THE ORGANIC CHEMISTRY OF DRUG SYNTHESIS

Volume 2

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The Organic Chemistry of Drug Synthesis

VOLUME 2

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It is our pleasure again to dedicate
a book to our helpmeets: Beryle and Betty.

"Has it ever occurred to you that medicinal chemists are just like compulsive gamblers: the next compound will be the real winner."*

*R. L. Clark at the 16th National Medicinal Chemistry Symposium, June, 1978.

Preface

The reception accorded "Organic Chemistry of Drug Synthesis" seems to us to indicate widespread interest in the organic chemistry involved in the search for new pharmaceutical agents. We are only too aware of the fact that the book deals with a limited segment of the field; the earlier volume cannot be considered either comprehensive or completely up to date. Because the earlier book did, however, lay the groundwork for many of the structural classes or organic compounds that have proven useful in the clinic, it forms a natural base for a series that will, in fact, be comprehensive and up to date. This second volume fills some of the gaps left by the earlier work and describes developments in the field up to the end of 1976. More specifically, we have included literature and patent preparations for

those compounds granted a USAN* generic name prior to and including 1976 that did not appear in Volume I.

In assembling the first volume, we faced an apparently staggering mass of material. It seemed at the time that attempts to be inclusive would lead to an undigestible compendium. In order to keep the reader's interest, we chose instead to be selective about material to be included. Specifically, the first volume deals predominantly with organic compounds actually used in the clinic. It is, of course, well known that many compounds die in various stages of clinical trials, either from lack of effect, lack of superiority over existing drugs, or the presence of disqualifying side effects. Particularly since 1962, sponsoring companies have become much more demanding in the standards to be met by a drug before undertaking the cost involved in the clinical work leading to an NDA.† For that reason, this period has seen a large increase in the number of compounds that have been granted generic names but have failed to achieve clinical use. Many such failed analogues were omitted from the previous volume. Since we now intend to make the series comprehensive, and since those analogues do have heuristic value, we have chosen to violate chronology and include them in the present volume. Volume 2 thus goes beyond simple updating.

*United States Adopted Name
†New Drug Application

The organization of the material by chemical classes used earlier has been retained since it provided a convenient method for lending coherence to the subject matter. However, changes in emphasis of research in medicinal chemistry have led us to change the organization of the individual chapters. The small amount of new work devoted to some structural types (e.g., phenothiazines) that formed large units in the earlier book failed to provide sufficient material to constitute a chapter here; what material was available has simply been included under some broader new heading. As was the case previously, syntheses have been taken back to commonly available starting materials as far as possible. An exception to this rule will be found in the section on steroids. Many of the compounds described are corticoids, that are the products of intricate multistep syntheses. In the earlier volume, we described the preparation of some quite highly elaborated corticoids using plant sterols as starting materials. Many of these corticoids are used for preparation of compounds in this volume. Since there seems little point in simply reiterating those sections, a starting material is judged to be readily available if its preparation is described in the first volume. The reference will be to that book rather than to the original literature.

We have endeavored, too, to approach biological activity in the same fashion as we did earlier. The first time some therapeutic indication occurs will be the occasion for a concise simplified discussion

of the disease state and the rationale for the specific method of drug therapy. Biological activities are noted for each generic compound at the same time as its preparation. It will be emphasized again that the activities quoted are those given by the authors; this book is not intended as a critical text in pharmacology.

"Organic Chemistry of Drug Synthesis, Volume 2" is addressed to the same audience as was Volume 1: graduate students in medicinal and organic chemistry, as well as practitioners in the two fields. This book also assumes that the reader will have a good understanding of synthetic organic chemistry and at least a rudimentary knowledge of biology.

Finally, we express our sincere appreciation to several individuals who contributed time and talent to this project. Ms. Carolyn Kelly patiently typed the many versions of the manuscript, including the final camera-ready copy, in the midst of the press of her daily responsibilities. Sheila Newland drew the structural formulae, and John Swayze read the entire manuscript and made several useful suggestions to help clarify the text and reduce the number of typos. Ken McCracken and Peggy Williams were extremely helpful in guiding us through the intricacies of the IBM "Office System 6".

