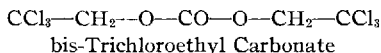


Carbonate Prodrugs in Formulation and Therapeutics

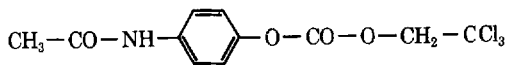
Sir:

The authors have noted that numerous carbonate diesters can be made of drugs containing the hydroxy group. Often such carbonates are prodrugs, *i.e.*, new compounds having physical-chemical properties different from the parent drugs but retaining qualitatively identical pharmacologic effects and reverting to the parent drug in the body. That they are prodrugs which are hydrolyzed to the parent drugs in the body is attested to by *in vitro* cleavage studies where blood serum has been shown to be a good source of enzymes for catalyzing the hydrolysis reactions.

The principle of prodrug formation has special utility where the parent drug possesses undesirable pharmaceutical features. For example, trichloroethanol possesses interesting sedative properties; but it is a volatile liquid with an unpleasant odor and taste. As such, it is not conveniently suited for therapeutic use; but by reaction with phosgene, it can be converted into bis-trichloroethyl carbonate having a melting point of 86–87°. This previously unreported crystalline compound is virtually tasteless, has sedative properties, and can be encapsulated or tableted.



Similarly, for example, a trichloroethyl carbonate diester of acetaminophen has been made by reacting it with trichloroethyl chloroformate. It is a crystalline compound, m.p. 151–153.5°, possessing the analgetic and sedative properties of the parent drugs from which it is derived, and is also virtually free of taste.



2,2,2-Trichloroethyl-4-acetamido-phenylcarbonate

These compounds, and some related ones, are interesting new compositions of matter. With but few exceptions (quinine ethyl carbonate, alkyl erythromycin carbonates) carbonate diesters have not been utilized as therapeutic agents, and to our knowledge it has not been demonstrated, heretofore, that diester carbonates are prodrugs. Studies on their physical-chemical properties, cleavage rates, biochemistry, and pharmacology along with studies on their pharmaceutical and therapeutic utilities will be subjects of more detailed publications.

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Books

REVIEWS

The Chemistry of the Carbonyl Group. Vol. II. Edited by SAUL PATAI. Interscience Publishers, London, England, 1966. xii + 1027 pp. 16 × 23.5 cm. Price \$32.50.

This book is the second in an ambitious series of treatises dealing with the chemistry of functional groups; the first volume was *The Chemistry of Alkenes*. Volume two is an extensive collection of information on the carbonyl group, written by an international team of highly competent authors. The work is somewhat encyclopedic in nature, although this is not necessarily a fault. The authors have emphasized recent advances and newer developments in critical discussions of the

chemistry involved. This reviewer is not aware that any other single volume possesses the scope of this one. Among the subjects considered are physicochemical and spectral properties of the carbonyl group; laboratory synthesis; biological formation and reactions; analytical procedures; photochemistry; and aspects of thioketone chemistry. As is indicated in the "Foreward," two chapters failed to materialize: "Equilibrium Additions to Carbonyl Groups" and "Syntheses and Uses of Isotopically Labeled Carbonyl Compounds." These omissions, while unfortunate, do not detract from the over-all merit of the work.

The chapters are well documented and about 1964 references are included. The general subject index is somewhat brief and is not useful,

but each chapter begins with an excellent table of contents. The binding of the book is fairly good; the print is readable; and the quality of the paper is good.

The book is addressed to research workers and graduate students, and it will be highly useful as a reference to organic chemists, biochemists, physical organic chemists, analytical chemists, and (to a lesser extent) to physical pharmacists. It is recommended for the research library, with the hope that the entire set of "Chemistry of Functional Groups" will be of the same quality.

*Reviewed by Joseph G. Cannon
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Nonexistent Compounds: Compounds of Low Stability. By W. E. DASENT. Marcel Dekker, Inc., 95 Madison Ave., New York, N. Y. 10016, 1965. ix + 182 pp. 16 × 23.5 cm. Price \$8.50.

