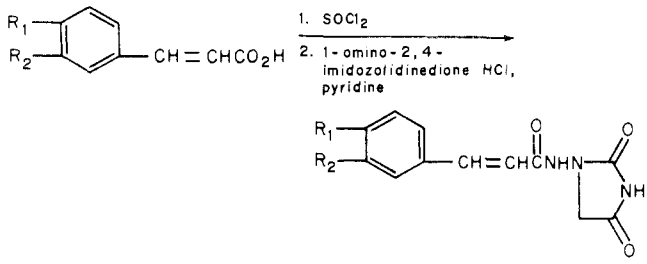
Scheme I




1-12

mercially were prepared by procedures described in the literature.[4,5] The synthetic procedure for the preparation of 1–12 is shown in Scheme I.

Title compounds 1–12 are shown in Table I.

**Anthelmintic Testing.** The compounds prepared in this work were tested against the mouse pinworm *Syphacia obvelata*.[1,2] The activity of these compounds, expressed in percent reduction in worm burden, is shown in Table I. The activity of the reference drug, piperazine adipate, is also included for comparison. Test compounds were administered perorally twice a day for 5 days. The most active compounds in reducing worm infestation are those substituted with halogen atoms (**1**, **3**, **4**, **7**, **10**) or a cyano group (**8**). However, no real structure activity trend is apparent among the cinnamamido-2,4-imidazolidinediones.

When compared to piperazine adipate for activity against *S. obvelata*, results indicate a number of compounds (**1**, **3**, **8**, and **10**) to be significantly more active, with as much as 97% reduction at 25 mg/kg (**8**).

## Experimental Section

Melting points were determined in open capillary tubes using a Mel-Temp melting point apparatus and are uncorrected. The NMR spectra were obtained on a Varian A-60A instrument using tetramethylsilane as an internal standard. The aldehyde intermediates used in the preparation of compounds **3**, **6**, **10**, **11**, and **12** were prepared by a general procedure.[6] These aldehydes as well as the cinnamic acid derivatives prepared therefrom were not characterized but used directly in the subsequent reactions.

**1-(3,4-Dichlorocinnamamido)-2,4-imidazolidinedione (1).** 3,4-Dichlorocinnamic acid (22 g, 0.1 mol) was treated dropwise with thionyl chloride (70 ml, 1 mol). After the addition was complete, the mixture was warmed for 0.5 hr, and then the excess thionyl chloride was removed in vacuo. The residue was stirred with benzene (50 ml) and the benzene removed in vacuo. To the residue was added a suspension of 1-amido-2,4-imidazolidinedione hydrochloride (15 g, 0.1 mol) in pyridine (200 ml). The reaction mixture was heated on a steam bath for 3 hr and then treated with charcoal and filtered. The pyridine solution was poured onto ice and the precipitated product (28 g, 89%) recrystallized from methanol to give off-white crystals.

Compounds **2**–**12** in Table I were prepared in a similar manner using the appropriately substituted cinnamic acids.[4-6]

**Biological Method.** *S. obvelata.* The method was described previously[2] and compound effectiveness was determined as a percentage reduction in the manner described earlier.[1] The results were analyzed for their statistical significance by means of the Mann–Whitney "U" test.[7]

**Acknowledgment.** The authors are grateful to Mr. James Sheffer for the preparation of chemical intermediates and to Mr. Stephen Ashton and Mr. William Foote for their assistance in the biological testing. Microanalyses were performed by Mrs. Cora Jeffrey and NMR spectra were determined by Mrs. Connie Lloyd.

## References and Notes

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# *Book Reviews*

**Annual Reports in Medicinal Chemistry. Volume 10.** Edited by Richard B. Heinzelman. Academic Press, New York, N.Y. 1975. ix + 348 pp. 17 × 25.5 cm. $14.50 (soft bound).

With Volume 10 of "Annual Reports in Medicinal Chemistry" Dr. Richard Heinzelman concludes his term as Editor-in-Chief and turns this important task over to Dr. Frank Clarke. His "swan-song" has been just as successful as his previous products. The organization of the subject matter follows the established format with major sections edited by competent section editors: I, CNS Agents (Gordon); II, Pharmacodynamic Agents (Clarke); III, Chemotherapeutic Agents (Warren); IV, Metabolic Diseases and Endocrine Functions (Moreland); V, Topics in Biology (Shen); VI, Topics in Chemistry (Counsell).

