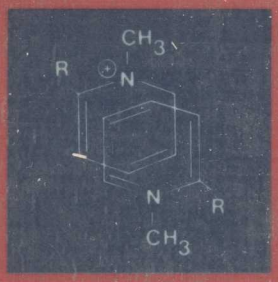
BIOREVERSIBLE CARRIERS IN DRUG DESIGN



Theory and Application

Edited by
Edward B. Roche

APhA

Published in cooperation with
The American Pharmaceutical Association

Pergamon Press

BIOREVERSIBLE CARRIERS IN DRUG DESIGN

Theory and Application

Edited by Edward B. Roche
University of Nebraska Medical Center
College of Pharmacy

PERGAMON PRESS
New York Oxford Beijing Frankfurt São Paulo Sydney Tokyo Toronto

Pergamon Press Offices:

U.S.A. Pergamon Press, Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.

U.K. Pergamon Press, Headington Hill Hall, Oxford OX3 0BW, England

PEOPLE'S REPUBLIC OF CHINA Pergamon Press, Qianmen Hotel, Beijing, People's Republic of China

FEDERAL REPUBLIC OF GERMANY Pergamon Press, Hammerweg 6, D-6242 Kronberg, Federal Republic of Germany

BRAZIL Pergamon Editora, Rua Eça de Queiros, 346, CEP 04011, São Paulo, Brazil

AUSTRALIA Pergamon Press (Aust.) Pty., P.O. Box 544, Potts Point, NSW 2011, Australia

JAPAN Pergamon Press, 8th Floor, Matsuoka Central Building, 1-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160, Japan

CANADA Pergamon Press Canada, Suite 104, 150 Consumers Road, Willowdale, Ontario M2J 1P9, Canada

---

First printing 1987

Library of Congress Cataloging in Publication Data

Bioreversible carriers in drug design.

Includes index.
1. Prodrugs. 2. Drugs--Vehicles.
I. Roche, Edward B.
RM301.57.B56 1986 615.5'8 86-30354
ISBN 0-08-034681-2

In order to make this volume available as economically and as rapidly as possible, the authors' typescripts have been reproduced in their original forms. This method unfortunately has its typographical limitations but it is hoped that they in no way distract the reader.

Printed in Great Britain by A. Wheaton & Co. Ltd., Exeter

PREFACE

The focus of this volume is on underlying concepts in physical organic chemistry, physical chemistry, biochemistry, cell biology, and immunology as they relate to bioreversible carrier design. The authors have created chapters which should well serve those who are working and studying in the various areas of drug design. It is our hope that this volume will serve as an instructional work for the serious student, and a stimulus for the scientist beginning to work in this area of research. The phrase "theory and application" in the title brings forth this intent.

In the first chapter, Professor Takeru Higuchi, whose pioneering research in this area is well known, gives us an overview of prodrugs and drug delivery systems. His discussion introduces aspects of specificity leading into the later chapters, and provides thoughts on the regulatory aspects of prodrug development including efficacy testing and patents.

The design of bioreversible derivatives and "chemical drug delivery systems" are discussed in detail in the next two chapters by Professors Bundgaard and Bodor, respectively. These discussions relate the state of the art in the design of chemical entities that are selective or specific for particular target tissues or systems.

The application of physical and chemical properties to the design of bioreversible compounds is discussed in the two chapters by Professor Anderson and Drs. Conradi and Fox, respectively. The importance of physicochemical considerations and the detailed analysis of physically based models is brought clearly into focus by these authors.

Professor Duncan and her colleagues discuss the use of synthetic soluble polymers, e.g., HPMA co-polymers, as specific intracellular macromolecular carriers. This is followed by Dr. Shen's chapter on targeting cell surface receptors and achieving selective permeation of cell membranes. This topic is discussed in another sense in the chapter by Audus and Borchardt on transport across the blood-brain barrier. The unique nature

of vascular endothelial cells is discussed with regard to the design of carrier systems for drugs intended to be transported across the cerebral vasculature.

