



Volume

5

The Organic Chemistry
of Drug Synthesis

Daniel Lednicer

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THE ORGANIC CHEMISTRY OF DRUG SYNTHESIS

Volume 5

DANIEL LEDNICER
National Cancer Institute
Bethesda, Maryland

江苏工业学院图书馆
藏书章



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The quotation below appeared as the frontpiece to Volume I of this series. It is still an apt description of drug discovery close to two decades later. The three names of Serenelli, Belakovich, Vlahos and Katsikis, as they traveled, were always making discoveries by accident and the serenity of things they were not in quest of.

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To Beryl—my wife, friend, and companion

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Three Principles of Serenelli, Belakovich, Vlahos and Katsikis, as they traveled, were always making discoveries by accident and the serenity of things they were not in quest of.

The quotation below appeared as the frontpiece in Volume 1 of this series. It is still an apt description of drug discovery close to two decades later.

*The three princes of Serendip, Balakrama, Vijayo and Rajasigha, as they traveled ... "... were always making discoveries by accident and sagacity, of things they were not in quest of."**

*Horace Walpole, in a letter of January 28, 1754, as quoted in *The Three Princes of Serendip*, by E. J. Hodges, Athaneum, New York, 1964.

PREFACE

This volume, like its predecessors, is based on the premise that the operational manipulations involved in preparing new therapeutic agents consist of synthetic organic chemistry. Once a target compound has been designed using the tools of medicinal chemistry, it is up to the practitioner to actually synthesize the compound so that it may be evaluated for biological activity. Broad areas of organic chemistry are used to prepare the highly diverse group of chemical structures utilized as therapeutic agents. The emphasis of this series continues to be the exposition of that chemistry as this is probably of interest to chemists outside the confines of medicinal chemistry. Since all target compounds included in this volume have shown biological activity, that information is included as well. An attempt has been made to place actual or potential utility of the agents in context by providing thumbnail sketches of the relevant therapeutic areas. Readers are referred to some of the more specialized medicinal chemistry or pharmacology texts for more detailed descriptions of those subjects.

The criterion for inclusion of a specific compound in the book is its appearance in the annual compilation of *United States Adopted Names* (USAN) published by the United States Pharmacopeia in "USAN and the USP Dictionary of Adopted Names." The existence of such a designation, known commonly as a **generic name** and shown in boldface type in the book, is an indication that the sponsoring laboratory considers the compound to show sufficiently promising activity to merit evaluation in the clinic. The current volume includes compounds from approximately 1988, where Vol-

ume 4 left off, to those that appear in USAN 1993. Readers familiar with the previous volumes will note the smaller number of compounds discussed in this book; whereas over 300 agents each with USAN were included in Volumes 3 and 4, approximately 250 appear in this volume. It would be interesting, but beyond the scope of this book, to speculate whether this represents a drop in the rate of discovery of new therapeutic agents or the adoption of stricter criteria for declaring compounds candidates for clinical trial. The changing nature of medicinal chemistry, as reflected by this series, has been noted in the earlier books. The most profound change indicated by Volume 5 is in the field of antibiotics: a mere nine compounds comprise the section on β -lactams (Chapter 10), while that on quinolone antibiotics in Chapter 8 has grown to over a dozen compounds. A sizeable number of new therapeutic targets such as lipoxygenase inhibitors, leukotriene antagonists, and renin inhibitors make their debut in this volume. It is too early to assess their significance since none have yet been approved for clinical practice.

The large number of entries whose synthesis appears only in the patent literature, most often in European Patent Applications, precluded consulting original sources; the syntheses for those agents were of necessity reconstructed from condensations in *Chemical Abstracts*. The reader should bear in mind too that the syntheses presented here, more often than not, represent those aimed at efficiently preparing analogue series. The actual route for preparing a commercialized drug may in fact be quite different.

Finally, I will take this opportunity to acknowledge the help provided by my colleague, Dr. Ravi Varma. Ravi offered cogent comments and suggestions on the manuscript and provided invaluable help in insuring that the numbers in the flow diagrams match those in the text. Any remaining errors of course remain my sole responsibility.

DANIEL LEDNICER

Rockville, Maryland
September 1994

THE ORGANIC CHEMISTRY OF DRUG SYNTHESIS

Volume 5

ACYCLIC AND ALICYCLIC COMPOUNDS

1. ACYCLIC COMPOUNDS

It is generally recognized that the action of a majority of biologically active compounds, and especially drugs, is due to their interaction with receptors or enzymes. The recognition sites on these substrates are composed of defined, intricate arrays of atoms that are part of biomolecules. The complexity of the receptor site is thus often mirrored by an equal level of complexity in the molecules with which it interacts. Consequently, it is not surprising to find few drugs based on acyclic skeletons. Those that fall into this category often owe their activity to pharmacological properties rather than to interaction with a receptor, as for example, in the case of anesthesia.

