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ABOUT THIS BOOK, AND HOW TO USE IT

An introductory chapter briefly describing the subject, the aim, the approach and the topics. Students are offered advice on how to select material for study, and encouraged to understand the information rather than learn the factual material. General information on ionization in biochemicals and on nomenclature is given, together with a list of common abbreviations.

THE SUBJECT

This book has been written primarily for pharmacy undergraduates to provide a modern text to complement lecture courses dealing with pharmacognosy and the use of natural products in medicine. Nevertheless, it should be of value in most other courses where the study of natural products is included, although the examples chosen are predominantly those possessing pharmacological activity.

For centuries, drugs were entirely of natural origin and composed of herbs, animal products, and inorganic materials. Early remedies may have combined these ingredients with witchcraft, mysticism, astrology, or religion, but it is certain that those treatments that were effective were subsequently recorded and documented, leading to the early Herbals. The science of pharmacognosy – the knowledge of drugs – grew from these records to provide a disciplined, scientific description of natural materials used in medicine. Herbs formed the bulk of these remedies. As chemical techniques improved, the active constituents were isolated from plants, were structurally characterized, and, in due course, many were synthesized in the laboratory. Sometimes, more active, better tolerated drugs were produced by chemical modifications (semi-synthesis), or by total synthesis of analogues of the active principles.

Gradually synthetic compounds superseded many of the old plant drugs, though certain plant-derived agents were never surpassed and remain as valued medicines to this day. Natural drugs derived from microorganisms have a much shorter history, and their major impact on medicine goes back only about 60 years to the introduction of the antibiotic penicillin. Microbially produced antibiotics now account for a very high proportion of the drugs commonly prescribed. There is currently a renewed interest in pharmacologically active natural products, be they from plants, microorganisms, or animals, in the continued search for new drugs, particularly for disease states where our present range of drugs is less effective than we would wish. Herbal remedies are also enjoying a revival as many sufferers turn away from modern drugs and embrace 'complementary medicine'.

THE AIM

Many modern university pharmacy courses include a pharmacognosy component covering a study of plant-derived drugs, and traditionally this area of natural products has been taught separately from the microbially derived antibiotics, or the animal-related steroidal and prostanoid drugs. These topics usually form part of a pharmaceutical chemistry course. The traditional boundaries may still remain, despite a general change in pharmacognosy teaching from a descriptive study to a phytochemical-based approach, a trend towards integrating pharmacognosy within pharmaceutical

chemistry, and the general adoption of modular course structures. A chemistry-based teaching programme encompassing all types of natural product of medicinal importance, semi-synthetic derivatives, and synthetic analogues based on natural product templates, is a logical development, and one we have practised at Nottingham for several years. This coursebook provides a suitable text for such a programme, and attempts to break down the artificial divisions.

THE APPROACH

This book establishes a groundwork in natural product chemistry/phytochemistry by considering biosynthesis – the metabolic sequences leading to various selected classes of natural products. This allows application of fundamental chemical principles and shows the relationships between the diverse structures encountered in nature, thus giving a rationale for natural products and replacing the traditional descriptive approach with one based more on deductive reasoning. Subdivision of the topics is predominantly via biosynthesis, not class or activity, and this provides a logical sequence of structural types and avoids a catalogue effect. There is extensive use of chemical schemes and mechanism, with detailed mechanistic explanations being annotated to the schemes, as well as outline discussions in the text. Extensive cross-referencing is used to emphasize links and similarities. As important classes of compounds or drugs (indicated by an asterisk) are reached, more detailed information is then provided in the form of short separate monographs in boxes, which can be studied or omitted as required, in the latter case allowing the main theme to continue. The monograph information covers sources, production methods, principal components, drug use, mode of action, semi-synthetic derivatives, synthetic analogues, etc, as appropriate. Those materials currently employed as drugs are emphasized in the monographs by the use of bold type.

