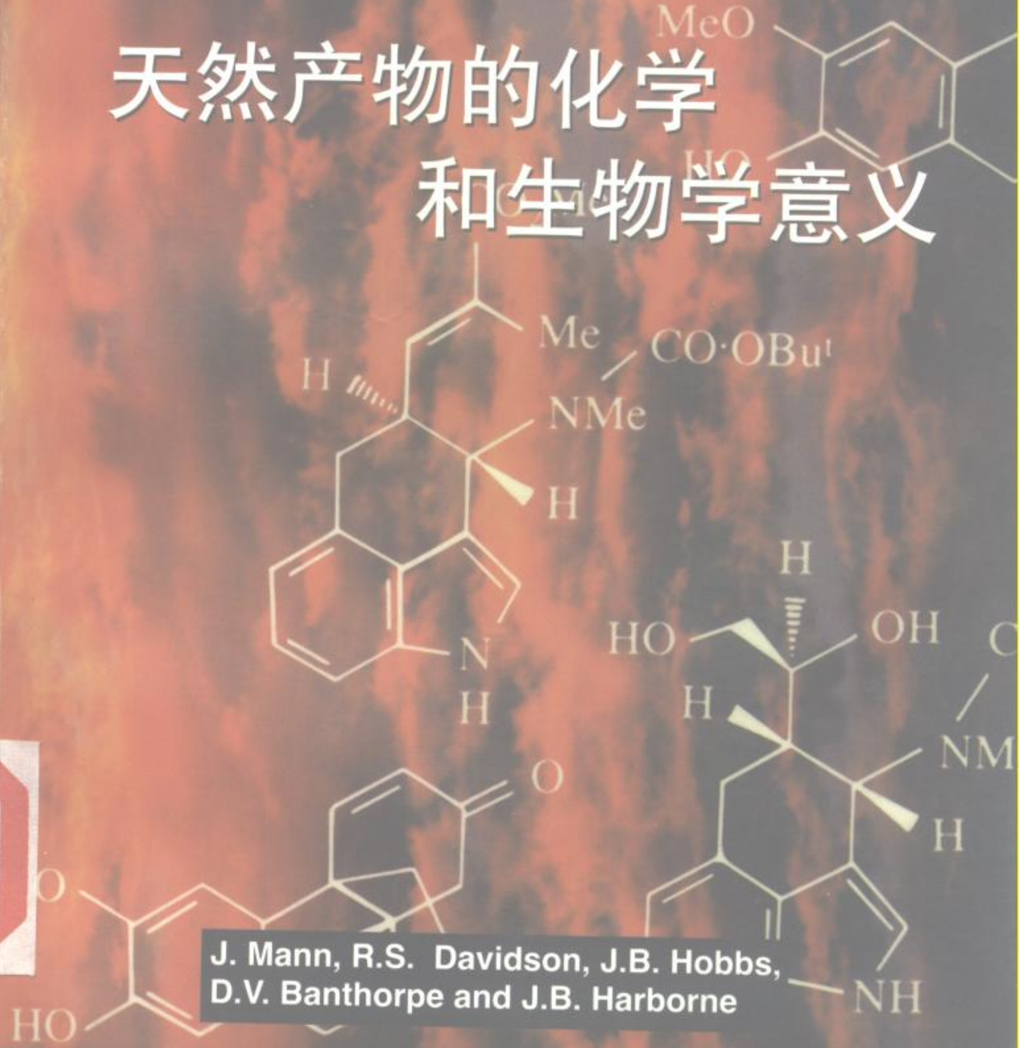
Natural Products

THEIR CHEMISTRY AND BIOLOGICAL SIGNIFICANCE

天然产物的化学和生物学意义



J. Mann, R.S. Davidson, J.B. Hobbs,
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Foreword

Naturally occurring organic chemical compounds (natural products) have always fascinated chemists. Interesting and intriguing chemistry is involved in their *in vivo* production and in their laboratory utilization, and their importance as structural materials and biologically active molecules (substrates for life processes, toxins, hormones, drugs, etc.) is of unparalleled importance. Yet they are largely ignored by the major textbooks of organic chemistry. This book seeks to remedy this omission.

