes is most gratifying.

The editor is very pleased to present as contributors here and in future volumes a group of internationally recognized experts in the field.

Arnold Brossi

CONTENTS

LIST OF CONTRIBUTORS	ix
PREFACE	xi
CONTENTS OF PREVIOUS VOLUMES	xiii

Chapter 1. Acridone Alkaloids: Experimental Antitumor Activity of Acronycine

KOERT GERZON AND GORDON H. SVOBODA

I. Historical Introduction	1
II. Physical and Chemical Properties	4
III. Structure of Acronycine: Principal Syntheses	5
IV. Experimental Antitumor Activity of Acronycine	7
V. Structure-Activity Relationships (SAR)	11
VI. Mammalian Metabolism	13
VII. Preclinical Studies of Acronycine	16
VIII. Mechanism of Action	18
IX. Summary and Conclusions	22
Appendix	23
Addendum	24
References	26

Chapter 2. The Quinazolinocarboline Alkaloids

JAN BERGMAN

I. Introduction and Nomenclature	29
II. Occurrence	35
III. Structure and Synthesis	36
IV. Biosynthesis	48
V. Pharmacological Properties of Quinazolinocarboline Alkaloids and Synthetic Analogs	49
References	52

Chapter 3. Isoquinolinequinones from Actinomycetes and Sponges

TADASHI ARAI AND AKINORI KUBO

I. Introduction and Occurrence	56
II. Saframycin-Type Antibiotics	57
III. Renieramycin-Type Antibiotics	71
IV. Naphthyridinomycin-Type Antibiotics	75
V. Mimosamycin-Type Antibiotics	78
VI. Biological Activity	89
Addendum	96
References	98

Chapter 4. Camptothecin

JUN-CHAO CAI AND C. RICHARD HUTCHINSON

I. Introduction	101
II. Total Synthesis	104
III. Biogenesis	118
IV. Medicinal Chemistry	123
References	135

Chapter 5. Amphibian Alkaloids

BERNHARD WITKOP AND EDDA GÖSSINGER

I. Introduction	139
II. Location and Function of Amphibious Venoms: Steroidal Alkaloids, Tetrodotoxin	141
III. Spiropiperidines, <i>cis</i> -Decahydroquinolines, and Octahydroindolizidines	168
IV. Neurotoxins, Receptors, and Ion Transport	219
V. Epilogue	236
References	237
Addendum	248

Chapter 6. Simple Isoquinoline Alkaloids

JAN LUNDSTRÖM

I. Introduction	255
II. Simple Isoquinoline Alkaloids	256
III. 1-Phenyl-, 4-Phenyl-, and <i>N</i> -Benzyl-Substituted Simple Isoquinoline Alkaloids	303
IV. Biogenesis	312
V. Biological Effects	318
References	321

Chapter 7. Mammalian Alkaloids

MICHAEL A. COLLINS

I. Introduction	329
II. Chemical Considerations	332
III. Analytical Separation and Detection of Mammalian Alkaloids	335
IV. Production of 1,2,3,4-Tetrahydroisoquinolines <i>in Vitro</i>	339
V. Tetrahydroisoquinolines in Human and Animal Models	341
VI. Mammalian β -Carboline Formation	343
VII. Alternative Modes of Mammalian Alkaloid Formation	344
VIII. Metabolic Studies of Mammalian Alkaloids	346
IX. Effects of Mammalian Alkaloids on Biochemical Processes	349
X. Physiological and Behavioral Effects of Mammalian Alkaloids	350
XI. Summary	352
References	353
INDEX	359

CONTENTS OF PREVIOUS VOLUMES

Contents of Volume I (1950)

edited by R. H. F. Manske and H. L. Holmes

CHAPTER

1. Sources of Alkaloids and Their Isolation BY R. H. F. MANSKE	1
2. Alkaloids in the Plant BY W. O. JAMES	15
3. The Pyrrolidine Alkaloids BY LEO MARION	91
4. <i>Senecio</i> Alkaloids BY NELSON J. LEONARD	107
5. The Pyridine Alkaloids BY LEO MARION	165
6. The Chemistry of the Tropane Alkaloids BY H. L. HOLMES	271
7. The <i>Strychnos</i> Alkaloids BY H. L. HOLMES	375