Targeting the enzymes of the gastro-intestinal tract as sites of bioconversion of carrier systems is the subject of the chapter by Amidon and Johnson. The location and specificity of these systems is discussed in detail. The closing chapter by Dr. Sinkula brings the industrial perspective into focus. The organization of multidisciplinary research groups to bring input from all of the cognizant sciences to bear on problems surrounding the selective targeting of drug entities and bioreversible carriers is discussed in detail.

It has been a pleasure for me to be involved with all of these authors, and with the editorial phase of the production of this book. I thank them for their efforts and cooperation. I would also like to thank Mrs. Andrea Steele for her invaluable assistance in the preparation of this volume.

Edward B. Roche
University of Nebraska Medical Center
College of Pharmacy
Omaha, Nebraska
November, 1985

CONTENTS

Chapter 1

Prodrug and Drug Delivery—An Overview

Takeru Higuchi

Department of Pharmaceutical Chemistry
University of Kansas
Lawrence, KS 66045

It has now been more than a decade since we helped organize a symposium on prodrugs as a part of an ACS meeting at Atlantic City. Although the interest in the approach even at that time led to a standing-room-only crowd, the concept probably has gained a far greater number of advocates today. The recent mainstream recognition of the importance of effective delivery in the development of new therapeutic agents has given major impetus to the growth of prodrug technology. This is because the approach permits, for a number of drug areas, a useful separation of the structural needs associated with optimal biological activity at the target site from the structural requirements associated with the best delivery of these agents to that site.

Delivery technology, in general, will play an increasing role in the near and indefinite future of new drug development. More complex and higher molecular weight chemical species are now being considered as new drug candidates; these bioactive agents are generally poorly absorbed -- being difficultly transported across various biological barriers. Development of many of the products of biotechnology into therapeutically useful dosages, for example, will particularly require new drug delivery technology. The prodrug concept will, without question, play an increasing major role in this respect.

It has already been well demonstrated that chemical modification of an active agent can significantly influence its availability to its targetted biospace. Thus, the dipivalyl ester of epinephrine developed for improved ocular delivery illustrates a recent success along this line. Another program which took place in our own laboratories demonstrated that 2-PAM, an antidote for nerve gas

poisoning, in its dihydro form was able to regenerate esterase activity in the brain following exposure of the whole animal to the choline esterase inhibitor. The parent drug, 2-PAM, in its quarternary form, is unable to penetrate the BBB and affect the enzyme system.

Since no serious student of drug activity would today suggest action at a distance, the effect induced at the target site by a given dose of drug will be the product of the drug's intrinsic activity and the efficiency with which it is delivered to the site. The two factors are thus of equal importance in the development of any new drug. And because of the structural orthogonality of those molecular attributes which would tend to optimize each of the factors, the prodrug approach which would often permit independent treatment of the two by separating them temporally offers real advantages.

Thus, for example, in the development of dipivalyl epinephrine as an agent for treatment of glaucoma, the intent was not to alter or improve the activity of epinephrine at its target site within the eye, but rather to confer on the drug those physical properties by chemical modifications which would permit its ready delivery into the intraocular space. During or after transit across the corneal barrier, the ester is cleaved to regenerate the active species. It is evident that the approach, when the basic technology is better developed, will certainly lead to significantly more useful drug substances.

There are two research directions related to future prodrug application which, I feel, need substantially greater effort. The first is concerned with the chemistry of chemical modifications which convert readily to the desired active species. The second relates to increasing our understanding of endogenous enzymic systems which can be used to trigger the generation of these active agents and the specificity of these enzymes. I will use the remainder of my time to elaborate on these points.