Daniel Lednicer — Evansville, Indiana
Lester A. Mitscher — Lawrence, Kansas
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1 Monocyclic and Acyclic Aliphatic Compounds

1. CYCLOPENTANES

a. Prostaglandins

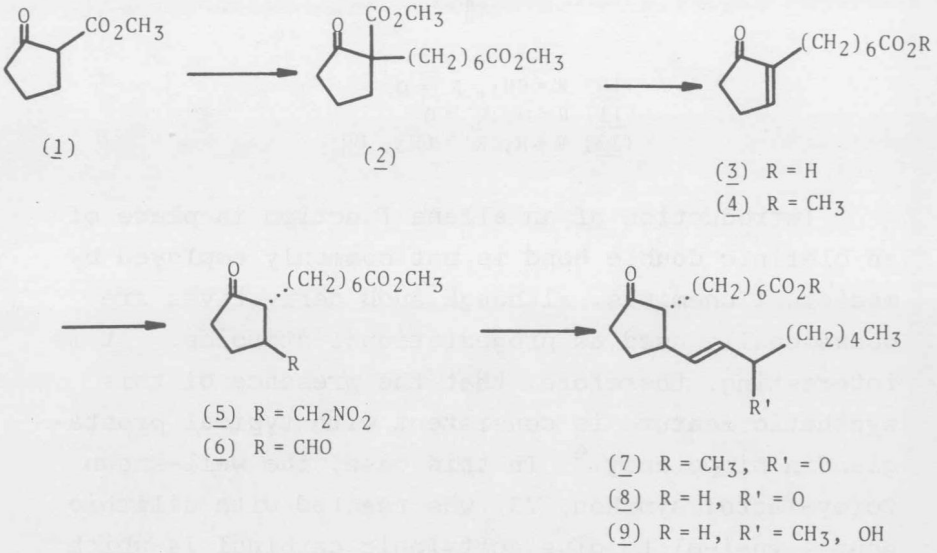
When realistic quantities of the natural prostaglandins became available, their extreme potency and wide-ranging biological activities were discovered and visions of therapeutic application in the regulation of fertility, control of ulcers, blood pressure, bronchial asthma, and many other conditions led to a torrent of chemical and biological studies which currently measures about four papers daily, and at least one a week dealing with synthesis alone. Initial chemical emphasis lay in developing efficient syntheses of the natural substances to solve the supply problem. Presently, the emphasis has shifted to preparation of analogues which are intended to be less expensive, more selective in their action, and longer lasting. The five drug candidates in this

section are significant representatives of the hundreds of such analogues available.

The naturally occurring prostaglandins, E_1, E_2 and A_1, have potent antisecretory activity when given parenterally and have been suggested for use in treatment of gastric ulcers. Unfortunately, these natural compounds have relatively poor oral activity and rapid metabolism makes their action short-lived. Molecular manipulation proved that an oxygen atom at C_{11} was not necessary for bioactivity but these compounds also lacked the desired oral activity. This problem was solved by a study of the metabolizing enzymes and by borrowing an artifice from steroid chemistry (*viz*-methyl testosterone, Volume I). The most rapid metabolic deactivating reaction is oxidation to the bioinert C_{15}-oxo prostaglandins. Converting the latter to a tertiary methyl carbinol led to the desired orally active gastric antisecretory agents.

Starting with 2-carbomethoxycyclopentanone (*1*), t-BuOK catalyzed alkylation of methyl ω-bromoheptanoate gave diester *2* which was then hydrolyzed and decarboxylated. The conjugated double bond was then introduced by a bromination-dehydrobromination sequence to give versatile prostaglandin synthon *3*. Esterification to *4* was followed by conjugate addition of sodio nitromethane to give *5*. Nitroketone *5* was converted to the sodium salt of the corresponding nitronic acid with sodium in methanol and this was hydrolyzed with icecold dilute H_2SO_4 to ketoaldehyde *6*. This sequence is the Nef reaction. Wittig

reaction of this sodio dimethyl-2-ketoheptyl phosphonate gave *7*.[1,2] Ester hydrolysis to *8* followed by careful reaction with methyl magnesium bromide produced the orally active bronchiodilator, *doxaprost (9)*.[2] *Doxaprost*, at least as originally prepared, is conformationally undefined at C_{15} and is probably a mixture of R and S isomers.



Enzymic studies demonstrated that the 15-dehydrogenase was also inhibited by saturation of the C_{13} double bond and *deprostil (12)* embodies this chemical feature as well.[3] Catalytic hydrogenation of *7* produced *10* which was hydrolyzed to *11* and reacted with methyl magnesium bromide in ether. As above, careful control of conditions allowed the organometallic reagent to add selectively to the