To anyone concerned with preparing or using stable compounds, the unstable ones are of interest, if only for the purpose of avoidance. And, of course, there are many shades of gray between the possible and impossible.

This little book has taken as its theme those inorganic compounds that are on the verge of stability, usually arranged in such classes that some of the members are stable and some are not. The compounds are discussed in terms of the reasons for their variations in stability.

The book opens with a chapter on various general approaches to stability, e.g., valence and structure, thermodynamics, tendencies in chain and multiple bond formation. A chapter illustrating each of several types of stability then follows. The semi-stable compounds of nitrogen, sulfur, phosphorus, and silicon have the most representatives, but there are illustrations from almost all the elements except the electropositive metals and the two rare earth series. There is a ten page discussion of compounds of the noble gases. It is difficult to give a typical example of the types of compounds included, so varied are they. The purely ionic compounds are specifically excluded.

Explanations and discussions are well grounded theoretically and are well documented. There are extensive tabulations of energetic data. The author leans heavily on Pauling's "Nature of the Chemical Bond" as concerns valence and bond energies, and writes generally in the same spirit as Pauling.

The book is not a mere curiosity, as suggested by the facetious title. It will find its best use as a rich source of illustrative material for the principles involved in the stability of inorganic and metal-organic chemistry. Some readers will be disappointed that it contains little of direct value for the organic chemist. A book in that subject would have a larger audience, and its point of view would be much different. Of course, it would have a different author.

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Remington's Pharmaceutical Sciences. XIII ed. Editor-in-Chief ERIC W. MARTIN. Mack Publishing Co., Easton, Pa., 1965. xii + 1954 pp. 21 × 29 cm. Price \$23.50

In keeping with the increased emphasis on the scientific basis of pharmacy, this classic has changed its title—from "Remington's Practice of Pharmacy" to "Remington's Pharmaceutical Sciences." The basic outline of earlier editions has been followed; however, many chapters have been revised and several new chapters have been added to reflect the latest developments in analytical and manufacturing procedures. The greatest amount of new material has been in the field of physical pharmacy—four areas are covered in new individual chapters—biopharmaceutics, quantum theory, reaction kinetics, and thermodynamics. A chapter on plastics has been added to the manufacturing section and includes the more recent developments in the nature, uses, and testing of plastics used in medicine.

Drugs are discussed individually as in previous editions. The use statements might more properly be called a therapeutic summary; uses are given, of course, but also included in the discussion are action, special advantages and/or disadvantages, side effects, and cautions.

Tests and assays for official (U.S.P. and N.F.) items are no longer included, since the respective compendia may be consulted for this information.

The physical make-up of the book is excellent; type size and column width make it easy to read, and it is well indexed.

The Remington is up to date, with the changes in the N.F. and U.S.P. being reflected.

It is difficult to review a book so familiar to all pharmacists and already of proved value. The summation which appears on the title page seems most appropriate. "Remington's Pharmaceutical Sciences" is: "A treatise on the manufacturing, standardizing, and dispensing of pharmaceutical products with biological and chemical properties and tests, assays, uses, and doses; also a guide to the legal obligations of the pharmacist and the professional services rendered in helping to maintain community health. A textbook and reference guide for pharmacists, physicians, and other medical scientists."

Encyclopedia of Industrial Chemical Analysis. Vol. 1, General Techniques A-E. Edited by F. D. SNELL and C. L. HILTON. Interscience Publishers, a div. of John Wiley & Sons., Inc., 605 Third Ave., New York, N. Y. 10016, 1966. xv + 763 pp. 18.5 × 26 cm. Price \$35.00 per copy with subscription. \$45.00 per single copy.

The structure of the chemical industry, the nature of the chemical products, and the methods and techniques of analysis have undergone radical changes in recent years. As a result, a comprehensive view of industrial analytical chemistry was felt to be a desirable undertaking. This is the first in a series of volumes to fulfill that need. Methods and techniques used throughout the world for the analysis of raw materials, intermediate, and finished products, as well as evaluation of the finished product for its intended use, will be included. The Encyclopedia will be presented in