Contents of Volume II (1952)

edited by R. H. F. Manske and H. L. Holmes

8.I. The Morphine Alkaloids I BY H. L. HOLMES	1
8.II. The Morphine Alkaloids II BY H. L. HOLMES AND (IN PART) GILBERT STORK	161
9. Sinomenine BY H. L. HOLMES	219
10. Colchicine BY J. W. COOK AND J. D. LOUDON	261
11. Alkaloids of the Amaryllidaceae BY J. W. COOK AND J. D. LOUDON	331
12. Acridine Alkaloids BY J. R. PRICE	353
13. The Indole Alkaloids BY LEO MARION	369
14. The <i>Erythrina</i> Alkaloids BY LEO MARION	499
15. The <i>Strychnos</i> Alkaloids. Part II BY H. L. HOLMES	513

Contents of Volume III (1953)

edited by R. H. F. Manske and H. L. Holmes

16. The Chemistry of the <i>Cinchona</i> Alkaloids BY RICHARD B. TURNER AND R. B. WOODWARD	1
17. Quinoline Alkaloids Other Than Those of <i>Cinchona</i> BY H. T. OPENSHAW	65
18. The Quinazoline Alkaloids BY H. T. OPENSHAW	101
19. Lupine Alkaloids BY NELSON J. LEONARD	119
20. The Imidazole Alkaloids BY A. R. BATTERSBY AND H. T. OPENSHAW	201
21. The Chemistry of <i>Solanum</i> and <i>Veratrum</i> Alkaloids BY V. PRELOG AND O. JEGER	247
22. β -Phenethylamines BY L. RETI	313
23. Ephredra Bases BY L. RETI	339
24. The <i>Ipecac</i> Alkaloids BY MAURICE-MARIE JANOT	363

*Contents of Volume IV (1954)**edited by R. H. F. Manske and H. L. Holmes*

CHAPTER

25. The Biosynthesis of Isoquinolines BY R. H. F. MANSKE	1
26. Simple Isoquinoline Alkaloids BY L. RETI	7
27. <i>Cactus</i> Alkaloids BY L. RETI	23
28. The Benzylisoquinoline Alkaloids BY ALFRED BURGER	29
29. The <i>Protoberberine</i> Alkaloids BY R. H. F. MANSKE AND WALTER R. ASHFORD	77
30. The Aporphine Alkaloids BY R. H. F. MANSKE	119
31. The Protopine Alkaloids BY R. H. F. MANSKE	147
32. Phthalideisoquinoline Alkaloids BY JAROSLAV STANĚK AND R. H. F. MANSKE	167
33. Bisbenzylisoquinoline Alkaloids BY MARSHALL KULKA	199
34. The Cularine Alkaloids BY R. H. F. MANSKE	249
35. α -Naphthaphenanthridine Alkaloids BY R. H. F. MANSKE	253
36. The <i>Erythrophleum</i> Alkaloids BY G. DALMA	265
37. The <i>Aconitum</i> and <i>Delphinium</i> Alkaloids BY E. S. STERN	275

*Contents of Volume V (1955)**edited by R. H. F. Manske*

38. Narcotics and Analgesics BY HUGO KRUEGER	1
39. Cardioactive Alkaloids BY E. L. MCCAWLEY	79
40. Respiratory Stimulants BY MICHAEL J. DALLEMAGNE	109
41. Antimalarials BY L. H. SCHMIDT	141
42. Uterine Stimulants BY A. K. REYNOLDS	163
43. Alkaloids as Local Anesthetics BY THOMAS P. CARNEY	211
44. Pressor Alkaloids BY K. K. CHEN	229
45. Mydriatic Alkaloids BY H. R. ING	243
46. Curare-like Effects BY L. E. CRAIG	259
47. The <i>Lycopodium</i> Alkaloids BY R. H. F. MANSKE	265
48. Mirror Alkaloids of Unknown Structure BY R. H. F. MANSKE	301

*Contents of Volume VI (1960)**edited by R. H. F. Manske*

1. Alkaloids in the Plant BY K. MOTHEs	1
2. The Pyrrolidine Alkaloids BY LEO MARION	31
3. <i>Senecio</i> Alkaloids BY NELSON J. LEONARD	35
4. The Pyridine Alkaloids BY LEO MARION	123
5. The Tropane Alkaloids BY G. FODOR	145
6. The <i>Strychnos</i> Alkaloids BY J. B. HENDRICKSON	179
7. The Morphine Alkaloids BY GILBERT STORK	219
8. Colchicine and Related Compounds BY W. C. WILDMAN	247
9. Alkaloids of the Amaryllidaceae BY W. C. WILDMAN	289

