Book Reviews

Pharmaco Chemistry Library, Vol. 22. The Chemistry and Pharmacology of Taxol® and its Derivatives. By Vittorio Farina, Boehringer-Ingelheim Pharmaceuticals. Elsevier Science, Tarrytown, NY. 1995. ix + 339 pp. 16.5 × 24 cm. $350.00. ISBN 0-444-81771-9.

As stated in the Introduction, the book is intended "for medicinal chemists, to stimulate further research in the area and to provide the necessary information to start a research program in the area." The book accomplishes what it promises and is an excellent source for the wealth of information available for the taxanes. Therefore, it will serve as an excellent reference book not only for newcomers to the field but also for those who have been involved in paclitaxel research for some time. There is, of course, some overlap with books on the same topic published earlier, but it also contains information not provided in these earlier publications. It focuses specifically on medicinal chemistry, and it was published at a later date than the other books.

The quality of the reviews is excellent. All authors participating in this book project have been major contributors to taxane research. The material is organized very well, and the texts are easy to read and understand. Information is appropriately presented in tables when series of compounds are discussed.

The quality of the layout is very good. All chapters have a unified style of text and chemical drawings.

The first two chapters are written by G. Appendino. The first one is entitled: "Naturally occurring taxoids". Rather than providing a comprehensive list of all taxanes that have been discovered until now, Appendino has wisely chosen to cover only the different structural types of taxoids that are known and their functionality patterns. The discussion on the botanical description of the yew tree should prove to be very valuable to chemists since it sheds a critical light on the confusion in the phytochemical literature with regard to the systematic classification of the *Taxus* genus. Also addressed in this chapter are the numbering of the taxoids and their trivial names. This is of importance because different numbering and names for the same compounds have appeared in the literature. Biogenesis, simple general chemical reactivities, including the photochemistry of the taxoids, and bioactivities other than cytotoxic properties of the taxoids are also covered in the first chapter.

The second chapter, "The structural elucidation of the taxoids", covers the spectroscopic characterization of the taxoids by MS, UV/CD, NMR, and X-ray crystallography. The ^{1}H and ^{13}C NMR data of 19 representative taxoids are displayed within very large drawings of the chemical structures and are very easy to read. Of great value are also the detailed discussions of the chemical shift changes at positions C1 to C20 after structural modifications have been made to the taxoids.

In the third chapter, entitled: "Paclitaxel (Taxol®) Formulation and Prodrugs", D. M. Vyas provides an excellent overview of "formulation related issues, stemming from the current clinical formulation" of paclitaxel with Cremophor EL®. Early formulation studies at the NCI and pharmaceutical and patient care issues of the current formulation are covered. The main emphasis of this chapter is a critical review of prodrug strategies to the paclitaxel drug delivery problem. Esters, carbonates, and phosphate ester derivatives as prodrugs are reviewed and liposome formulations are discussed.

M. Wright and colleagues provide a review on "Metabolism and pharmacology of taxoids" in the fourth chapter. The distinctly different metabolic fates of paclitaxel and docetaxel are reviewed, including species differences of metabolic pathways. The major metabolic inactivation of both clinically used taxoids, paclitaxel and docetaxel, is due to hydroxylation by cytochrome P-450 enzymes. Part of the chapter is, therefore, devoted to a review of the isozymes that have been found responsible for the hydroxylation reactions, including studies carried out in the presence of substrates, enzyme inducers, and inhibitors. The section on the pharmacological disposition of the taxoids ends with a very interesting discussion concerning potential clinical implications of drug metabolism and drug disposition.

The fifth chapter by Chen and Farina on chemistry and structure−activity relationships is the longest one in the book and provides a wealth of information on the major aspects of taxoid chemistry, as it relates to the diterpene core structure of the taxoids. Following the numbering system of the diterpene moiety, chemical reactions are discussed starting with C1 and ending with C14. Major topics are as follows: general chemical reactivities, hydrolysis reactions, deoxygenations, ring cleavages, rearrangements, and photochemistry. The structure−activity relationship section starts with a brief overview of the biological assays used for evaluation of paclitaxel analogues: *in vitro* tubulin assays, *in vitro* and *in vivo* cytotoxicity assays. This discussion is followed by a critical review of the results of the most important paclitaxel structure−activity relationship studies.

In the sixth chapter, J. Kant provides an excellent concise review of the most important synthesis method for the preparation of the C13 phenylisoserine side of paclitaxel and docetaxel, as well as methods for attachment of this group to the baccatin III diterpene moiety. The chapter also includes a representative selection of the most important SAR studies of the C13 side chain. The chapter ends with a discussion of conformational studies of paclitaxel, docetaxel, and related analogues, based on X-ray analyses and high-field NMR studies.

