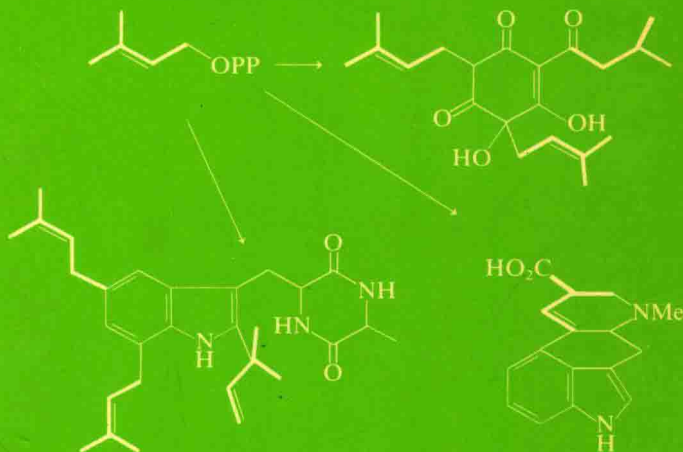


J. MANN

Secondary Metabolism

SECOND EDITION



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J. MANN

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Secondary metabolism

Second edition

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Editor's foreword

The chemistry of natural products has always excited the interest of the scientist and it provided the early stimulus for the foundation of organic chemistry as a separate discipline. The rapidly growing knowledge of natural-product structure led naturally to questions concerning the transformations and functions of biological molecules and hence to the subject of biochemistry.

Traditionally biochemists have studied the essential life processes of primary metabolism while the organic chemist has tended to concentrate his interests on secondary metabolites, where the problems of structure elucidation provided the necessary initial intellectual challenge. Great progress has been made in both areas and a composite picture of biosynthesis has emerged of sufficient clarity to satisfy the differing philosophies of biochemist and organic chemist alike. The subject now provides an essential bridge between the physical and life sciences.

The remarkable advances which have been made in the understanding of biosynthesis have depended on specialized techniques drawn from a wide range of disciplines. The use of mutants, isolated enzyme systems, radioactive tracer techniques, and, more recently, the application of n.m.r. methods to metabolites enriched with precursors containing stable isotopes, have all contributed to the picture. The subject is now so important that biologist, biochemists, and organic chemists must be exposed to this exciting field of study.

Dr Mann is an organic chemist with a very strong interest in natural-product chemistry and is well equipped to present a balanced picture of the field. Although the book is written primarily for the organic chemist, and provides the basic knowledge of biosynthesis essential to the armoury of any organic chemist, the material covered will also be of great interest to the biochemist and biologist. Indeed, any scientist who is concerned with the chemistry of life processes will discover in this book an account of the remarkable progress that has been made in the last twenty years.

J. S. E. H.

For Sara, Sebastian,
Cressida, and Octavia

Preface to the second edition

During the eight years since the first edition was published, sophisticated n.m.r. techniques (especially observation of isotope-induced shifts when ^{13}C and ^2H or ^{18}O isotopes are jointly present in the administered substrates), and the use of isolated enzymes, have revolutionized the study of biosynthetic pathways. In particular, subtle details of these routes may now be identified, and the biogenesis of ever more complex natural products can be probed. These innovations are highlighted in this completely updated edition, though the emphasis is still on a consideration of the main pathways of biosynthesis, and on the biological activities and ecological significance of secondary metabolites. In order to include as much new material as possible, without complicating the main part of the text, some of the more exotic or complex compounds have been included in the problems section (answers are now provided), or are referred to in the list of research references.

Reading

January 1986

J. M.

Preface to the first edition

The chemistry of natural products has been studied seriously for about one hundred and fifty years; but investigation of their biosynthesis is a much more recent research endeavour, and has been greatly facilitated by the advent of modern spectroscopic techniques and the availability of isotopically labelled compounds. The results of these investigations—the proven pathways of biosynthesis and interconversion of natural products—are the subject of this book.