Contents of Volume VII (1960)

edited by R. H. F. Manske and H. L. Holmes

CHAPTER

10. The Indole Alkaloids BY J. E. SAXTON	1
11. The <i>Erythrina</i> Alkaloids BY V. BOEKELHEIDE	201
12. Quinoline Alkaloids Other Than Those of <i>Cinchona</i> BY H. T. OPENSHAW	229
13. The Quinazoline Alkaloids BY H. T. OPENSHAW	247
14. Lupine Alkaloids BY NELSON J. LEONARD	253
15. Steroid Alkaloids: The <i>Holarrhena</i> Group BY O. JEGER AND V. PRELOG	319
16. Steroid Alkaloids: The <i>Solanum</i> Group BY V. PRELOG AND O. JEGER	343
17. Steroid Alkaloids: <i>Veratrum</i> Group BY O. JEGER AND V. PRELOG	363
18. The Ipecac Alkaloids BY R. H. F. MANSKE	419
19. Isoquinoline Alkaloids BY R. H. F. MANSKE	423
20. Phthalideisoquinoline Alkaloids BY JAROSLAV STANĚK	433
21. Bisbenzylisoquinoline Alkaloids BY MARSHALL KULKA	439
22. The Diterpenoid Alkaloids from <i>Aconitum</i> , <i>Delphinium</i> , and <i>Garrya</i> Species BY E. S. STERN	473
23. The Lycopodium Alkaloids BY R. H. F. MANSKE	505
24. Minor Alkaloids of Unknown Structure BY R. H. F. MANSKE	509

Contents of Volume VIII (1965)

edited by R. H. F. Manske and H. L. Holmes

1. The Simple Bases BY J. E. SAXTON	1
2. Alkaloids of the Calabar Bean BY E. COXWORTH	27
3. The Carboline Alkaloids BY R. H. F. MANSKE	47
4. The Quinazolinocarbolines BY R. H. F. MANSKE	55
5. Alkaloids of <i>Mitragyna</i> and <i>Orouparia</i> Species BY J. E. SAXTON	59
6. Alkaloids of <i>Gelsemium</i> Species BY J. E. SAXTON	93
7. Alkaloids of <i>Picralima nitida</i> BY J. E. SAXTON	119
8. Alkaloids of <i>Alstonia</i> Species BY J. E. SAXTON	159
9. The <i>Iboga</i> and <i>Voacanga</i> Alkaloids BY W. I. TAYLOR	203
10. The Chemistry of the 2,2'-Indolylquinuclidine Alkaloids BY W. I. TAYLOR	238
11. The <i>Pentacera</i> s and the Eburnamine (<i>Hunteria</i>)-Vicamine Alkaloids BY W. I. TAYLOR	250
12. The <i>Vinca</i> Alkaloids BY W. I. TAYLOR	272
13. <i>Rauwolfia</i> Alkaloids with Special Reference to the Chemistry of Reserpine BY E. SCHLITTLER	287
14. The Alkaloids of <i>Aspidosperma</i> , <i>Diplorrhyncus</i> , <i>Kopsia</i> , <i>Ochrosia</i> , <i>Pleiocarpa</i> , and Related Genera BY B. GILBERT	336
15. Alkaloids of Calabash Curare and <i>Strychnos</i> Species BY A. R. BATTERSBY AND H. F. HODSON	515
16. The Alkaloids of Calycanthaceae BY R. H. F. MANSKE	581
17. <i>Strychnos</i> Alkaloids BY G. F. SMITH	592
18. Alkaloids of <i>Haplophyton cimicidum</i> BY J. E. SAXTON	673

CHAPTER

19. The Alkaloids of <i>Geissospermum</i> Species BY R. H. F. MANSKE AND W. ASHLEY HARRISON	679
20. Alkaloids of <i>Pseudocinchona</i> and <i>Yohimbe</i> BY R. H. F. MANSKE	694
21. The Ergot Alkaloids BY S. STOLL AND A. HOFMANN	726
22. The Ajmaline-Sarpagine Alkaloids BY W. I. TAYLOR	789