There are a total of 33 topics. Interestingly, 18 of these topics in the present volume did not appear in Volume 9. Hence, medicinal chemists should not consider "Annual Reports" merely as a yearly updating process but should consult, when carrying out searches, the most recent as well as the preceding volumes.

It is hard to single out any of these excellent overviews. This reviewer found great pleasure in learning of areas in which he had little previous exposure such as "Current Concepts in Periodontal Disease" by Taichman and McArthur; "Radioimmunoassays" by Kohen et al.; and "Molecular Aspects of Membrane Function" by Baran.

In a previous review this reviewer questioned the utility of the "topics" sections vis-à-vis the methodically oriented ones. Suffice it to say that even referees can change their minds and acquire new knowledge when browsing through "Annual Reports".

This book is recommended without any reservation to all who are involved in any aspect of medicinal chemistry research.

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**Drug Design. Volume 5.** Edited by E. J. Ariens. Academic Press, New York, N.Y. 15 × 23.5 cm. xvi + 356 pp. $39.50.

The present volume in this series consists of six chapters. As the editor states in his preface they deal primarily with "the physicochemical approach to the relationship of structure and mechanism of action and the applicability of the insight gained to drug design...".

The first chapter, "Utilization of Operational Schemes for Analog Synthesis and Design", is quite short. It is essentially an

expanded version of Topliss' paper on the subject [*J. Med. Chem.*, 15, 1006 (1972)]. It begins with a description of the method which may be characterized as a nonmathematical approach to multiple regression analysis and they describe several examples of the application of the method.

"The Design of Enzyme Inhibitors: Transition State Analogs" by R. N. Lundquist is an excellent summary of the current state of the art. Although this approach has not yielded any useful drugs so far, it is apparent that it has great potential. In contrast to the first chapter which instructs us how to optimize a biological lead, the second chapter offers a technique to uncover new active compounds.

The third chapter by E. J. Lien is entitled "Structure–Absorption–Distribution Relationships: Significance for Drug Design". He devotes much of this chapter to the application of multiple regression analysis to drug absorption and distribution. Very little space is devoted to a discussion of the factors which influence the transport of drugs. For example, the pH–partition hypothesis is mentioned several times but what this hypothesis is, is not discussed. That binding of drugs may influence their transport is first mentioned well along in the chapter when Ruth Levine's studies on the absorption of quaternary ammonium salts is considered. An introductory section dealing with these factors would have been very helpful in understanding why a term for dissociation appears in the equation correlating the absorption of bases from the rat stomach but does not appear in the equation for acids. It is never made clear that there are differences in pH in the stomach as compared with other parts of the gastrointestinal tract and that these differences have a profound effect on drug transport.

The fourth chapter, "The Role of Charge-Transfer Processes in the Action of Bioactive Materials", by P. H. Doukas is another relatively short one. It is reasonable to expect that charge-transfer processes play a role in drug–receptor interactions but the author fails to make a convincing case that this is a major role. In fact, he admits that other factors tend to dominate and obscure the effect of charge transfer in drug–receptor interactions.

The chapter by Grindey, Moran, and Werkheiser is entitled "Approaches to the Rational Combination of Antimetabolites in Cancer Chemotherapy". The authors begin with an excellent discussion of the problem of enzyme kinetics involving more than one inhibitor. This serves as an excellent background for the discussion of combination chemotherapy. While most of their examples are drawn from the chemotherapy of cancer, essentially the same considerations can be applied to the general problem of combination chemotherapy.

The final chapter by Kaufman and Koski has the imposing title, "Physicochemical, Quantum Chemical and Other Theoretical Techniques for the Understanding of the Mechanism of Action of CNS Agents: Psychoactive Drugs, Narcotics, and Narcotic Antagonists and Anesthetics". This is essentially a review of the work that these authors have been doing in the past few years. The first section of the chapter is a broad overview of the methodology of quantum chemical calculation. As the authors point out this is a relatively superficial review designed to give the reader a "feel" for the technique. For a deeper understanding it is necessary to consult other texts devoted to the subject.

