88

Fortschritte der Chemie organischer Naturstoffe

Progress in the Chemistry of Organic Natural Products

Founded by
L. Zechmeister

Edited by
W. Herz, H. Falk,
and G. W. Kirby

SpringerChemistry

SpringerWienNewYork

SpringerWienNewYork

88

Fortschritte der Chemie organischer Naturstoffe

Progress in the Chemistry of Organic Natural Products

Founded by
L. Zechmeister

Edited by
W. Herz, H. Falk,
and G. W. Kirby

Authors:
J. F. Grove, E. Reimann, S. Roy

SpringerWienNewYork

Prof. W. Herz, Department of Chemistry,
The Florida State University, Tallahassee, Florida, U.S.A.

Prof. H. Falk, Institut für Chemie,
Johannes-Kepler-Universität, Linz, Austria

Prof. G. W. Kirby, Chemistry Department,
The University of Glasgow, Glasgow, Scotland

This work is subject to copyright.
All rights are reserved, whether the whole or part of the material is concerned, specifically those of translation, reprinting, re-use of illustrations, broadcasting, reproduction by photocopying machines or similar means, and storage in data banks.

© 2007 Springer-Verlag/Wien
Printed in Austria

SpringerWienNewYork is part of
Springer Science + Business Media
springer.com

Product Liability: The publisher can give no guarantee for the information contained in this book. This also refers to that on drug dosage and application thereof. In each individual case the respective user must check the accuracy of the information given by consulting other pharmaceutical literature. The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Library of Congress Catalog Card Number AC 39-1015

Typesetting: Thomson Press (India) Ltd., Chennai
Printing and binding: Druckerei Theiss GmbH, A-9431 St. Stefan

Printed on acid-free and chlorine-free bleached paper

SPIN: 10975961

With 12 Figures and 1 coloured Plate

ISSN 0071-7886
ISBN-10 3-211-20688-4 SpringerWienNewYork
ISBN-13 978-3-211-20688-1 SpringerWienNewYork

Contents

List of Contributors IX

Synthesis Pathways to *Erythrina* Alkaloids and *Erythrina* Type Compounds
E. Reimann 1

1. Introduction 2

2. Structural Classification of *Erythrina* Alkaloids 4

3. New *Erythrina* Alkaloids 18

4. Biosynthesis of *Erythrina* Alkaloids 18
   4.1. Erythrinane Alkaloids 18
   4.2. Homoerythrinane Alkaloids 20

5. Syntheses of *Erythrina* Alkaloids and *Erythrina* Type Compounds 21
   5.1. Methodical Classification 22
   5.2. Erythrinanes 23
      5.2.1. Final Formation of One Ring 23
         5.2.1.1. Ring C (Route C) 23
            5.2.1.1.1. Cyclization of *N*-Phenethylhydroindole Derivatives (Route C(a)) 23
            5.2.1.1.2. Cyclization of Angulary Arylated Hydroindole Derivatives (Route C(b)) 29
         5.2.1.2. Formation of Ring B (Route B) 32
            5.2.1.2.1. Cyclization of N-substituted C5-Spiroisoquinoline Derivatives (Route B(a)) 32
            5.2.1.2.2. Cyclization of C6-Substituted C5-Spiroisoquinoline Derivatives (Route B(b)) 35
         5.2.1.3. Formation of Ring A (Route A) 35
            5.2.1.3.1. Cycloaddition to Pyrroloisoquinolines (Route A(a)) 35
            5.2.1.3.2. Intramolecular Aldol Condensation of Angularly Substituted Pyrroloisoquinoline (Route A(b)) 37
      5.2.2. Simultaneous Formation of More Than One Ring 38
         5.2.2.1. Simultaneous Formation of Rings B and C (Route B/C) 39

5.2.2.1.1. Cyclization of Secondary Diphenethyl- or (Cycloalkyl)ethyl-phenethylamine Derivatives (Route B/C(a)) . . . 39
5.2.2.1.2. Cyclization of Tertiary Cyclohexyl-ethyl-phenethyl-amide Derivatives (Route B/C(b)) . . . 42
5.2.2.2. Cyclization of N-Substituted 1-Acyldihydroisoquinolinium Derivatives (Route A/B) . . . 44
5.2.2.3. Cyclization of a Highly Functionalized Homoveratrylimide (Route A/B/C) . . . 45
5.3. Homoerythrinanes . . . 45
5.3.1. Biomimetic Routes . . . 47
5.3.2. Final C Ring Formation Starting from N-Substituted Phenylhydroindoles . . . 49
5.3.3. A Ring Formation by [2 + 2] Photocycloaddition to Pyrrolobenzazepines . . . 50
5.3.4. Simultaneous B Ring Formation/C Ring Expansion Starting from Spiro-2-tetralones . . . 52

