## REVIEWS

*Design of Active-Site-Directed Irreversible Enzyme Inhibitors.* By B. R. BAKER. John Wiley & Sons, Inc., 605 Third Ave., New York, NY 10016, 1967. xiii + 325 pp. 15.5 × 23.5 cm. Price $13.50.

Professor Baker has written an interesting book about the work he has been doing for the last six years on the design, synthesis, and evaluation of what he calls "active-site-directed irreversible inhibitors." The book itself deals primarily with design of these inhibitors.

Dr. Baker's ideas initially were based largely on the established mechanism of action of azaserine, which is known to combine, because of its similarity to glutamine, reversibly at the active site of phosphoribosylformylgycineamidine synthetase using the glutamine binding points, and then irreversibly inactivate the enzyme by reaction of its diazomethyl group with a thiol group in the active site. The design of such inhibitors, which have been termed endo-alkylating agents, is severely limited because of the steric requirements of the active site. On the other hand, Professor Baker has found that an inhibitor can be designed to fit an enzyme active site and at the same time bear a group capable of reacting with a functional group on the enzyme surface but outside the active site. This concept of an exo-alkylating agent has two advantages. First, the *position* of the change made in a metabolite to give an antimetabolite becomes more important than the nature or size of the change. Second, and more important ultimately, such an inhibitor has an extra dimension of specificity, since even closely related isozymes differ in their secondary and tertiary structure.

Professor Baker uses the "6-mercaptopurine story" to illustrate the parameters involved in the use of enzyme inhibitors as chemotherapeutic agents. He then discusses the development of his exo-mechanism concept. Chapter 2 is devoted to a general discussion of the forces involved in the reversible binding of substrates to enzymes. Chapters 3–5 deal with the mode of binding to specific enzymes. Chapter 6 is concerned with the types of changes in the structure of a metabolite that can be expected to produce inhibitors and the types of changes that may lead to modified substrates, while Chapter 7 discusses bulk tolerance in enzyme–inhibitor complexes. Chapter 8 details the kinetic parameters important to active-site-directed irreversible inhibition and studies, other than the author's, on this type of inhibition. Chapters 9–12 are devoted to the details of the *modus operandi* developed by Professor Baker in his studies of lactic and glutamic dehydrogenases, dihydrofolic reductase, and other folate cofactor area enzymes, while Chapter 12 describes the work of other investigators on adenosine deaminase. Unexpectedly, the last chapter is devoted to enzyme-specific columns, but the relationship of this subject to the author's interests is obvious.

This book should be studied by any serious student of medicinal chemistry. I would agree with the author's statement "Although these active-site-directed irreversible inhibitors have not yet led to useful chemotherapeutic agents, the future for such discoveries appears based on scientifically sound premises." That is a lot more than can be said for much of the work being carried out today on the design and synthesis of potentially useful medicinals.

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*Topics in Medicinal Chemistry.* Vol. 1. Edited by J. L. RABINOWITZ and R. M. MYERSON. Interscience Publishers, Inc., 605 Third Ave., New York, NY 10016, 1967. xi + 453 pp. 15 × 23 cm. Price $17.75.

This volume is the first in a new series that will deal with the biomedical aspects of drugs, or groups of drugs. It draws from a wide source of authors, especially from industry. In general presentation and format it resembles the chapters in the various Annual Reviews that started the now essential function of regularly reviewing the literature with the "Annual Review of Biochemistry" 35 years ago.

In the first chapter, Litwack, in discussing the mechanism of action of cortisol, comes to the obviously reluctant conclusion that direct effect on the genetic apparatus of the cell is probably not the essential mechanism, at least in liver cells. In the chapter on anti-inflammatory agents, Shen describes the increase in knowledge of the nature of the inflammatory process and the difficulties of associating them with immunological disease. The series, analgesics to anti-immune agents, runs from the salicylates through phenylbutazone, corticosteroids, antimalarial, and gold salts to indomethacin and mefenamic acid and, for general usefulness, back to the salicylates again. Shimkin, in his usual clear fashion, classifies the chemotherapeutic agents against cancer that are turned to when surgery and irradiation are not effective or not applicable. For only a very few tumors, notably choriocarcinoma, can chemotherapy compare with optimal use of the scalpel, but Shimkin feels that this situation will inevitably change. Osden in a review on antiviral agents shows that despite an immense amount of work no agents are available against systemic disease therapeutically in man, as opposed to prophylactically. However, the effectiveness of agents in simple *in vitro* settings, as with cancer chemotherapy, holds the interest and hope of workers in the field. Childress shows how far chemists have gone from original antibiotic structures by chemical modification. Nature's contribution was unique, but

man is exploiting it further. Rudel and Martinez-Manauton show, in a consideration of antifertility agents, that estrogens alone, progestins alone, or a combination, simultaneously or sequentially, may provide effective oral contraception. Other chapters deal with antihypertensives, the thyroid, digitalis, and radiologic and radioactive agents.

