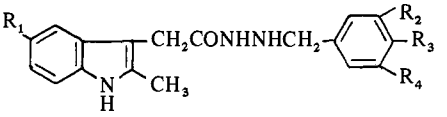
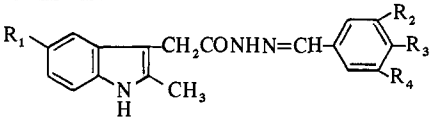
Table I. N^1-Substituted Indole-3-acetyl-N^2-(3',4'-dimethoxy/3',4',5'-trimethoxybenzyl)hydrazines and Their Anticonvulsant Activity



No.	R_1	R_2	R_3	R_4	Mp,[a] °C	Yield, %	Solvent of crystn[b]	Formula[c]	Anticonvulsant activity: Protection, %	Anticonvulsant activity: Mortality, 24 hr, %
1	CH_3	CH_3O	CH_3O	H	225	60	EtOH	$C_{21}H_{25}N_3O_3$	30	30
2	H	CH_3O	CH_3O	H	220	70	EtOH	$C_{20}H_{23}N_3O_3$	10	40
3	CH_3O	CH_3O	CH_3O	H	215	75	PE	$C_{21}H_{25}N_3O_4$	20	50
4	CH_3	CH_3O	CH_3O	CH_3O	280	60	D	$C_{22}H_{27}N_3O_4$	50	20
5	H	CH_3O	CH_3O	CH_3O	120	40	D	$C_{21}H_{25}N_3O_4$	30	50
6	CH_3O	CH_3O	CH_3O	CH_3O	112	50	Et_2O	$C_{22}H_{27}N_3O_5$	10	70

[a]Melting points were taken in open capillary tubes. [b]PE = Petr ether; D = dioxane. [c]All compds were analyzed for C, H, and N and analyses were found within acceptable limits.

Table II. N^1-Substituted Indole-3-acetyl-N^2-(3',4'-dimethoxy/3',4',5'-trimethoxybenzylidene)hydrazines



No.	R_1	R_2	R_3	R_4	Mp, °C[a]	Yield, %	Solvent[b]	Formula[c]
1	CH_3	CH_3O	CH_3O	H	198	65	EtOH	$C_{21}H_{23}N_3O_3$
2	H	CH_3O	CH_3O	H	192	60	PE	$C_{20}H_{21}N_3O_3$
3	CH_3O	CH_3O	CH_3O	H	191	70	PE	$C_{21}H_{23}N_3O_4$
4	CH_3	CH_3O	CH_3O	CH_3O	210	65	EtOH	$C_{22}H_{25}N_3O_4$
5	H	CH_3O	CH_3O	CH_3O	180	70	EtOH	$C_{21}H_{23}N_3O_4$
6	CH_3O	CH_3O	CH_3O	CH_3O	190	60	EtOH	$C_{22}H_{25}N_3O_5$

[a]Melting points were taken in open capillary tubes. [b]PE = petr ether. [c]All compds were analyzed for C, H, and N and analyses were found within acceptable limits.

the hydrazides which separated out were filtered and recrystd with appropriate solvents.

Substituted Indolebenzylidenehydrazines. A mixt of 0.01 mole of substituted indole-3-acetylhydrazine and substituted (dimethoxy- or trimethoxy)benzaldehyde (0.01 mole) in EtOH (50 ml) was refluxed for 2 hr. The reaction mixt was filtered hot and concd *in vacuo*. The solid compounds which sepd out on cooling were crystd from the appropriate solvents (Table II).

Substituted Indolebenzylhydrazines. A soln of 0.05 mole of substituted indolebenzylidenehydrazines in 100 ml of dioxane or THF was hydrogenated with 0.1 g of PtO_2 catalyst in a Parr hydrogenation apparatus at an initial pressure of 2.8 kg/cm². The required amount of hydrogen was absorbed in 15 hr. Filtration and removal of the solvent under reduced pressure left a residue which was crystd by dissolving in a minimum amount of EtOH and adding petroleum ether (bp 40–60°).

