Activity against the sensitive and resistant sublines of leukemia P388 is compared in Table III. The sensitive line showed the 3-fold decreased potency of **2** relative to **1**, but the resistant line showed that **2** was twice as potent as **1**. The significant comparison is of the resistance index, showing that **2** was intermediate between **1** and the non-cross-resistant cyanomorpholine **3**. It is not clear why the usual doxorubicin cross resistance should be even partly deleted with an *N*-alkyl derivative such as **2**. The resistance index (17) of **2** was the same as that (14) recently reported[6,14] for *N*-(cyanomethyl)doxorubicin, the simplest of the α-cyano amines. It was clear, however, that the capacity of **3** to overcome cross resistance was significantly diminished in going from **3** to **2**, just as was antitumor activity in other screens.

Relationships between chemical properties (structure, reactivity) and biological properties (antitumor efficacy, potency, cross resistance) are of continuing interest in this series.

Experimental Section

Chemical and biological methods were the same as previously described in this series.[1,4,14,15] Reverse-phase HPLC analyses were done on a Spectra-Physics SP-8100LC using a Waters Z-Module Radial Pak Nova C-18 5-μm column, with a flow rate of 2 mL/min and monitoring at 254 nm. DCI-MS and NDCI-MS were determined on a Ribermag R10-10C GC-MS with NH_3 as the reagent gas; in the assignments, the term sugar refers to that portion of the parent structure, without the glycosyl O.

***N*-(2-Hydroxyethyl)doxorubicin Hydrochloride (2·HCl).** A stirred solution of 0.580 g (1.00 mmol) of **1**·HCl and 0.120 g (2.00 mmol) of glycoaldehyde (crystalline dimer, Aldrich) in 30 mL of CH_3CN–H_2O (2:1) was treated with a solution of 0.042 g (0.67 mmol) of $NaBH_3CN$ in 1.5 mL of CH_3CN–H_2O (2:1). The mixture was stirred at room temperature in the dark for 1 h and poured into 50 mL of 0.1 N acetic acid. The solution was washed with $CHCl_3$, basified with solid $NaHCO_3$, and extracted repeatedly with 25-mL portions of $CHCl_3$–CH_3OH (4:1) and then $CHCl_3$. The combined extracts were dried and evaporated to 0.400 g of a solid residue containing the following: 30–40% of **2** free base, R_f = 0.15 by TLC in $CHCl_3$–CH_3OH–H_2O (40:10:1); along with 30–40% of the 13-dihydro derivative of **2** (identified by MS), R_f = 0.04; 10% of **1**, R_f = 0.10; and 10–15% of unidentified byproducts R_f = 0.45, 0.55, and 0.65. The solid was redissolved in 2 mL of CH_2Cl_2–CH_3OH (6:1) and added to a column (1.5 × 27 cm) of silica gel in CH_2Cl_2–CH_3OH (98:2). The column was eluted with CH_2Cl_2–CH_3OH in 100-mL lots (98:2, 96:4, 94:6, 92:8 (200 mL), 90:10, 88:12, 86:14, 84:16) and finally 1000 mL (80:20). Eluate fraction A (840 mL) afforded 78 mg consisting of lipophilic byproducts, fraction B (60 mL) 18 mg from which 12 mg of **2** was obtained by preparative TLC, and fraction C (240 mL) 75 mg of **2**. A suspension of the combined 87 mg in 10 mL of H_2O was stirred and acidified to pH 4.5 with 1.22 mL of 0.1 N HCl added dropwise. The resultant solution was lyophilized, and the residual hydrochloride was dissolved in 2 mL of CH_3OH and precipitated with 15 mL of ether to yield 0.084 g (13%). Purity was 89% by reverse-phase HPLC in 0.1 M NaH_2PO_4–CH_3CN (75:25), containing 1% of the 13-dihydro derivative and 6% of the *N*,*N*-bis(2-hydroxyethyl) analogue (identified by MS of a purified fraction). Presence of 2% of **1** was analyzed by TLC. For **2**, UV-vis (MeOH) λ_{max} 234 nm ($\epsilon \times 10^{-3}$ 37.2), 252 (25.7), 289 (8.66), 478 (12.0), 530 (6.74); NDCI-MS, *m*/*z* 587 (M); DCI-MS, *m*/*z* 192 (sugar + H_2O), 174 (sugar). Anal. ($C_{29}H_{33}NO_{12}$·HCl·1.5 H_2O) C, H, N.