Contents of Volume IX (1967)

edited by R. H. F. Manske and H. L. Holmes

1. The Aporphine Alkaloids BY MAURICE SHAMMA	1
2. The Protoberberine Alkaloids BY P. W. JEFFS	41
3. Phthalideisoquinoline Alkaloids BY JAROSLAV STANĚK	117
4. Bisbenzylisoquinoline and Related Alkaloids BY M. CURCUMELLI-RODOSTAMO AND MARSHALL KULKA	133
5. Lupine Alkaloids BY FERDINAND BOHLMANN AND DIETER SCHUMANN	175
6. Quinoline Alkaloids Other Than Those of <i>Cinchona</i> BY H. T. OPENSHAW	223
7. The Tropane Alkaloids BY G. FODOR	269
8. Steroid Alkaloids: Alkaloids of Apocynaceae and Buxaceae BY V. ČERNÝ AND F. ŠORM	305
9. The Steroid Alkaloids: The <i>Salamandra</i> Group BY GERHARD HABERMEHL	427
10. <i>Nuphar</i> Alkaloids BY J. T. WRÓBEL	441
11. The Mesembrine Alkaloids BY A. POPELAK AND G. LETTENBAUER	467
12. The <i>Erythrina</i> Alkaloids BY RICHARD K. HILL	483
13. <i>Tylophora</i> Alkaloids BY T. R. GOVINDACHARI	517
14. The <i>Galbulimima</i> Alkaloids BY E. RITCHIE AND W. C. TAYLOR	529
15. The <i>Stemona</i> Alkaloids BY O. E. EDWARDS	545

Contents of Volume X (1967)

edited by R. H. F. Manske and H. L. Holmes

1. Steroid Alkaloids: The <i>Solanum</i> Group BY KLAUS SCHREIBER	1
2. The Steroid Alkaloids: The <i>Veratrum</i> Group BY S. MORRIS KUPCHAN AND ARNOLD W. BY	193
3. <i>Erythrophleum</i> Alkaloids BY ROBERT B. MORIN	287
4. The <i>Lycopodium</i> Alkaloids BY D. B. MACLEAN	306
5. Alkaloids of the Calabar Bean BY B. ROBINSON	383
6. The Benzylisoquinoline Alkaloids BY VENANCIO DEULOFEU, JORGE COMIN, AND MARCELO J. VERNENGO	402
7. The Cularine Alkaloids BY R. H. F. MANSKE	463
8. Papaveraceae Alkaloids BY R. H. F. MANSKE	467
9. α -Naphthaphenanthridine Alkaloids BY R. H. F. MANSKE	485
10. The Simple Indole Bases BY J. E. SAXTON	491
11. Alkaloids of <i>Picralima nitida</i> BY J. E. SAXTON	501
12. Alkaloids of <i>Mitragyna</i> and <i>Ouorouparia</i> Species BY J. E. SAXTON	521
13. Alkaloids Unclassified and of Unknown Structure BY R. H. F. MANSKE	545
14. The <i>Taxus</i> Alkaloids BY B. LYTHGOE	597

Contents of Volume XI (1968)

edited by R. H. F. Manske and H. L. Holmes

CHAPTER

1. The Distribution of Indole Alkaloids in Plants BY V. SNIIEKUS	1
2. The Ajmaline-Sarpagine Alkaloids BY W. I. TAYLOR	41
3. The 2,2-Indolylquinuclidine Alkaloids BY W. I. TAYLOR	73
4. The <i>Iboga</i> and <i>Voacanga</i> Alkaloids BY W. I. TAYLOR	79
5. The <i>Vinca</i> Alkaloids BY W. I. TAYLOR	99
6. The Eburnamine-Vincamine Alkaloids BY W. I. TAYLOR	125
7. <i>Yohimbine</i> and Related Alkaloids BY H. J. MONTEIRO	145
8. Alkaloids of Calabash Curare and <i>Strychnos</i> Species BY A. R. BATTERSBY AND H. F. HODSON	189
9. The Alkaloids of <i>Aspidosperma</i> , <i>Ochrosia</i> , <i>Plejacarpa</i> , <i>Melodinus</i> , and Related Genera BY B. GILBERT	205
10. The Amaryllidaceae Alkaloids BY W. C. WILDMAN	307
11. Colchicine and Related Compounds BY W. C. WILDMAN AND B. A. PURSEY	407
12. The Pyridine Alkaloids BY W. A. AYER AND T. E. HABGOOD	459

