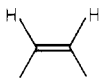
3000, 2975, 2920, 2900, 1670, 1620, 1600, 1100 cm^{-1}; UV (EtOH) λ_{max} 280 (ϵ 31 100); NMR ($CDCl_3$) δ 7.45 (d, 1, J_{trans} = 13 Hz, =CHN), 6.62 and 6.41 (AB, 2, J = 8.5 Hz, Ar H), 5.56 and 5.30 (m, m, 2, J_{cis} = 10 Hz, i), 4.54 (d, 1, J_{trans} = 13 Hz, COCH=), 2.89



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[s, 6, $N(CH_3)_2$], 1.22 [s, 9, $C(CH_3)_3$]; mass spectrum (70 eV), m/e 438 (M^+), 382, 285, 267, 98. Anal. ($C_{26}H_{34}N_2O_4$) C, H, N.

3-*O*-*tert*-Butylmorphine (5). To a solution of 15.0 g (34 mmol) of 4 in 600 mL of ethanol was added 280 mL of 2 N sodium hydroxide. After this mixture had been heated under reflux for 24 h, the ethanol was removed under reduced pressure, and the resulting suspension was extracted with chloroform (900 mL). The organic layer was washed with 2 N sodium hydroxide (100 mL) and then with water (120 mL) and dried. Removal of the solvent gave a residue, which was distilled to give 10.69 g (92%) of **5**: bp 220–230 °C (0.2 mm); $[\alpha]^{25}_D$ –79.8° (*c* 0.8, MeOH); IR ($CHCl_3$) 3550, 3000, 2975, 2925, 2800, 1730, 1600 cm^{-1}; UV (EtOH) λ_{max} 239 sh (ϵ 4680), 285 (3100); NMR ($CDCl_3$) δ 6.68, 6.50 (AB, 2, J = 8.5 Hz, Ar H), 5.65 and 6.27 (m, m, 2, J_{cis} = 10 Hz, i), 2.45 (s, 3, NCH_3), 1.32 [s, 9, $C(CH_3)_3$]; mass spectrum (70 eV), m/e 341 (M^+), 299, 285, 268, 215, 162, 124, 115, 57. Anal. ($C_{21}H_{27}NO_3$) C, H, N. The tartrate salt of **5** was prepared in ethanol with *d*-tartaric acid. Recrystallization from ethanol gave **5** as the *d*-tartrate diethanolate: mp 105–106 °C dec; $[\alpha]^{25}_D$ –28.2° (*c* 1.18, MeOH); mass spectrum (70 eV), m/e 341 (M^+), 308, 285, 268, 215, 162, 124, 115, 76, 57. Anal. ($C_{21}H_{27}NO_3 \cdot C_4H_6O_6 \cdot 2C_2H_6O$) C, H, N.

Hydrolysis of 3-*O*-*tert*-Butylmorphine (5) to Morphine (1). A solution of 0.12 g (0.35 mmol) of **5** in 1 N hydrochloric acid was stirred at room temperature for 17 h and then neutralized with concentrated ammonium hydroxide. The product, collected by filtration and recrystallization from methanol, gave 0.09 g (90%) of pure morphine (1), mp 254–256 °C (lit.[18] mp 251–256 °C). Its mmp with an authentic sample was undepressed and its spectroscopic properties (UV, IR, and MS) were identical with those of an authentic sample of morphine (1).

(–)-3-*tert*-Butoxy-*N*-methylmorphinan (8). A mixture of 11.3 g (44 mmol) of (–)-3-hydroxy-*N*-methylmorphinan (**6**) and 18.1 g (88 mmol) of *N,N*-dimethylformamide di-*tert*-butyl acetal was heated at 100–110 °C for 2 h under nitrogen. Then an additional two 9.0-g (44 mmol) portions of *N,N*-dimethylformamide di-*tert*-butyl acetal were added successively in 2-h intervals, and the heating was continued for an additional 6 h. The excess reagent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (300 mL). The ethyl acetate solution was washed successively with 2 N sodium hydroxide (2 × 60 mL) and water (50 mL). The organic solution was dried and concentrated to give a residue, which was distilled to give 8.1 g (59%) of (–)-3-*tert*-butoxy-*N*-methylmorphinan (**8**): bp 180–200 °C (0.1 mm); $[\alpha]^{25}_D$ –49.3° (*c* 0.93, MeOH); IR ($CHCl_3$) 3000, 2950, 2875, 2825, 1620, 1505 cm^{-1}; UV (EtOH) λ_{max} 279 (ϵ 2820); NMR ($CDCl_3$) δ 6.9 (m, 3), 2.8 (m, 3, Ar H), 2.4 (s, 3, NCH_3), 1.32 [s, 9, $C(CH_3)_3$]; mass spectrum (70 eV), m/e 313 (M^+), 298, 257, 242, 228, 214, 200, 189, 157, 150, 59. Anal. ($C_{21}H_{31}NO$) C, H, N.