Prodrug Chemistry

Much of the earlier efforts on prodrugs has been based on simple esterification of the active substance. Thus, the ester aspirin was developed from salicylic acid nearly a century ago with the intent to deliver the acid without its corrosive effect. More recent examples are chloramphenicol palmitate, triacetyloleandomycin, etc. These esters were developed essentially by trial and error and underwent

hydrolysis to varying degrees on their journey to the circulating blood.

More recently, newer chemistry has been developed which permits use of endogenous esterases to convert derivatized drugs to their active forms. Thus, a number of amines, amides and imides have been converted to esterase-sensitive prodrugs. Some of these are shown in Figure 1 and Figure 2.

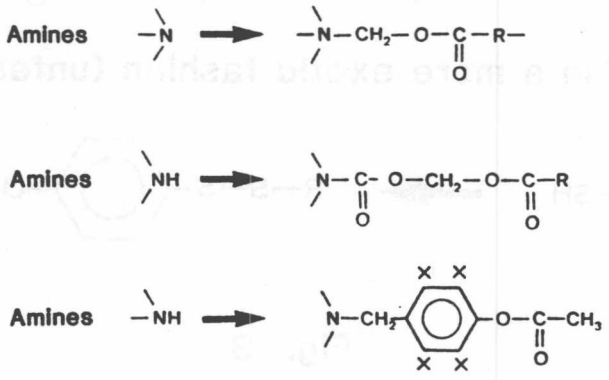


Fig. 1

Some Chemistry Leading to Esterase Sensitive Prodrug Forms of Amines.

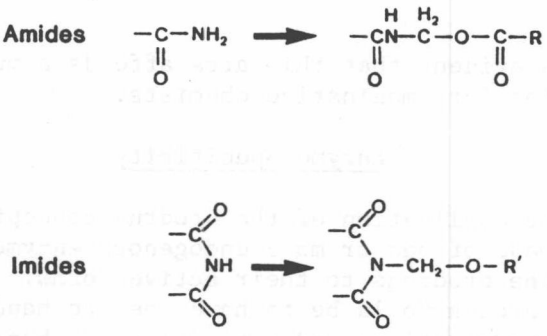
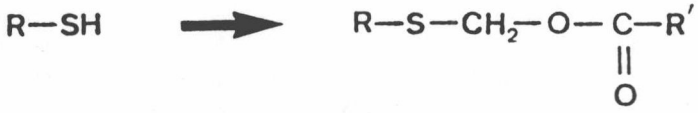


Fig. 2

Prodrugs Formed from Amides and Imides which are Esterase Sensitive.

Other similar contrived chemistry can be imagined. For example, thiols can be simply acylated or soft alkylated.



Or in a more exotic fashion (untested)

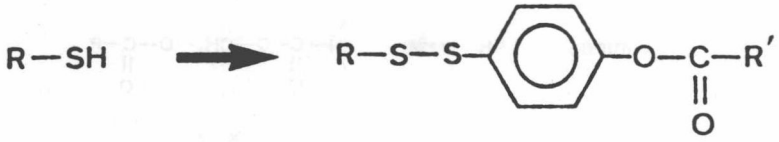


Fig. 3

Derivitization of Sulfahydryl Drugs.

It is evident that this area affords a multitude of opportunities for imaginative chemists.

Enzyme Specificity

In the application of the prodrug concept, use is generally made of one or more endogenous enzymes to transform the prodrugs to their active forms. A truly rational approach would be to have, before hand, the relative concentrations and activities of those biological catalysts which can perform these functions and can be expected to be encountered during passage, for example, from the gut to the brain. Unfortunately, our knowledge in this

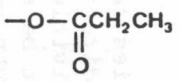
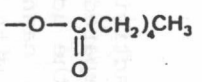
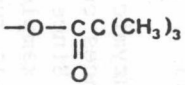
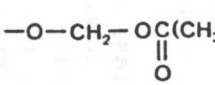
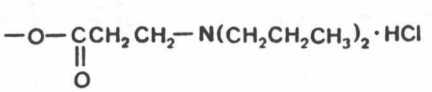
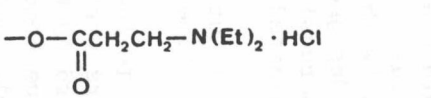
area is still very limited. Specificity, for example, of various esterases toward variations in substrate structures is as yet poorly known. Recently, for this reason, we have been looking at the relative sensitivities of a limited number of structurally different esters toward several esterases which may be encountered during and after gut absorption. I would, at this point, like to share with you some of the results of this study.