Contents of Volume XII (1970)

edited by R. H. F. Manske and H. L. Holmes

The Diterpene Alkaloids: General Introduction BY S. W. PELLETIER AND L. H. KEITH	xv
1. Diterpene Alkaloids from <i>Aconitum</i> , <i>Delphinium</i> , and <i>Garrya</i> Species: The C ₁₉ -Diterpene Alkaloids BY S. W. PELLETIER AND L. H. KEITH	2
2. Diterpene Alkaloids from <i>Aconitum</i> , <i>Delphinium</i> , and <i>Garrya</i> Species: The C ₂₀ -Diterpene Alkaloids BY S. W. PELLETIER AND L. H. KEITH	136
3. Alkaloids of <i>Alstonia</i> Species BY J. E. SAXTON	207
4. <i>Senecio</i> Alkaloids BY FRANK L. WARREN	246
5. Papaveraceae Alkaloids BY F. ŠANTAVÝ	333
6. Alkaloids Unclassified and of Unknown Structure BY R. H. F. MANSKE	455
7. The Forensic Chemistry of Alkaloids BY E. G. C. CLARKE	514

Contents of Volume XIII (1971)

edited by R. H. F. Manske and H. L. Holmes

1. The Morphine Alkaloids BY K. W. BENTLEY	1
2. The Spirobenzylisoquinoline Alkaloids BY MAURICE SHAMMA	165
3. The <i>Ipecac</i> Alkaloids BY A. BROSSI, S. TEITEL, AND G. V. PARRY	189
4. Alkaloids of the Calabar Bean BY B. ROBINSON	213
5. The <i>Galbulimima</i> Alkaloids BY E. RITCHIE AND W. C. TAYLOR	227
6. The Carbazole Alkaloids BY R. S. KAPIL	273
7. Bisbenzylisoquinoline and Related Alkaloids BY M. CURCUMELLI-RODOSTAMO	303
8. The Tropane Alkaloids BY G. FODOR	351
9. Alkaloids Unclassified and of Unknown Structure BY R. H. F. MANSKE	397

*Contents of Volume XIV (1973)**edited by R. H. F. Manske and H. L. Holmes*

CHAPTER

1. Steroid Alkaloids: The <i>Veratrum</i> and <i>Buxus</i> Groups BY J. TOMKO AND Z. VOTICKÝ	1
2. Oxindole Alkaloids BY JASJIT S. BINDRA	83
3. Alkaloids of <i>Mitragyna</i> and Related Genera BY J. E. SAXTON	123
4. Alkaloids of <i>Picralima</i> and <i>Alstonia</i> Species BY J. E. SAXTON	157
5. The <i>Cinchona</i> Alkaloids BY M. R. USKOKOVIĆ AND G. GRETHE	181
6. The Oxaporphine Alkaloids BY MAURICE SHAMMA AND R. L. CASTENSON	225
7. Phenethylisoquinoline Alkaloids BY TETSUJI KAMETANI AND MASUO KOIZUMI	265
8. <i>Elaeocarpus</i> Alkaloids BY S. R. JOHNS AND J. A. LAMBERTON	325
9. The <i>Lycopodium</i> Alkaloids BY D. B. MACLEAN	347
10. The Cancentrine Alkaloids BY RUSSELL RODRIGO	407
11. The <i>Securinega</i> Alkaloids BY V. ŠNIECKUS	425
12. Alkaloids Unclassified and of Unknown Structure BY R. H. F. MANSKE	507

*Contents of Volume XV (1975)**edited by R. H. F. Manske and H. L. Holmes*

1. The Ergot Alkaloids BY P. A. STADLER AND P. STUTZ	1
2. The Daphniphyllum Alkaloids BY SHOSUKE YAMAMURA AND YOSHIMASA HIRATA	41
3. The Amaryllidaceae Alkaloids BY CLAUDIO FUGANTI	83
4. The Cyclopeptide Alkaloids BY R. TSCHESCHE AND E. U. KAUBMANN	165
5. The Pharmacology and Toxicology of the Papaveraceae Alkaloids BY V. PREININGER	207
6. Alkaloids Unclassified and of Unknown Structure BY R. H. F. MANSKE	263