The tartrate salt of **8** was prepared in 2-propanol with *d*-tartaric acid. Recrystallization from 2-propanol gave **8** as the *d*-tartrate hydrate: mp 105–107 °C dec; $[\alpha]^{25}_D$ –36.3° (*c* 0.99, MeOH). Anal. ($C_{21}H_{31}NO \cdot C_4H_6O_6 \cdot H_2O$) C, H, H.

Acknowledgment. We are indebted to Dr. E. J. Simon, Department of Medicine, New York University Medical Center, for the binding affinity data. We are grateful to the following members of the Research Department, Hoffmann-La Roche Inc: S. Traiman (IR), Dr. V. Toome (UV), Dr. W. Benz (MS), Dr. T. Williams (NMR), and Dr. F. Scheidl (microanalyses).

(18) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, 78, 1380 (1956).

Book Reviews

The **Molecular Basis of Antibiotic Action. 2nd Edition.** By E. F. Gale, E. Cundliffe, P. E. Reynolds, M. H. Richmond, and M. J. Waring. Wiley, New York. 1981. xxiii + 646 pp. 23.5 × 15.5 cm. $83.00.

The current high level of interest in antibiotics makes this volume a timely addition to the literature of medicinal chemistry. Revising their book 9 years after the first edition appeared, the authors have rewritten most of the chapters. The literature cited is up to date for a book published in early 1981. It has an impressive number of references to 1980 publications, but such is the rate of progress in the field of antibiotics that the material on β-lactam antibiotics is already getting dated because of the discovery of the large family of "monobactams" since the publication of the book.

This volume of sizeable dimension does not aim to be compendium of all the antibiotics, but it does deal with a wide spectrum of antibiotics as well as some of their synthetic analogues. A cursory scan of the index shows references to numberous "mycins", penicillins, cephalosporins and many other antibiotics, as well as less well-known substances, e.g., poke-weed antiviral peptide, pederine, and bruceantin. The last-named compound, which is cited along with other inhibitors of eukaryotic protein synthesis, is incorrectly described as an alkaloid, although the compound is devoid of nitrogen.

Synthetic and medicinal chemists trying to devise new antibiotic drugs will find valuable information in the long chapters on "Inhibitors of Bacterial and Fungal Cell Wall Synthesis", "Antibiotics Affecting the Function of the Cytoplasmic Membrane", "Inhibitors of Nucleic Acid Synthesis", and "Antibiotic Inhibitors of Ribosome Function" (128 pages). The chapter on "Bacterial Resistance to Antibiotics" will interest many, especially since it presents a lucid exposition on the genetic basis of resistance.

The last chapter, under the title "Perspectives", discusses the lack of any large-scale success in designing new antibiotics on the basis of "rational chemotherapy". This chapter then provides a brief account of the modification of existing antibiotic nuclei to obtain successful new antibiotic drugs: semisynthetic penicillins and cephalosporins are used as illustrative examples. This volume meets the high standard in production that one has come to expect of Wiley-Interscience. Extensive illustrations and an abundance of structural diagrams aid the reader, as does the extensive index.

Teamwork by five authors with impressive credentials has led to a book with depth of treatment and breadth of coverage. It is, however, not a textbook for beginning graduate students. Unfortunately, the high price of this volume will prevent many professionals from buying a copy for their personal use.

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Methods in Enzymology. Volume 77. Detoxication and Drug Metabolism: Conjugation and Related Systems. Edited by William B. Jakoby. Academic Press, New York, London, Toronto, Syndey, and San Francisco. 1981. xxii + 476 pp. 16 × 23.5 cm. ISBN 0-12-181977-9. $45.00.

