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Studies in Natural Products Chemistry

Atta-ur-Rahman, FRS
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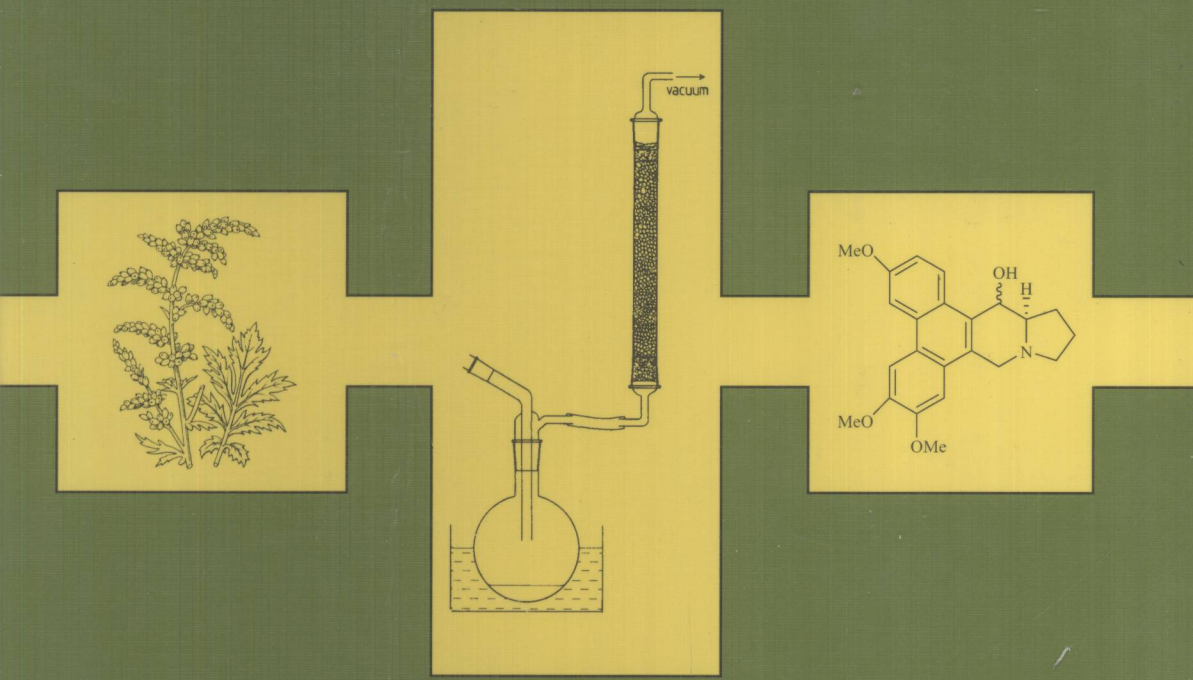

Volume 34

Bioactive Natural Products (Part N)

Studies in Natural Products Chemistry

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Edited by

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edited by Atta-ur-Rahman

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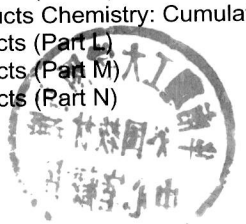

FOREWORD

Nineteen years have passed since Professor Atta-ur-Rahman launched the series "Studies in Natural Products Chemistry" in 1988. At that time when Volume 1 was published, I had the privilege of contributing my review on chiral building blocks of biocatalytic origin. Now I was asked to contribute the Preface to Volume 34.

The most important task of we scientists is to create or add meaningful new knowledge to our own field of science. To do so, we must work hard theoretically or experimentally. This may make it difficult for us to have broad knowledge in all aspects of our research area. However, without broad knowledge, we may not be able to find out and interpret the new results. It is therefore necessary for us to read good review articles. Reviews will give us a lot of knowledge far beyond our own experience. Studying good reviews allows us to extend our experience by assimilating the experience of others.