6. Pharmacology . . . 53

7. Concluding Remarks . . . 55

References . . . 56

The Trichothecenes and Their Biosynthesis

J. F. Grove (†) . . . 63

1. Introduction . . . 63

2. The Trichothecenes . . . 64
2.1. Macrocyclic and Non-Macrocyclic Compounds . . . 64
2.2. Trichothecene Relatives . . . 90
2.3. Sources . . . 96
2.4. Oxygenation Pattern . . . 97

3. Biosynthesis . . . 98
3.1. Simple Trichothecenes . . . 98
3.1.1. Mevalonic Acid to Trichodiene . . . 98
3.1.2. Trichodiene to 12,13-Epoxytrichothecene and Isotrichodermol . . . 101
3.1.3. Further Oxygenation and Esterification of the Trichothecene Nucleus: Biosynthesis of Specific Metabolites . . . 104
3.1.3.1. Trichothecolone . . . 104
3.1.3.2. Vomitoxin and Derivatives . . . 104
3.1.3.3. T-2 Toxin . . . 107
3.1.3.4. Nivalenol and Derivatives . . . 108
3.1.4. Trichothecene Biosynthetic Gene Clusters . . . 108
3.2. Trichoverroids and Macrocyclic Trichothecenes . . . 109
3.3. Trichothecene Relatives . . . 112

References . . . 113

Melanin, Melanogenesis, and Vitiligo
S. Roy . . . 131

1. Melanin . . . 132
   1.1. Introduction . . . 132

2. Chemistry of Melanin . . . 134
   2.1. Isolation and Analysis . . . 134
   2.2. Solubilization . . . 135
   2.3. Protein Content . . . 135
   2.4. Carboxylic and Phenolic Function . . . 136
   2.5. Chemical Degradation . . . 136
      2.5.1. Reductive Methods . . . 136
      2.5.2. Oxidative Methods . . . 137
      2.5.3. Pyrolytic Methods . . . 137
   2.6. Spectroscopic Studies . . . 138
      2.6.1. UV and IR Spectroscopy . . . 138
      2.6.2. NMR Spectroscopy . . . 138
      2.6.3. X-Ray Defraction Study . . . 138
      2.6.4. ESR Study . . . 139
   2.7. Structure of Melanin . . . 139
      2.7.1. Melanin as Homopolymer . . . 139
      2.7.2. Melanin as Poikilopolymer . . . 140
      2.7.3. Melanin as Bipolymer . . . 141
      2.7.4. Biophysical Model of Melanin Structure . . . 141
      2.7.5. Structure of Phaeomelanin . . . 143
   2.8. Synthesis of Melanin . . . 143
      2.8.1. Electrochemical Synthesis . . . 143
      2.8.2. Photochemical Synthesis . . . 145

3. Characteristic Biophysicochemical Properties of Melanin . . . 145
   3.1. Interaction of Melanin with Light . . . 146
      3.1.1. Melanin in UV and Visible Light . . . 146
      3.1.2. Melanin in the Photoprotection of Skin . . . 146
      3.1.3. Melanin as Light Screen in Eyes . . . 147
   3.2. Melanin and Its Redox Function . . . 148
   3.3. Binding Complexation and Medicinal Aspects of Melanin . . . 149
   3.4. Use of Melanin for Defence . . . 150

4. Melanogenesis . . . 150
   4.1. Melanogenesis *in vivo* . . . 150
      4.1.1. Melanocytes . . . 151
      4.1.2. The Characteristics of the Enzyme . . . 152
      4.1.3. Regulation of Melanogenesis . . . 153
         4.1.3.1. Physiological Factors . . . 154
         4.1.3.2. Organic Sulfur Compounds . . . 154
         4.1.3.3. Metal Ions and Other Chemicals . . . 154
         4.1.3.4. Vitamins . . . 154
         4.1.3.5. Hormones . . . 155
         4.1.3.6. Neural Influence . . . 157
         4.1.3.7. Malpighian Cells . . . 157
         4.1.3.8. UV Light . . . 157

4.2. Melanogenesis *in vitro* 157
4.2.1. Enzymatic Melanin Synthesis. 157
4.2.1.1. Rearrangement of Dopachrome. 158
4.2.1.2. Polymerization of DHI 159
4.2.2. Non-Enzymatic Melanin Synthesis: Model Reaction 161
4.2.2.1. Udenfriend System: A Model for Mixed Function Oxidase 161
4.2.2.2. Melanin Formation Under Udenfriend Conditions. 162

