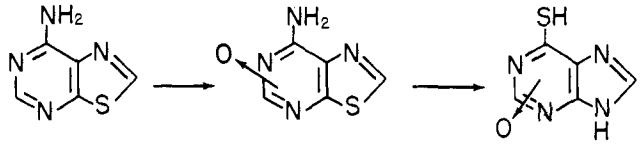
# Communication to the Editor

## Synthesis of a 6-Mercaptopurine N-Oxide[1]

*Sir:*

A theoretical advantage[2] of an N-oxide of a chemotherapeutically effective purine is based, in part, upon the possibility that it, like adenine-1-N-oxide,[3] may undergo a reduction *in vivo* to the parent purine. The greatly reduced toxicity and improved therapeutic index[4] of 6-methylpurine-1-N-oxide over the parent purine was the first supporting example.

Direct oxidation of 6-mercaptopurine to an N-oxide of it has failed because of oxidation of the mercapto group. Oxidation of 6-chloropurine has resulted in a prior hydrolysis to the nonoxidizable hypoxanthine, and attempts to introduce mercapto or halogeno groups into appropriate purine N-oxides have resulted in the reduction of the N-oxide group.



I II III

Scheme I

The synthesis of a 6-mercaptopurine N-oxide has now been accomplished by introduction of the N-oxide function while the sulfur is protected from oxidation in a thiazole.

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, Public Health Service (Grant No. CA-03190-07), and from the Atomic Energy Commission (Contract No. AT(30-1)-910).

(2) G. B. Brown, "Fourth International Congress of Biochem. Colloquia," Vol. XIII, Pergamon Press, London, 1958, p. 111.

(3) D. Dunn, M. H. Maguire, and G. B. Brown, *J. Biol. Chem.*, **234**, 620 (1959).

(4) M. A. Stevens, A. Giner-Sorolla, H. W. Smith, and G. B. Brown, *J. Org. Chem.*, **27**, 567 (1962).

Oxidation of 7-aminothiazolo[5,4-*d*]pyrimidine (I)[5] in acetic acid with $H_2O_2$ yielded 60% of the N-oxide II, m.p. 278° dec.

*Anal.* Calcd. for $C_5H_4N_4OS$: C, 35.71; H, 2.37; N, 33.33; S, 19.05. Found: C, 35.94; H, 2.48; N, 33.50; S, 19.04.

Heating the N-oxide II in an equivalent of *N* NaOH results in rearrangement to a 6-mercaptopurine-N-oxide (III) in 25% yield, m.p. 230° dec.

*Anal.* Calcd. for $C_5H_4N_4OS \cdot H_2O$: C, 32.26; H, 3.22; N, 30.11; S, 17.20. Found: C, 32.39; H, 3.00; N, 30.26; S, 17.40.

Evidence that the purine ring is present in III derives from the fact that treatment with Raney nickel yields purine and that irradiation with ultraviolet light results in a removal of the oxygen to yield 6-mercaptopurine, a reaction characteristic of several purine N-oxides.[6] The position of the oxygen has not yet been established but, in analogy to adenine, I may undergo oxidation at N-6, resulting in a purine 3-N-oxide after the rearrangement.

Initial observations by Dr. H. C. Reilly, with Sarcoma 180 in Swiss mice,[7] indicate no toxicity at 500 mg./kg./day and a chemotherapeutic activity, including inhibitions and delayed regressions, which exceeds that obtained with toxic levels of 6-mercaptopurine.

(5) G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 2858 (1956).

(6) G. Levin and G. B. Brown, *Federation Proc.*, **21**, 372 (1962), and unpublished observations.

(7) C. C. Stock, *Am. J. Med.*, **8**, 658 (1950).

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Received September 12, 1963

# Book Reviews

**Experimental Chemotherapy.** Vol. 1. R. J. Schnitzer and Frank Hawking, Editors. Academic Press, Inc., New York, N. Y., 1963. xv + 1008 pp. $38.00.

This is the first of three projected volumes of a comprehensive treatise on all aspects of chemotherapy. If the other two volumes will follow the tradition of high quality set by the present book, this treatise may well become the standard reference work for biologists interested in all phases of the subject. Introduced fittingly by a photograph of the patron saint of chemotherapy, Paul Ehrlich, one of the editors surveys the history of the field from antiquity to the present. Like all other chapters, this first one is amply and well documented. The fact that the majority of the references concerned with the discovery of chemotherapeutic drugs come from the biological literature points to the division of labor, as well as to the teamwork of medicinal chemists and biologists in this area. Stress is laid on decisive testing procedures in laboratory animals, on statistical analyses of these procedures, on the pharmacological and toxicological aspects of the drugs, and on the development and treatment of resistant strains.