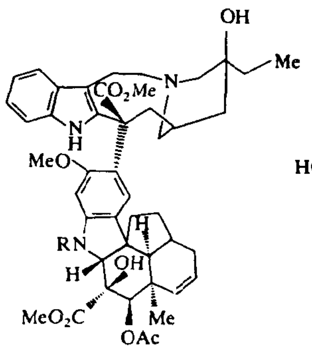
Each chapter is devoted to a particular class of compounds. Some, like carbohydrates, nucleosides and nucleotides, and amino acids and proteins, are products of primary metabolism and are vital for the maintenance of life processes. Others, like terpenoids, phenolics, fatty acid metabolites and alkaloids, are products of secondary metabolism and have toxicological, pharmacological and ecological importance.

The authors of the various chapters were given a free rein in terms of the contents of their chapters, though each chapter contains information about structural types, structure elucidation, synthesis, biosynthesis, and biological significance. This is not a research text and no attempt has been made to include the very latest (and possibly rather esoteric) advances. It is, however, intended to provide a comprehensive and readable introduction to most classes of natural products, and thus complements the standard texts on basic organic chemistry.

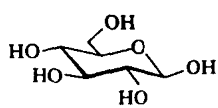
Contents

Introduction

It is just over a hundred years since Emil Fischer announced (in 1891) his elucidation of the structure of glucose. The complex alkaloids vinblastine and vincristine, which are highly potent anti-tumour agents, only succumbed to structure elucidation in 1964. The three compounds are clearly natural products, yet glucose is ubiquitous and essential for life, whilst the two alkaloids are only produced by a few species of plants, notably the rosy periwinkle *Catharanthus roseus*, and have no apparent functions in the plants.



R = –Me:vinblastine
R = –CHO:vincristine



β-D-glucose

The two types of compounds are, however, connected via complex metabolic pathways as shown in Fig. 1. Admittedly the link is somewhat tenuous, but carbohydrate metabolism does give rise to the aromatic amino acid tryptophan and to the terpenoid precursor mevalonic acid. These two building blocks provide most of the skeleton of vinblastine and vincristine.

A more detailed examination of Fig. 1 reveals the numerous metabolic interconnections between the various classes of natural products that are included in this book. Usually the compounds are identified as products of primary metabolism, i.e. carbohydrates, nucleosides, amino acids and the polymers derived from them, or as products of secondary metabolism, i.e.

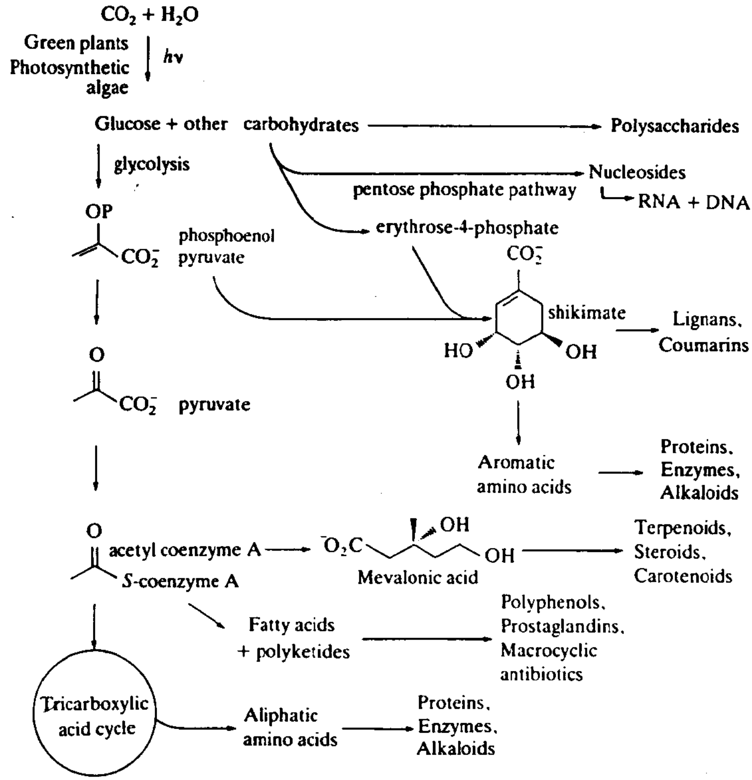


Fig. 1.