Ionizing radiation remains one of the more effective but not therapeutic means for treatment of cancers. It is however often accompanied by a large number of unwanted effects due to the inability to limit cell damage to the cancerous tissue. Considerable work has consequently been devoted to developing compounds that would prevent damage to healthy cells. Many of these compounds resulted from the finding that mercaptans tend to have antiradiation activity, possibly because of their ability to remove radiation-generated free radicals. The α -thioethers **1** (1), may be viewed as a highly modified atropine derivative. Preparation of the compound starts in straightforward fashion by alkylation of 1,3-dithianopropane (**1**) with 2-chloroethanol; reaction of the product, **2**, with hydrogen bromide gives the corresponding bromo derivative **3**; the presence of excess hydrogen

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PREFACE

This volume, like its predecessors, is based on the premise that the essential manipulations involved in preparing new therapeutic agents consist of synthetic organic chemistry. Once a target compound has been designed using the tools of medicinal chemistry, it is up to the practitioner to actually synthesize the compound so that it may be evaluated for biological activity. Broad areas of organic chemistry are used to prepare the highly diverse group of chemical structures utilized as therapeutic agents. The emphasis of this series continues to be the exposition of this chemistry in that is probably of interest to chemists outside the confines of medicinal chemistry. Since all target compounds included in this volume have shown biological activity, that information is included as well. An attempt has been made to place each agent in its potential utility of the agents in context by providing thumbnail sketches of the relevant therapeutic areas. Readers are referred to some of the more specialized medicinal chemistry or pharmacology texts for more detailed descriptions of these subjects.

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CHAPTER 1

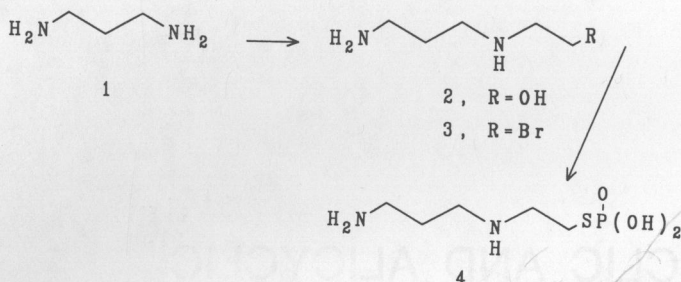
ACYCLIC AND ALICYCLIC COMPOUNDS

1. ACYCLIC COMPOUNDS

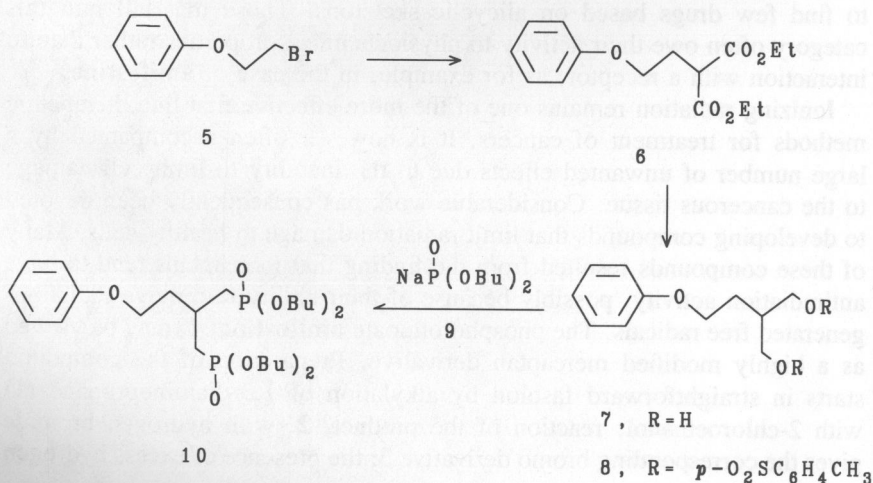
It is generally recognized that the action of a majority of biologically active compounds, and especially drugs, is due to their interaction with receptors or enzymes. The recognition sites on those substrates are composed of defined, intricate arrays of atoms that are part of biopolymers. The complexity of the receptor site is thus often mirrored by an equal level of complexity in the molecules with which it interacts. Consequently, it is not surprising to find few drugs based on alicyclic skeletons. Those that fall into this category often owe their activity to physiochemical properties rather than to interaction with a receptor, as for example, in the case of **amifostine**.