On the whole, the clinically useful drugs are discussed primarily and their biological and host–parasite relationships are illustrated. In several cases, however, the influence of the chemical structure in a series of related drugs is considered, and the effect of drug metabolites is detailed wherever it is known. This first volume treats the chemotherapy of protozoan and metazoan infections. Each chapter is written by authorities in the particular field who have had long actual experience in the area. Most authors are well known members either of British industrial research organizations or of American and British university or governmental laboratories. Specific diseases and their chemotherapy treated are trypanosomiasis, leishmaniasis, trichomoniases, histomoniasis, giardiasis, amebiasis, coccidiosis, malaria, babesiasis, theileriasis, anaplasmosis, toxoplasmosis, balantidiasis, spirochetal and miscellaneous infections, helminthiases, filariasis, and myriasis. A general author and subject index concludes the book.

The editors, who themselves have contributed several chapters, have managed to keep the style and presentation uniform, lucid, and easy to read. One may look forward with pleasure to the next two volumes of this work. The book may be recommended to medicinal chemists, experimental biologists, and physicians who have to study and treat infectious diseases.

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**Enzyme and Metabolic Inhibitors. Vol. 1. General Principles of Inhibition.** By J. LEYDEN WEBB. Academic Press, New York, N. Y., 1963. xxi + 949 pp. $26.00.

Most enzymes possess more inhibitors than substrates. In addition, enzyme–inhibitor interaction constants are always also equilibrium constants while an enzyme–substrate interaction constant may or may not be an equilibrium constant. For this reason enzyme–inhibitor constants, though more difficult to evaluate precisely, are more immediately comparable than enzyme–substrate constants. The large volume under review here is the first in a projected set of four primarily concerned with inhibitors and inhibition. While the three succeeding volumes will deal with specific inhibitors, this first volume develops in considerable detail general principles of inhibition. The contents might best be indicated by listing the titles of the 17 chapters: 1, Perspectives of Metabolic Inhibition; 2, The Kinetics of Enzyme Reactions; 3, The Kinetics of Enzyme Inhibition; 4, Substrate Inhibition and Product Inhibition; 5, Determination of the Mechanisms and Constants of Inhibition; 6, Interactions of Inhibitors with Enzymes; 7, Inhibition in Multienzyme Systems; 8, Distribution and Fate of Inhibitors in Living Organisms; 9, Inhibition in Cells and Tissues; 10, Effects of More Than One Inhibitor; 11, Localization of the Site of Inhibition; 12, Rates of Inhibition; 13, Reversal of Inhibition; 14, Effects of pH on Enzyme Inhibition; 15, Effects of Various Factors on Inhibition; 16, Specificity of Inhibition; and 17, Suggestions for Planning and Reporting Inhibition Studies.

As indicated by the chapter titles, the book is concerned with broad areas of inhibition, from interactions between parts of molecules to aspects of inhibition in whole organisms. Chapter 6 on molecular interactions contains a valuable discussion of the forces between molecules. It is unfortunate, however, that the author did not include a more thorough discussion of hydrophobic interactions. No reference is made to the article by W. Kauzmann, *Advan. Protein Chem.*, **14**, 33 (1959), one source where hydrophobic bonds are discussed. Their importance seems underestimated in this book. The free energy change for the transfer of a methyl group from an aqueous to a hydrocarbon environment [*J. Am. Chem. Soc.*, **84**, 4240 (1962)] is about equal to the deficiency of dispersion forces in accounting for the binding of a single substrate methyl group to cholinesterase as discussed on p. 286. A second point inadequately discussed appears in Chapter 14 where the bell-shaped plots obtained when reaction rate is plotted against pH are interpreted almost entirely in terms of ionizing groups. Yet either ascending or descending portions of a bell-shaped plot may not be due to a simple ionization constant but to an ionization constant modified by ratios of other equilibrium and rate constants [see for example, *J. Am. Chem. Soc.*, **81**, 4552 (1959)] or simply to ratios of rate constants alone as demonstrated in a simple nonenzymatic system [*J. Am Chem. Soc.*, **81**, 5089 (1959)]. Thus the last sentence on p. 655 is not true. No discussion of the general principles of metal ion inhibition is presented but perhaps this subject will appear when specific metal ion inhibitors are considered in a later volume. Now that it has been established that substrates alter the conformation of at least some enzymes it will be of interest to see to what extent various inhibitors act in the same fashion.