The present Volume deals with various aspects of bioactive natural products referring to 2,807 references. Everyone can agree that it is not at all easy to examine 2807 references in a short period. By reading this Volume, we can have access to these scientific treasures. Fourteen reviews in this Volume treat diverse and different topics in natural products chemistry - basic ones, medicinally oriented ones, agro-oriented ones, and ecologically oriented ones. They are all good introductions to the specific fields of bioactivities including a timely review on pheromones.

I congratulate Professor Atta-ur-Rahman on his eminent success in securing capable authors, and look forward to studying the future volumes of this series.

Kenji Mori
Emeritus Professor
The University of Tokyo
Japan

PREFACE

The present volume, the 34th in this series, presents frontier reviews on recent developments on bioactive natural products in cutting edge areas by eminent experts in their respective fields. The first three articles describe the chemistry and antitumor activity of tylophorine-related alkaloids, antitumor and anti-metastatic actions of various natural products, and stilbenes and their analogues as antineoplastic agents. These articles by US (Lee & coworkers), Japanese (Kimura) and Italian (Orsini & coworker) groups provide a wealth of interesting information in this important area. Certain enzymes, the "Diels–Alderases", catalyse the Diels-Alder reaction in biological systems. The article by Ichihara reviews the recent developments in this area. Lipids play an essential role as biomolecules in living cells. The article by Demetzos & coworker describes the chemistry, biological role and applications of membrane lipids as drug carriers. Cytokinins are plant hormones which are involved in the regulation of a number of plant development processes. The article by Galuszka & coworkers presents an overview of recent researches on genes and corresponding proteins involved in cytokinin biosynthesis, modification, degradation and transactions. Another review by Alonso-Amelot on high altitude plants describes the chemistry of their acclimation and adaptation which in turns influences the nature of bioactive compounds present. (+)-Biotin has received considerable attention in recent years because of its significant biological activities for human health and nutrition. The review by Seki describes the industrially viable synthetic approaches which can allow efficient access to (+)-biotin. Another review by Zárate and coworkers presents the applications of biotechnology, especially recombinant DNA technology, as a tool to control biosynthesis and accumulation of plant natural products. The article by Velázquez & coworkers describes the role of insect and mammal pheromones. The article presents evidence relating to the vomeronasal organ (VNO), human pheromones and their possible role in influencing human behavior. A comprehensive account of the occurrences, chemistry, biological roles and activities of stilbenoids is presented by Xiao and coworkers. Plant tissue culture studies for micropropagation, transformation and production of useful secondary metabolites is described in the review by Yoshimatsu. The review by Borne & coworkers presents the chemical and pharmacological properties of isoquinuclidines. Kogan and coworkers have contributed a review on hyaluronic acid, a linear polysaccharose which is present in almost all biological fluids and tissues and plays a critically important role in maintaining the viscoelastic properties required for lubrication of joints. Its degradation leads to increased wear of joints, causing arthritic pain. The fundamental role of hyaluronic acid and its involvement in various pathological conditions and inflammatory processes are reviewed.

This volume is expected to be another useful addition to this important series of volumes on natural product chemistry which now covers over 25,000 pages and is generally acknowledged to be the leading series of volumes in Natural Product Chemistry.

We would like to express our thanks to Mr. Liaquat Raza Siddiqui for his assistance in the preparation of the index. We are also grateful to Mr. Wasim Ahmad for composing and typing and to Mr. Mahmood Alam for the editorial assistance.

