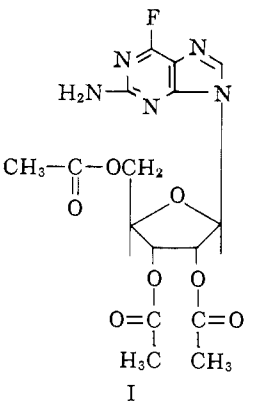
# Communications to the Editor

## The Preparation of a Derivative of 6-Fluoro-9-β-D-ribofuranosylpurine[1]

We wish to report the first instance of the introduction of fluorine into position 6 of a purine nucleoside. Compounds of this type are of considerable interest because of the biological activity of such nucleosides as 5-fluoro-2′-deoxyuridine[2] and 2-fluoroadenosine.[3] The synthesis of 2-amino-6-fluoro-9-(2,3,5-triacetyl-β-D-ribofuranosyl)purine (I) has now been accomplished



I

and is the subject of the present report. When 2-amino 6-chloro-9-(2,3,5-triacetyl-β-D-ribofuranosyl)purine[4] was treated with silver fluoride[5] in refluxing toluene, I was isolated in 10–25% yield. The unreacted silver fluoride was filtered, and the cooled toluene gave a white crystalline product (I), m.p. 144–146°. Recrystallization from toluene did not alter the melting point.

*Anal.* Calcd. for $C_{16}H_{18}FN_5O_7$: C, 46.8; H, 4.42; N, 17.0; F, 4.6. Found: C, 47.0; H, 4.04; N, 16.7; F, 4.9. In 95% ethanol the ultraviolet absorption spectrum showed $\lambda_{max}$ 246 and 289 mμ; ε 11,100 and 7,000.

This type of halogen exchange has recently been found to be general for various 7- or 9-alkylated purines[6] possessing a chlorine substituent in positions 2, 6, or 8. The synthesis of the acetylated derivative (I) was selected since acetylation of certain pyrimidine nucleosides[7,7a] and nucleoside antibiotics[8] has been reported to alter transport characteristics in such a way as to improve on the efficacy of the drug.

Attempts to deacetylate I with methanolic ammonia were unsuccessful. Under conditions which readily convert 2-amino-6-chloro-9-(2,3,5-triacetyl-β-D-ribofuranosyl)purine to 2-amino-6-chloro-9-β-D-ribofuranosylpurine,[4] methanolic ammonia changed I to 2,6-diamino-9-β-D-ribofuranosylpurine.[9]

Compound I has been submitted for antitumor and antiviral screening. The possibility of the synthesis of other 6-fluoropurine nucleoside derivatives is presently being explored.

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(1) This work was supported by research grant CY-4008(C4) from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *J. Am. Chem. Soc.*, **81**, 4112 (1959).

(3) J. A. Montgomery and K. Hewson, *ibid.*, **79**, 4559 (1957).

(4) J. F. Gerster, J. W. Jones, and R. K. Robins, *J. Org. Chem.*, **28**, 945 (1963).

(5) The silver fluoride (argentous) was purchased from the Harshaw Chemical Co., Cleveland, Ohio. The yield of I varied considerably with different lots of silver fluoride used.

(6) A. G. Beaman and R. K. Robins, *J. Org. Chem.*, in press.

(7) E. S. Perkins, R. M. Wood, M. L. Sears, W. H. Prusoff, and A. D. Welch, *Nature*, **194**, 979 (1962).

(7a) W. A. Creasey, M. E. Fink, R. E. Handschumacher, and P. Calabresi, *Cancer Res.*, **23**, 444 (1963).

(8) H. Hoeksema, C. B. Whitfield, and L. E. Rhuland, *Biochem. Biophys. Res. Commun.*, **6**, 213 (1961).

(9) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951).

# Book Reviews

**The Opium Alkaloids.** Selected Topics. By David Ginsburg, Israel Institute of Technology, Haifa. 111 pages. Interscience Publishers, Inc. (a Division of John Wiley and Sons), New York, N. Y., 1962. $6.50. Reviewed by Alfred Burger, University of Virginia.