5. Vitiligo 164
5.1. Introduction 164
5.2. Melanocytotoxicity: Antimelanocyte-Antibodies Formation. 164
5.2.1. The Immune Hypothesis 165
5.2.2. The Neural Hypothesis 165
5.2.3. The Self-Destruction Hypothesis 165
5.2.4. The Composite Hypothesis 165
5.3. Chemotherapy of Vitiligo 166
5.3.1. Psoralens 166
5.3.2. Psoralen Action and UV Light 166
5.3.3. Psoralen Action on Melanogenesis 167
5.4. Abnormal Biochemical Parameters in Vitiligo 168
5.5. Status of Tryptophan in the Melanogenic System 169
5.6. A Composite Hypothesis on Vitiligo 171

References 171

Author Index 187

Subject Index 201

List of Contributors

Grove, Dr. J. F., 3 Homestead Court, Welwyn Garden City, Herts AL7 4LY, England (deceased)

Reimann, Prof. Dr. E., Department of Pharmacy, Ludwig-Maximilians-Universität, Butenandtstrasse 5–13, 81377 München, Germany,
e-mail: ebrei@cup.uni-muenchen.de

Roy, Dr. S., Institute of Natural Products, 8 J. N. Roy Lane, Kolkata 700006, India,
e-mail: shyamali_radha@yahoo.co.in

Synthesis Pathways to *Erythrina* Alkaloids and *Erythrina* Type Compounds

Eberhard Reimann

Department of Pharmacy,
Ludwig-Maximilians-Universität München, Germany

Contents

1. Introduction 2

2. Structural Classification of *Erythrina* Alkaloids 4

3. New *Erythrina* Alkaloids 18

4. Biosynthesis of *Erythrina* Alkaloids 18
   4.1. Erythrinane Alkaloids 18
   4.2. Homoerythrinane Alkaloids 20

5. Syntheses of *Erythrina* Alkaloids and *Erythrina* Type Compounds 21
   5.1. Methodical Classification 22
   5.2. Erythrinanes 23
      5.2.1. Final Formation of One Ring 23
         5.2.1.1. Ring C (Route C) 23
            5.2.1.1.1. Cyclization of *N*-Phenethylhydroindole Derivatives (Route C(a)) 23
            5.2.1.1.2. Cyclization of Angulary Arylated Hydroindole Derivatives (Route C(b)) 29
         5.2.1.2. Formation of Ring B (Route B) 32
            5.2.1.2.1. Cyclization of N-substituted C5-Spiroisoquinoline Derivatives (Route B(a)) 32
            5.2.1.2.2. Cyclization of C6-Substituted C5-Spiroisoquinoline Derivatives (Route B(b)) 35
         5.2.1.3. Formation of Ring A (Route A) 35
            5.2.1.3.1. Cycloaddition to Pyrroloisoquinolines (Route A(a)) 35
            5.2.1.3.2. Intramolecular Aldol Condensation of Angularly Substituted Pyrroloisoquinoline (Route A(b)) 37
      5.2.2. Simultaneous Formation of More Than One Ring 38
         5.2.2.1. Simultaneous Formation of Rings B and C (Route B/C) 39

5.2.2.1.1. Cyclization of Secondary Diphenethyl- or (Cycloalkyl)ethyl-phenethylamine Derivatives (Route B/C(a)) 39
5.2.2.1.2. Cyclization of Tertiary Cyclohexyl-ethyl-phenethyl-amide Derivatives (Route B/C(b)) 42
5.2.2.2. Cyclization of N-Substituted 1-Acyldihydroisoquinolinium Derivatives (Route A/B) 44
5.2.2.3. Cyclization of a Highly Functionalized Homoveratrylimide (Route A/B/C) 45
5.3. Homoerythrinanes 45
5.3.1. Biomimetic Routes 47
5.3.2. Final C Ring Formation Starting from N-Substituted Phenylhydroindoles 49
5.3.3. A Ring Formation by [2 + 2] Photocycloaddition to Pyrrolobenzazepines 50
5.3.4. Simultaneous B Ring Formation/C Ring Expansion Starting from Spiro-2-tetralones 52
6. Pharmacology 53
7. Concluding Remarks 55
References 56

1. Introduction

The history of erythrina research begins at the end of the 19th century. During the last two decades of that time extracts from species of *Erythrina* have been found to exhibit curare-like neuromuscular blocking activities which are caused by alkaloids occurring therein (*1–4*).