Chemists will find biological background, pharmacologists will find chemical background, and clinicians will find both in these excellent volumes.

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*Separation Techniques in Chemistry and Biochemistry.* Edited by ROY A. KELLER. Marcel Dekker, Inc., 95 Madison Ave., New York, NY 10016, 1967. xvi + 415 pp. 16 × 23 cm. Price $12.75.

In June 1966, a symposium on analytical chemistry was held at the University of Alberta, Edmonton, Alberta, Canada. Separation techniques presented at the symposium have been collected in this single volume. Gas-liquid chromatography and thin-layer chromatography comprise a substantial portion of the separation techniques. Applications of GLC include adrenocortical steroids and protein amino acids, while TLC is represented by separations of *N*-substituted maleimides on alumina. One section of the book is devoted to criteria of identity and purity in chromatographic separations. Specialized topics in gas chromatography include ultra high pressure to 2000 atmospheres, indeterminate errors in the measurement of chromatographic peaks, behavior of pretreated silica gels, support-coated open tubular columns, and nonlinear distribution coefficients. A theoretical aspect of TLC is noted in a chapter on observed plate height.

Newer separation techniques discussed are continuous particle electrophoresis for fractionating and studying particles of biological interest, gel chromatography for separating molecules by means of solvent-swollen gels, and liquid chromatography. A comparison of mobile-phase peak dispersion in gas and liquid chromatography is offered in this volume.

*Staff Review*

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*Statistical Techniques for Collaborative Tests.* By W. J. YOUDEN. The Association of Official Analytical Chemists, Box 540, Benjamin Franklin Station, Washington, DC 20044, 1967. ix + 60 pp. 17 × 26 cm. Price $2.00. Paperbound.

This brief paper-covered book sums up the ideas and experience of Dr. W. J. Youden, who recently retired from the National Bureau of Standards. It was written, not so much with the statistician in mind, but rather the nonstatistician or management-oriented chemist. Over the years, Dr. Youden has developed methods of presenting data in tabular and graphic form, which, from a statistical sense, are readily understandable and usable by the bench chemist. Dr. Youden has repeatedly urged that collaborative tests be run using few tests per laboratory but many laboratories. This book sums up his thoughts on the subject.

One of the highlights of his discussion is that on "systematic error," *e.g.*, an inherent error in the analytical method. The average pharmaceutical laboratory talks about systematic error but seldom routinely evaluates quantitatively the degree to which it exists or creeps into the test over a period of time. The only time a chemist might detect he has added systematic error to a test is when he gets a bad lot of material to test, the formula of the product has been changed, he compares a series of past results on a control chart and finds them predominantly high or low, or when he is setting up a new test involving knowns and the results are uniformly high or low.

The reading of this book is a good review for the chemist, because, being written in lecture style, Dr. Youden takes the reader through a series of eight chapters and tells him what he should keep in mind during his everyday work in addition to the occasional collaborative testing he may do. This book is not a textbook on statistics nor is it meant to be such. It deals with the application of a limited set of statistical techniques and the inherent problems in their use. The logic and methodology contained herein could be used as the basis on which collaborative testing for official compendia and intra-industry test development is undertaken.

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## NOTICES

*Dictionary of Organic Compounds.* Fourth Edition, Third Supplement. Oxford University Press, 200 Madison Ave., New York, NY 10016, 1967. 279 pp. 20 × 27 cm. Price $28.00. [For a review of the *Dictionary* see *J. Pharm. Sci.*, **55**, 1635 (1966)].

*Progress in Biophysics and Molecular Biology.* Vol. 17. Edited by J. A. V. BUTLER and H. E. HUXLEY. Pergamon Press, Inc., 44-01 21st St., Long Island City, NY 11101, 1967. vii + 392 pp. 16 × 25.5 cm. Price $18.50.

*Submicro Methods of Organic Analysis.* By Ronald Belcher. Elsevier Publishing Co., Inc., 52 Vanderbilt Ave., New York, NY 10017, 1966. viii + 173 pp. 15 × 23 cm. Price $10.00.

*Chemical-Medical Abstracts.* Section D, Endocrinology. Derwent Publications, Ltd., 128 Theobalds Road, London, W.C. 1, England, 1967. 24 × 29 cm. Paperbound. (Sample issue.)