This small volume represents formalized lectures on some aspects of the chemistry of morphine, codeine, thebaine and papaverine, given by the author during a sabbatical year, and as he imagines they might be given to graduate students as part of a course on alkaloids. The approach to the chemistry of these compounds is deductive, and both structural proof and syntheses are treated so as to teach selected students to think rather than to memorize. The chapters on the stereochemistry and biogenesis of morphine are especially well conceived. Unfortunately, *not one single reference* documents the text, and the index is scanty and useless. The pharmacological and medicinal implications of these alkaloids which have so influenced the mechanisms and the design of drugs, are not even hinted at. The chapter on papaverine is largely historical and does not measure up to those on morphine. The minor opium alkaloids are not mentioned. Since the book is neither a monograph nor a text book, few chemists will want to turn to it for information.

**Absorption Spectroscopy.** By Robert P. Bauman, Assistant Professor of Physical Chemistry, Polytechnic Institute of Brooklyn. John Wiley and Sons, Inc., New York, N. Y., 1962. $12.00 (10 chapters, 611 pages). Reviewed by Paul N. Schatz, University of Virginia, Charlottesville, Virginia.

Professor Bauman has written an admirable book on a subject too broad to be covered thoroughly in any one volume. It starts with an introductory chapter on various basic fundamentals, followed by two chapters on instrumentation and a fourth chapter on sample preparation. The middle chapters (5–7) and chapter 10 are primarily theoretical in nature discussing such topics as

classical and quantum mechanics, electronic structure, molecular vibrations and rotations, group theory, and the application of such topics to spectroscopy. Chapters 8 and 9, entitled, respectively, Qualitative Analysis and Quantitative Analysis, are chiefly concerned with practical applications.

In general, the discussion of practical applications is excellent throughout the book. If one wishes to do experimental work in spectroscopy, this volume will prove a splendid starting point. Both experimental details and more general principles are discussed clearly and accurately. The range of topics is broad, including such things as details concerning instrumentation, a survey of commercially available instruments, sample preparation, cells, and a variety of methods of analysis.

The theoretical discussion also covers a wide range of topics, but, of necessity, the subject matter is abbreviated. It will serve as an adequate refresher for someone already familiar with the material. For someone lacking this familiarity, the book will serve to state what the results of theory are and what subjects one should consult in a more specialized text, but the theoretical treatments will prove to be too condensed for the beginner. In brief, this volume represents an excellent presentation of practical absorption spectroscopy coupled with a good summary of the theoretical background.

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**Infrared Spectra of Pharmaceuticals.** Issued by Sadtler Research Laboratories, 1517 Vine Street, Philadelphia 2, Pa. 750 spectra + 8 sets of indices, $400.00. Reviewed by O. R. Rodig, University of Virginia.

This useful addition to the Sadtler collection of spectra contains a group of 750 infrared spectra, recorded from the 2 to 15 micron range on a linear wave length *versus* percentage transmission scale. The backbone of the work consists of spectra of active principles of drugs found largely in the latest editions of "New and Nonofficial Drugs," "The United States Pharmacopoeia," "The National Formulary," "The British Pharmacopoeia," and "The National Dispensatory." Each spectrum also contains the generic, trade and descriptive chemical names of the substances, the structural and empirical formulas, source, major use, the preparative technique used (*e.g.*, KBr wafer, between salts, etc.), and the instrument used to run the spectrogram. Most of the spectra were scanned on either the Beckman IR4 or Perkin-Elmer 21 instruments. The spectra are 7.6 × 21.6 cm., having been reduced photographically from a 12.7 × 44.5 cm. master copy, and appear one to a page with the back of the page blank. In this reviewer's opinion, it would have been more desirable to place two spectra on a page since this could be done without undue crowding and would have cut the bulk of this work in half. (The entire work is printed on heavy paper and comprises two volumes, each volume being approximately 7 cm. thick).