Acknowledgments. The authors wish to express their thanks to Professor K. P. Bhargava and Dr. J. P. Barthwal for their advice and encouragement and to Dr. M. L. Dhar and Dr. Nitya Anand of the Central Drug Research Institute, Lucknow, for providing microanalysis facilities. Grateful acknowledgment is made to the State Council of Scientific and Industrial Research, Lucknow for providing financial assistance to one of us (V. K. A.).

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Book Reviews

Search for New Drugs. Edited by Alan A. Rubin, with 12 contributors. Marcel Dekker, New York, N. Y. 1972. x + 452 pp. 16 × 24 cm. $19.50.

Fortuitous discovery of clinically useful drugs, so prevalent earlier in the century, is becoming less probable every day. The smaller number of clinical trials, dictated by more severe governmental restrictions, is the final pinacle protruding from an ocean of obstacles in drug research. These obstacles begin with the uncertainties of even the most sophisticated methods of drug design in the chemical laboratory. The most formidable difficulty is the predictability of the success of a drug in human medicine even if animal model experiments hold out promise. The book under discussion examines these pharmacological hurdles in several fields. In three of them drugs are known to suppress symptoms of the diseases, but with varying success only. They are antiinflammatory, antiulcer, and psychotropic drugs. The three chapters probe the possibility of discovering tests for curative agents.

Four other chapters deal with drugs–β-adrenergic blocking agents,

antiatherosclerotics, interferon inducers, and fibrinolytic agents—which may serve as indicators of new research direction. The chapter on antithrombotic and thrombolytic agents is especially clearly written (Kenneth M. Moser) and presents hopes and great experimental difficulties alike, readably and realistically. Two final chapters, on drugs affecting aging, learning, and memory do not have much new to suggest for future testing programs but summarize nicely existing methods and ideas.

For over 400 years, since Gutenberg printed the Bible, printers and publishers have taken pride in the format and appearance of books and periodicals. Now the inflated wages of American printers are forcing publishers against the wall, and are reversing this century-old trend. Almost one-half of the labor cost can be saved by not justifying right-hand margins, and using off-set type processes, as in the present volume. The reader will have to become accustomed to this format in spite of the fact that the resulting savings are not passed on to him.

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Drug Design. Edited by E. J. Ariëns. Vol. I. Academic Press, New York, N. Y. 1971. xiv + 581 pp. 23.5 × 16.5 cm. $33.00.

This is the first volume in a series which will attempt to rationalize what we know about drug design. In spite of the prodigious efforts expended jointly and separately by medicinal chemists and pharmacologists for 7 decades, drug design is still in a most tenuous stage. A biologist informs a chemist that a given chemical exerts a certain biological activity. Seldom is this activity so specific and so useful in medicine that no further work is warranted. In most cases chemists will want to improve the action of the "lead" compound and increase its potency and/or specificity by subtle alterations of its chemical structure or stereochemistry.

The development of a useful drug thus rests on two sets of investigations although these overlap in a few respects. Professor Ariëns devotes a long general introduction to phase I, the discovery of a lead compound. Such a compound can be a natural product, occasionally with a folklore of healing properties. Screening or accidental detection, or the application of more than often incorrect hypotheses can barely be classified as "design." Much more is learned from the testing of drug metabolites; the study of the action of multipotent compounds on fundamental life processes and comparative biochemistry and, especially, detailed analysis of side effects and mechanisms of action can occasionally divulge a new lead.

The second phase is molecular modification, and this is where art, intuition, experience, and science are applied to drug design. Among the reasons for molecular modification discussed by Ariëns are the search for an alternative to the lead compound, for whatever reason; sharpening of specificity; the modulation of the pharmacokinetics and biological distribution of the lead compound; and modification of time–concentration relationships. The techniques of achieving these changes range from bioisosteric replacements (which are given a good discussion) to new forms of drug availability. There is an interesting tabulation of "bis-ing" of structures to achieve higher selectivity. A good section deals with relations of physical properties to biological activities.