Ionizing radiation remains one of the more effective first line therapeutic methods for treatment of cancers. It is however often accompanied by a large number of unwanted effects due to the inability to limit cell damage to the cancerous tissue. Considerable work has consequently been devoted to developing compounds that limit radiation damage to healthy cells. Many of these compounds resulted from the finding that mercaptans tend to have antiradiation activity, possibly because of their ability to remove radiation-generated free radicals. The phosphorothioate **amifostine**, **4**, may be viewed as a highly modified mercaptan derivative. Preparation of the compound starts in straightforward fashion by alkylation of 1,3-diaminopropane (**1**) with 2-chloroethanol; reaction of the product, **2**, with hydrogen bromide gives the corresponding bromo derivative **3**; the presence of excess hydrogen

bromide may prevent self-alkylation of the product by protonating the amino groups. Nucleophilic displacement of bromine by sulfur in sodium thio-phosphonate leads, after acidification, to **amifostine**, **4**.¹

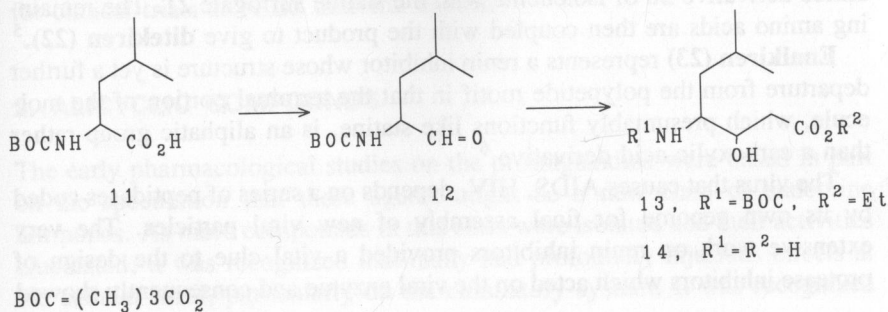


Calcium channel-blocking agents have found increasing use over the past decade as antianginal and antihypertensive drugs. Most compounds in this class typically consist of heterocycles such as dihydropyridines or benzothiazepines. An acyclic bisphosphonate also reportedly exhibits this activity. Alkylation of the anion from diethyl malonate with bromoethylphenol **5** (itself the product of phenoxide and dibromoethane) leads to malonate **6**. Reduction of the ester with LAH followed by acylation of the thus produced diol (**7**) with *p*-toluenesulfonyl chloride gives the bistosylate **8**. Displacement of the tosylates by means of sodium dibutyl phosphonate (**9**) gives the calcium channel-blocking agent **belfosdil**, **10**.²

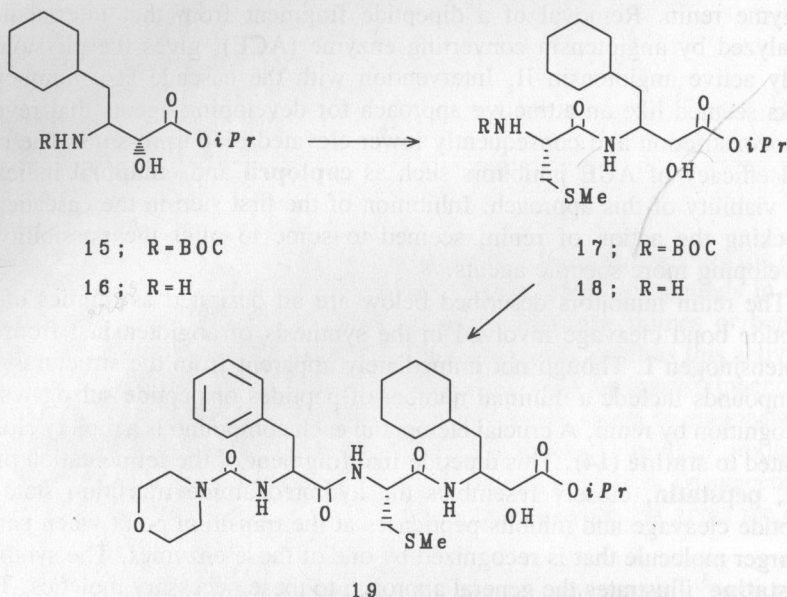


The most important mechanism for regulating blood pressure involves constriction or dilation of blood vessels on the arterial side. This vascular musculature is in turn under the control of both the involuntary nervous system, via its neurotransmitter catecholamines, and the set of peptide hormones that comprise the renin-angiotensin system. The very potent vasoconstrictor angiotensin II is this system's ultimate effector. The cascade that leads to production of this octapeptide starts with the cleavage of the peptide angiotensinogen to the decapeptide angiotensin I, which is catalyzed by the enzyme renin. Removal of a dipeptide fragment from that intermediate, catalyzed by angiotensin converting enzyme (ACE), gives the physiologically active angiotensin II. Intervention with the cascade at a number of links seemed like an attractive approach for developing agents that reverse vasoconstriction and consequently lower elevated blood pressure. The clinical efficacy of ACE inhibitors such as **captopril** and **enalapril** indicated the viability of this approach. Inhibition of the first step in the cascade, by blocking the action of renin, seemed to some to offer the possibility of developing more specific agents.