phenolics, terpenoids and steroids, and alkaloids. Primary metabolites are essentially ubiquitous and certainly essential for life, whilst the secondary metabolites are of restricted occurrence and of no apparent utility. This division is useful but somewhat arbitrary. Testosterone, for example, is of limited occurrence, but has vital hormonal activity, and nicotine from the tobacco plant (and a few other species) has a definite role as an insect feeding deterrent. It is thus much more important to appreciate the chemical and biochemical interconnections between the various classes of natural products, than to worry about whether they are primary or secondary metabolites.

Although the book is primarily concerned with the chemistry of natural products, most of the chapters do include some discussion of the biogenesis of the various natural products. The metabolic pathways by which they are produced and subsequently transformed are almost invariably enzyme-controlled, so a brief discussion on enzymes and their cofactors is essential.

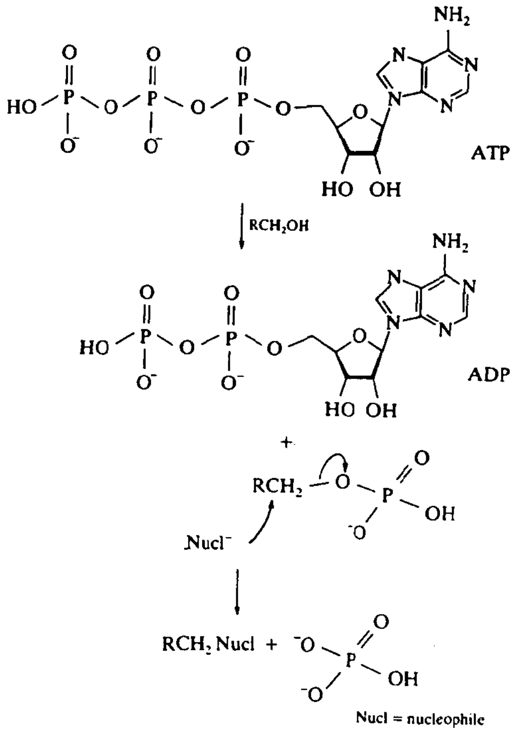


Fig. 2.

Enzymes and cofactors

There are two major classes of proteins: structural proteins such as keratin of skin and collagen of tendon; and enzymes such as chymotrypsin or trypsin, which catalyse the breakdown of ingested proteins in the gut. The former are usually fibrous, whilst the latter are often globular in shape.

One feature that all enzymes possess is an active site, which is the 'cavity' in which the chemical interconversions that are catalysed by the enzyme actually take place. In general, the chemistry that occurs is mechanistically similar to that which could be accomplished in the laboratory, but the rates of reaction are up to 10^{12} times faster. Most of the reactions are also stereospecific, or at least highly stereoselective, and the rate acceleration and this stereospecificity are a direct result of the way in which the substrate(s) and the enzyme interact. The substrate(s), specific participating amino acids, and necessary cofactors (small organic molecules or metal ions), are held in a pseudo transition state configuration, so that the activation energy for the reaction is reduced and the stereospecificity ensured.

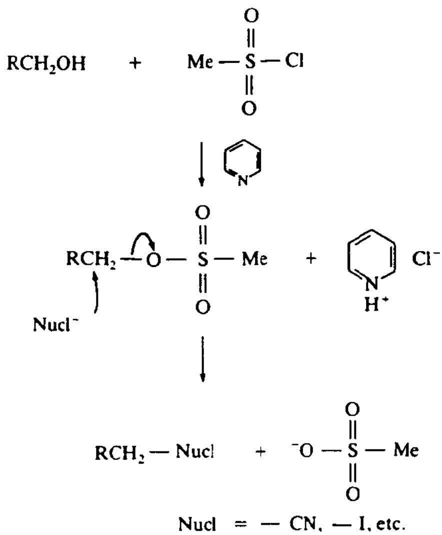

RCH₂OH + Me—S(O)₂—Cl
RCH₂—O—S(O)₂—Me
Cl⁻
H⁺
Nucl⁻
RCH₂—Nucl + ⁻O—S(O)₂—Me
Nucl = —CN, —I, etc.

