

Studies in Natural Products Chemistry

Volume 17

Structure and Chemistry (Part D)

Edited by

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**Studies in
Natural Products Chemistry**

Volume 17

Structure and Chemistry (Part D)

Studies in Natural Products Chemistry
edited by Atta-ur-Rahman

- Vol. 1 Stereoselective Synthesis (Part A)
- Vol. 2 Structure Elucidation (Part A)
- Vol. 3 Stereoselective Synthesis (Part B)
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FOREWORD

The rapid advances in chromatographic procedures, spectroscopic techniques and pharmacological assay methods have resulted in an increasing number of new and interesting natural products being discovered from terrestrial and marine sources. The present volume contains comprehensive reviews on some of the major advances in this field which have taken place in recent years. The reviews include those on novel metabolites from marine gastropods, the chemistry of marine natural products of the halenaquinol family, secondary metabolites from Echinoderms and Bryozoans, triterpenoids and aromatic compounds from medicinal plants, chemistry and activity of sesquiterpenes from the genus *Lactarius*, the chemistry of bile alcohols, antifungal sesquiterpene dialdehydes, annonaceous acetogenins, nargenicin macrolides, lignans and diarylheptanoids. Tropane alkaloids and phenolies formed by root cultures are also reviewed. Articles on natural Diels-Alder type adducts, the use of computer aided overlay for modelling the substrate binding domain of HLADH, applications of ^{17}O NMR spectroscopy to natural product chemistry and the use of biological raw materials in synthesis should also be of interest.

It is hoped that the present volume will continue to meet the standards set by the earlier ones of this series and provide much material of interest to a large number of natural product chemists.

I wish to express my thanks to Dr. M. Saleh Ajaz and Mr. Athar Ata for their assistance in the preparation of the index. I am also grateful to Mr. Wasim Ahmad, Mr. Asif Khan and Mr. Shabbir Ahmad for the typing work and Mr. Mahmood Alam for secretarial assistance.

December 1994

Atta-ur-Rahman
Editor

PREFACE

Since days immemorial natural products have had a profound impact on humankind. They were our earliest sources of drugs, derived from traditional herbal medicines. They reaped havoc on man in the form of toxins that would kill or maim people, either in natural disasters, like outbreaks of red tide or ergotism, or in incidences inflicted by man, as the executions in old Greece or the poisonings of adversaries that were often a means of settling power struggles throughout history. And they enriched human life in the form of spices and fragrances. Last not least, they have led to the development of the science of organic chemistry, which started out as the chemistry of natural products.

Stimulated by important advances in the biological sciences, particularly in the molecular biology of diseases and in the new field of ecology, the last two decades have seen a tremendous renaissance in the field of natural products. We are now accutely aware of the value of the chemical diversity represented by natural products as a source of new leads for bioactive drugs and of the utility of bioactive natural products as tools in dissecting and analyzing life processes at the molecular level. And we are developing an ever keener sense of the importance of natural products in governing the complex relationships of living organisms in our ecosystems. Concomitantly our view of the role of natural products has changed drastically over the years. While at one time they were considered mere waste products of a luxuriating metabolism, the view now prevails that the synthesis of such compounds represents an evolutionary advantage to the producing organism.

With the renewed broad interest in natural products it is most appropriate that a continuing series of publications is dedicated to the topic of natural products chemistry. Professor Atta-Ur-Rahman with his worldwide connections to all the leading natural products chemists of our time is the ideal person for the task of editing this series. He has brought this series to life and has done an outstanding job of sustaining it. The present volume again presents an eclectic mix of articles on many different topics ranging from marine natural products, microbial and plant metabolites all the way to topics like molecular modeling, ^{17}O -NMR spectroscopy or the role of biological raw materials in synthesis. I hope its readers will enjoy this volume as much as I did, and I wish it the same success that its predecessors have enjoyed.

