and dried at 80 °C under vacuum to yield 3. Pure **3g** was obtained by chromatography of the crude reaction mixture on silica gel (60–200 mesh) with ether/hexane (1:1).

Pharmacology. The carrageenin-induced edema, adjuvant-induced arthritis, and acute toxicity tests have been previously described.[3,4]

Mouse Active Arthus Test (MAA). The procedure used was based on that of Goldlust et al.[5] Male CD-1 mice (Charles River Breeding Laboratories), 19–21 g, were sensitized with an intraperitoneal injection of 0.5 mL of a 1:1 emulsion of Freund's complete adjuvant (DIFCO) containing 250 mg of bovine serum albumin (BSA) in saline. The mice were used for testing 5 to 6 weeks later. The skin of the back was shaved on the day before the experiment.

On the day of the experiment, test compounds were suspended with sterile 1% sodium carboxymethylcellulose in pyrogen-free saline (PFS). The test compound was administered orally to each mouse in a 0.5-mL volume 1 h before antigenic challenge, which consisted of an interdermal injection of 0.05 mL of 5 mg of BSA/mL of PFS into the skin of the back.

Three and one-half hours after antigenic challenge, the animals were sacrificed by exposure to carbon dioxide, and the lesions were excised using the acutal perimeter of the edema as a guide. The average lesion weights of groups receiving test compounds were compared with that of a control group, which received only vehicle, and the percent inhibition by test compounds was calculated. Dose–response curves were run for each compound, from which ID_{50} doses were calculated.

Acknowledgment. We thank The Squibb Analytical Section under the direction of Dr. Allen I. Cohen for microanalyses and spectra.

(3) R. C. Millonig, M. B. Goldlust, W. E. Maguire, B. Rubin, B. Schulze, R. J. Wojnar, A. R. Turkheimer, W. F. Schreiber, and R. J. Brittain, *J. Med. Chem.*, 16, 780 (1973).
(4) R. C. Millonig and E. Yiacas, in "Pharmacological and Biochemical Properties of Drug Substances", M. E. Goldberg, Ed., American Pharmaceutical Association, Washington, DC, 1977, pp 215–231.
(5) M. B. Goldlust, T. W. Harrity, and D. M. Palmer, in "The Recognition of Anti-Rheumatic Drugs", D. C. Dumonde and M. K. Jasani Eds., MTP Press, Lancaster, England, 1978, pp 119–136.

Book Reviews

Oxygen and Life. Second BOC Priestley Conference. Sponsored by the BOC Gases Division Trust and Organized by The Royal Society of Chemistry and the University of Birmingham, September 15–18, 1980. The Royal Society of Chemistry, Burlington House, London. 1981. xii + 224 pp. 14.5 × 21 cm. £11.00.

This volume is a series of presentations by various established investigators on the biology, biochemistry, and toxicology of oxygen. Additionally, the Priestley Lecture by G. A. Soffen is included that relates to Mars and the role of oxygen and environment in organogenesis and life.

R. J. P. Williams presents an overview of oxygen and life, discussing the various biological catalysts, the chemistry and mechanism of action, and their wide range in the using of oxygen. This presentation provides the basis for the four main themes of this symposium. First, there are two papers by M. Calvin and A. Harriman, respectively, on photosynthesis and synthetic organometallic structures designed to mimic the chloroplast, using them as a basis for understanding the photoactivation process. The second section relates to the mechanism of oxygen toxicity and its critical importance, especially through the respiratory burst, in providing microbicidal oxidants. Of the three papers, the first, by J. A. Fee, is critical of the concept that oxygen toxicity stems from oxy radicals, such as superoxide. However, those by H. A. O. Hill/M. J. Okolow-Zubkowska and B. M. Babior discussing how oxygen is used by neutrophils do strongly favor oxidizing radicals as the source for the lethal effects observed. The paper by Babior would be of special interest and benefit to those nonbiologists, since the biological terms that are used are defined very clearly and succinctly. The third group of talks are concerned with various aspects of oxygen transport in biological systems. The extremes are the studies by C. A. McAuliffe in the use of small synthetic manganese–phosphine complexes on the one hand and high-molecular-weight hemocyanins by E. F. J. van Bruggen on the other. Two very intriguing papers in this section were by R. P. Geyer and by K. Yokoyama, T. Suyama, and R. Naito on the development and use of perfluorochemicals as blood substitutes by reason of their oxygen transporting capability. The last topic related to oxygen-utilizing enzymes. This section is more diverse and includes a talk by T. Ljones and T. Skotland on dopamine β-mono-oxygenase; two articles on cytochrome oxidase, one by K. J. Berry, M. J. Gunter, and K. S. Murray on synthetic models and a second by G. M. Clore on low temperature kinetic studies; and a paper by C. Greenwood on the importance of iron and copper metalloenzymes in protecting various living forms. Finally, there is an excellent article by O. Hayaishi on his outstanding contributions relating to indoleamine-2,3-dioxygenase and its requirement of the superoxide anion for metabolic activity.