Preparative TLC ($CHCl_3$–CH_3OH, 6:1) of fraction A above afforded an 8-mg fraction that was identified as ***N*-(2-hydroxyethyl)-*N*,4′-*O*-(2-hydroxyethylidene)doxorubicin (5)** by NDCI-MS, *m*/*z* 629 (M); DCI-MS, *m*/*z* 234 (sugar + H_2O), 216 (sugar). Other fractions were mixtures of **5** with the 13-dihydro derivative.

Hydrolysis of 3. A solution of 5.0 mg of **3** in 3.5 mL of CH_3OH was diluted with 3.5 mL of 0.1 M H_3PO_4 and stored at 23 °C in the dark. After 3, 5, and 24 h, aliquots were analyzed by reverse-phase HPLC in pH 4 0.05 M citrate buffer–CH_3OH (35:65). Disappearance of the well-resolved diastereoisomers of **3** (55% **a**, 42% **b**) was accompanied by the appearance of two new products, with an overall decrease in total absorbance. The solution after 24 h was diluted with 10 mL of H_2O and extracted with 10 mL of $CHCl_3$–CH_3OH (95:5). The dried extract was evaporated to yield 0.4 mg containing 77% of doxorubicinone along with unreacted **3** diastereoisomers (8% **a**, 13% **b**), identified by HPLC. The aqueous portion was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$–CH_3OH (95:5; 2 × 8 mL). These extracts were dried and evaporated to yield 2.4 mg containing 10–20% of **2** (identified by MS and by TLC and HPLC comparison with synthetic **2**) and 9% of doxorubicinone.

Essentially identical results were observed in CH_3OH solution diluted with 0.1 M citric acid (pH 2). In undiluted CH_3OH solution, **2** underwent no change after 24 h. After 6 weeks in CH_3OH at −10 °C, only minor contaminants were formed (3%, 2%, 1%, unidentified).

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(14) Acton, E. M.; Tong, G. L.; Taylor, D. L.; Streeter, D. G.; Filppi, J. A.; Wolgemuth, R. L. *J. Med. Chem.* **1986**, *29*, 2074.
(15) Acton, E. M.; Tong, G. L.; Taylor, D. L.; Filppi, J. A.; Wolgemuth, R. L. *J. Med. Chem.* **1986**, *29*, 1225.
(16) Note added in proof: The complete acid decomposition of cyanomorpholine in contrast to cyanopiperidine was recently noted. Barton, D. H. R.; Billion, A.; Boivin, J. *Tetrahedron Lett.* **1985**, *26*, 1229.

Book Reviews

Synthesis and Applications of Isotopically Labeled Compounds 1985. Second International Symposium, Kansas City, Missouri, 3–6 September 1985. Edited by R. R. Muccino. Elsevier, New York. 1986. xxxiv + 557 pp. 17 × 24.5 cm. ISBN 0-444-42612-4.

This volume relates the work presented at the Second International Symposium on the Synthesis and Applications of Isotopically Labeled Compounds held at Kansas City, MO, during Sept 3–6, 1985. The conference gathered 337 participants from 19 countries to review current and future directions on isotope research via 178 oral and poster presentations.

The text is arranged in essentially the chronological order of the conference proceedings. Whereas the first Kansas City Symposium in 1982 stressed the complimentary nature of radioactive and stable isotopes, the emphasis of this most recent meeting was on the newer applications of labeled compounds. Therefore, this book reviews such topics as the preparation and use of labeled peptides, radioligands in receptor studies, applications of ^3H and ^{15}N NMR, and clinical applications of NMR imaging. Aside from the purely technical papers, the volume also contains the historically valuable reflections of Professor Melvin Calvin during his award address. As a pioneer in the synthesis and applications of isotopically labeled compounds, Professor Calvin's after-dinner discourse was a memorable highlight of the 4-day meeting. An author and subject index and a useful list of conference attendees' names and addresses are also included in the book.