This is followed by some examples of calculations performed by the authors on molecules of biological interest such as a group of phenothiazines, morphine, and nalorphine. What is not made clear to this reader is what is the correlation between these calculations and the biological activity of the compound. Tables of values of orbital energies and charge densities for a number of phenothiazines such as promazine and chlorpromazine are given but a discussion of the significance of these calculations with respect to the relative potencies of these phenothiazines is not presented. A similar statement concerning morphine and nalorphine can be made. The question as to why one is an analgesic devoid of antagonist properties and the other is both an agonist and antagonist remains unanswered. It is not clear why the authors discussed the problem of narcotic dependence and it is even less clear how they managed to overlook the contributions Collier and his group have made to this problem. The last section of the chapter deals with some physicochemical measurements. Here the relevance of this work is much more apparent.

Despite these criticisms there is much in this volume that is worthwhile. The major objection to the book is its price. There are 340 pages of text (exclusive of the index but inclusive of the bibliographies); this comes to over eleven cents per page. This book is just one example of the runaway inflation which has completely taken over the pricing of scientific books.

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**Hallucinogenic Agents.** By Roger W. Brimblecombe and Roger M. Pinder. Wright-Scientechnica, Bristol, England. 1975. 15 × 22.5 cm. xi + 272 pp. £12.50.

Many books and monograph articles on hallucinogenic drugs in general and on specific psychotomimetics have been published during the last 15 years. They were authored by psychologists and psychiatrists, by bewildered sociologists, and by scientist and lay explorers of tropical jungles and primitive peoples. Albert Hofmann, the discoverer of psychotomimetic lysergic acid derivatives, came closest to treating the subject from a medicinal chemist's point of view in his extensive writings. But he concentrated mainly on indole compounds of which he is a master at the expense of other structural types, especially cannabinoids. The present volume covers all types of such agents equally thoroughly and delves exhaustively into structure–activity relationships within each series and between several structural series.

Written in Pinder's now acknowledged superior style and documented well beyond the call of duty, all scientific aspects of hallucinogens are reviewed: their history, discovery, chemistry (the best sections), tissue and psychopharmacology, and medical applications. Special attention is devoted to hypotheses and facts bearing on modes of action. The bitter accusations of women's magazines linking these drugs with carcinogenicity and teratogenicity have been refuted with careful and meaningful documentation. Social workers specializing in "hot lines" for victims of bad trips will be disappointed; there is not much compassion in this factual volume.

The book is remarkably free of errors. The only one this reviewer found concerns the name Jimson weed (*Datura*) which (p 186) "originates from an episode in the American Civil War when many British troops at Jamestown suffered from *Datura* poisoning".... All those American wars must look alike from the other side of the Atlantic.

This is by far the best comprehensive book on hallucinogens for medicinal chemists, biochemists, and pharmacologists.

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**Pharmacological Basis of Cancer Chemotherapy.** Published for the University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Williams and Wilkins, Baltimore, Md. 1975. xiv + 737 pp. 16 × 23.5 cm. $30.00.

This volume is a collection of papers presented at the 27th Annual Symposium on Fundamental Cancer Research, held in Houston in 1974. In the keynote address Dr. C. Gordon Zubrod set an optimistic tone for the symposium as he reviewed the progress achieved by application of chemotherapy to a number of cancers of high mortality. This was followed by the Bertner Foundation Award Lecture, delivered by Dr. George Hitchings, under the title "Salmon, Butterflies, and Cancer Chemotherapy". In this presentation, stress was laid on the current state of knowledge of the folate antagonists and thiopurines. In this, Dr. Hitchings made a telling point we would all do well to remember, namely, the self-defeating nature of excessively targeted research. The remainder of the book is divided into six sections.

The first section on pharmacological principles of cancer chemotherapy contains five chapters ranging over the topics of disposition and metabolism of drugs, kinetics of drug action, the pharmacology of leukovorin rescue during therapy with methotrexate, and cellular pharmacology, the latter mainly comprising a study of dose–response survival curves for various agents

and the phenomenon of selective effects during the cell cycle. The chapters on drug metabolism and kinetics of drug action are particularly valuable.

The second section deals with the design of cancer chemotherapeutic agents. The chapter on principles of drug design and cancer by Dr. Ariens includes a discussion of autolysis induction as an approach to therapy. This might be the most interesting article in the book. Other topics covered in this section are selective toxicity, the chemical approach to design of agents, the relationship between biochemical pharmacology and drug design, and structure–activity relationships. A final paper on the synthesis of the 5-iodo-3-indolyl phosphodiester of 6-methylthiopurine ribonucleoside seems out of place in this rather generalized section.