This volume did not contain all of the presentations of the conference. Eight talks were not included. The great diversity of subject matter, only united by oxygen, might result in researchers having only limited interest in the entire volume. The work presented, however, is certainly most eminent.

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Fundamentals of Oncology. Second Edition. Revised and Expanded. By Henry C. Pitot. Marcel Dekker, New York. 1981. viii + 291 pp. 14 × 22 cm. $16.50.

This wide-ranging, yet remarkably compact, introduction to the subject of oncology forms the syllabus for a series of slide lectures presented annually at the University of Wisconsin Medical School by Professor Pitot and other faculty and staff of the McArdle Laboratory for Cancer Research. The first edition, issued in 1978, was so successful that a second edition had to follow almost immediately.

There are 13 chapters in this revised, slightly expanded edition, one more than in the original. After two introductory chapters devoted to an historical overview and exposition of general terminology and concepts, three chapters consider the physical, chemical, and biological factors currently regarded as being significant etiologic aspects of tumorigenesis. The next seven chapters deal with major aspects of the biochemistry and immunobiology of the cancer cell and with the pathogenesis and natural history of various types of tumors. Special emphasis is placed on host–tumor relationships and on the influence of nutritional, hormonal, and immunologic effects on the course of neoplastic disease. The final chapter, absent in the first edition, deals (rather briefly) with cancer chemotherapeutic principles, and there is a short epilogue in which the author attempts to predict the probable evolution of the field of oncology in the years ahead.

Each chapter has been updated to reflect newer discoveries that have been made since the first edition appeared. There is, for

example, a more extensive discussion than before on suspected etiologic factors in human cancer, including the possible harmful effect of immunosuppressants (azathioprine, prednisone, and even phenacetin used in high doses for long periods by persons with chronic inflammatory disease). Increased attention is likewise accorded to the potential etiologic role of food additives (coloring and flavoring agents, preservatives), polyhalogenated pesticides and defoliants that can enter the food chain, and, needless to say, tobacco and alcohol in excess. There is also more emphasis than in the first edition on suspected tumor promoters, such as phenobarbital and saccharin, and tumor-retarding substances, such as the retinoids. More space is devoted, as well, to advances that have been made recently in our understanding of the mechanism of metastasis and the delicate role of the immune response in this process. While our knowledge of the biochemistry of neoplastic disease continues to grow only slowly, the author has nonetheless found important new material to add to this edition, including sections dealing with the altered isozyme patterns in minimal deviation hepatomas and the appearance of "unique proteins" and other fetal gene products in the blood of patients with early or prerecurrent cancer. New material has been added also in support of the current view that cancer may be a "disease of differentiation", a hypothesis fortified by the discovery that certain agents such as Me_2SO and vitamin E can cause phenotypic differentiation in transformed cells in culture. A further topic which is dealt with in more detail in this edition concerns ectopic tumors and the paraneoplastic syndromes associated with the production of biochemical markers of potential clinical diagnostic significance, such as hormones, fetal antigens, and polyamines. Finally there is an expanded discussion of the rising field of immunogenetics, with new material on the mapping of the HLA and H-2 histocompatibility regions of human and mouse chromosomes, respectively.

There are few major changes in this second edition. The lists of references at the end of each chapter have been brought up to date, and appropriate new entries have been added to the index. Some of the figures have been enlarged or redrawn; others, however, have been reduced in size and are thus more difficult to read. The organization of topics remains substantially unaltered. One exception is that the progression and regression of tumors, as well as the subject of occult neoplasia, are now discussed in the chapter on the natural history of neoplasia in vivo, rather than in the chapter on pathogenesis which focuses more narrowly on the initiation/promotion theory. In a number of instances, errors in structural formulas which marred the first edition have been corrected. New molecular weight values and coding potentials for certain of the oncoviruses have been provided, along with genetic maps for the SV40 virus, adenovirus, and Rous sarcoma virus. Detailed maps of the HLA and H-2 histocompatibility complexes have likewise been included. While this obviously represents an effort to update the book, it will probably be beyond the grasp of readers not already acquainted with the complex language of molecular immunogenetics. Since there is essentially no attempt to explain this arcane terminology, the pedagogic utility of at least some of the new material will be limited by the willingness and ability of the reader to consult other sources. Apart from this minor complaint, this reviewer heartily concurs with others who have previously recommended this concise and well-documented survey of the field of oncology to students as well as more seasoned investigators in the health sciences.