The renin inhibitors described below are all designed as mimics of the peptide bond cleavage involved in the synthesis of angiotensin I from angiotensinogen I. Though not immediately apparent from the structures, the compounds include a minimal number of peptides or peptide surrogates for recognition by renin. A crucial element in each compound is a moiety closely related to **statine** (**14**). This dipetide-like fragment of the fermentation product, **pepstatin**, closely resembles the hydrated amide transition state for peptide cleavage and inhibits peptidases at the transition point when part of a larger molecule that is recognized by one of those enzymes. The synthesis of **statine**³ illustrates the general approach to these necessary moieties. Thus reduction of leucine as its *tert*-butylcarbonyl (BOC) derivative¹¹ with diisobutylaluminum hydride at low temperature leads to the corresponding aldehyde **12**. Condensation of **12** with the lithium salt of ethyl acetate gives the protected statine derivative **13**.



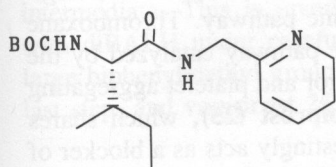
Preparation of the renin inhibitor **terlakiren** starts by removal of the BOC protecting group from statine analogue **15** in which the isopropyl group of statine has been replaced by cyclohexyl. Condensation of the amino group under standard peptide synthesis conditions with the *S*-methyl ether of BOC-cysteine gives the intermediate **17**. This is again deprotected (**18**) and the product is condensed with the *N'*-morpholylurea derivative of phenylalanine. There is thus obtained the renin inhibitor **terlakiren** (**19**).⁴



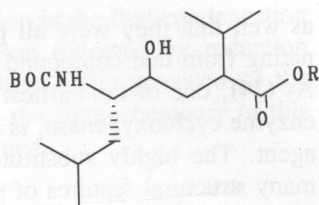
A somewhat lengthier series of amino acid condensations leads to the renin inhibitor **ditekiren**.⁵ In this case, the transition state mimic moiety is not located at the terminal position and is more complex than statine. A key reaction in the sequence involves condensation of the aminomethylpyridyl-amide derivative **20** of isoleucine with the statine surrogate **21**. The remaining amino acids are then coupled with the product to give **ditekiren** (**22**).⁵

Enalkiren (**23**) represents a renin inhibitor whose structure is yet a further departure from the polypeptide motif in that the terminal portion of the molecule, which presumably functions like statine, is an aliphatic group rather than a carboxylic acid derivative.⁶

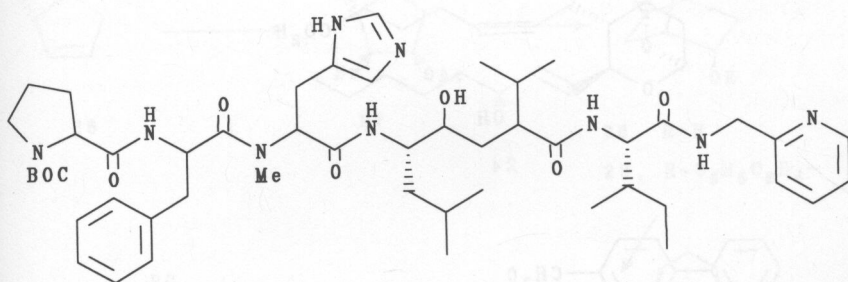
The virus that causes AIDS, HIV, depends on a series of peptidases coded by its own genome for final assembly of new viral particles. The very extensive work on renin inhibitors provided a vital clue to the design of protease inhibitors which acted on the viral enzyme and consequently showed



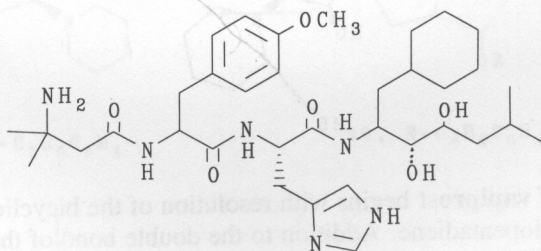
20



21



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23

in vitro antiviral activity. Several of these compounds are currently headed for clinical trials as AIDS antiviral agents.

2. ALICYCLIC COMPOUNDS

The early pharmacological studies on the prostaglandins were based in part on the speculation that these agents might be a new class of endocrine hormones. As more compounds in this class were isolated and their activities elucidated, it was recognized that many had profoundly injurious effects at the cellular level, particularly on the circulatory system. It was recognized