It was Altamirano (*2*), who obtained a silky shining, crystallinic acetate as well as Greshoff (*3*) who already isolated several basic unspecified compounds. Because of their remarkable biological activity he suggested a systematic phytochemical examination of the genus *Erythrina*. But it still has taken at least half a century before this has been realized for the first time by Folkers. He has shown that more than fifty *Erythrina* species – as an example, *E. crista-galli* is shown in Plate 1 – are containing the typical alkaloids exhibiting the same curare-like activity reported earlier (*5*, *6*). Moreover, his group succeeded in isolating the first crystallized erythrinane alkaloid named erythroidine (**14**; Fig. 2) (*7*). Soon after numerous alkaloids have been isolated, *e.g.* erythramine (**8**) (*8*), erythraline (**3**) (*9*), erythratine (**9**) (*10*), erysodine (**6**), erysopine (**4**), and erysovine (**5**) (*11*). Another decade later the fundamental investigations of Prelog

Plate 1. Erythrina crista-galli L (Coral Tree)

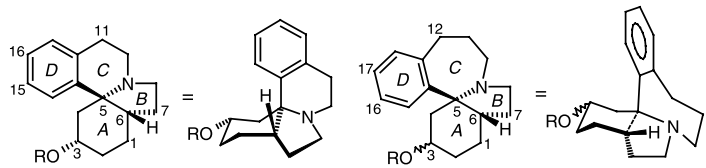


Fig. 1. Stereostructure and atom labeling of the *Erythrina* alkaloid frameworks

(*12*, *13*) and Boekelheide (*14*) have finally led to the correct structural framework of the erythrinane alkaloids (parent compound **1**, Fig. 1).

In the late 1960s ring C-homologues of erythrinane alkaloids have been anticipated from the biosynthetic pathway of certain alkaloids, which are known to be generated from 1-phenethyl-isoquinoline derivatives as precursors (*15*, *16*). Only a short time later such compounds named homoerythrinanes, homoerythrina alkaloids, or schelhammeranes indeed have been found in the plant kingdom (*17*) (parent compound **2**, Fig. 1).

Due to the increasing attraction and rapid extension in this field the *Erythrina* alkaloids have been regularly reviewed concerning occurrence, structure, analytic and spectral properties, biosynthesis, total synthesis, and biological activities covering the literature up to 1997. The most important reviews are cited in Refs. *18–24*.

The present contribution will give a brief classification of the *Erythrina* alkaloids, a compilation of new alkaloids isolated from 1997 to 2004 covering source, structure, analytical/spectral data, a new pathway of their biosynthesis, an overview of all the synthesis strategies hitherto known for the erythrinane alkaloids including several approaches to the homoerythrinane group, and finally a short review of their biological activities.

2. Structural Classification of *Erythrina* Alkaloids

The erythrina-type alkaloids are characterized by their unique tetracyclic spiroamine framework. They are generally classified into two main groups: Alkaloids predominantly possessing a 6-5-6-6-membered indoloisoquinoline core are called erythrinanes and those exhibiting a 6-5-7-6-membered indolobenzazepine skeleton are generally called schelhammeranes or homoerythrinane alkaloids (see Fig. 1).

Depending on the nature of the D ring both groups in turn may be subdivided into aromatic and non-aromatic alkaloids, the latter of which

References, pp. 56–62

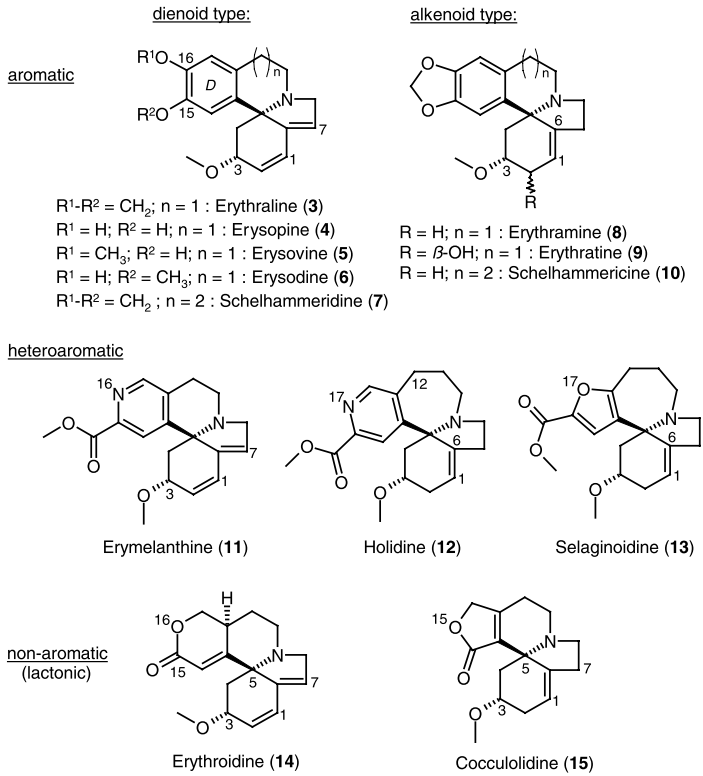


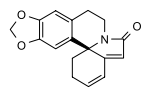
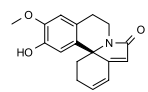
Fig. 2. General classification of *Erythrina* alkaloids: Dienoid and alkenoid type alkaloids and D ring modifications