A very valuable part of this spectra collection is an elaborate indexing system, comprised of eight different sets of indices. Thus one can find substances indexed according to Trade Name, Generic Name, Common Chemical Name, Chemical Abstracts Name, Common Use, Molecular Formula, Chemical Class, and Spectrum Number. The spectra will also be listed in the Commercial Spec-Finder edition to be issued in late December. This indexing method categorizes the spectra according to their strongest absorption bands and thus serves as a valuable aid in identifying spectra of unknown substances. The Commercial Spec-Finder is not included in the Pharmaceutical Collection and must be purchased separately.

Since some of the indices were compiled using an IBM punch card system, code symbols are occasionally employed in the names. However, these are easily remembered and are no drawback to the use of the indices.

The Chemical Class Index lists the compounds in terms of their functional groups and categorizes them in approximately 100 different sections, such as quaternary amines, carboxylic acids, alcohols, thiophenols, metallo-organic coördination compounds and epoxides, just to mention a few. Many of these groups are, in turn, further broken down into subgroups.

The Common Use Index lists the spectra in one of 25 categories, as found in NND. These include such areas as local anesthetics, antibiotics, autonomic drugs, hematological agents, skeletal muscle relaxants and their antagonists, etc. Thus far, no entries appear under contraceptives, enzymes, immunologic agents and radioactive isotopes.

The entire work is housed in two green vinyl hard-cover looseleaf binders thus allowing easy replacement of any of the spectra. It is stated that replacement spectra will be reissued to correct errors or when improved data become available. The spectra are obviously most useful to persons dealing with drug identification and purity. However, due to the large number and diversity of examples available and the excellent indexing, this collection should also be of significant value for spectra–structure correlations in any organic laboratory and comprise a useful addition to the Sadtler Spectra Collection.

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**Enzymatic Synthesis of DNA.** By ARTHUR KORNBERG. John Wiley and Sons, Inc., New York, N. Y., 1962. ix + 103 pp. $4.00. Reviewed by R. Bruce Martin, University of Virginia, Charlottesville, Virginia.

The three chapters of equal length in this little book were delivered as CIBA lectures in microbial biochemistry. Though these lectures were presented in the spring of 1961, they summarize work of the author appearing in journals through 1962. The first chapter begins with a brief description of the structure of DNA and proceeds to describe the cell-free enzyme catalyzed replication of DNA. It concludes with a discussion of nearest neighbor base frequencies of ordinary and single stranded DNA. The second chapter discusses the synthesis and structure of synthetic polydeoxyribonucleotides. In the third chapter DNA synthesis in bacteriophage infected cells is sumniarized. The book is liberally illustrated with either a figure or table every $1^1/_2$ pages. Though there is no index, the table of contents is detailed.

As can be seen from this brief description, the book does not present an even synopsis of Kornberg's contributions on DNA polymerase but is weighted in favor of his more recent studies. The book is not a primary reference source, nor will those familiar with Kornberg's papers find anything new here. Rather, the work presents the essence of the author's recent research without the complications of the papers. This statement does not imply that difficulties are ignored; indeed, unanswered questions frequently are pointed out. For those who want an encapsulization of Kornberg's truly significant and beautiful research, his little book is recommended for an evening's reading.

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**Progress in Drug Research.** Vol. 3, ERNST JUCKER, Ed. Birkhäuser Verlag, Basel, 1961, and Interscience Publishers, Inc., New York, N. Y., 1961. 563 pp. $23.50. Reviewed by Alfred Burger, University of Virginia.

