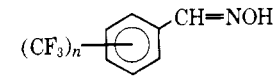
TABLE I

TRIFLUOROMETHYLBENZALDOXIMES



No.	Config	Isomer	n	Yield, %	Mp, °C[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, %[b] C	Found, %[b] H	Found, %[b] N
1	*syn*	*ortho*	1	85	54–55	$C_8H_6F_3NO$	50.80	3.26	7.41	50.74	3.35	7.26
2	*syn*	*meta*	1	77	46–47	$C_8H_6F_3NO$	50.80	3.26	7.41	50.69	3.26	7.19
3	*syn*	*para*	1	70	100–101	$C_8H_6F_3NO$	50.80	3.26	7.41	51.07	3.25	7.51
4	*syn*	3,5-di	2	85	92–93	$C_9H_5F_6NO$	42.02	1.95	5.44	42.37	2.04	5.36
5	*anti*	3,5-di	2	1	134–135	$C_9H_5F_6NO$	42.02	1.95	5.44	42.19	2.28	5.35

[a] Melting points were determined on a Thomas–Hoover capillary apparatus and are corrected. [b] Analyses were performed by Galbraith Laboratories, Inc., Nashville, Tenn.

with Raney nickel and formic acid.[6] Yields of 58, 74, 75% were obtained for the *ortho*, *meta*, and *para* isomers, respectively. The aldehydes were used without further purification in the next reaction.

***syn*-Trifluoromethylbenzaldoximes.**—Vogel's[7] procedure was followed, but the pure *syn* configuration was obtained only with 1. Compounds **2** and **3** contained traces of the *anti* compounds, while **4** contained a larger amount of the *anti* configuration. The crystalline *syn* configurations, 1–**4**, were obtained by column chromatography on silica gel with benzene–ethyl acetate (10:1 as the eluting solvent.

***anti*-Trifluoromethylbenzaldoxime Hydrochlorides.**—Saturation of the ethereal solutions of the *syn*-oximes with anhydrous HCl gas and subsequent cooling caused precipitation of the salts which were collected on sintered-glass funnels.[7] The yields of the salts were essentially quantitative. No salt could be formed from **1**. The unusual behavior of the *ortho* isomer will be the subject of a later communication.

***anti*-Trifluoromethylbenzaldoximes.**—Decomposition of the *anti*-hydrochloride salts of **2** and **3** with 10% aqueous Na_2CO_3 followed by ether extraction resulted in a mixture of configurational isomers. Column chromatography of the mixtures failed to give crystalline *anti* isomers. Compound **5** was separated from **4** by silica gel column chromatography.

(5) Purchased from Pierce Chemical Co., Rockford, Ill.
(6) B. Staskum and O. G. Backeberg, *J. Chem. Soc.*, 5880 (1964).
(7) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 719.

Book Reviews

Anticancer Agents. By FRANCES E. KNOCK. A Monograph in American Lectures in Living Chemistry. Edited by I. NEWTON KUGELMANS. Charles C Thomas, Publisher, Springfield, Ill. 1966. ix + 272 pp. 25 × 18 cm. $15.50.

As they walked along a path one evening, a group of men came upon a friend searching the ground under a lamp post. The searcher explained that he was looking for a key, whereupon the strollers joined in the search. After examining the area for some minutes, they asked, "are you certain that the key is here?" The friend answered, "oh no, it is someplace along this path, but the light is here." Examination of this well-known story with respect to the friend's approach to his dilemma, discloses something about his judgment. He knew that the key was to be found someplace within rather broad limits. Since the light was within these limits, the decision to look under it was sound because the key would be more easily found if it were there. His decision to commit, by his silence before questioning, his friends to look in the same place was clearly unsound. The man fell into the "trap" of assessing his situation as presenting a choice between two alternatives which were not mutually exclusive. Dr. Knock seems to have fallen into a similar "trap" in her editorial comments on the status of cancer chemotherapeutic studies in the United States; but more about this later.

The book purports ". . . to present related aspects of surgical–chemical treatment of cancer, at preclinical and clinical levels." Further, the author pleads ". . . for patient-centered cancer therapy, . . . for coordinated surgical–chemical treatment of cancer individualized in accord with the chemical requirements of each patient's own cancer cells." The desirability of these objectives is unquestioned. The author's approach to selection of a drug on the basis of biological, chemical, and drug-sensitivity testing of the patient's tumor is interesting and worthy of note even though such techniques have not yet been fruitful in general. Otherwise, the book presents a concise review of factors known to influence the etiology, development, and treatment of experimental or clinical cancer, and will be informative for scientific investigators who are not directly involved in cancer therapy; for those who are in the field, it will seem to be somewhat superficial.

