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