Although the book has rapidly appeared only 6 months after the symposium, it is well arranged and assembled. Prepared by direct photographic reproduction of typewritten manuscripts, the book's closely followed editorial guidelines maintained uniformity in the volume. Contributing authors made good use of photographs, tables, graphs, and structural formula, and I found no typographical errors. Both the editor and publisher should be congratulated for a book that will be valuable to those who make and utilize isotopically labeled compounds.

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Biological Oxidation of Nitrogen in Organic Molecules—Chemistry, Toxicology and Pharmacology. Edited by J. W. Gorrod and L. A. Damani. Ellis Horwood Ltd., Chichester, England. 1985. 4455 pp. 17 × 25 cm. $58.00.

The metabolism of organic nitrogen compounds has become of increasing importance to medicinal chemists, pharmacologists, biochemists, and toxicologists. Since a large number of drugs, pesticides, and food additives contain nitrogen and the presence of the nitrogen moiety is very important for pharmacological and toxicological activity, a clear understanding of the metabolism involving nitrogen and especially its oxidation is crucial in determining the biological action of these compounds.

After a very brief introductory chapter, the book is divided into nine sections with several chapters in each: (1) *Analysis of N-Oxygenated Compounds*, (2) *Substrates and Molecular Mechanism of the Flavin-Containing Monooxygenase*, (3) *Aromatic Amine Oxidation and Formation*, (4) *Oxidation of Amides and Carbamates*, (5) *Azaheteroaromatic N-Oxygenations*, (6) *Amidine, Imine, Triazene, Hydrazine and Azo Oxidation*, (7) *Prostaglandin H Synthetase Mediated N-Oxidations*, (8) *Peroxidase-H_2O_2-Catalyzed N-Oxidations*, and (9) *Interaction of N-Oxidized Compounds with Cellular Constituents—Toxicological Implications*. In general, the chapters in this book are quite variable in the depth in which the subject matter is covered. This arises inevitably from multiple authors but also due to the fact that some chapters are organized quite differently from others. Some are presented as if they were brief research papers with an experimental or methods section and one on results and discussion; whereas other chapters are presented in a more classical form. Despite this significant variability in presentation, the editors and the authors are clearly knowledgeable and at the cutting edge on this important area of xenobiotic metabolism.

The editors have incorporated important sections and chapters on the recent role of prostaglandin H synthetases and peroxidases in N-oxidation reactions. There are also significant chapters on the mechanism by which N-oxidation influences biological and toxicological action; notable among these is Chapter 23 (J. W. Gorrod) on amine–imine tautomerism, Chapter 41 (E. Kriek, J. G. Westra, and M. Welling) on the reaction of N-oxidation compounds with nucleic acids, and Chapter 43 on the reactions of such metabolites with sulfhydryl functions of biological importance.

In summary, this book contributes to the important area of metabolism, especially involving organonitrogen structures and the potential of N-oxidation products, both stable and labile intermediates, in carrying out biological transformations. In this regard, it offers useful information to researchers and others engaged in the development of new drugs and pesticides and an understanding of their pharmacological/toxicological activities.

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Textbook of Clinical Chemistry. Edited by Norbert W. Tietz. W. B. Saunders, Philadelphia. 1986. 1952 pp. $7^1/_4 \times 10^1/_4$ cm. ISBN 0-7216-8886-1. $59.95.

An updated version of this classic reference text of clinical chemistry was long overdue. This area of science has changed significantly since the prior edition was published in 1976. I was pleased to see that this 1986 edition has kept pace with modern developments in clinical chemistry, adding topics such as microprocessors in the clinical laboratory, therapeutic drug monitoring, biochemical aspects of pregnancy, receptor assays, method evaluation, high-performance liquid chromatography, and mass spectrometry. All the old subjects are there as well, e.g., instrumentation, automation, enzymes, endocrinology, acid–base balance, liver function, trace elements, porphyrins, calcium and phosphate metabolism, toxicology, amino acids and proteins, and so on. The field is still evolving at a rapid pace, as today's biochemistry becomes tomorrow's clinical chemistry. For example, DNA probes, biosensors, and HPLC–mass spectrometry will be topics in some future edition. While no topic in this current edition is treated comprehensively, the overall choice and degree of coverage in this immense text are appropriate, and the organization is consistent throughout. Thus, this is *THE* book to have if you want to be in touch with clinical chemistry.

