

# ROLE OF ACETATE IN BIOSYNTHESIS<sup>1</sup>

JOHN H. RICHARDS<sup>2</sup>

*Gates and Crellin Laboratories of Chemistry,  
California Institute of Technology, Pasadena, California*

## Abstract

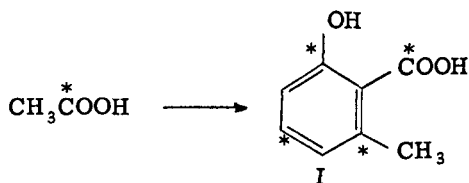
The role of acetate in the biosynthesis of a large number of antibiotics and other natural products is discussed. Included are simple substances apparently derived from acetate by molecular rearrangements, such as patulin and the fungal tropolone acids, puberlonic and stipitatic acids. The origin of more complex antibiotics such as oxytetracycline is considered, as well as the genesis of depsidones (such as nidulin) from lichens and fungi. The involvement of acetate in the biosynthesis of various classes of alkaloids, such as the indoles, strychnine, and ajmaline, is also discussed. More recent developments in the biochemical details of these processes, such as the role of malonate, is particularly stressed.

In the last decade, acetate as a metabolic entity has come to occupy a position of central importance in a wide variety of biosynthetic activities of many diverse organisms. Its incorporation as the primary building block into steroids (e.g., cholesterol) and terpenes, by way of isopentenyl pyrophosphate, the biological isoprene unit, was well established by Bloch, Lynen, and many others (Wright, 1961). Acetate is also known as the major substrate (in the form of malonyl coenzyme A) for the construction of the linear carbon chains characteristic of fatty acids (Mead, 1963). We shall not be concerned here with these two important biosynthetic roles of ace-

tate, but shall concentrate on its utilization in the construction of various aromatic substances in fungi and on its newly discovered function as an important substrate in the biosynthesis of indole alkaloids such as strychnine. Moreover, this discussion is by no means inclusive as, even within the areas chosen, there is a wealth of material too extensive for inclusion here.

Collie (1907) advanced the proposal that acetate could give rise to various substances by appropriate condensations. Independently, Birch (1956), in a more sophisticated way, advanced a similar proposal, and this suggestion bore much fruit in subsequent years.

One of the simplest aromatic substances of biological origin is 6-methyl salicylic acid (I), and its origin from acetate in the expected fashion was one of the earliest experimental verifications of the acetate hypothesis (Birch, Massy-Westropp, and Moye, 1955):

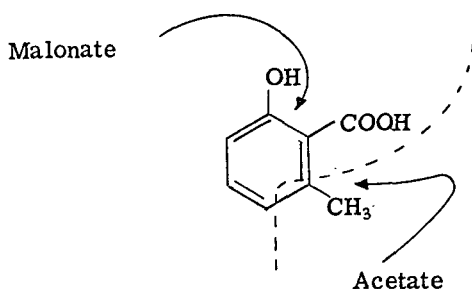


Along with the recent realization that fatty acid synthesis involves addition of malonyl coenzyme A to an acyl coenzyme A, it has been found that malonate is incorporated into 6-methyl salicylic acid as three of the four two-carbon units

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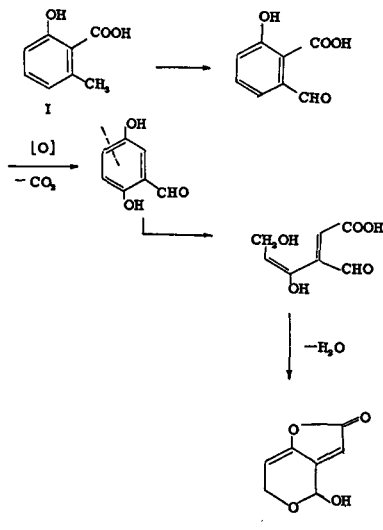
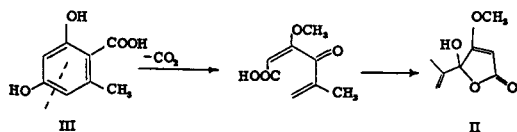
<sup>2</sup>Alfred P. Sloan Fellow.