As in the previous volumes in this series, broad subjects in medicinal chemistry are reviewed thoroughly by authorities in their respective fields in this book. No claim for completeness of references is made, and long tabulations of related compounds and their activities are presented only on occasion. Instead, the organic chemistry, biochemistry, and biological modes of action are illustrated critically, the pertinent facets of these subjects receiving primary attention. The present volume contains six review articles of exceptional timeliness. N. P. Buu-Hoï comprehensively discusses (in French) fluorinated organic compounds of pharmacological interest; this is by far the best article on this subject this reviewer has read. Structure–activity relationships of phenothiazine and piperazine anthelmintics are presented by J. Cymerman Craig and M. E. Tate, with a conclusive section on the mode of action of such compounds. V. Erspamer, one of the fathers of the serotonin field, has written an exhaustive review of almost monograph length on 5-hydroxytryptamine and related indolealkylamines. A pharmacological approach to allergy by G. B. West surveys the contributions of cells, tissues, hormones, and enzymes to the allergic syndrome, centering on the release of histamine and 5-hydroxytryptamine. In this complex area, an unbiased appraisal of these many factors is a welcome and educational contribution. Two articles are in German. One of them discusses antineoplastic antibiotics from actinomycetes (Kh. and Christa Zepf) while the other one is the now famous annual review of new clinical drugs by W. Kunz.

As usual, paper, print, and book make-up are excellent. The authors, the editor, and the publishers are to be congratulated on another job well done. A subject index—not completely reliable, unfortunately—guides the reader through the book.

**Chemistry of The Sex Hormones.** By PETER M. F. BISHOP, Guy's Hospital Medical School, London. xi + 100 pp. Charles C Thomas, Publishers, Springfield, Ill., 1962. $5.75. Reviewed by Alfred Burger, University of Virginia.

In this small book, the author has tried to explain to the expert steroid chemist, in simple language understandable to the physician as well, the structures, conformations and the physiological effects of the natural sex hormones and their synthetic analogs and congeners. It is always difficult to steer a course between thoroughness and expediency, and the result is usually dilution to the brink of superficiality. Dr. Bishop has almost avoided this, but not quite. There are no descriptions of either degradations or syntheses of the sex hormones, as implied by the word "chemistry" in the title of the book, and there is no bibliography. The index is minimal, and the list of clinically used materials is that available in England. Nevertheless, the chemical novice who wants to get a quick look at the formulas of these compounds will find this book handy, pleasant to read, and easy to understand.

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**The Biochemical Bases of Psychoses or The Serotonin Hypothesis about Mental Diseases.** By D. W. WOOLLEY, Rockefeller Institute. xii + 331 pages. John Wiley and Sons, Inc., New York, N. Y., 1962. $11.95. Reviewed by Alfred Burger, University of Virginia.

Only the last followers of the early psychoanalytical schools still believe that mental disturbances of various shades and depths are caused solely by early experiences and by environmental factors. Although no psychiatrist and biochemist would deny the contribution of such factors to the *ultimate* causation of mental diseases, they are equally convinced of the chemical causes of these conditions. The plural has been chosen with care, because so far the imbalance of several hormones and neurohormones has been indicted in different manifestations of psychoses and neuroses. In a few cases of genetically caused idiocies, the inherited lack of some enzymes or coenzymes has been found to be responsible for these conditions, and measures to interrupt the progression to irreversibility have had success. Of the metabolites found to alter behavior and the mood, serotonin, norepinephrine and acetylcholine have received most attention. Dr. Woolley has contributed much to the chemistry and physiology of serotonin, and it is not surprising that he emphasizes this compound over others. But in contrast to his previous books and reviews, the present volume is not narrowly biased; it discusses critically and with an open mind the many different biochemical facets of psychoses. Most of all, its easy and straightforward style makes the book readible and understandable both to the professional biochemist and to the chemically educated physician. There is considerable strictly technical information to satisfy the expert, and enough—although necessarily loose—speculation to stimulate thinking and possible experimentation. There is, for better or for worse, a philosophical appendix wishing for peace of mind in a world that cannot be. The discussion of psychopharmacological agents now in clinical use is marginal. But the intelligent approach to mental disease drugs by the pathway of broadly considered metabolite antagonism is well presented and will make the book worth reading.

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**A Medical Greek and Latin Workbook.** By JAMES A. MCCULLOCH, Duquesne University. ix + 154 pages. Charles C Thomas, Publishers, Springfield, Illinois, 1962. $5.75. Reviewed by Alfred Burger, University of Virginia.

