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PHARMACEUTICAL CHEMISTRY

Volume 1
drug synthesis

H. J. Roth and A. Kleemann
in collaboration with Thomas Beisswenger

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Volume 1: Drug Synthesis

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PHARMACEUTICAL CHEMISTRY

Volume 1: Drug Synthesis

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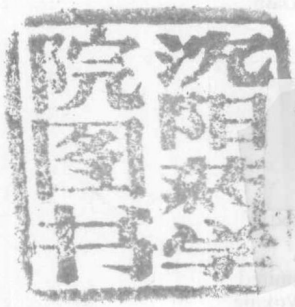

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Preface

To present the wide range of modern pharmaceutical chemistry it seems appropriate to use different approaches which cover the major topics. Among the important subjects are the synthetic methods for production of drugs and the analysis of drugs with detection of contaminants and impurities. Of interest within the complex area of action-related properties are structure activity relations, structure dependent pharmacokinetic aspects, the bioreactivity and the metabolism of the drugs.

This book, the first in a series of Pharmaceutical Chemistry, deals with the synthetic aspects of the chemical production processes as well as with some of the commercial aspects. A second book published in its German version deals with the therapeutic use and methods for preparation of drugs which are obtained from natural sources. Ellis Horwood Ltd will be publishing in English the third book in the series — *Drug analysis*.

For continuity within the book the important structural groups of drugs have been used for classification. The book begins with the large group of basic substituted, aliphatic–aromatic compounds, and not with the synthesis of hydrocarbons, which anyway have minimal importance as agents.

The material has been considered in nine groups (chapters). A further chapter contains the few remaining compounds which did not fit into the earlier groups.

An alternative principle of organizing by reaction type, or even by reaction mechanism, soon proved to be unpractical since an immense number of cross references would have become necessary.

This book assumes knowledge of organic chemistry and basic knowledge of preparative organic chemistry.

There are more than 70 organic name reactions referred to in the text, and information on these can be found in well-known textbooks of organic chemistry. It has therefore been necessary only in special cases, and then for clarity, to discuss the mechanism of such reactions.

The **choice of drugs** has been made on two basic features,

— the frequency of doctors' prescriptions and of selfmedication
— the size of market shares.

The decisions on detail and breadth, or the limitations to the most essential, in different chapters have been directed by the significance of the described drugs. Furthermore, we have tried to illustrate the actual commercial syntheses being carried out today by the pharmaceutical industry. In this context a wide-ranging study of the respective patent literature was necessary.

The present book deals only with synthetic and semisynthetic drugs. This is not meant to denigrate the therapeutic value of biogenic (natural) agents, but the inclusion of these products would unacceptably increase the size of the book. Many drugs are obtained by partial syntheses as for example in the enormous area of semisynthetic steroids. We therefore decided to prepare a special book which was published under the title *Drug isolation* in its German edition. It covers the isolation of biogenic drugs and their derivatives.

The most extensive chapter in the present book describes the synthesis of heterocyclic drugs, and this reflects the large proportion of such compounds in use as medicines. Benzo-condensed heterocycles are in each case included after the cyclic compound without the benzene ring. Thus, for example, benzimidazoles are found under the monocyclic heterocycles, after imidazole, and not amongst the bicyclic heterocycles such as purines.

All chiral carbon atoms in the formulae in this book have been asterisked (*) to show
— the number of chiral centers in today's agents,
— where resolution of racemates is necessary,
— when asymmetric syntheses are performed,
— when enantiomers or just racemates are used.

We thought it would be appropriate to begin with a stepwise introduction of themes or topics that relate to drug syntheses or are necessary for their understanding. We furthermore tried to provide an overview on the actual numbers, effects, patent situation, and the size of production of pharmaceuticals. This is to illustrate the progress and the obstacles in the way of developing new and better drugs.

The present book represents the translation of the original German 1982 edition but is updated with more than 40 new therapeutically significant pharmaceuticals which in part depend on new concepts of therapy and which came into use during recent years. The enormous increase of peptide-based pharmaceuticals prompted us to introduce a new chapter (Chapter 10) that deals with the synthetic opportunities and therapeutic utility of this class of agents.

We are indebted to Dr K. Eger, Dr G. Folkers, Dr J. Troschuetz, Dr R. Troschuetz, Bonn (FRG), and Dr K. Huthmacher, Hanau (FRG) who were engaged in the preparation of the original German edition. For the translation into the English version we wish to thank Dr Michael Cooke. The new entries as well as some corrections were carried out by Dr T. Beisswenger, Hanau (FRG) to whom we are especially indebted.