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Structure and Chemistry

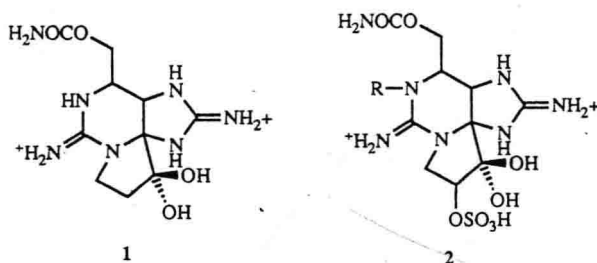
Novel Secondary Metabolites of Marine Gastropods

M. Alam and K.L. Euler

Mollusks have attracted the attention of humans since prehistoric times. People historically have associated certain powers with plants and animals that resembled parts of the human anatomy. Mollusks would be a classical example in that a certain type of power was associated with cowry (anatomical resemblance to female genitalia) and was thought to be transferred to the possessors of cowry. The first written report about mollusks appeared in Aristotle's "History of animals", which contained a detail discussion of Mediterranean mollusks. During the late fourteen and fifteenth centuries the collecting and studying of shells of marine mollusks became hobbies of gentlemen from well-to-do families with interests in natural history.

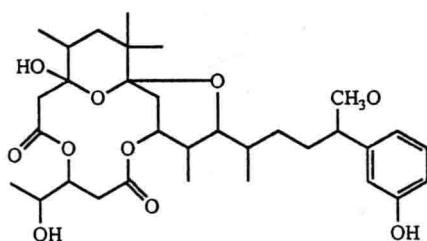
Since the publication of the first book on marine natural products by Professor Scheuer--Chemistry of Marine Natural Products (1) a number of books (2-6) have been published on marine natural products. Similarly, a number of reviews (7-9) dealing with various aspects of the chemistry of marine mollusks have also appeared in the literature. In the present review the authors have attempted to present a summary of the literature dealing with novel compounds from marine mollusks since 1987. For compounds before 1987 the readers are referred to excellent reviews authored by P. Karuso (10) and H. C. Krebs (11).

In order to give readers a broader scope of the novel compounds, examples from all three subclasses of the phylum Mollusca--Prosobranchia, Opisthobranchia and Pulmonata have been selected. During the early seventies the occurrence of a variety of compounds from marine mollusks raised serious questions about their origin. Because gastropods are voracious eaters with virtually every type of feeding habit, it was postulated early on that novel compounds from mollusks may have had their origin in the dietary sources of these invertebrates. One of the earliest reports supporting this hypothesis came from the laboratory of Professor Schantz, who showed that saxitoxin [1] (one of a group of neurotoxins commonly known as paralytic shellfish poisons), which was originally isolated from the mollusk *Saxidomus gigantius*, was actually produced by



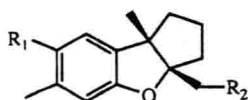
the dinoflagellate *Gonyaulax catenella* (12). Similarly, saxitoxin derivatives commonly known as

gonyautoxins [2] isolated initially from the clam *Mya arenaria* were later determined to be secondary metabolites of another species of *Gonyaulax*-- *G. tamarensis* (= *Alexandrium tamarensis*) (13). The first report linking a brominated secondary metabolite of the sea hare *Aplysia kurodai* with its diet, the red alga *Laurencia* sp., appeared in 1967 (14). Similarly, earlier work from Professor Moore's laboratory (15) reported the isolation of deromoaplysiatoxin (3) from the blue green alga *Lyngbya gracilis*. Debromoaplysiatoxin had been isolated previously from the digestive gland of the sea hare *Stylocheilus longicauda* (16). The presence of 3 in *L. gracilis* again suggested a direct relationship between the diet and novel metabolites of the sea hare.