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The Total Synthesis of Natural Products. Volume 4. Edited by John ApSimon. Wiley-Interscience, New York. 1981. 610 pp. 16 × 23.5 cm. $60.00.

This is the fourth volume in a series which was initiated by ApSimon in 1973 and which now covers 16 distinct areas of natural product total synthesis. Future volumes, according to Editor ApSimon, "will contain predominately updating chapters". The present volume discusses three new topics (insect pheromones, cannabinoids, and ionophores) and two updated topics (prostaglandins and monoterpenes).

Volume 4 gets off to a brilliant start with Mori's chapter on the synthesis of insect pheromones. His is a deeply researched and beautifully presented review, one of the finest this reviewer has seen on any subject of synthesis. It comprises nearly one-third of the book and covers 96 pheromones with special emphasis on 30 chiral pheromones (about one-third of the chapter). Mori's reaction schemes are models of clarity and harmony and are easily the best in the series to date. Thus, one can "read" each total synthesis without recourse to the text. Coverage is through April 1979. Biological activity and isolation data are discreetly presented where appropriate.

Razdan examines syntheses of the tetracannabinols, their metabolites, related cannabinoids, and THC analogues. Although the shortest chapter in Volume 4, it also briefly covers pharmacological profiles, structure–activity relationships, and potential therapeutic applications. Coverage extends into 1979.

Wierenga's ionophore chapter, with some coverage into 1980, compiles total syntheses of ionophoric peptides (e.g., gramacidins), depsipeptides (e.g., valinomycin), siderophores (iron chelating agents, such as ferrichrome and enterobactin), oxymacrocycles (e.g., nonactin, crown ethers, and boromycin), and polyether antibiotics (e.g., monensin, lasalocid, and calcimycin). He concludes with a brief presentation of miscellaneous ionophores either which have not yet been synthesized or remain unclassified. These include the polyene antibiotics (e.g., amphotericin B), phospholipids (e.g., cardiolipin), and isolated structures such as streptolydigin. Noteworthy are the pellucid presentations of Kishi's and Evans' elegant syntheses in the polyether field.

Bindra updates prostaglandin total synthesis, begun in Volume 1, with coverage from 1971 to 1979, including prostacyclin and thromboxanes. Unlike Mori and Wierenga, Bindra elects not to show reagents over reaction arrows, a practice to be condemned forthwith, especially considering the many graduate students—trying to learn synthesis—who will presumably read this book.

Thomas and Bessiere update monoterpene total synthesis, begun in Volume 2, with coverage from 1971 through most of 1979. Only a relatively few syntheses are presented in detail (i.e., à la Mori), but the literature appears to have been exhaustively reviewed (774 citations).

In summary, the entire series (Volume 4 being no exception) can be recommended to synthetic and medicinal chemists, as well as to graduate students in these fields, as a means with which to follow natural product total synthesis—from antibiotics to triterpenes—and to learn modern synthetic organic chemistry in the content considered by many to be the ultimate intellectual challenge.

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Medicinal Chemistry, A Series of Monographs. Volume 17. Doxorubicin. By Federico Arcamone. Academic Press, New York. 1981. xiii + 369 pp. 15.5 × 23.5 cm. $49.00.

This seventeenth volume in the "Medicinal Chemistry" series deals with doxorubicin (adriamycin). As the series title suggests, this is basically a chemical text, although aspects of the subject ranging from isolation and synthesis to pharmacokinetics and studies on the mechanism of antitumor activity are included. The book is logically organized and well balanced in its treatment of individual topics. The first chapter deals with the discovery and development of doxorubicin, and the second with the chemical synthesis of doxorubicin and related compounds. Following a chapter entitled "Molecular Interactions", which describes the physical properties of doxorubicin and its interaction with biologically important molecules, there is a chapter detailing the effects of the compound on living systems. Four additional chapters deal with analogues of doxorubicin and with new types of naturally occurring anthracyclines. Each chapter contains literature references, which cover the period through 1979 (and part of 1980).

This book should be a valuable reference source for workers in the field and for those synthetic and medicinal chemists who want to acquaint themselves with some particular aspect of doxorubicin studies. It is written clearly and contains numerous structural formulas, which enhance its value and readability.

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