Tuebingen and Hanau, August 1987

H. J. Roth/A. Kleemann

Translator's note

Giving the 'right' name to a chemical compound will seldom find universal agreement. In this translation I have tried to keep a fair balance between the trivial and systematic names; in the case of generic drug names, all have been checked against the *Merck Index* (10th edition, published by Merck & Co., Inc., Rahway, New Jersey, USA, 1983) and/or *Martindale — The Extra Pharmacopoeia* (28th edition, published by the Pharmaceutical Press, London, 1982).

The choice of 'right' proprietary name is, however, far more problematic. (For example, the generic agent ampicillin is marketed worldwide in over 300 proprietary names/formulations — and even this number does not include the numerous salt forms!) I have therefore worked on the principle that

— if the trade name used in the original German edition is not used in the English-speaking world, then any English/American 'equivalent' will be more helpful to the reader, but
— if there is no English/American 'equivalent', then the original (German) name has been retained.

The choice of such an 'equivalent' does not in any way imply

(a) that this alternative proprietary material is an exact equivalent of the original, or
(b) that in the necessarily limited selection any substantial preference for one brand (cited) rather than another (not cited) has been made, or
(c) that the use of any such trade name/registered name etc. in this publication gives judgement on the rights associated with the use of that name.

M. D. Cooke
24 May 1985

Introduction

1. EXPLANATION AND DEFINITION OF IMPORTANT BASIC CONCEPTS

Drugs or **medicines** are substances which are made available by chemical syntheses or come from natural sources. If they are administered they cause a reaction which can help to prevent, to sooth, to cure, or to recognize an illness or disorder in man or in animals.

Depending on their mode of action, **pharmaceuticals** are subdivided into three main categories:

(1) **Pharmacodynamic agents**, which interact in a corrective manner on disturbed physiological control processes.
(2) **Chemotherapeutics**, which are used to control pathogens and parasites or exhibit antineoplastic activity.
(3) **Diagnostics**, which serve both to recognize and to monitor the state of illness or of therapy.

The term **pharmaceutical** has much the same meaning as **drug** in its **prescribing form** and represents a finished preparation of the **medicament**. It is in general composed of the drug or agent, inert carriers, and additives. If it is formulated without active ingredients it is called a **placebo**.

A **proprietary drug** is one that is prepared with a consistent quality and composition and that is used in unchanged form over a long period. It is available on the market in a standardized packing that carries a registered trade name or trade mark.

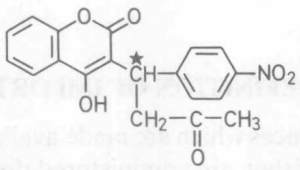
2. INTERNATIONAL ABBREVIATIONS

As a step towards an internationally uniform description the Geneva-based World Health Organization (WHO) has conferred on drug abbreviations, the so-called **generic names**. These are derived from strict guidelines which relate both to the chemical structure as well as to the intended use.

After a manufacturer's request and consideration by a WHO committee, the WHO issues a **proposed** international abbreviation for the respective drug. This is published in the *WHO Chronicle*. After a four-month period to allow settlement of legal disputes over trade names etc., this proposed international abbreviation then becomes a **recommended** abbreviation. These **International Nonproprietary Names (INN)** are generally applied for as soon as a compound is considered for clinical evaluation.

The INN's are meant to replace the many different national abbreviations or trade names, as well as the scientific names which are frequently very complicated. They are intended to allow a uniform international nomenclature which leads to simplification and to greater understanding. The INN is used throughout this book for all drugs.

The earlier systems of national abbreviations are still much used today, but are increasingly being replaced by the INN. As an example the agent **acenocoumarol** can be cited:



Scientific name: 4-Hydroxy-2-oxo-3-[3-oxo-1-(4-nitrophenyl)-butyl]-2*H*-chromene
INN or generic name: **acenocoumarol**

Previously used national names were:

a	Germany	Acenocumarin
b	Great Britain (BAN)[1]	nicoumalone
c	France (DCF)[2]	acenocoumarol
d	Scandinavia (NFN)[3]	acenocumarolum
e	USA (USAN)[4]	acenocoumarin

Trade names (trade marks) in various countries are: Ascumar®, Neo-Sintrom®, Sinthrome®, Sintrom®, Sintroma®.

During the last ten years it has become common in many countries to sell commercially important substances under their INN as so-called 'generics'. This is of course only possible when the patent protection of the originating company has expired in that country. Such a 'copy' preparation can be offered by the 'generic firms', in many cases, much more cheaply, since for them the research and development costs do not apply and have already been borne by the originating company. Thus after expiry of the Wellcome Company's patent protection on their allopurinol (Allopurinol®, Caplenal®, Zyloric®), well over ten 'generic' pre-

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[1] BAN = British Approved Name
[2] DCF = Dénomination Commune Française
[3] NFN = Nordisk Farmakopénaevn (Nordic Pharmacopoeia Council)
[4] USAN = United States Adopted Name

parations were marketed in Germany. This example shows how important it is for the reseraching pharmaceutical industry to maintain, both long-term and comprehensively, the patent protection on the compounds which have recently been developed at great cost.

