THE BIOSYNTHESIS OF STEROIDS, TERPENES, AND ACETOGENINS

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and

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Preface

In the last decade, acetate as a metabolic entity has assumed a position of central importance in biological processes, particularly as a prime substrate for the biosynthesis of a wide variety of natural substances. Indeed, the symbol adopted for the Fifth International Congress of Biochemistry, held in Moscow in the summer of 1961, was a somewhat stylized representation of an acetic acid molecule. As a result of this progress, acetate is now recognized as the common progenitor of a host of widely divergent structural types found in nature; e.g., terpenes, steroids, fatty acids, complex oxygen heterocycles phenolics, and even some alkaloids.

In every area of study there comes a time when hypotheses solidify into theory, when various, at one time independent, understandings merge into a clear and satisfying theoretical unity that generates predictions, the basic tenets of which are safe from experimental destruction. This is the propitious moment for a detailed exposition, since such an exposition may confidently be expected to remain substantially correct thereafter, while providing a useful condensation and organization that exposes the remaining areas of theoretical and experimental uncertainty, thus affording a springboard into future efforts. The study of biosynthesis from acetate seems to be at this stage; although many important questions still remain open, the theoretical outline is generally clear and is unlikely to undergo major revision in the future. We were therefore encouraged to undertake this summary of the field up to the end of 1962 and, in most cases, through 1963.

We should like to acknowledge that the original initiative for this work came from Professor Marshall Gates, who invited us to participate in a general volume on the biogenesis of natural substances. For reasons beyond his control (the life of an editor is not an easy one!), Professor Gates was

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obliged to dissolve the enterprise. This work represents the crystallization of our manuscripts with considerable expansion, revision, and updating.

In order to identify ourselves as targets for criticism, one of us (J. B. H.) claims primary responsibility for the first part of the book (Chapters 2 through 5) and the other (J. H. R.) is the principal author of the remainder. J. B. H. would like to record his gratitude to Dr. David Dalton for assistance in literature searching, and J. H. R. is grateful to an anonymous reviewer for a great many very helpful criticisms.

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J. B. HENDRICKSON I. H. RICHARDS

Cambridge, Massachusetts Pasadena, California March 1964

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chapter one

Introduction

The role of acetate in the biosynthesis of almost all groups of natural products has received extensive theoretical and experimental consideration, especially within the last two decades. As a result the casual reader of this book may easily find himself inundated by the mass of structural correlations that is now apparent and by the large amount of detailed biochemical knowledge that is presently available on many aspects of this question. We propose, therefore, in this brief discussion to give a panoramic view of the role of acetate in the biosynthesis of natural products, and hope that it may serve as a gentle and concise introduction to the subject.

The importance of acetate as an intermediate in a host of biochemical processes has long been known. Acetate results from fatty acid breakdown, is a product of carbohydrate metabolism, and can be produced from certain amino acids. Acetate can also serve as a source of these substances and is thus a molecule that interconnects the three major classes of biological compounds: fats, carbohydrates, and proteins. Acetate can also serve as a source of energy through oxidation to carbon dioxide and water via the familiar Krebs cycle (or tricarboxylic acid cycle).

I-I ACETOGENINS

The implication of acetate in the biosynthesis of a wide variety of straight-chain and aromatic natural compounds was first deduced on structural grounds; the acetate hypothesis stated that a linear polyketomethylene chain formed from head-to-tail self-condensation of acetate units could cyclize into a remarkable array of complex structures.

These deductions were subsequently confirmed by tracer and enzymatic studies.

The compounds encompassed by the acetate hypothesis are a broad group that has never, unfortunately, been graced with a generic name, so that, unlike the terpenes and alkaloids, no unified reviews of this group have been assembled. The group includes such categories as flavonoids, quinones, coumarins, chromones, depsides, benzophenones, and a host of others, all highly oxygenated compounds and about 85 per cent incorporating at least one benzene ring. Now that these compounds can be considered unified under the acetate biogenesis concept, it is appropriate that a generic name be given them; to this end it is suggested that they be called acetogenins.* It is hoped that future laboratory investigators of biogenesis will thus be dissuaded from concentrating solely on such biologically artificial groupings as flavones or xanthones and will consider the acetogenin group as a whole.

The conversion of acetate to the acetogenins is a process that possesses a close similarity to the construction of fatty acids (themselves acetogenins). New carbon-carbon bonds are formed in both cases by the addition of malonyl coenzyme A to an activated carbonyl group.

$$CH_3COSCoA + CO_2 \rightarrow CH_2 - COSCoA$$

$$COOH$$

$$O$$

$$CH_3COSCoA + CH_2 - COSCoA \rightarrow CH_3 - C - CH_2 - COSCoA + CO_2 \xrightarrow{redn.}$$

$$COOH$$

$$CH_3(CH_2)_{2n}COSCoA \rightarrow Fatty Acid$$

* The term acetogenin ("genesis from acetate") is intended to include compounds biogenetically derivable by the acetate hypothesis and its several variants discussed below, and to exclude the terpenes, which, although ultimately derived from acetate, are obviously themselves a homogeneous family arising more immediately from linear combination of isoprenoid units.