including ring D oxa-compounds, are usually also called the lactonic alkaloids. In addition, in both series there have been isolated alkaloids containing a pyridyl instead of a phenyl unit, which are known as erymelanthine (**11**) and holidine (**12**) (16-azaerythrinane and 17-aza-homoerythrinane derivatives) belonging to two further different subtypes of these alkaloids (*25*, *26*) (see below and Fig. 2). Several D-*seco*-derivatives in the homoerythrinane group should also be mentioned (see *e.g.* **32**, Table 2).

Finally, the typical position and the number of olefinic bonds in the A and B ring have led to a further subdivision into dienoids and alkenoids in both alkaloid series. The former are characterized by a conjugated diene unit covering C atoms 1, 2, 6, and 7, while the latter possess only one double bond in the 1,6-position (see Fig. 2).

The aromatic erythrinanes and homoerythrinanes as the most important members of the *Erythrina* alkaloids show substitution patterns of

Table 1. New Erythrinane Alkaloids

Nr.	Trivial name(s)/ Formula/Structure	M.p./°C $\pm[\alpha]_D$/° $cm^2 g^{-1}$	IR: $\bar{\nu}/cm^{-1}$ UV: λ_{max}/nm ($\log \varepsilon/mol^{-1} dm^3 cm^{-1}$) MS: m/z	^1H NMR: δ/ppm ^{13}C NMR: δ/ppm	Natural source	Ref.
16	Erythrosotidienone $C_{17}H_{15}NO_3$ (281.31) 	250	2930, 2860, 1740, 1610, 1460, 1440, 1380, 1280–1260, 1160, 1130, 1075, 1040, 975, 960, 860–840, 730, 720, 675, 645, 610, 580	6.02 (d, $J = 10$ Hz, 1-H), 5.94 (s, OCH_2O), 5.72, 6.02 (d, $J = 10$ Hz, 1-H), 5.94 (s, OCH_2O), 5.72 (m, 2-H), 3.63 (t, $J = 1.5$ and 4.5 Hz, 2H, 10-H), 3.27–1.87 (m, 6H)	*E. variegata* *Flowers*	(*33*)
		–	– 281 (5.0), 280 (22.5), 279 (100), 267 (7.5), 265 (7.5), 253 (17.5), 227 (2.5), 226, 199 (15.4), 174 (15.0), 167 (10.0), 133 (5.0), 81 (31.6), 20 (8.0), 77 (5.0), 76 (80.0), 56 (27.3), 55 (42.5)	184.0 (CO), 152.0 (C-16), 152.4 (C-15), 132.0 (C-2), 131.0 (C-1), 129.6 (C-7), 128.3 (C-12), 128.1 (C-13), 114.0 (C-17), 110.1 (C-14), 104.0 (C-6), 102.8 (OCH_2O), 68.1 (C-5), 40.3 (C-10), 32.0 (C-3), 30.4 (C-4), 23.2 (C-11)		
17	Erythromotidienone $C_{18}H_{19}NO_3$ (297.35) 	172	2920, 2880, 1760, 1600, 1450, 1380, 1280–1260, 1250, 1170, 1110, 1075, 1055, 1025, 975, 960, 925, 885, 835, 800, 765, 730, 700	7.32 (dd, $J = 2.5/9.0$ Hz, 16- or 15-H), 7.21 (d, $J = 2.7$ Hz, 14-H), 7.13 (d, $J = 2.3$ Hz, 17-H), 6.62 (s, 7-H), 6.34 (d, $J = 9.6$ Hz, 1-H), 6.02 (dd, $J = 2.5/7.5$ Hz, 2-H), 3.86 and 3.36 (2s, 2 OCH_3), 3.76–1.92 (m, 7H)	*E. variegata* *Flowers*	(*33*)
		–	297 (5), 296 (8), 295 (11), 269 (19), 255 (30), 239 (8), 235 (10), 213 (16), 185 (16) 83, 81 (43)	^{13}C not reported		