This volume of the popular series provides a convenient reference to a variety of methods employed in the study of xenobiotics. The principle emphasis of the volume has been methods for the study of conjugative and hydrolytic processes. The subject matter is divided into four sections entitled "Animal Organ and Cell Preparations", "Enzyme Preparations", "Assay Systems", and "Synthesis". The first section is further divided into categories of "General Methods", "Organ Perfusion", and "Cells".

The chapters under "General Methods" deal principally with whole animal preparations under such diverse topics as "Exhalation of Isotopic CO_2", "Germfree Rats", "Chemical Depletion of Glutathione in Vivo", and "Whole-Body Radiography". Although operating at a much higher level of organization than the homogeneous enzyme, the chapters provide a significant insight into important methods of xenobiotic study, meriting their inclusion. The two following divisions deal with progressively lower levels of organization—the perfused organ and isolated cells.

The enzyme preparations described cover a number of processes in the metabolism of xenobiotics, including conjugation, sulfation, methylation, acyl transfer, and hydrolysis. It is noteworthy that this section closely parallels a recent two-volume overview of xenobiotic metabolism by the editor ("The Enzymatic Basis of Detoxication", Volumes I and II, Academic Press, 1980, W. B. Jakoby, Ed.) without serious duplication of material. Together, the two texts provide an insight into the biochemical basis of xenobiotic metabolism and methods for the study of these processes.

The remaining two sections, "Assay Systems" and "Synthesis", cover assay methods for glutathione, glutathione transferases, UDP-glucuronyltransferases and bilirubin glucuronides, as well as syntheses of such compounds as PAPS, bilirubin glucuronides, mixed disulfides, and thio esters of glutathione and coenzyme A. Also included is a very good discussion of the theory and practicality of solvent extraction methods as applied to the study of drug metabolism.

In summary, this volume is a well-organized treatment of methods employed in the study of xenobiotic metabolism. The principle emphasis is on conjugative and hydrolytic processes of metabolism, although techniques applicable to the study of most metablic pathways are presented. The volume should prove of value to both the researcher entering the field of drug metabolism and the established investigator familiar with many of the methods.

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Progress in Drug Research. Volume 25. Edited by Ernst Jucker. Birkhäuser Verlag, Boston. 1981. 501 pp. 17 × 24.5 cm. ISBN 3-7643-1179-7. $160.00.

This is the anniversary volume of a series initiated in 1959. In keeping with previous issues in this series, the present volume consists of a group of reviews of subjects of general interest to those involved in drug research. Each of the seven monographs presented in this volume represents a thorough, well-written, almost error-free, scholarly review.

The first monograph, "Antihypertensive Agents 1969–1980", is a sequel to the authors' previous review in Volume 13 of this series. It does not discuss diuretics, but it does describe important endogenous substances influencing blood pressure to provide a background for a detailed description of the various classes of antihypertensive agents, their mechanism of action, and structure-activity relationships. The bibliography of over 1340 references attests to the thoroughness of the review. The monograph on "Clinical Importance of Cardiovascular Drug Interactions" is probably of lesser interest to most medicinal chemists, but it provides a good account of the wide variety of mechanisms responsible for these clinically relevant events. Similarly, the review "An Overview of Studies on Estrogens, Oral Contraceptives, and Breast Cancer" is primarily of clinical interest. The subject of "Recent Developments in Cancer Chemotherapy" is a valuable reference for both clinical oncologists and medicinal chemists. Unfortunately, the review accurately reflects the general lack of success of truly Herculian efforts in the area of chemotherapy. It is realistically concluded that "biotechnologies...will play an increasing role in the future production of cancer chemotherapeutic agents." Two of the monographs, namely, "The Perinatal Development of Drug Metabolizing Enzymes: What Factors Trigger Their Onset?" and "Biliary Excretion of Drugs and Other Xenobiotics", are superb treatments of drug metabolism-related topics that should be of interest to all medicinal chemists. Rapid developments in these fields are reflected by the statement (p 194) that "cytochrome P-450 is thought to take no part in N-hydroxylation." This 1977 observation has been revised in more recent studies. The final monograph "Noninvasive Pharmacodynamic and Bioelectrometric Methods for Elucidating the Bioavailability Mechanisms of Ophthalmic Drug Preparations" reviews the determination of opthalmic bioavailability by measuring a pharmacological response. Problems associated with this methodology are adequately discussed. The author's formulas, along with several examples of their utility for measuring bioavailability, are presented. Unfortunately, many examples present analyses and interpretations based on very limited data. For example, Figures 18 and 19 purport to show an "effect" that is based on data from only two animals.