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Pakistan Encyclopaedia Planta Medica. Vol. 1. Edited by Atta-Ur-Rahman, Hakim Mohammed Said, and Viqar Uddin Ahmad. Hamdard Foundation, Karachi. 1986. v + 373 pp. 19 × 24.5 cm. $50.00.

This is the first in what promises to be an extended series of volumes dealing with the chemistry, pharmacology, and indigenous medicinal use of the plants of Pakistan. It includes 94 species in 41 genera—*Abelmoschus* to *Allium*—many recognized for their reputed medicinal use not only in Pakistan but generally throughout the Indian subcontinent as well as in other tropical, subtropical, and even temperate geographical areas. In this respect it resembles the classical compilations of, e.g., Chopra or Nadkarni, but it differs from them in at least one important feature: Virtually every statement concerning identifiable chemical constituents, biodynamic activity, or medicinal use in one part of the world or another carries a reference to the original literature, as far as this is possible, along with an appropriate citation from *Chemical Abstracts*. There are, for example, 575 such references dealing with the common onion. The literature has been surveyed through mid-1984; 13 plants are illustrated with color plates.

While the editors point out that the specific chemical constituents isolated from any given species to date are not necessarily those responsible for its reported pharmacological activities and medicinal uses, they express the hope that this comprehensive survey will prompt medicinal plant chemists to further research and the eventual discovery of "new and more powerful drugs for the treatment of various diseases which afflict mankind today".

Unfortunately the quality of the binding is not commensurate with the price of the volume nor with the use that one might expect to make of it.

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Biological Methylation and Drug Design. Edited by Ronald T. Borchardt, Cyrus R. Creveling, and Per Magne Ueland. Humana, Clifton, NJ. 1986. xxi + 457 pp. 15 × 23 cm. ISBN 0-89603-102-0. $69.50.

This volume features the proceedings of the symposium entitled The Biochemistry of *S*-Adenosylmethionine as a Basis for Drug Design that was held at Bergen, Norway, on June 30–July 4, 1985. The symposium brought together scientists from various disciplines (biochemistry, pharmacology, virology, immunolgy, chemistry, medicine) to discuss recent advances in the biological roles of *S*-adenosylmethionine (AdoMet) and to discuss the feasibility of utilizing AdoMet-dependent enzymes as targets for drug design. The information provided in this volume will be of value not only to basic scientists involved in elucidating the role of AdoMet in biology but also to medicinal chemists who are using this basic knowledge in the process of drug design. The volume should also

be of interest to pharmacologists and clinicians involved in biological evaluation of potential therapeutic agents arising from the efforts of the biochemists and medicinal chemists.

The individual chapters in this volume represent comprehensive, up-to-date reviews of the subject material. Topics covered in this volume include protein and phospholipid methylations (Section A), nucleic acid methylations (Section B), the regulation of AdoMet, *S*-adenosylhomocysteine, and methylthioadenosine metabolism (Section C), clinical aspects of AdoMet (Section D), and the design, synthesis, and biological evaluation of transmethylation inhibitors (Section E). A subject index is also included.

Staff

Natural Product Chemistry. Edited by Atta-Ur-Rahman. Shamin Printing, Karachi, Pakistan. 1985. 603 pp. 18.5 × 25 cm.