3. NUMBER OF DRUGS

There are no reliable figures for the exact number of drugs used worldwide, but there might be somewhat over 3500 substances. Those which occur especially frequently in drugs as the only active ingredient are:

acetylsalicylic acid	heparin
allopurinol	hydrocortisone
ampicillin	isosorbid dinitrate
ascorbic acid	nitrofurantoin
atropine	phenoxymethylpenicillin
bisacodyl	prednisolone
chloramphenicol	prednisone
cyanocobalamine	retinol
dexamethasone	tetracycline
digoxin	triamcinolone
erythromycin	vincamine
glyceroltrinitrate	

The active agent **allopurinol** alone is supplied in 30 different proprietary pharmaceuticals in the Federal Republic of Germany (FRG), not counting the different dosage forms.

Annually worldwide some 200 000 to 300 000 tons of bulk chemicals are required. The value of this is some US-$ 8000 million. However, worldwide fewer than 500 compounds are in the 'big league'. Top in this category, based on quantity, is **acetylsalicylic acid**, with 50 000 tons produced annually. Next are **paracetamol** (acetaminophen) (27 000 tons), **β-lactam antibiotics** (16 000 tons), and **sulfonamides** (8000 tons). The vitamins must also be mentioned, of which the most important is **ascorbic acid** (vitamin C) with a worldwide production of 50 000 tons.

However, the value of these substances in US-$ covers a very wide range, from US-$ 10/kg for **acetyl salicylic acid** to about US-$ 3000/kg for speciality **heart glycosides**. Highly active peptide hormones command much higher prices still. The average cost of a drug substance is about US-$ 30/kg.

The elemental composition of pharmaceutical agents is also interesting. From a sample of 1000 substances, 91% contain nitrogen, 25% sulfur, and 62% a heterocycle. Of these heterocyclic agents again 95% contain nitrogen, 24% sulfur, and 16.5% oxygen as a ring element. Since these figures do not equal 100% it is clear that many compounds contain not only nitrogen but also sulfur and oxygen in the molecule or heterocycle.

When the frequency of different heterocycles in these same 1000 pharmaceutical agents is reviewed the following ranking is found:

piperidines	(79)	1,2,4-benzothiadiazinedioxides	(14)
pyridines	(64)	'pyrazolones'	(13)
piperazines	(58)	1,3-thiazoles, -ines, -idines	(12)
pyrimidines	(55)	imidazoles	(11)
phenothiazines	(40)	isoquinolines	(11)
thiophenes	(30)	indoles	(10)
penicillins	(29)	isoxazoles, -idines	(10)
pyrrolidines	(26)	1,3-oxazoles, -idines	(10)
purines	(24)	benzimidazoles	(9)
furans	(20)	hydantoins	(9)
1,4-benzodiazepines	(18)	5*H*-dibenz[b,e]azepines	(8)
quinolines	(18)	coumarins	(7)
morpholines	(18)	1,3,4-thiadiazoles	(7)
cephalosporins	(15)	azepanes	(6)
imidazolines, -idines	(15)	benzofurans	(6)

The number in brackets gives the count of heterocycles in the 1000 agents.

A very interesting and broad analysis of new agents introduced worldwide over the period 1961 to 1985 has been published by the Bundesverband der Pharmazeutischen Industrie (pharma dialog Nr. 95; E. Reis-Arndt: Neue pharmazeutische Wirkstoffe 1961 bis 1985). In this period 1787 chemically defined substances were introduced as new drugs in at least one country.

When the countries in which new drugs were invented are ranked, the following table results (the figures in brackets give the percentage share):

USA	422	(23.6)
France	288	(16.1)
Federal Republic of Germany	247	(13.8)
Japan	216	(12.1)
Italy	142	(7.9)
Switzerland	133	(7.4)
Eastern Bloc countries	113	(6.3)
Great Britain	86	(4.8)
Scandinavia	57	(3.2)
Benelux countries	42	(2.4)
Austria	28	(1.6)
Spain	18	(1.0)
Other countries	14	(0.8)
Total	1787	

This study also shows the significant trend that worldwide the number of newly developed compounds introduced into therapy has declined. While at the beginning of the '60s there were over 90 per year, by the mid '70s there were just 68, and in the early '80s it declined to 53. This shows clearly that the demand for efficiency and cost of registration are steadily increasing.