*Contents of Volume XVI (1977)**edited by R. H. F. Manske and H. L. Holmes*

1. Plant Systematics and Alkaloids BY DAVID S. SIEGLER	1
2. The Tropane Alkaloids BY ROBERT L. CLARKE	83
3. <i>Nuphar</i> Alkaloids BY JERZY T. WRÓBEL	181
4. The Celestraeae Alkaloids BY ROGER M. SMITH	215
5. The Bisbenzylisoquinoline Alkaloids—Occurrence, Structure, and Pharmacology BY M. P. CAVA, K. T. BUCK, AND K. L. STUART	249
6. Synthesis of Bisbenzylisoquinoline Alkaloids BY MAURICE SHAMMA AND VASSIL ST. GEORGIEV	319
7. The Hasuoan Alkaloids BY YASUO INUBŪSHI AND TOSHIRO IBUKA	393
8. The Monoterpene Alkaloids BY GEOFFREY A. CORDELL	431
9. Alkaloids Unclassified and of Unknown Structure BY R. H. F. MANSKE	511

*Contents of Volume XVII (1979)**edited by R. H. F. Manske and H. L. Holmes*

1. The Structure and Synthesis of C ₁₉ -Diterpenoid Alkaloids BY S. WILLIAM PELLETIER AND NARESH V. MODY	1
2. Quinoline Alkaloids Related to Anthranilic Acid BY M. E. GRUNDON	105
3. The <i>Aspidosperma</i> Alkaloids BY GEOFFREY A. CORDELL	199
4. Papaveraceae Alkaloids II BY F. ŠANTAVÝ	385
5. Monoterpene Alkaloid Glycosides BY R. S. KAPIL AND R. T. BROWN	545

*Contents of Volume XVIII (1981)**edited by R. H. F. Manske and R. G. A. Rodrigo*

CHAPTER

1. *Erythrina* and Related Alkaloids BY S. F. DYKE AND S. N. QUESSY 1
2. The Chemistry of C₂₀-Diterpenoid Alkaloids BY S. WILLIAM PELLETIER AND NARESH V. MODY 99
3. The ¹³C-NMR Spectra of Isoquinoline Alkaloids BY D. W. HUGHES AND D. B. MACLEAN 217
4. The Lythraceae Alkaloids BY W. MAREK GOŁĘBIEWSKI AND JERZY T. WRÓBEL 263
5. Microbial and *in Vitro* Enzymic Transformation of Alkaloids BY H. L. HOLLAND . . 323

*Contents of Volume XIX (1981)**edited by R. H. F. Manske and R. G. A. Rodrigo*

1. *Sceletium* Alkaloids BY PETER W. JEFFS 1
2. *Solanum* Steroid Alkaloids BY HELMUT RIPPERGER AND KLAUS SCHREIBER 81
3. Phenanthroindolizidine and Phenanthroquinolizidine Alkaloids BY I. RALPH C. BICK AND WANNIE SINCHAI 193

*Contents of Volume XX (1981)**edited by R. H. F. Manske and R. G. A. Rodrigo*

1. Bisindole Alkaloids BY GEOFFREY A. CORDELL AND J. EDWIN SAXTON 1
2. The Eburnamine-Vincamine Alkaloids BY WERNER DÖPKE 297

— CHAPTER 1 —

ACRIDONE ALKALOIDS: EXPERIMENTAL ANTITUMOR ACTIVITY OF ACRONYCINE

KOERT GERZON

*Department of Pharmacology, Indiana University School of Medicine,
Indianapolis, Indiana*

AND

GORDON H. SVOBODA

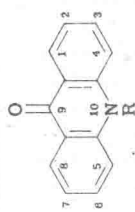
Indianapolis, Indiana

I. Historical Introduction	1
II. Physical and Chemical Properties	4
III. Structure of Acronycine: Principal Syntheses	5
IV. Experimental Antitumor Activity of Acronycine	7
V. Structure-Activity Relationships (SAR)	11
VI. Mammalian Metabolism	13
VII. Preclinical Studies of Acronycine	16
VIII. Mechanism of Action	18
IX. Summary and Conclusions	22
Appendix	23
Addendum	24
References	26

I. Historical Introduction

In the review of acridine alkaloids by J. R. Price, which appeared just 30 years ago in Volume II of this treatise (1), the author recognized a relatively small group of acridone alkaloids present in the bark and leaves of certain Rutaceae species found in northern Australia's tropical rain forests. These acridone alkaloids reported in the period from 1948 to 1952 by Price (1, 2), Lahey (2), and their associates at the Universities of Sydney and Melbourne, include alkylated derivatives of (a) 1,3-dihydroxy-*N*-methylacridone [e.g., acronycine (1, 2) and 1,3-dimethoxy-*N*-methylacridone (1)], of (b) 1,2,3-trihydroxy-*N*-methylacridone (evoxanthine) (1, 3), and (c) 1,2,3,4-tetrahydroxy-*N*-methylacridone (melicopine, melicopidine, and melicopicine) (1, 2), all of which have an *O*-1-methyl substituent in common while differing in the respective pattern of alkylation at *O*-2, *O*-3, and *O*-4. Two further