Prediction of antineoplastic activity is the thread that links together, albeit loosely, the third group of contributions. Transplantable animal tumor models have been the subject of much discussion; Dr. Venditti discussed the modified approach at the National Cancer Institute designed to identify activity in human solid cancers. Much data are given regarding the experimental activity of a range of drugs. The first generation transplanted C3H mammary tumor could be a valuable tool, but Drs. Bruce and Lau find that no currently available agents can deal effectively with this tumor. Prediction of clinical response, which is a major need of cancer chemotherapy, where response rates may be low and incidence of toxicity high, receives adequate attention. The next two chapters relate to RNA tumor viruses, their relation to human leukemia and control of oncorna virus infections with rifamycins and streptonigrin. In the final chapter of this group the relevance of molecular mechanisms of action to development of the therapeutic regimens is discussed with regard to arabinosylcytosine and 5-azacytidine.

The toxicology of anticancer drugs is considered in six chapters. In the first two, entitled "The Systems Approach, Cybernetics and Toxicology" and "Increasing the Reliability of Extrapolation of Preclinical Toxicologic Data of Antineoplastic Agents", Doctors Guarino and Prieur stress the very restricted approach of conventional toxicology. There is need, for example, to incorporate pharmacokinetic data in the design of toxicological experiments. Other topics covered in this section include prediction of clinical toxicities of anticancer drugs through animal models; the clastogenic, mutagenic, teratogenic, and carcinogenic effects of antineoplastic agents, a very thorough and extensive treatment of these side effects at both preclinical and clinical levels; selective toxicity and chemotherapeutic efficacy, a biochemical treatment of nucleic acid metabolism in ascitic tumors and normal tissues of the mouse with stress on changes induced by cytosine arabinoside; and, finally, a reappraisal of phase I and II clinical trials, a useful introduction to the area.

The next section begins with discussions of DNA–drug interactions of antibiotics and alkylating agents, the interactions of pactamycin with macromolecules and ribosomes, and the interaction of drugs with enzymes. Dr. Elion's treatment of the latter topic stresses the multiplicity of interactions and the difficulty in identifying lesions critical for drug action. The last two chapters in the section deal with drug interactions, both among anticancer agents and between these agents and other drugs.

In the final section on drug resistance, Doctors Henderson and Brockman present an initial survey of the biochemical mechanisms that can lead to drug resistance. Two subsequent chapters illustrate these mechanisms by describing the changes that occur when cells develop resistance to the 6-thiopurines and the folate antagonists. Other topics covered include models and methods for biochemical studies of resistance, circumvention of resistance through the use of drug combinations and the phenomenon of collateral sensitivity, and the pharmacological basis of cancer chemotherapy.

The volume also includes the discussions that took place during the sessions, many of which are very valuable, and introductory remarks to many of the sections which are brief and of little value.

In general the contributors deserve credit for this series of well-referenced and significant articles. This reviewer has the impression that the subject index is rather short for a volume of this size, while the author index is strictly a list of the contributors and discussants and not a compilation of the names of all those workers referred to in the text. This I feel is a drawback. Nevertheless, the book will be of value both to workers in the field and to students seeking an understanding of chemotherapeutic principles.

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**Organic Syntheses via Boranes.** By Herbert C. Brown with techniques by Gary W. Kramer, Alan B. Levy, and M. Mark Midland. Wiley, New York, N.Y. 1975. xix + 283 pp. 15.5 × 23.5 cm. $17.50.

Medicinal chemists should find H. C. Brown's new book of particular interest, for it is in the pharmaceutical industry that organoborane intermediates find their most widespread application. This volume surveys the field in a way which provides greater accessibility to the procedures and techniques than any previous offerings.

The initial eight chapters present chemical principals in the odd numbers, while the even-numbered chapters give exemplary procedures, all as completely as is possible in such a burgeoning field. Chapter nine, by the coauthors, provides an enlightening review of the techniques for handling air-labile substances. This material updates the techniques invented by Alfred Stock for use in the first borane preparations to include the most modern developments.

Although a number of topics may be familiar to readers of the author's penultimate work, *Boranes in Organic Chemistry*, the biographical accounts which made that volume a bedside delight have been omitted in favor of the more thorough description of procedures and techniques. In doing so, the author has provided another valuable resource to the advanced student and the working research chemist.

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