The last chapter of the book (chapter 7) by Landino and MacDonald covers "The biochemical pharmacology of Taxol® and mechanism of resistance". The authors provide an easy to read concise overview of the current knowledge of paclitaxel's biochemical effects. The chapter starts out with a general description of the

tubulin−microtubule system, its biological functions,and its response to tubulin-binding anticancer agents. The basis for the therapeutic effects of paclitaxel is discussed, including issues of selective cytotoxicity, cellular tubulin concentration, tubulin isotype sensitivity, and microtubule bundling. The section on the mechanisms of paclitaxel resistance reviews research into P-glycoprotein-mediated paclitaxel-resistance, its potential effects on bcl-2, and paclitaxel resistance due to alteration of α- and β-tubulin. The review ends with a discussion of paclitaxel's effect on murine macrophages.

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Medicinal and Aromatic Plants−Industrial Profiles, Vol. 1. Valerian−The Genus *Valeriana*. Edited by Peter J. Houghton. Harwood Academic Publishers, The Netherlands. 1997. xi + 142 pp. 17 × 24.5 cm. $75.00. ISBN 90-5702-170-6.

This is the first in a series of volumes on the principal medicinal herbs of commerce. The editor-in-chief of the series is Roland Hardman, and a further 29 volumes, each with their own editor, are in progress. The prospect of thorough literature reviews on such a broad range of medicinal plants is an admirable one, and is much needed in the field.

This particular volume comprises six chapters, each with a different author(s). The volume opens with an introductory chapter by Dweck that examines some botanical aspects of the genus and the commercial plants. A chapter on the chemistry of *Valeriana* by Houghton is followed by a discussion of the pharmacology and therapeutics of *Valeriana* by Hölzl and of the cultivation by the herb by Bernáth. The final two chapters describe the quality assurance issues and the preparation of the crude drug (Woerdenbag, Bos, and Scheffer), and the volume closes with an interesting summary of the range of products containing *Valeriana* species that are sold commercially worldwide (Foss and Houghton). There is also a useful index. The literature is covered to about the Fall of 1996.

In many ways, valerian is a very difficult monograph because, as is mentioned in each chapter, the active principle is (supposedly) not known. Implications for the active principle(s) to be the valepotriates (a standardized preparation of which is sold in Germany), valerenic acid, baldrinal, the essential oil, the volatile oil, etc. are made based on the available literature. However, for reasons that are not clear, a significant patent describing the active principle of the ammoniated tincture of valerian was ignored. U.S. Patent 5,506,268 discusses the determination that isovaleramide is the anxiolytic component of the tincture and, thus, that isovaleric acid is the probable active constituent of the normal root preparation. The commercial implications of such a discovery are quite apparent. "Isovaleramide" and "anxiolytic" are not indexed in the volume.

The whole answer to the issue of the active ingredient is presented (unknowingly!) on page 3 of the book in two *almost* concurrent sentences, "...there is a growing body of evidence to show that the odour of valerian alone is sufficient to have a sedative effect." and "It is now known that the major part of the odour is due to the isovaleric acid released by enzyme hydrolysis from some of the compounds present in the plant."

Although this is a very serious omission from a book of this type, there is also another series of errors: for the most part, the editing of the chapters is poor. A few examples will suffice. Frequently, the genus name *Valeriana* is not italicized, while other words are; there are typographical errors, words omitted, and typesetting errors; on page 18 an "echo" is heard *before* the initial retort; and the last phrase on p 17 is not a sentence! None of the "Alkaloids" in Figure 12 on page 42 are alkaloids, and the compounds **104** and **105** (p 43) are misnamed. Quite surprisingly, there is absolutely no consistency of style to the references in Chapter 2. The other chapters are better than this, although one can find errors of some description on almost every page. I would suspect that if subsequent volumes in the series perpetuate the same attributes of this volume, the series will not be well received. Many issues relate to a lack of proofreading and editing, and thus, perhaps other editors will raise the standard of the series. It has certainly not started very auspiciously.

In summary, this is a flawed volume, which nevertheless contains much useful information and is well referenced. It is recommended for libraries hoping to keep up with the burgeoning literature on herbal products, although unfortunately its relatively high price (50¢/page!) will keep it out of the hands of the individual scientist.

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Medicinal Natural Products: A Biosynthetic Approach. By Paul M. Dewick (University of Nottingham, U.K.). John Wiley & Sons, Ltd., West Sussex, England. 1997. ix + 466 pp. 19 × 25 cm. Hardback, $160.00. ISBN 0-4719-7477-3. Paperback, $59.90. ISBN 0-4719-7478-1.