We looked at the hydrolytic behavior of some acetaminophen esters in the presence of various crude esterases. The system had been studied in some detail by Lew Dittert, Cliff Wong and Joe Swintosky here in Philadelphia nearly twenty years ago. Our recent effort had been directed primarily toward evaluation of the relative catalytic activities of esterases obtained from the gut wall, the liver, and the blood with variation in substrate structure. The program was designed to test the possibility of designing esters (prodrugs) which would cleave more or less specifically at a selected point along the absorption pathway.

In these studies, enzymic activities toward different esters were in all instances compared directly to that toward APAP propionate. Since the activities of crude tissue homogenates, for example, cannot be easily reproduced, each preparation was run with APAP proprianate as well as with the ester under study and the results expressed as the ratio of the two rates obtained at substrate concentrations usually well below saturation.

The esters studied are shown in Table I, along with their observed hydrolytic half lives at pH 7.0 and 25° under nonenzymatic conditions. In Figs. 4, 5, 6, 7, and 8, their relative susceptibilities toward rat intestinal homogenate, rat liver homogenate, commercial partly purified porcine liver esterase, rat plasma and partly purified horse serum butyrl cholinesterase are shown. It is evident that the susceptibility profiles are relatively reproducible and distinctly different. It is of interest to note the very close similarity between that obtained for rat liver homogenate and that tor the porcine liver esterse. Essentially the same response was observed for similar structural changes in related reverse esters (P-acetamido benzoic acid ester series).

TABLE I. Structure and Chemical Hydrolytic Half - Lives of APAP Esters Studied

Compound	Structure	Half-Life (hrs.) pH=7.0 T=25°
E-1		>250
E-2		>460
E-3		>1400
E-4		>3500
E-5		0.65
E-6		0.69

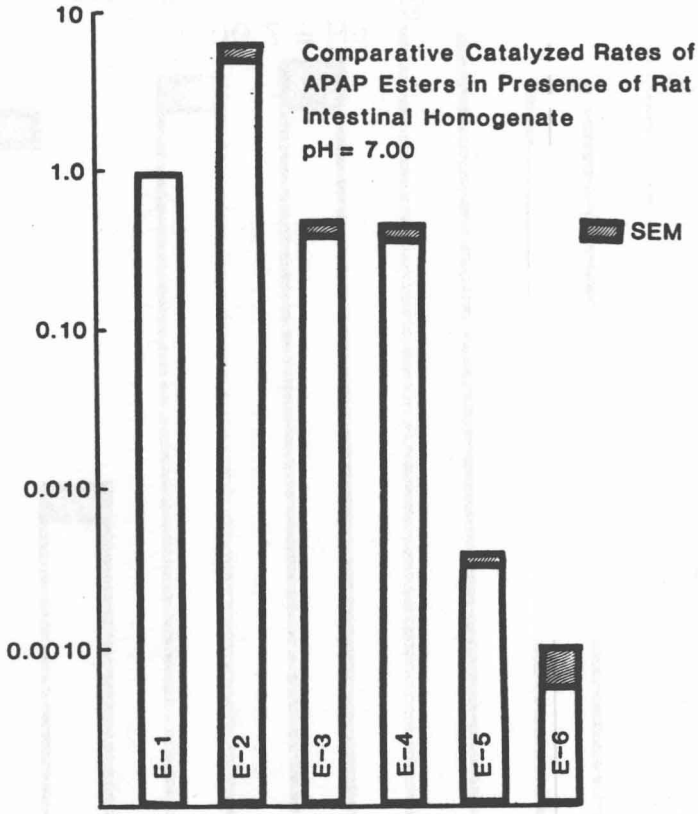

10
1.0
0.10
0.010
0.0010
Comparative Catalyzed Rates of APAP Esters in Presence of Rat Intestinal Homogenate
pH = 7.00
SEM
E-1
E-2
E-3
E-4
E-5
E-6