How does a chemist learn the vocabulary of the pharmacologist? And how does the undergraduate student acquire the words needed in the curriculum of the medical school? Does he just memorize them the hard way, one by one, or base his progress on etymological comparison? If he uses etymological principles, how does he get along without Latin and Greek that he may never have studied? The present text book is designed to help him to get past this hurdle. It contains Greek and Latin prefixes, words, and suffixes pertaining to medical terminology. The student is taught to join prefixes and suffixes to words; he drills and practices as he goes along and increases his vocabulary. Ultimately, his whole vocabulary is bound to expand, and even in his vernacular he will profit from the increased etymological knowledge.

The exercises are clear and easy to follow, the approach to scientific terminology is novel, and self-examinations and tests assure the serious student of satisfactory progress. The text can be recommended to the medicinal chemist who has been trained in chemistry and who finds himself confronted with strange terms in writing, speaking, spelling, and pronouncing in his semi-medical surroundings.

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**Diseases Caused by Chemicals.** Two new books. **1. Human Ecology and Susceptibility to the Chemical Environment.** THERON G. RANDOLPH, The Swedish Covenant Hospital, Chicago, Ill. vii and 148 pages. $5.50. **2. Drug-Induced Diseases.** A symposium organized by the Boerhave Courses for post-graduate medical education. L. MEYLER, Groningen, and H. M. PECK, West-Point, Pa., Editors. 237 pages. $12.50. Both published by Charles C. Thomas, Publishers, Springfield, Ill., 1962. Reviewed by Alfred Burger, University of Virginia.

In the wake of Rachel Carson's "Silent Spring" which disgusted the scientific community with its dramatic and totally uninformed and unfounded attack upon man-made environmental chemicals, a rational medical evaluation of real and potential damage to our health by chemicals is to be welcomed. The two books under discussion are designed to furnish such information, but they do it in different degrees. Dr. Randolph's small volume lists every kind of chemical which has proved noxious, allergenic or pathogenic to man in recent years. Written by a physician whose long-ago courses in elementary chemistry no longer evoke an echo in his mind, it mentions exhaust gases, cosmetics, smog, drugs, and dozens of other classes of agents and describes their damaging effects on *susceptible* humans. It states that natural pure vitamins do not cause any damage while synthetic samples, chemically identical with the natural products, may cause disease (sic!). The book is addressed to the practicing physician who may encounter allergic consequences of repeated exposure to usually not just one chemical, but to a mixture of substances. Unlike Miss Carson, Dr. Randolph does not dwell on food additives and pesticides, but his preoccupation with clinical observations and preventive measures does not recommend the volume to the medical scientist, except to the allergist. Nevertheless, medicinal chemists and pharmacologists may want to thumb through this book and become aware of the possibility of sensitization by everything they themselves touch, or that they prepare for clinical trial and use.

For questions posed, and sometimes answered in the field of drug-induced disturbances, they will do well to turn to the second book, a symposium of twenty experts who present discussions of their research groups in English, French, and German. This is a much more interesting and well documented work. It deals with such subjects as morphological aspects of sensitization, anaphylaxis in man, cytopenia of immunological origin and non-immunological aspects of drug-induced blood diseases, anemias and skin disorders caused by drugs, sensitization to drugs as a cause of collagen diseases, ototoxic effects of drugs, and discussions of interminable "side-effects" of a wide variety of drugs in a variety of tissues, including the brain and its functions. A timely chapter on risks for the neonatus caused by the administration of drugs during pregnancy concludes this symposium. By necessity, much of these lamentable manifestations can only be treated descriptively, with a bow toward the known causation, but without much hope of prophylaxis, except to suggest that drugs should not be used unless really needed, and then in dosages that will do the required job as quickly as possible. The medicinal chemist can try to overcome side effects resulting from true toxicity by structural variation; secondary pharmacological effects may be met by modifying administrative routes and schedules; combinations of drugs which exaggerate toxic reactions can readily be altered. But in most instances we have to live with inherited sensitivities to drugs if we are to use our modern agents without forbidding restrictions.