THE TOPICS

A preliminary chapter is used to outline the main building blocks and the basic construction mechanisms employed in the biosynthesis of natural products. Many of these fundamental principles

should be familiar, having been met previously in courses dealing with the fundamentals of organic chemistry and biochemistry. These principles are then seen in action as representative natural product structures are described in the following chapters. These are subdivided initially into areas of metabolism fed by the acetate, shikimate, mevalonate and deoxyxylulose phosphate pathways. Remaining chapters then cover alkaloids, peptides and proteins, and carbohydrates. The book tries to include a high proportion of those natural products currently used in medicine, the major drugs that are derived from natural materials by semi-synthesis, and those drugs which are structural analogues. Some of the compounds mentioned may have a significant biological activity which is of interest, but not medicinally useful. The book is also designed to be forward looking and gives information on possible leads to new drugs. A selection of supplementary reading references is provided at the end of each chapter; these are limited as far as possible to recent review articles in easily accessible journals rather than books, and have been chosen as student friendly.

BE SELECTIVE

Coverage is extensive to allow maximum flexibility for courses in different institutions, but not all the material will be required for any one course. However, because of the many subdivisions and the highlighted keywords, it should be relatively easy to find and select the material appropriate to a particular course. On the other hand, the detail given in monographs is purposely limited to ensure students are provided with enough factual information, but are not faced with the need to assess whether or not the material is relevant. Even so, these monographs will undoubtedly contain data which exceed the scope of any individual course. It is thus necessary to apply selectivity, and portions of the book will be surplus to immediate requirements. The book is designed to be user friendly, suitable for modular courses and student-centred learning exercises, and a starting point for later project and dissertation work. The information presented is as up to date as possible, but undoubtedly new research will be published that modifies or even contradicts some of the statements made. The reader is asked always to be critical and to maintain

a degree of flexibility when reading the scientific literature, and to appreciate that science is always changing.

TO LEARN, OR TO UNDERSTAND?

The primary aim of the book is not to rely just on factual information, but to impart an understanding of natural product structures and the way they are put together by living organisms. Rationalization based on mechanistic reasoning is paramount. The sequences themselves are not important; the mechanistic explanations for the processes used are the essence. Students should concentrate on understanding the broad features of the sequences, and absorb sufficient information to be able to predict how and why intermediates might be elaborated and transformed. The mechanistic explanations appended to the schemes should reinforce this approach. Anyone who commits to memory a sequence of reactions for examination purposes has missed the point. Of course, passing exams is probably the main reason why students are prompted to read this book, and the retention of some factual information will be essential. There is no alternative to memory for some of the material covered in the monographs, but wherever possible, information should be reduced to a concept that can be deduced, rather than remembered. The approach used here should help students to develop such deductive skills.

CONVENTIONS REGARDING ACIDS, BASES, AND IONS

In many structures, the abbreviation **P** is used to represent the phosphate group and **PP** the diphosphate (or pyrophosphate) group:
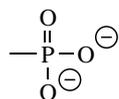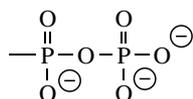
P (phosphate)   **PP** (diphosphate)

At physiological pHs, these groups will be ionized as shown, but in schemes where structures are given in full, the unionized acids are usually depicted. This is done primarily to simplify structures, to eliminate the need for counter-ions, and to avoid mechanistic confusion. Likewise, amino acids are shown in unionized form, although they will typically exist as zwitterions:
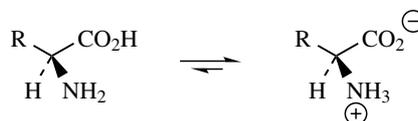
Ionized and unionized forms of many compounds are regarded as synonymous in the text, thus acetate/acetic acid, shikimate/shikimic acid, and mevalonate/mevalonic acid may be used according to the author's whim and context, and have no especial relevance.