In keeping with other volumes of this series, the topics are generally unrelated. Thus, the book is of greater utility as a library reference source in contrast to being a desk copy for medicinal chemists. This is consistent with the editor's goal of making this series an encyclopedic reference. Toward this objective, not only is an index included for the present volume, but also there are limited ones of titles and first authors for subjects covered in the complete set. These abbreviated indexes of the 25-volume series severely restrict facile location of subject matter and detract from the encyclopedic objective of the editor. Since each volume in the series has an adequate index, it would seem simple and extremely useful to present comprehensive author and subject indexes for the entire set.

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Proceedings of the International Vinca Alkaloid Symposium: Vindesine. Volume 6. Contributions to Oncology. Edited by W. Brade, G. A. Nagel, and S. Seeber. S. Karger AG, Basel, Munich, Paris, London, New York, and Sidney. 1981. xii + 376 pp. 16 × 23 cm. ISBN 3-8055-1381-X. $57.00.

This volume is a compilation of lectures, reviews, and discussions held during the "International Vinca Alkaloid Symposium: Vindesine" in Frankfurt during November 1980. At this symposium all of the available experimental, pharmacological, and clinical data on vindesine were presented, as well as discussions of their current and future research activities on vindesine. In addition, the latter compound was compared with its two older parent compounds, vincristine and vinblastine. The newest alkaloid, vindesine, is apparently showing a limited degree of effectiveness both in lung and breast cancer and in melanoma, a field which in the past it was felt that Vinca alkaloids played no role. It is evident from this symposium that the addition of this drug to the other two generally available Vinca alkaloids has clearly extended the range of potential therapeutic application of Vinca alkaloids in cancer chemotherapy.

In general, this is a highly specialized volume of interest primarily to oncologists. The symposium review is divided into five main sections: (1) experimental and clinical pharmacology and toxicology of vindesine as compared to vincristine and vinblastine, (2) treatment of leukemias and hematosarcomas with Vinca alkaloids with special reference to vindesine, (3) treatment of solid tumors with vindesine compared to vincristine and vinblastine, (4) a round-table discussion, and (5) a short but good summary section by E. J. Freireich. There is a comprehensive author index, but the subject index is limited.

Only the first main section, section I, is likely to be of interest to medicinal chemists. In this section, probably the one paper in the entire volume that might be of maximal interest to individuals with interest in medicinal chemistry and cancer chemotherapy is a critical review of pharmacology, toxicology, and pharmacokinetics of vincristine, vindesine, and vinblastine by W. P. Brade. This is an excellent chapter. The price of this paperback book, $57.00, unfortunately, makes it almost prohibitive for it to be in the library of the nonspecialist.

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The Alkaloids. Volume 11. Specialist Periodical Reports. M. F. Grundon, Senior Reporter. The Royal Society of Chemistry, London. 1982. xii + 259 pp. 14 × 22 cm. ISBN 0-85186-347-7. $111.00.

The regular team of authors reviews the whole of the alkaloid literature between July 1979 and June 1980, and a 2-year coverage of *Erythrina* alkaloids is included.

Over 700 references are concerned with the isolation and chemistry of alkaloids, and approximately one-third of these are devoted to synthesis and biosynthesis. It is perhaps in these areas that the most notable research is to be found. Although it is probably invidious to attempt the exercise, a personal selection of highlights would include new results on the biosynthesis of quinolizidine alkaloids, the first synthesis of an 11-membered marcocyclic pyrrolizidine diester, the synthesis of *Poranthrea* alkaloids, and, in the indole field, the synthesis of tryptoquivalines G and L, of a chiral intermediate in the construction of heteroyohimbine alkaloids, and of a catharanthine intermediate, using palladium catalysts.