Fig. 4

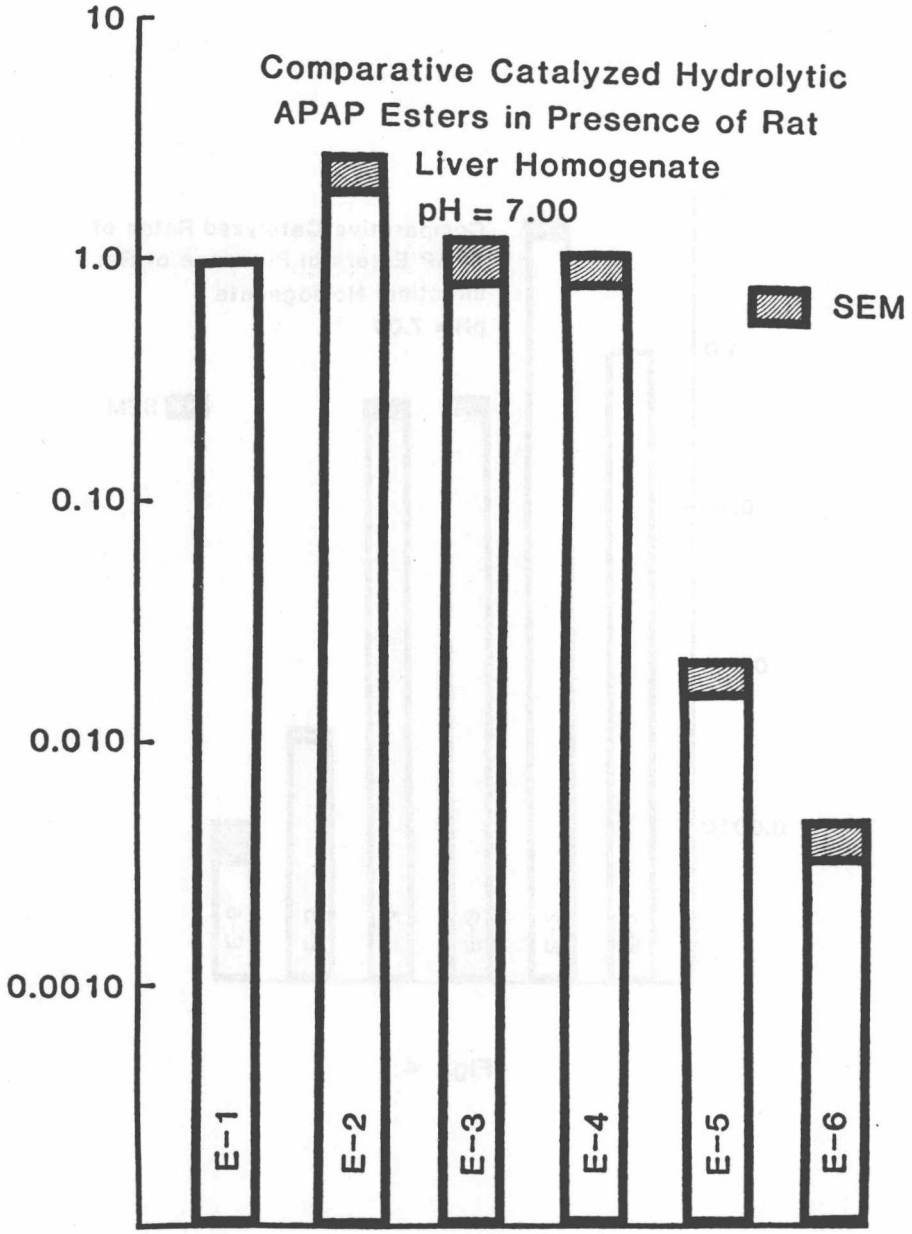

Comparative Catalyzed Hydrolytic
APAP Esters in Presence of Rat
Liver Homogenate
pH = 7.00
SEM
10
1.0
0.10
0.010
0.0010
E-1
E-2
E-3
E-4
E-5
E-6

Fig. 5