In the first chapter the idea of primary and secondary metabolic pathways is introduced. These produce, respectively, essential and ubiquitous compounds (e.g. carbohydrates, proteins, and nucleic acids), and apparently non-essential compounds, or secondary metabolites. This latter group is then classified according to the small precursor molecules (or 'building blocks') from which they are derived, and most of the remainder of the book is concerned with a detailed discussion of the various biosynthetic pathways. The final chapter considers ecological chemistry, and attempts to show how secondary metabolites are used as mediators of complex interactions between different species.

My aim was to write a text that was suitable for undergraduate courses in natural products/secondary metabolism, and of use to research workers entering the field, who required a general introduction to the subject. It is not a reference text, and does not cover the chemistry of secondary metabolites in any great detail: there are many excellent texts which serve these purposes. However, all major classes of secondary metabolites are dealt with, and their biosynthesis is covered in some detail. In the main, only well-established results are included, but at the end of each chapter there are questions, whose answers may be found in the recent research literature.

Finally, I have stressed the biological properties of these compounds and their pharmacology, toxicology, and ecological significance, because I feel these aspects have received scant attentions in the past. Secondary metabolites can no longer be thought of as the useless detritus produced by obscure metabolic pathways: many have a profound influence on the interactions of one species with another. When we understand these interactions a little better, we should be able to ensure that we do not disturb the environment to our own detriment or to that of the species with which we coexist.

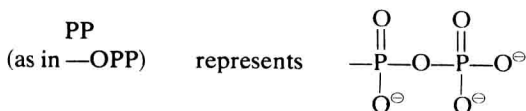
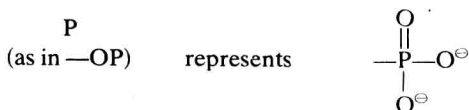
I should like to thank Dr Holker for his invaluable help and guidance, and also Dr Derek Banthorpe, Dr Jeffrey Harborne, and Dr David Crout, who read parts of the manuscript. Their comments and criticism were of great assistance.

Reading
1977

J. M.

Abbreviations used and stereochemical nomenclature

Abbreviations

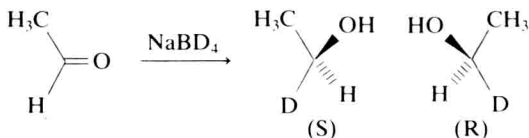


Stereochemical nomenclature

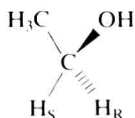
It is assumed that the reader is familiar with the Cahn-Ingold-Prelog (R,S) nomenclature, but two other types of stereochemical nomenclature that are commonly encountered in discussions of secondary metabolism are given below.

Prostereoisomerism

When deuterium or tritium isotopes are introduced into organic molecules, new chiral centres are often produced. So, for example, in the reduction of ethanal by sodium borodeuteride, two stereoisomers of ethanol are produced:

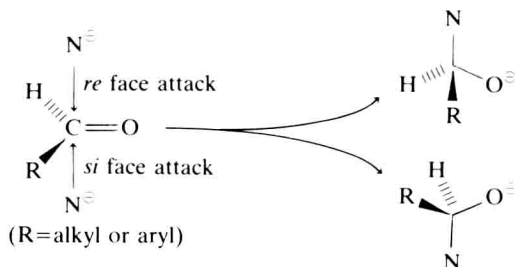


Upon oxidation either two hydrogens or a hydrogen and a deuterium may, in principle, be lost, to yield monodeutero ethanal or ethanol. In ethanol itself, the two methylene hydrogens are apparently identical, though an oxidation mediated by an enzyme will usually be stereospecific, and only one of the two possible hydrogens will be lost. In order to distinguish between these atoms we can call them pro-R and pro-S (H_R and H_S), implying that if the former atom is replaced by a deuterium or tritium atom, the molecule will then have R-stereochemistry, and if the latter is replaced the S-stereochemistry will result, viz:



Enantiotopic faces

Prochirality can be extended to the faces of molecules, and this is also of prime importance when discussing the stereochemistry of enzyme-mediated reactions. Thus, attack of a nucleophile at a carbonyl produces different chiral products, depending upon the direction of attack:



To distinguish the two faces, one considers the 'view seen' by the attacking species: if the groups are arranged (in the priority sense of the Cahn–Ingold–Prelog rules) in a clockwise direction this is then the *re* (rectus) face, and if in an anticlockwise direction this is then the *si* (sinister) face.