Factors known to influence the development of cancer in the laboratory animal or in humans including chemical, physical, and viral carcinogens are discussed briefly. The author has noted the value of early diagnosis. She has reviewed broadly the techniques of surgery and radiation and their value, and has properly pointed out their limitations in cases of disseminated disease. New and older approaches which have been exploited to varying extents are discussed. These range from the use of surgery plus chemotherapy to the use of immunotherapeutic techniques; the latter yet to be shown as beneficial. Reviewed with clarity are some of the known biochemical and pharmacological actions of some widely known anticancer agents as well as other agents that are of interest because of their similarity in action to known anticancer drugs. The student of biochemistry and pharmacology may find these discussions interesting inasmuch as many important biochemical pathways, and the ways in which they are inhibited, are covered. The main types of compounds considered are alkylating agents, sulfhydryl inhibitors, antimetabolites, plant and antibiotic filtrate products, steroids and hormones, and miscellaneous drugs including methylglyoxal bisguanylhydrazone, methylhydrazines, terephthalanilides, *o,p'*-DDD, hydroxyurea, quinacrines, urethan, and indomethacin. Scant mention is made of bischloroethylnitrosourea, and cytosine arabinoside is not mentioned. Both of the latter have been in clinical trial.

This leaves Dr. Knock's comments on the ethics involved in entering a new drug into clinical trial and her thoughts on the philosophy of searching for new chemotherapeutic agents. It is unfortunate that on this latter point, concerning the national program for uncovering new anticancer drugs, Dr. Knock has

fallen into the "trap" described in our opening parable. In her chapter on Perspectives, in which she comments on the "Clinical Problems in Cancer Chemotherapy," the author has, in the opinion of this reviewer, seriously detracted from her otherwise informative book. Specifically, she has presented the time-worn argument of "empiricism *vs.* the rational approach" and from a clearly prejudiced viewpoint. Avoidance of this "trap" depends on an awareness that beneficial developments in clinical medicine have most generally resulted from the prudent application of both approaches and that they are not mutually exclusive. Thus, the author criticizes national cancer chemotherapy programs paraphrasing from the 1965 report of the "Wooldridge Committee," which she erroneously states as having been appointed by President Johnson rather than President Kennedy (the final report was made to President Johnson). The author fails to mention that one of the basic recommendations of the Wooldridge Committee was that an *ad hoc* committee be instituted to review the national cancer chemotherapy program. The latter committee, chaired by Arthur P. Richardson, Dean of the Emory University School of Medicine, while recommending some decrease in large-scale empirical anticancer screening and increased emphasis on basic research, did recognize that "... current knowledge of the biology of cancer and mode of action of chemotherapeutic agents is still too limited to support an entirely rational approach."

In the opinion of this reviewer, the national cancer chemotherapy program has, from its inception, recognized the need for both the empirical and rational approach, one complementing the other. One need look no further than the history of modern chemotherapy to become aware that most of man's useful drugs originated with serindipitous or empirical observations followed by developmental work rationally based on structure–activity studies, specificity studies, etc. Discovery by serendipity cannot be planned. It depends on perspicacious observation. Discovery by empiricism is planned and has been successful. It is based on acceptance of the premises that (a) the desired goal exists, and (b) an infinitely broad search will attain the goal or fortuitously uncover a clear way to it which can be followed rationally. If the reviewer seems to make too much of this issue, it is because the author implies that the ability to choose a drug for each patient on the basis of the biological and chemical characteristics of his tumor and the tumor's *in vitro* sensitivity to drugs is a *fait accompli*. The concept is potentially sound, the goal is desirable, but instances of successful application have been rare. In the meantime, while we await the technological developments necessary to achieve this goal, Dr. Knock's immoderate attack on the status of the national program seems premature.

NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014
JOHN M. VENDITTI

Progress in Drug Research. Volume 10. Edited by E. JUCKER, Birkhäuser Verlag, Basel. 1966. x + 603 pp. 17.3 × 24.7 cm. 128 Swiss Francs.