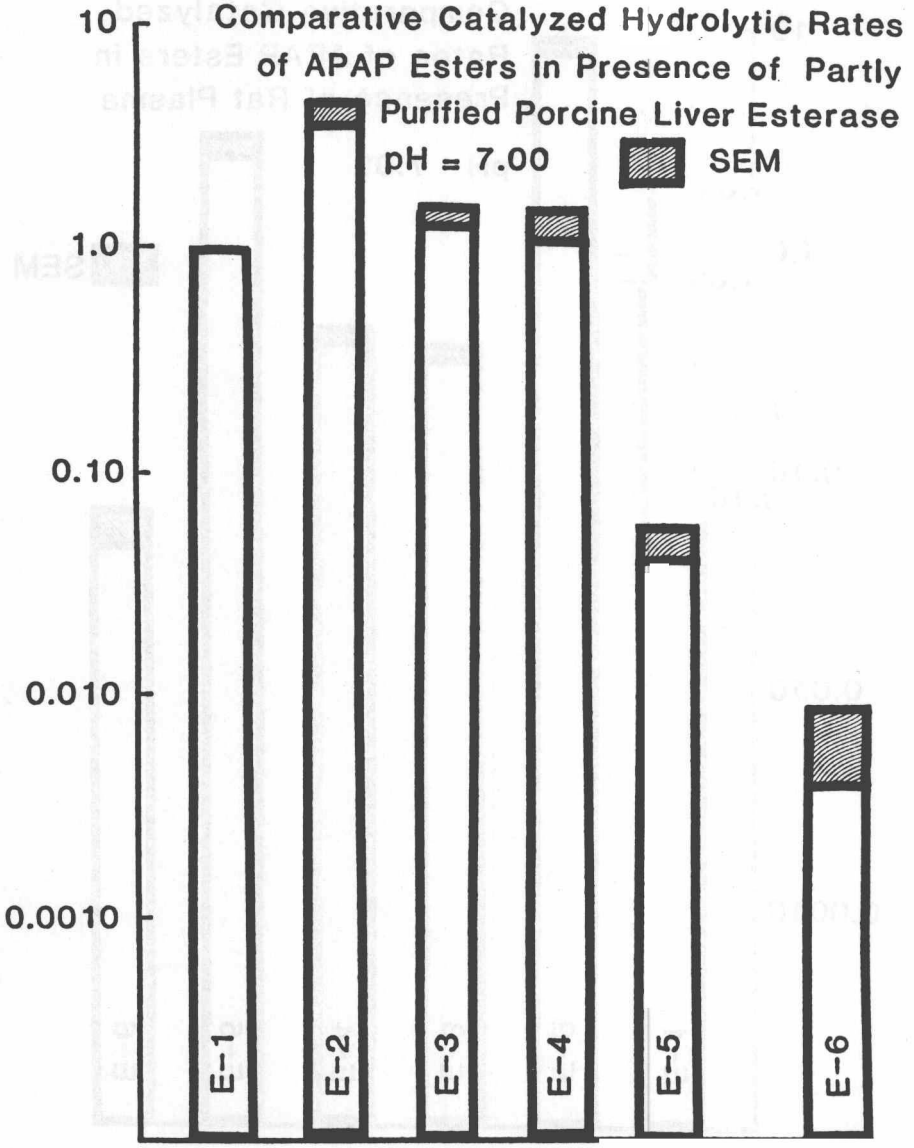

Comparative Catalyzed Hydrolytic Rates
of APAP Esters in Presence of Partly
Purified Porcine Liver Esterase
pH = 7.00
SEM
10
1.0
0.10
0.010
0.0010
E-1
E-2
E-3
E-4
E-5
E-6