TABLE I
ACRIDONE ALKALOIDS OF SIX RUTACEAE SPECIES



Alkaloid	Molecular formula	CH ₃ O group(s) location	Methyletheredioxy location	Substituent at N	Rutaceae species ^a	Reference
Acronycine	C ₂₀ H ₁₉ O ₃ N ₁	1 (C-1) ^b	— ^c	—CH ₃	<i>Acr. b.</i>	1, 2, 5, 6
1,3-Dimethoxy-N-methyl-acridone	C ₁₆ H ₁₃ O ₃ N ₁	2 (C-1, C-3)	— ^c	—CH ₃	<i>Acr. b.</i>	1
Evoxanthine	C ₁₆ H ₁₃ O ₄ N ₁	1 (C-1)	C-2, C-3	—CH ₃	<i>Ev. x., Ev. a.</i>	1, 3, 8
Melicopine	C ₁₇ H ₁₃ O ₃ N ₁	2 (C-1, C-2)	C-3, C-4	—CH ₃	<i>Acr. b., Mel. f.</i>	1 ^d
Melicopidine	C ₁₇ H ₁₃ O ₃ N ₁	2 (C-1, C-4)	C-2, C-3	—CH ₃	<i>Act. ac.</i>	3
Melicopine	C ₁₈ H ₁₅ O ₃ N ₁	4 (C-1-4)	— ^c	—CH ₃	<i>Acr. b., Mel. f.</i>	6
Evoxanthidine	C ₁₈ H ₁₅ O ₄ N ₁	1 (C-1)	C-2, C-3	—H	<i>Ev. x.</i>	9
Xanthevodine	C ₁₆ H ₁₃ O ₃ N ₁	2 (C-1, C-4)	C-2, C-3	—H	<i>Acr. b., Mel. f.</i>	1, 3, 8, 11
Noracronycine ^e	C ₁₉ H ₁₇ O ₃ N ₁	—	— ^c	—CH ₃	<i>Ev. x.</i>	1, 3, 11
De-N-methylacronycine	C ₁₆ H ₁₃ O ₃ N ₁	1 (C-1)	— ^c	—H	<i>Gly. p.</i>	4
De-N-methyl/nor-acronycine ^e	C ₁₈ H ₁₅ O ₃ N ₁	—	— ^c	—H	<i>Gly. p.</i>	4
Normelicopine ^e	C ₁₆ H ₁₃ O ₃ N ₁	1 (C-2)	C-3, C-4	—CH ₃	<i>Acr. b.</i>	5, 6
Normelicopidine ^e	C ₁₆ H ₁₃ O ₃ N ₁	1 (C-4)	C-2, C-3	—CH ₃	<i>Acr. b.</i>	5, 6
Normelicopine ^e	C ₁₇ H ₁₇ O ₃ N ₁	3 (C-2-4)	—	—CH ₃	<i>Acr. b.</i>	5, 6

^a Abbreviations for botanical species studied: *Acronychia haueri* Schott = *Acr. b.*; *Evodia xanthoxyloides* F. Muell. = *Ev. x.*; *Evodia alata* F. Muell. = *Ev. a.*; *Acronychia acidula* F. Muell. = *Acr. ac.*; *Melicope fareana* Engl. = *Mel. f.*; and *Glycosmis pentaphylla* (Retz.) Correa. = *Gly. p.*
^b C-1 in the acridone numbering system (see first column) corresponds to C-6 in the acronycine system (see Fig. 1).
^c In acronycine a *gem*-dimethylchromene ring system is located at the C-3—C-4 bond site (Figure 1).
^d References 1, 3, 6, 9, 10 refer to the group of melicope alkaloids.
^e The designation "nor" for de-O-1-methyl analogs of parent alkaloids is the one used in Reference 1.

No analytical data confirming the molecular formulas of these natural products are given, but conversion of the parent natural O-1-methyl product to the nor species under acidic conditions has been reported (1,4).