Staff

The Alkaloids. Volume XIX. Chemistry and Physiology. Edited by R. G. A. Rodrigo with R. H. F. Manske, Founding Editor. Academic Press, New York. 1981. xvi + 227 pp. 15.5 × 23.5 cm. ISBN 0-12-469519-1. $39.00.

Advances in the chemistry of three groups of alkaloids are reviewed in this volume. The *Sceletium* (Peter W. Jeffs) and phenanthroindolizidine–phenanthroquinolizidine groups (Ralph C. Bick and Wannee Sinchai) were previously reviewed in Volume IX of this series, and a chapter on the *Solanum* alkaloids (Helmut Ripperger and Klaus Schreiber) appeared in Volume X. The present reports deal with the considerable research activity in these areas over the intervening years.

Staff

The Alkaloids. Volume XX. Chemistry and Physiology. Edited by R. G. A. Rodrigo. Academic Press, New York. 1982. xvi × 341 pp. 15.5 × 23.5 cm. ISBN 0-12-469520-5. $59.50.

This volume is largely devoted to a review of the bisindole type and includes all alkaloids containing two tryptophan-derived nuclei (Geoffrey A. Cordell and J. Edwin Saxton). Various aspects of the chemistry of such indole alkaloids have been covered in several earlier volumes up to and including Volume XI of this series. All structural types are included in the present review, and the remarkable advances of the recent years in our knowledge of these very complex compounds are discussed and evaluated. A smaller chapter (Werner Dobke) reviews the eburnamine–vincamine group of indole alkaloids, which has not received any attention in this series since Volume XI.

Staff

Organic Compounds of Sulphur, Selenium, and Tellurium. Volume 6. Specialist Periodical Reports. By D. R. Hogg, Senior Reporter. The Royal Society of Chemistry, Burlington House, London. 1981. xviii + 331 pp. 13.5 × 21.5 cm. $127.00.

This Report, which covers the literature from April 1978 to March 1980, differs from its predecessor in this series in that coverage of sulfur-containing heteroaromatic compounds has been limited to the aspects involving the sulfur atom. Basically, the heteroaromatic compounds have now been relegated to the Report on Heterocyclic Chemistry. Also, the section of Se and Te ylides has been expanded, and the section devoted to thioureas and related thiocarbonyl compounds now includes a review of dithiocarbamates, xanthates, and trithiocarbamates. Otherwise, the format of Volume 6 remains essentially the same as that of Volume 5.

Senior Reporter D. R. Hogg and his ten collaborators have provided an excellent examination of the recent literature of the chalcogens. Chapter 1 (by G. C. Barrett) reviews aliphatic organic sulfur compounds with exocyclic sulfur functional groups and selenium and tellurium analogues. Chapter 2 describes ylides and carbanionic compounds of sulfur (by E. Block) and of selenium (by D. L. J. Clive), as well as compounds with S=N functionalities (by S. Oae and N. Furukawa). Chapter 3 covers thioaldehydes, thioketones, thioketenes, and their selenium analogues (by A. Ohno); sulfines and sulfenes (by D. L. Hogg); and thioureas, thiosemicarbazides, thioamides, thiono- and dithiocarboxylic acids, and their selenium analogues (by J. K. Landquist). Small ring compounds of sulfur and selenium are the subject of chapter 4 (by C. G. Venier). Saturated cyclic compounds of sulfur, selenium, and tellurium are discussed in chapter 5 (by P. K. Claus), and heteroaromatic compounds of sulfur, selenium, and tellurium are discussed in chapter 6 (by M. Davis). An author index is provided but no subject index.

The articles are of uniformly high quality, being both comprehensive in their coverage and succinctly written. The editor and the authors are to be complimented on a job well done.

Undoubtedly, the $127 price will deter many interested chemists and chemistry students from acquiring this book. High prices have been a negative aspect of the Specialist Periodical Reports since their inception. Considering that the Reports are essentially yearbooks with a shorter useful life span than a textbook, perhaps a less costly production process can be found, such as that used by Academic Press in making available the Annual Reports in Medicinal Chemistry. The latter, with its camera-ready copy, soft cover, and selective type reductions, serves to bring an annual review to an interested readership on schedule and at a more affordable price. Possibly the editors of Specialist Periodical Reports can be persuaded to adopt similar no-frills production methods.

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