NOMENCLATURE

Natural product structures are usually quite complex, some exceedingly so, and fully systematic nomenclature becomes impracticable. Names are thus typically based on so-called trivial nomenclature, in which the discoverer of the natural product exerts his or her right to name the compound. The organism in which the compound is found is frequently chosen to supply the root name, e.g. podophyllotoxin and peltatins from *Podophyllum peltatum*. Name suffixes might be -in to indicate 'a constituent of', -oside to show the compound is a sugar derivative, -genin for the aglycone released by hydrolysis of the sugar derivative, -toxin for a poisonous constituent, or may reflect chemical functionality, such as -one or -ol. Traditionally -ine is always used for alkaloids (amines). Structurally related compounds are then named as derivatives of the original, using standard prefixes, such as hydroxy-, methoxy-, methyl-, dihydro-, homo-, etc for added substituents, or deoxy-, demethyl-, demethoxy-, dehydro-, nor-, etc for removed substituents, positioning being indicated from systematic numbering of the carbon chains or rings. Some groups of compounds, such as steroids, fatty acids, and prostaglandins, are named semi-systematically from an accepted root name. In this book, almost all structures depicted in the figures carry a name; this is primarily to help identification and, for the student, structural features are more pertinent than the names used. It will soon become apparent that drug names chosen by pharmaceutical manufacturers are quite random, and have no particular relationship to the chemical structure.

We are also currently experiencing a transitional period during which many established drug names are being changed to recommended international non-proprietary names (rINN); both names are included here, the rINN preceding the older name.

SOME COMMON ABBREVIATIONS

ACP	acyl carrier protein
ADP	adenosine diphosphate
Api	apiose
Ara	arabinose
ATP	adenosine triphosphate
B:	general base
CoA	coenzyme A as part of a thioester, e.g. acetyl-CoA ($CH_3COSCoA$)
CDP	cytidine diphosphate
CTP	cytidine triphosphate
Dig	digitoxose
DMAPP	dimethylallyl diphosphate (dimethylallyl pyrophosphate)
Enz	enzyme
FAD	flavin adenine dinucleotide
$FADH_2$	flavin adenine dinucleotide (reduced)
FMN	flavin mononucleotide
$FMNH_2$	flavin mononucleotide (reduced)
FPP	farnesyl diphosphate (farnesyl pyrophosphate)
Fru	fructose
Gal	galactose
GFPP	geranylfarnesyl diphosphate (geranylfarnesyl pyrophosphate)
GGPP	geranylgeranyl diphosphate (geranylgeranyl pyrophosphate)
Glc	glucose
GPP	geranyl diphosphate (geranyl pyrophosphate)
HA	general acid
HMG-CoA	β-hydroxy-β-methylglutaryl coenzyme A
HSCoA	coenzyme A
IPP	isopentenyl diphosphate (isopentenyl pyrophosphate)
LT	leukotriene
Mann	mannose
NAD^+	nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide (reduced)
$NADP^+$	nicotinamide adenine dinucleotide phosphate
NADPH	nicotinamide adenine dinucleotide phosphate (reduced)
O	oxidation – in schemes
P	phosphate – in text
P	phosphate – in structures
PEP	phosphoenolpyruvate
PG	prostaglandin
PLP	pyridoxal 5′-phosphate
PP	diphosphate (pyrophosphate) – in text
PP	diphosphate (pyrophosphate) – in structures
Rha	rhamnose
Rib	ribose
SAM	*S*-adenosyl methionine
TDPGlc	thymidine diphosphoglucose
TPP	thiamine diphosphate (thiamine pyrophosphate)
TX	thromboxane
UDP	uridine diphosphate
UDPGlc	uridine diphosphoglucose
UTP	uridine triphosphate
W–M	Wagner–Meerwein rearrangement
Xyl	xylose
hν	electromagnetic radiation; usually UV or visible
Δ	heat

FURTHER READING

Pharmacognosy, Phytochemistry, Natural Drugs

Books

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