We have come to look forward to each new volume in this series with pleasurable anticipation. These surveys contain some of the most adequate reviews of current interest in various medicinal fields, set against a historical background of developing ideas and experiments. It is disappointing to sense a foreboding about the future of medicinal chemistry in several leading articles in the present volume. The motivating basis of this attitude is, of course, the fact that medicinal discovery has slowed down; indeed, the last decade has been almost sterile compared to the surging tide of discovery from 1930 to 1955. Innovations since the mid-fifties have been largely developments and modifications based on earlier discoveries. Nobody will deny that few if any breakthroughs in drug research have appeared in the expanded medicinal literature of the last 10 years.

Some of the reasons for this decline have been extraneous and essentially at the clinical level: stricter regulation of drugs and their abuses, sparked by the tragedy of teratogenic side effects and by the smearing of the picture of drug studies and sales by politicians seeking reelection. But where there is smoke there is fire, and some of the abuses uncovered in the course of such discussions and the placebo nature of some widely advertised agents have contributed to the growing distrust of drugs by the public. But the real cause of the decimation of novel drug discovery has been the lack of acceptable and defendable new ideas which could be applied to the design of truly new drugs with a definite promise of carry-over from the laboratory to the clinic.

G. Ehrhart paints a particularly pessimistic picture of the present situation. He even discounts the value of molecular modification based on structure–activity relationships. His attitude may be limited by his emphasis on research achievements in his own company which, while noteworthy, do not represent the total scope of drug investigation. A much broader and more optimistic outlook is to be found in R. G. Denkewalter and Max Tishler's contemplations on the present and future of medicinal research. However, these authors also recognize the failure of current basic knowledge to spawn new ideas in therapeutic areas which have been resistant to advance so far. New insights must be gained from molecular biology, and the obvious conclusion is that we do not teach medicinal science of the future in our universities.

W. Kunz' review of new drugs is of value especially to the student of prescription items in Europe; the minimal additions to American drugs under the influence of restrictive legislation may have something to do with the local emphasis of this survey. J. H. Biel and B. K. B. Lum recount β-adrenergic blocking agents in Biel's usual masterful manner; the long and excellent article by E. J. Ariëns on the many facets of drug design complements the hopes expressed in the paper by the two Merck authors above. From the same company comes a particularly timely review of nonsteroid antiinflammatory agents by C. A. Winter. A critical evaluation of all the biological aspects of this important and therapeutically controversial field has long been needed.

The presentation of articles of general medicinal interest is an innovation to be welcomed in this series. These papers should persuade many medicinal chemists to place Volume 10 on their private book shelves.

UNIVERSITY OF VIRGINIA
CHARLOTTESVILLE, VIRGINIA
ALFRED BURGER

Topics in Medicinal Chemistry. Volume 1. Edited by J. L. RABINOWITZ and R. M. MYERSON. Interscience Division, John Wiley and Sons, Inc., New York, N. Y. 1967. xi + 453 pp. 24.5 × 17 cm. $17.75.

Edited monographs are usually compiled by coaxing contributors into writing chapters. Even though the original plan and outline prepared by the editors may represent a unified and timely effort, such plans are liable to fall by the wayside if key contributors drop out for some reason. If such an event endangers the publication of the book, some late substitution may be arranged in haste, and this will barely ever be as satisfactory as the original plan. Something like this must have happened to the present volume, or else a serious misunderstanding must have beset the choice and arrangement of the topics.

Medicinal chemistry and biochemical pharmacology have no quarrel how their fields of interest should be divided up. However, it is generally agreed that biologists gladly keep their fingers out of organic-preparative methodology, and medicinal chemists do the same when it comes to pharmacological methodology. There may be some occasional overlapping, but there is none when it comes to clinical pharmacology except for that rare species of a Ph.D. in chemistry who also holds an M.D. degree, and who actually works both as a chemist and as a clinician. I am sure that 99.9% of all medicinal chemists cannot aspire to such proficiency and would shy away from the legal and professional restrictions imposed on the physician who tests new drugs in patients. It is therefore strange to find a section on "Clinical Medicinal Chemistry" in the present book.

One of these chapters, on digitalis, lists the structural formulas, names, components, sources, etc., of the major cardiac glycosides which are of clinical importance, before delving into animal and human pharmacology of these substances. The formulas and names are merely descriptive; there is no attempt at correlation, at comparisons of structures and properties with activity, although these topics form the intellectual core of medicinal chemistry. It is worse in the chapter on oral contraceptives; it does not even have the formulas, and it is purely clinically oriented. This holds also for the descriptive chapter on radioactive drugs. The listing of the chemicals used in diagnostic procedures gives a