# Carbonate Prodrugs in Formulation and Therapeutics

*Sir:*

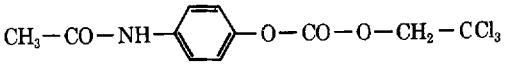
The authors have noted that numerous carbonate diesters can be made of drugs containing the hydroxy group. Often such carbonates are prodrugs, *i.e.*, new compounds having physical–chemical properties different from the parent drugs but retaining qualitatively identical pharmacologic effects and reverting 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.

$CCl_3—CH_2—O—CO—O—CH_2—CCl_3$

bis-Trichloroethyl Carbonate

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 pharmaceutic and therapeutic utilities will be subjects of more detailed publications.

JOSEPH V. SWINTOSKY
H. J. ADAMS
H. C. CALDWELL
L. W. DITTERT
THEODORE ELLISON
DONALD E. RIVARD

Smith Kline & French Laboratories
Philadelphia, Pa. 19101

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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 Labelled 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,