Fig. 6

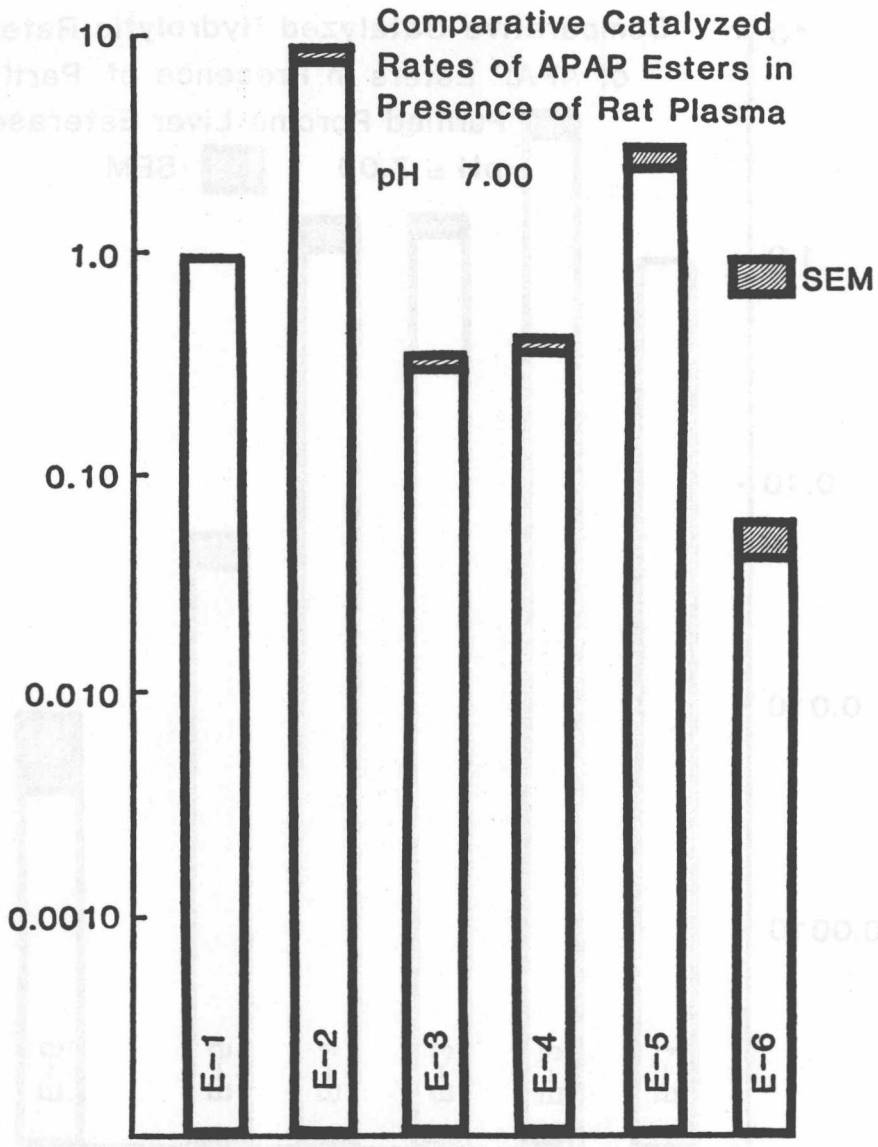


Fig. 7