Clearly, the above aspects of stereochemistry apply equally well to asymmetric organic synthesis, as they do to secondary metabolism and biochemical processes in general.

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1. Introduction

Natural products

This book is primarily concerned with the formation, structure, and biological activity of natural products. The term 'natural product' is commonly reserved for those organic compounds of natural origin that are unique to one organism, or common to a small number of closely related organisms. In most instances they appear to be non-essential to the plant, insect, or microorganism producing them, in marked contrast to the other organic compounds in Nature, sugars, amino acids, nucleotides, and the polymers derived from them, which are both essential and ubiquitous.

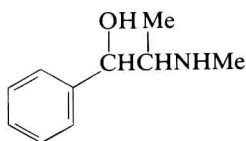
Two examples of typical natural products will help to clarify the definition. Morphine only occurs in two species of poppy, *Papaver somniferum* and *P. setigerum*, and although widely used and abused by Man, has no known function in these plants. Similarly, penicillins are produced by a few species of fungi, and by no other organisms. They have great value as antibiotics in the service of Man, but appear to serve no useful purpose in the microorganisms that produce them.

Man has used natural products, albeit as crude plant extracts, since the dawn of time and we still possess 'recipes' from mediaeval times. Thus Ambroise Paré (1517–90), a French surgeon of some note, treated gunshot wounds with a concoction of chamomile, melilot flowers, lavender, rosemary, sage, thyme, and the extract from red roses boiled in white wine. Thomas Sydenham (1624–89), a Bachelor of Medicine (and friend of Robert Boyle) prescribed finely powdered Peruvian bark (from the cinchona tree) mixed with syrup of cloves as a remedy for malaria. Quinine is a major component of the bark of the cinchona tree.

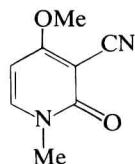
Primitive man found these extracts efficient as medicines for the relief of pain or alleviation of the symptoms of disease, as poisons for use in warfare and hunting, as effective agents for euthanasia and capital punishment, and as narcotics, hallucinogens, or stimulants to relieve the tedium, or alleviate the fatigue and hunger in his life. He must also surely have used the more odiferous and spicy compounds to obscure the odour of unwashed humanity, and to disguise the putrid or bland flavour of his food. Some of the compounds that he unwittingly employed are shown in Fig. 1.1.

Many of these natural products are still used today, and usually for the same general purpose. Curare, a plant extract which contains several toxic alkaloids, was used by South American Indians as an arrow poison since they discovered that it could paralyse even quite large animals. A

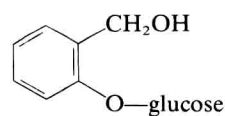
Medicines



Ephedrine (respiratory ailments)

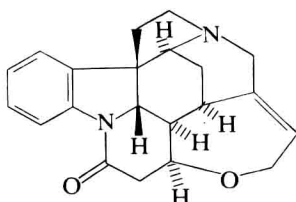


Ricinine (Castor oil: purgative)

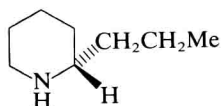


Salicin (from willow bark: used by 'rural folk' for fevers; aspirin is a synthetic analogue)

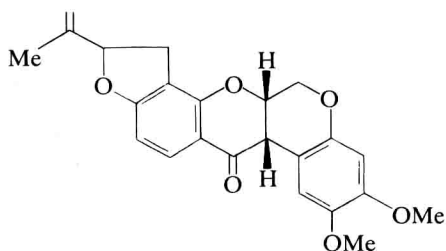
Poisons



Strychnine



Coniine (hemlock)



Rotenone (fish poison and natural insecticide)

Fig. 1.1