This book edited by Dr. Atta-Ur-Rahman from the H. E. J. Research Institute of Chemistry at the University of Karachi, Pakistan, is the Proceedings of the 1st International Symposium on the Chemistry of Natural Products ever organized in Pakistan and held in conjunction with the Pakistan–U.S. Binational Workshop in Karachi, Feb 5–9, 1984. The book is dedicated to Professor Salimuzzaman Siddiqui, F.R.S., a well-known expert on the chemistry of natural products. The 29 contributions cover a wide area of research, including plant chemicals, insect chemistry, glycoproteins, peptides, steroids, biopolymers, pharmacological investigations of interesting extracts, synthetic methodology, and physical methods used for structure determination. Besides well-known scientists from the United States, West Germany and Japan, a large group of Pakistani chemists presented plenary lecturs. The Pakistani delegation with Atta-Ur-Rahman, Viqar Uddin Ahmad, Mohammad Ataullah Khan, and Salimuzzaman Siddiqui, from the University of Karachi, Mashooda Hasan from the University of Islamabad, Yusuf Ahmad and Syed Khaqan Hasan from the Laboratories of the Pakistan Council of Scientifique & Industrial Research in Karachi discussed constituents of medicinal plants from Pakistan. Nasir-ud-Din, from the University of Baluchistan in Quetta reviewed glycoproteins, and Sabira Naqvi, from the University of Karachi, presented data of a primary hemoglobin structure from a reptile. Individual chapters are extensively referenced, and an author index is given at the beginning and a subject index at the end of this book, covering 574 photoreproduced pages. Although individual chapters are remarkably free of typographical errors, they are often printed inconsistently, and one chapter is reproduced in such a way that it is rather difficult to read. One would probably take such mishaps more lightly if these proceedings would have been published in a cheaper paperback edition, also much faster available in print. It is hoped that the proceedings of the 2nd International Symposium, held in Karachi in February of this year, will follow this suggestion. This book leaves the impression that the 1st Symposium organized by Atta-Ur-Rahman was an excellent one; the topics selected were relevant at the time and discussed by well-known experts in the field. Again, availability of a cheaper paperback addition would possibly be of interest to a much wider community.

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The Alkaloids. Vol. 25. Edited by Arnold Brossi. Academic, New York. 1985. xviii + 369 pp. 16 × 24 cm. ISBN 0-12-469525-6. $72.50.

The 25th member of this series is in some respects the most unique volume in the entire series. Prepared by Matthew Suffness of the National Cancer Institute and Geoffrey A. Cordell of the College of Pharmacy, University of Illinois at Chicago, Volume 25 differs from the preceding volumes by its extensive and thorough coverage of many aspects of the structure–activity relationships and biological activity of a number of antitumor alkaloids. Synthesis of the various alkaloids is discussed, usually briefly, but major attention is not focused on this area. Instead such topics as biological detection, antitumor activity in experimental models, mechanism of action, mutagenicity, metabolism, and microbial transformation of alkaloids are discussed. In some cases the results of toxicology studies and clinical trial are mentioned. As a consequence, this volume will be of great interest to medicinal chemists, biologists, and oncologists who are interested in the relation of chemical structure to antitumor activity. The authors have excavated a literal gold mine of cytotoxic and antitumor data. Much of this information has been unpublished, buried in NCI data files.

The coverage of the various alkaloids is somewhat uneven. The clinically important Vinca alkaloids are omitted because they will be covered in a future volume; on the other hand the cephalotaxus and maytansinoid alkaloids, which were reviewed in depth in Vol. 23, 1984, are given again covered albeit with much greater emphasis on SAR. Some 16 classes of alkaloids are covered individually, plus a miscellaneous group. Ellipticine is covered in great detail as is camptothecine. One of the few adverse comments by the reviewer is the placing of an "e" after camptothecin that, while possibly theoretically correct, is not in accord with numerous literature citations. But this is a minor cavil. The treatment of these two alkaloids, along with the caphalotaxus alkaloids, and the maytansinoids is outstanding. The other groups are also covered well, although in a more condensed manner. Suffness and Cordell have brought together in an elegant manner the structure–activity relationships in each of the alkaloid groups covered.

A nice feature of the review is the unsurpassed literature coverage and coverage of much unpublished NCI testing data. In the main body of the review, over 2100 papers are reviewed. Of these, there are a few as late as 1983. However, the authors have prepared a useful addendum section, which surveys the alkaloids in the same order as those in the basic text. This section includes 300 references, many of which are recent. There are some 1985 references and a sizeable number of 1983 and 1984 references.

Volume 25 of the Alkaloid series will remain for many years one of the most up-to-date summaries available to medicinal and organic chemists, biologists, and oncologists who are interested in one aspect or another of the fascinating subject of antitumor alkaloids. A particularly good feature is that the authors have carefully defined the biological activity and differentiated between data based on in vitro cytotoxicity, in vivo i.p., and in vivo systemic methods of testing and administering the antitumor drugs. Drs. Suffness and Cordell are to be congratulated on this outstanding volume. It should be on the shelves of all libraries and is an important reference book for individual scientists with interests in natural products and medicinal chemistry.

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