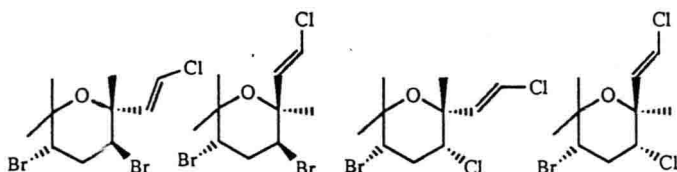
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Herbivorous marine prosobranchs of the genus *Aplysia* feed on red, brown, green or blue-green algae. During the late seventies and early eighties a number of terpenoidal secondary metabolites were isolated from various species of *Aplysia* and were assumed to be accumulated by the mollusks from the dietary sources consisting of red algae (17), brown algae (18-22) and green and blue-green alga (23). During the middle eighties research on the secondary metabolites of various species of *Aplysia* continued to reward researchers with novel compounds. An examination of various species of *Aplysia* for the presence of aromatic compounds resulted in the isolation of aplysin and related compounds [4-8] (24), which were also found to be present in the red alga of *Laurencia* species that was consumed by the sea hare (25, 26). A chemical investigation (27) of



- 4. $R_1 = \text{Br}, R_2 = \text{H}$
- 5. $R_1 = R_2 = \text{H}$
- 6. $R_1 = \text{H}, R_2 = \text{OH}$
- 7. $R_1 = \text{Br}, R_2 = \text{OH}$
- 8. $R_1 = \text{H}, R_2 = \text{Br}$

the mid-gut gland of another *Aplysia* -- *A. kurodai*, collected from Izy -Shimode Beach, Southwest



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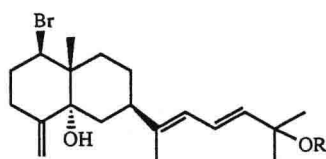
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12

Japan, has resulted in the isolation of four isomeric compounds --aplysiapyranoid A - D [9 -12]. The absolute configuration of aplysiapyranoid B was later established by x-ray crystallography (28)

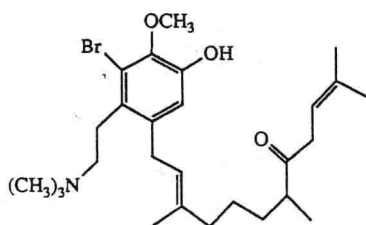
Quite often the type of compound isolated from *Aplysia* species depends on the location from which they were collected, and therefore, on the algae upon which they feed. *A. kurodai* collected from Mei Prefecture of Japan was found to contain an extended diterpene (with a prenylated eudismane skeleton)--aplysiadiol [13] and its methyl derivative [14] (29). It could safely be assumed that a brown alga on which this prosobranch feeds was the actual source of aplysiadiol. Recently a biogenetic type synthesis of 14 has been reported (30).



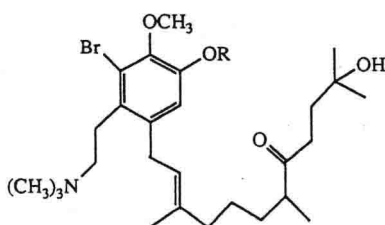
13. R = H

14. R = CH₃

An investigation of the more polar fraction of, presumably, the above mentioned collection of *A. kurodai*, from the Mei Prefecture of Japan resulted in the isolation of three cytotoxic alkaloids --aplaminone [15], neoaplaminone [16] and neoaplaminone sulfate [17] (31). The biogenetic origin



15



16. R = H 17. R = SO₃H

of these alkaloids is still open for discussion. However, they could have been derived from tyrosine or tyramine.

An examination of another collection of *A. kurodai*, presumably from Japan, has resulted in the isolation of aplykurodin A [18] and aplykurodin B [19] (32), which could have been derived from a steroidal precursor, which was degraded by the sea hare to produce aplykurodin A. However, its presence in the dietary source of the sea hare (such as a brown alga) can not be ruled out at the present time.

A bioassay directed fractionation of *A. kurodai* collected from Mei Prefecture in Japan has