In any book of general principles with such breadth, considerable selection is required in choosing examples to illustrate the principles. Though this section is admittedly largely subjective, some of the examples seem to have been chosen without sufficient discrimination. For instance, the citing on p. 196 of the thiol ester grouping as the reactive form of the sulfhydryl group in the enzyme papain ignores the fact that the proposer of this grouping at the active center has never accounted for his own extensive kinetic data in these terms and indeed it does not seem possible to do so. On p. 809 in a discussion of the possible general effects of dielectric constant changes on $\alpha$-chymotrypsin hydrolysis in methanol solutions, no reference is made to the specific effect of low concentrations of methanol [*J. Am. Chem. Soc.*, **82**, 3336 (1962)].

These comments should be taken less as criticisms than as indications of the book's scope and thought-provoking qualities. Even the first volume of the projected four represents an enormous labor. This first volume is not a reference work but often contains incisive discussions of points concerning inhibition. As such it should be in personal libraries where workers may become familiar with its contents and be able to refer to it frequently and conveniently. Unfortunately, the high price reveals that the publishers are planning only upon the assured sale to libraries, on whose shelves the valuable volume is apt to remain little used.

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**Spectrometric Identification of Organic Compounds.** By ROBERT N. SILVERSTEIN and G. CLAYTON BASSLER. John Wiley and Sons, Inc., New York and London, 1963. viii + 177 pp. $8.50.

Recent years have witnessed the explosive development and use of instrumental techniques as aids for the elucidation of structures of organic compounds. These developments have been largely paralleled by the appearance of erudite monographs which have helped the organic chemist apply such methods to his own research. This dependence on instrumentation has now reached such proportions that a course in the subject is definitely indicated and an increasing number of institutions are, in fact, incorporating such material in their formal study programs. Generally, such ventures have been largely limited by the lack of an adequate book, written for the beginner, which describes how information obtained from different instrumental methods can be used in complementary fashion to greatest advantage.

The book by Silverstein and Bassler is a step in this direction. It is an outgrowth of a course given by the authors at San Jose State College in the spring of 1962, consisting of eleven lecture hours and four hours of discussion. The object of the book is to acquaint the reader with four instrumental techniques important to the organic chemist, these being mass, infrared, nuclear magnetic resonance, and ultraviolet spectrometry; it emphasizes the value of combining information obtained from them in the solving of structural problems.

The book consists of eight chapters, the first of which is a one and one-half page introduction explaining the purpose of the book and the scheme followed in the remaining chapters. Each of the next four chapters is devoted to one of the techniques indicated above, and contains a brief discussion of the theory, instrumentation, sample preparation, and interpretation of spectra. An excellent list of references in each case includes most of the more extensive reference works in that particular field.

The discussions of these techniques are usually clear and concise, and the chapters contain numerous diagrams, charts, tables, and extensive appendices (many borrowed from other sources) which help the reader to correlate and use the information presented. In some instances, this reviewer had the opinion that the material presented is almost too concise. In the infrared chapter, for example, combination and overtone bands are mentioned in the discussion of possible pitfalls in interpreting infrared spectra, but where one might suspect their presence in a spectrum is not indicated. Another potential source of trouble here, Fermi resonance, is not mentioned at all. As another case in point, in the section on theory, it may have been helpful for the beginner if diagrammatic representations of the vibrational modes of the $AX_3$ group, as well as the $AX_2$ group, had been included. However, these shortcomings are relatively minor and do not detract appreciably from the value of the book. A particular point on the bright side is the presentation of all infrared data in both $\mu$ and cm.$^{-1}$ units, which makes the discussion easy to follow regardless of the system the reader is familiar with.

Since the book is written for the organic chemist, it is not surprising to find that the authors stress interpretation of spectra to a greater extent than the theoretical aspects of energy absorption. The theory is, however, usually treated in sufficient detail so as to provide an adequate understanding of the general principles involved.

The chapter on nuclear magnetic resonance is well presented and deals almost exclusively with proton magnetic resonance.