The biochemical reasons for the apparent lack of structure-activity relationships are presented in another section of the introduction. Why do structurally dissimilar compounds often have similar biological activity? How much do species differences affect structure-activity relationship studies? Much of this leads up to antimetabolite theories, illustrated with many examples. From there the introduction proceeds to false transmitters and other indirectly acting compounds. The chapter ends with a critical review of receptor hypotheses.

The slightly pharmacological bias in these presentations is counterbalanced by a strictly physicochemical approach in Chapters 2–5. Corwin Hansch gives us perhaps the most authoritative elaboration of the quantitative structure-activity relationships of which he is the unquestioned main proponent. J. K. Seydel writes a long and searching chapter on physicochemical approaches to rationalizations in drug design, and these chapters are capped by discussions of MO theories, regression analysis, and electronic aspects of drug action by A. J. Wohl and by R. L. Schnaare. Included are transfer complexes of CNS-active drugs, and conformational ideas of drug-receptor interaction. These five are the most instructive chapters of the book, but the reader should brush up on the mathematics of physical chemistry if he wants to tackle them profitably.

Two chapters with more limited application to structural design are "Biopharmaceutics" by J. G. Wagner and "Pharmacokinetics" by J. M. Van Rossum.

The complex crossword puzzle of drug design has not been solved by the multifaceted treatment of principles in this volume. One will wait expectantly for the continuation of the series which will deal with specific examples. It is not easy to predict what rabbit Ariëns will pull out of an almost emptied hat that may keep worried medicinal chemists from tossing in their troubled REM sleep.

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Amino Acids, Peptides, and Proteins. Volume 3 (Specialist Periodical Reports). Edited by G. T. Young, with 15 other contributors. The Chemical Society, London. 1971. xiv + 379 pp. 14 × 22 cm. £6.00.

This volume, which covers the literature in this field for 1970, continues the excellent series of specialist reports. New papers, particularly in the areas of protein structure and peptide synthesis, appear at such a rate that even workers actively engaged in the field find it nearly impossible to keep up with the literature. In this volume, 532 papers on structural investigations of peptides and proteins and 348 papers on peptide synthesis, along with several hundred other papers in the areas of amino acids, peptides with structural features not typical of proteins, and metal derivatives of amino acids, peptides, and proteins are reviewed. The papers on peptide synthesis appeared in 73 journals.

The reviewers have done a superlative job of assimilating the data from these many papers, and accentuating the important aspects of them. In the chapter on protein structure chemical, spectroscopic, and X-ray methods are covered. In the chapter on peptide synthesis, a valuable feature is the appendix which lists all peptides synthesized and reported during 1970, as well as useful new synthetic intermediates described during the same period. A special table lists applications of Sephadex LH-20 in peptide chemistry. This is an indispensable key to the literature for the scientist working in any of these areas.

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Electron and Coupled Energy Transfer in Biological Systems. Edited by T. E. King and M. Klingenberg. Marcel Dekker, Inc., New York, N. Y., $28.50

This book is not a systematic treatment of electron and coupled energy transfer in biological systems. It consists of five chapters which review specifically the following topics: cytochrome oxidase, nonporphyrin-bound metals, lipid components in electron transfer systems, bioenergetics of invertebrates, and bioenergetics of microbial systems.

With this reservation in mind, the book would be useful to investigators in the field of bioenergetics as a reference or teaching aid and to advanced graduate students or postdoctoral fellows who are commencing research in one of the above mentioned areas. It is not suitable for students without any knowledge of the field of bioenergetics and they would benefit best by investing their limited resources in one of several other less specialized books which treat the subject in a more basic and organized manner.

I found each of the chapters to be well written and to give a broad overview of the subject discussed. In some cases there is overlap; *e.g.*, the role of copper in cytochrome oxidase is dealt with in two different chapters. This proves to be beneficial because the reader gets the viewpoint of more than one author. For the most part, the authors are not dogmatic about the subjects covered and state quite fairly what we do know and what remains to be established about the subject. This type of treatment thus provides the necessary background as well as prospective problems for those advanced students entering the field.

Perhaps the biggest drawback to the book is that some of the chapters were submitted by the authors more than 4 years ago and have not been revised to include more recent material. As a result, some new and very exciting experiments are not discussed.

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