THE ALKALOIDS

Chemistry and Pharmacology

Edited by
Arnold Brossi

Founding Editor
R. H. F. Manske

VOLUME XXI

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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

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MICHAEL A. COLLINS

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—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

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

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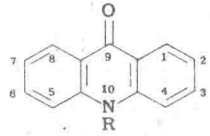
TABLE I

ACRIDONE ALKALOIDS OF SIX RUTACEAE SPECIES



Alkaloid	Molecular formula	CH_3O group(s) location	Methylenedioxy location	Substituent at N	Rutaceae species[a]	Reference
Acronycine	$C_{20}H_{19}O_3N_1$	1 (C-1)[b]	—[c]	$-CH_3$	*Acr. b.*	*1, 2, 5, 6*
1,3-Dimethoxy-*N*-methyl-acridone	$C_{16}H_{15}O_3N_1$	2 (C-1, C-3)	—[c]	$-CH_3$	*Acr. b.*	*1*
Evoxanthine	$C_{16}H_{13}O_4N_1$	1 (C-1)	C-2, C-3	$-CH_3$	*Ev. x., Ev. a.*	*1, 3, 8*
Melicopine	$C_{17}H_{15}O_5N_1$	2 (C-1, C-2)	C-3, C-4	$-CH_3$	*Acr. b., Mel. f.*	*1*[d]
					Act. ac.	*3*
Melicopidine	$C_{17}H_{15}O_5N_1$	2 (C-1, C-4)	C-2, C-3	$-CH_3$	*Acr. b., Mel. f.*	*6*
					Ev. x., Ev. a.	*9*
Melicopicine	$C_{18}H_{19}O_5N_1$	4 (C 1-4)	—[c]	$-CH_3$	*Acr. b., Mel. f.*	*10*
Evoxanthidine	$C_{15}H_{11}O_4N_1$	1 (C-1)	C-2, C-3	$-H$	*Ev. x.*	*1, 3, 8, 11*
Xanthevodine	$C_{16}H_{13}O_5N_1$	2 (C-1, C-4)	C-2, C-3	$-H$	*Ev. x.*	*1, 3, 11*
Noracronycine[e]	$C_{19}H_{17}O_3N_1$	—	—[c]	$-CH_3$	*Gly. p.*	*4*
De-*N*-methylacronycine	$C_{19}H_{17}O_3N_1$	1 (C-1)	—[c]	$-H$	*Gly. p.*	*4*
De-*N*-methylnor-acronycine[e]	$C_{18}H_{15}O_3N_1$	—	—[c]	$-H$	*Gly. p.*	*4*
Normelicopine[e]	$C_{16}H_{13}O_5N_1$[f]	1 (C-2)	C-3, C-4	$-CH_3$	*Acr. b.*	*5, 6*
Normelicopidine[e]	$C_{16}H_{13}O_5N_1$	1 (C-4)	C-2, C-3	$-CH_3$	*Acr. b.*	*5, 6*
Normelicopicine[e]	$C_{17}H_{17}O_5N_1$[f]	3 (C 2-4)	—	$-CH_3$	*Acr. b.*	*5, 6*

[a] Abbreviations for botanical species studied: *Acronychia baueri* 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*.

[f] 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*).