The term is clearly expressive of the biogenetic origin and unity of this diverse group of compounds, the suffix -genin defined as "A termination denoting a substance formed from another substance, e.g., digitogenin from digitonin, etc." However, it has been criticized as implying "producing acetate" rather than "arising from acetate," especially in the adjectival form, and indeed the suffixes -genic and -genous are defined in both ways. In order to avoid confusion with the -genic suffix, which is often used in the former sense, we have chosen to employ acetogenous as the adjectival form.

1. Webster's New International Dictionary of the English Language, unabridged 2d ed., 1960; 3d ed., 1961, Merriam, Springfield, Mass.

Malonyl coenzyme A is itself formed from acetate by carboxylation of acetyl coenzyme A.

In the production of other natural products derived from acetate, it is useful to envision the intermediacy of an unreduced polyketo chain that can undergo internal, aldol-type reactions to yield cyclic products. The formation of orsellinic acid [1] points out two of the major features of acetogenins: first, they are derived from the appropriate folding of a chain whose backbone is composed of acetate units linked linearly head to tail; and, sécond, these substances often carry oxygen at those positions derived from the carboxyl group of the acetate precursor. In this fashion oxygen functions frequently mark the carboxyl carbons of acetate and so serve as an important key to the structural deduction of acetate biogenesis.

These comments apply to griseofulvin [2], which also demonstrates another aspect of acetogenin biosynthesis: the acquisition of secondary substituents (in this case chlorine). These substituents can be of a wide variety and include halogen, oxygen, and carbon in various forms, e.g., methyl, formyl, carboxyl, or even isoprenoid chains.

$$CH_3COOH$$
 \longrightarrow CH_3O OCH_3 OCH_3

An additional secondary feature is further oxidation (or reduction) to give products in different over-all oxidation states from those of the

formal polyketo-chain precursor. Cyclopaldic acid [3] demonstrates some of these features. Other modifications and variations of these few basic themes are possible and afford an extraordinarily wide

$$\begin{array}{c} CH_3 \rightarrow [O] \\ C \rightarrow O \\ COOH \\ CH_3 \end{array} \longrightarrow \begin{array}{c} OHC \\ OCH_3 \\ CH_3 \end{array}$$

array of substances whose basic carbon skeleton is composed of a linear arrangement of acetate units. For example, such complex and apparently diverse substances as erythroaphin [4] and the alkaloid lycopodine [5] are probably derived directly from acetate.

I-2 BIOLOGICAL ISOPRENE UNIT

For the incorporation of acetate into terpenes and their derivatives, a route is followed that differs at an early stage from that just discussed for the biosynthesis of the acetogenins. Whereas the acetogenins are formed by a linear linking of acetate units, the terpenes are generated by conversion of acetate to a branched-chain intermediate, Δ^3 -isopentenyl pyrophosphate, the biological isoprene unit. The condensation of two moles of acetyl coenzyme A [6] produces acetoacetyl coenzyme A [7], which, upon acquisition of another acetyl residue at the central carbonyl group, forms a branched, six-carbon substance, hydroxymethylglutaryl coenzyme A [8]. A stepwise reduction of the esterified carboxyl carbon of this substance produces mevalonate [9].

The intermediates in the biosynthetic sequence prior to mevalonate are capable of interconversion to many other substances. However, the formation of mevalonate is an essentially irreversible process, and mevalonate once formed has essentially only one biochemical role—the production of isoprenoid substances. Its discovery was, therefore, one of the important breakthroughs in terpene biosynthesis.

$$2CH_{3}COSC_{0}A \rightarrow CH_{3}COCH_{2}COSC_{0}A$$

$$[6] \qquad [7]$$

$$\downarrow CH_{4}COSC_{0}A$$

$$H_{3}C \qquad OH \qquad OH$$

$$CH_{3} - C - CH_{2}COSC_{0}A$$

$$CH_{2} \qquad CH_{2} \qquad CH_{2}$$

$$HO-CH_{2} \qquad COOH$$

$$[9] \qquad [8]$$

The path after mevalonate commences with a series of stepwise phosphorylations ([9] \rightarrow [10] \rightarrow [11]) by which the terminal hydroxyl function of the mevalonate is activated as a pyrophosphate ester. The tertiary hydroxyl group is also phosphorylated ([11] \rightarrow [12]), thus activating the resulting molecule for decarboxylation concerted with loss of phosphate and generation of Δ^3 -isopentenyl pyrophosphate [13].

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