It is refreshing to read a current natural products textbook that embraces a biosynthetic approach to instruction, which allows for the application of basic chemical principles. This text is invaluable for both undergraduate and graduate students with interests in natural products chemistry. It provides a comprehensive examination of natural products used in medicine from a biosynthetic point of view, rather than the more usual natural product class or activity viewpoint. There is an extensive use of biosynthetic schemes and mechanisms including detailed mechanistic explanations as annotations and outline discussions in the text. Exten-

sive cross-referencing has been implemented to accentuate links and similarities. Extended detailed information is provided as short monographs, covering sources, production methods, principal components, drug use, mode of action, and synthetic and semisynthetic derivatives, as appropriate. The book includes a vast array of natural products currently used in medicine.

The first chapter (better suited as a forward by author), "How to Use This Book", is subdivided under the headings "The Subject", "The Aim", "The Approach", "The Topics", "Be Selective", "To learn or To Understand", "Conventions Regarding Acids, Bases, and Ions", and "Some Common Abbreviations". This chapter focuses on Dewick's mission and design of the textbook. As Dewick states, "Rationalization based on mechanistic reasoning is paramount. The sequences themselves are not important; the mechanistic explanations for the processes used are the essence."

The remaining six chapters logically follow traditional biosynthetic textbook flow, and including the following: Chapter 2, "Secondary Metabolism: The Building Blocks and Construction Mechanisms"; Chapter 3, "The Acetate Pathway: Fatty Acids and Polyketides"; Chapter 4, "The Shikimate Pathway: Aromatic Amino Acids and Phenylpropanoids"; Chapter 5, "The Mevalonate Pathway: Terpenoids and Steroids"; Chapter 6, "Alkaloids"; Chapter 7, "Peptides, Proteins, and Other Amino Acid Derivatives"; and Chapter 8, "Carbohydrates". The structures and biosynthetic pathways are extremely well illustrated and organized within each chapter. Each chapter ends with a Further Reading Section, containing a total of over 400 references to the primary and secondary literature. The Table of Contents and the Index are superbly fashioned and sufficiently detailed and are easy to use and follow. The cost of the paperback is extremely reasonable for students (and faculty!). The textbook is essentially error-free (except for a few structural and typographical oversights) and is highly recomended for use in the classroom, equally suited as either a supplemental or a stand-alone textbook.

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Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds, Vol. IV. Heterocyclic Compounds, Part B. Five-membered Heterocyclic Compounds: Alkaloids, Dyes, Pigments. Edited by M. Sainsbury. Elsevier Science, V.B., Amsterdam, The Netherlands. 1997. xvi + 509 pp. 15 × 22.5 cm. $324.25. ISBN 0-444-827587.

This volume comprises eight chapters that update the corresponding volume in the series on the basis of information published in the period from 1985 to the end of 1995. The chapters are devoted to the following: pyrrolidine alkaloids, pyrrolizidine alkaloids (both by R. J. Robins, 19 and 47 pages), indole alkaloids (G. W. Gribble, 96 pages), Amaryllidaceae alkaloids (J. R. Lewis, 85 pages), tropane alkaloids (G. Fodor, 26 pages), pyrrole pigments (K. M. Smith, 81 pages), indigo group dyes (M. Sainsbury, 22 pages), and cyanine dyes and related compounds (G. Bach and S. Dähne, 99 pages). There is an index of compounds.

The editor is to be congratulated on assembling a group of exceptional authors for these chapters, each of whom is an authoritative expert in their respective field. When considering one word to describe this book I thought of either "terse" or "succinct". The former has a somewhat negative connotation these days, although its original derivation refers to being polished and refined. Succinct would be applied in the context of clarity of presentation of a vast amount of information. So perhaps both words apply. For this is indeed a polished volume of briefly presented information covering some very large areas of alkaloid and synthetic chemistry. The styles and contents of the various alkaloid chapters are reasonably equivalent. Each of these chapters deals with the isolation of new alkaloids, and most of the alkaloid chapters deal with recent synthetic strategies (not the indole alkaloid chapter). Fodor also covers the biosynthesis of tropanes. As one might imagine, very little attention is paid to the biological activity of the isolates. The last two chapters on the indigo and cyanine dyes, respectively, are very well-presented, and the section on the present divergent industrial uses of cyanine dyes was most illuminating.

Overall these are excellent reviews. There were very few errors noted, and the structures are well-proportioned. Unfortunately, the very high price means that this volume is not intended for the bookshelf of the typical academic. However, as a part of maintaining a library collection of the series, it is an essential acquisition.

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