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Bioactive Natural Products

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ANTITUMOR AGENTS 248. CHEMISTRY AND ANTITUMOR ACTIVITY OF TYLOPHORINE-RELATED ALKALOIDS

LINYI WEI, ARNOLD BROSSI, SUSAN L. MORRIS-NATSCHKE, KENNETH F. BASTOW AND KUO-HSIUNG LEE*

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Abstract: Tylophorine (**1**) and related phenanthroindolizidine alkaloids, also known as *tylophora* alkaloids, have been isolated principally from plants of the family *Asclepiadaceae*, including members of the genus *Tylophora*. Because of their profound cytotoxicity, these compounds have been targets of synthetic modification. Evaluation of (+)-(*S*)-tylophorine and its analogs in the National Cancer Institute's antitumor screen showed a uniform and potent inhibitory effect on the cell growth ($GI_{50} \cong 10^{-8}$ M) against all 60 cancer cell lines, with notable selectivity toward several refractory cell lines, including melanoma and lung tumor cell lines. However, to date, this compound class has not been successfully developed for clinical use in cancer due to the CNS toxicity of tylocrebrine reported in 1966. Most recently, tylophorine analogs have shown significant inhibitory effects on NF-κB mediated transcription, a unique mode of antitumor action that differs from those of the current known antitumor drugs. This recent discovery points to a great potential for developing tylophorine derivatives as a new antitumor drug class. Motivation is high in many research laboratories and a renewed and expedited exploration of *tylophora* alkaloids is anticipated. Therefore, this article contains a comprehensive review of isolation, total synthesis, antitumor activity and structure-activity relationship (SAR) correlations of tylophorine-related alkaloids.

INTRODUCTION

Several plants containing *tylophora* alkaloids have been used for the treatment of various diseases in East Asian countries. Traditional Chinese medicine uses extracts from the dried bark of silk trees for the treatment of pain, insomnia, asthma, and muscle strains, as well as for stimulation of blood circulation. In addition, the flowers of silk trees are used to make tea to treat sore throat and the roots of *Tylophora atrofolliculata* have long been used to treat rheumatism [1]. In Taiwan, *Fiscus septica,* a small evergreen tree growing in the tropical and subtropical regions is used as a folk medicine to treat ulcers, colds, fever, fungal infections, asthma, allergic and rhinitis and for its antitumor and anti-inflammatory effects [2, 3]. In India, *Tylophora asthmatica* is used as an emetic [4].

Tylophora alkaloids have long been targeted for synthetic modification because of their profound cytotoxicity [5-9]. However, the clinical failure of tylocrebrine (**2**) in 1966 due to central nervous system toxicity manifested by ataxia and disorientation discouraged further consideration of these alkaloids for drug development [4]. Encouragingly, recent studies have demonstrated that tylophorine analogs have unique mode(s) of action different from those of current known anticancer drugs. One of these actions is an inhibitory effect on NF-κB binding-mediated transcription [10]. NF-κB is known as one mechanism of resistance to chemotherapy because of an antiapoptotic role [11, 12]. Due to significant advances in the field of molecular biology over the past decade, tylophorine compounds have significant potential to be developed into a new class of chemotherapeutic drug, especially for refractory cancers. Motivation is high in many research laboratories and the development of *tylophora* alkaloids as novel anticancer drugs is anticipated.

The objective of this review article is to provide comprehensive information about isolation, total synthesis, antitumor activity, and structure-activity relationship (SAR) correlations of tylophorine-related alkaloids in order to facilitate the anticipated drug discovery and development of the tylophora class.

ISOLATION OF TYLOPHORA ALKALOIDS FROM MEDICINAL PLANTS

Tylophorine (**1**) and its analogs, the phenanthroindolizidine alkaloids also referred to as *tylophora* alkaloids, have been isolated primarily from plants of the family *Asclepiadaceae* [13-16], Fig. (**1**), including members of the genus *Tylophora*, *Vincetoxicum, Pergularia*, *Cynanchum*, but also from *Hypoestes verticillaris* (Acanthaceae) [17], *Cryptocarya phyllostemmon* (Lauraceae) [18], *Ficus hispida* and *F. septica* (Moraceae) [2, 19]. The isolations of these alkaloids are summarized in Table 1. The most significant phenanthroindolizidine alkaloids are tylophorine (**1**), tylocrebrine (**2**), antofine (**3**), and tylophorinine (**4**), Fig. (**2**).