Fig. 3.

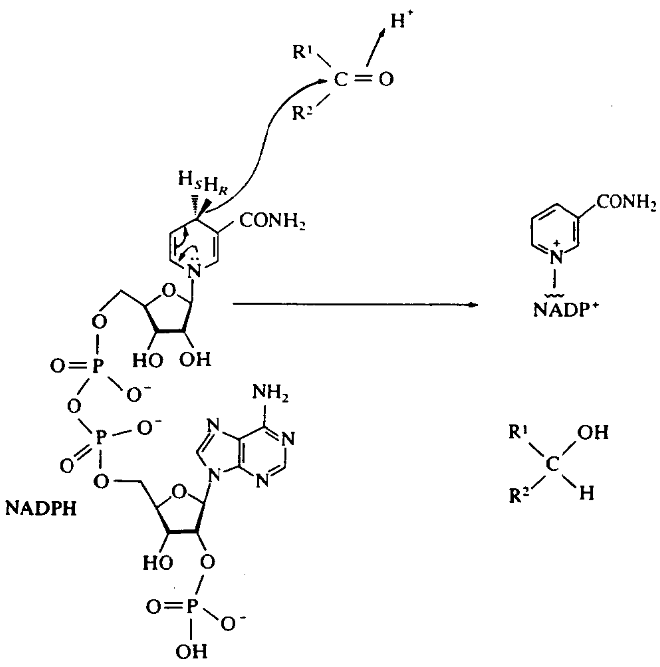

H⁺
R¹
C=O
R²
HSHR
CONH₂
CONH₂
N
NADP⁺
HO OH
NH₂
NADPH
HO
OH
R¹ OH
C
R² H

Fig. 4.

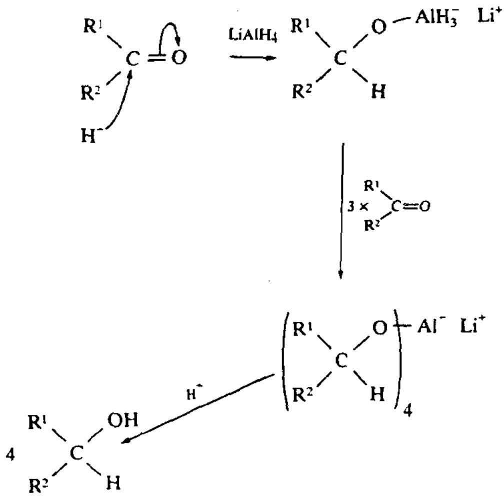


Fig. 5.

Numerous cofactors have been identified, but two are of particular importance. These are adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide phosphate (NADPH). The general mode of reaction of ATP is shown in Fig. 2, and involves activation of a substrate molecule for nucleophilic displacement. Usually a hydroxyl function is converted into the phosphate or pyrophosphate, and this then suffers nucleophilic displacement. This type of chemistry is familiar to anyone who has ever made a methanesulphonate or toluenesulphonate in order to convert an alcohol into an iodide, nitrile, etc. (Fig. 3).

The cofactor NADPH is a mediator of numerous reductions that occur during biosynthesis, and the mechanism of action is shown in Fig. 4. Once again this chemistry is analogous to laboratory chemistry, since reductions effected with lithium aluminium hydride, sodium borohydride, and other hydride transfer reagents also result in addition of hydride followed by addition of a proton (upon work-up with water) (Fig. 5). One major difference is that the two hydrogens of NADPH are pro-chiral (i.e. if one is replaced with deuterium or tritium, the carbon centre becomes chiral), and the reductions mediated by the cofactor are usually stereospecific. This means that either the H_R or H_S hydrogen is used by a particular enzyme for a specific reduction. Other cofactors will be encountered in the main body of the text, and their chemistry will be discussed at that point.

An examination of Fig. 1 will reveal that photosynthesis and the production of carbohydrates are central to all primary and secondary metabolic pathways, and the book thus commences with a discussion of the chemistry and biological significance of carbohydrates.