(Bu'Lock, Smalley, and Smith, 1962):

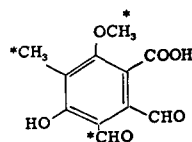


Thus, the biosynthesis of these aromatic acetogenins (acetogenins is a convenient word to describe those substances originating from an essentially linear poly-acetate chain) is seen to have many similarities to fatty acid construction.

Interesting extensions of this route to a simple benzenoid product are also found. For example, ring cleavage and decarboxylation can lead to substances such as penicillic acid (II) from orsellinic acid (III; Mosbach, 1960) and patulin (IV) from 6-methyl salicylic acid (Tanenbaum and Bassett, 1959).

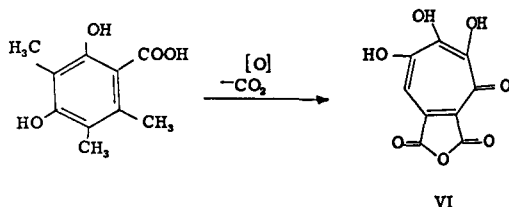


Many substances contain carbon atoms which originate from the one-carbon pool, probably by a transmethylation from methionine. Such additional carbon atoms are evident in cyclopaldic acid (V; Birch and Kocor, 1960; Birch et al., 1958), which is clearly a close biosyn-



V

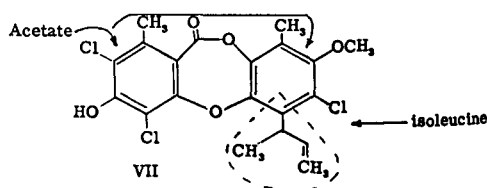
thetic relative of 6-methyl salicylic acid. (Asterisks indicate carbons from the "one-carbon pool.") It was suggested (Ferretti and Richards, 1960; Bentley, 1963) that the mold tropolones arise by a molecular rearrangement of a benzenoid intermediate, a ring enlargement converting the six-membered benzene skeleton into the seven-membered aromatic tropolone ring, e.g., puberulonic acid (VI).



VI

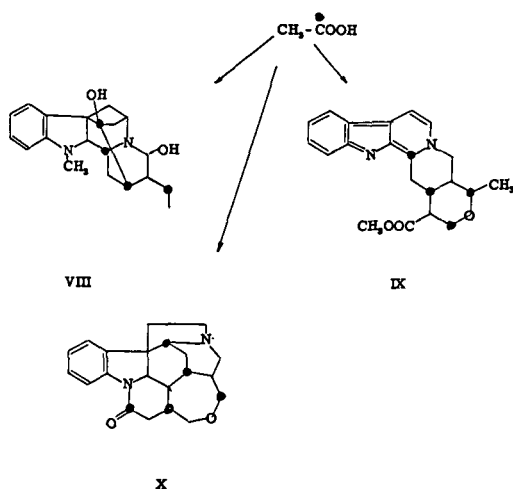
Thus, there are a variety of secondary biosynthetic pathways open to simple benzenoid acetogenins which can lead to such diverse substances as penicillic acid, patulin, or the mold tropolones, puberulonic or stipitatic acid.

Another group of substances whose origin from acetate was demonstrated is the depsidones, for example nidulin (VII; Beach and Richards, 1963). The flexibility of general acetogenin biosynthesis



is here amplified by the demonstration that fragments other than acetate can be included in the skeleton. In this case, isoleucine gives rise to the isobutenyl side chain attached to one of the aromatic rings of nidulin. Many other mixings of this type could be cited to enforce the general observation that acetogenins need not be derived solely from acetate (or malonate) units, but may derive important parts of their skeletons from quite different metabolic areas.

The recent demonstration that indole alkaloids have regions of apparently polyacetate origin is an example of this generality, and settles a question that has long perplexed those interested in biogenetic theories. The demonstrations of acetate incorporation into ajmaline (VIII), serpentine (IX; Leete and Ghosal, 1962), and strychnine (X; Hall, Willner, and Richards, *unpublished data*) would seem to provide a broad enough spectrum of structural types from different plant sources to support the suggestion that acetate has a wide spread importance in indole alkaloid biosynthesis.



### Addendum in Proof

Recent experimental results of Battersby et al. (Proc. Chem. Soc., p. 369-

370, 1963) on acetate and formate incorporation into ajmaline are in complete disagreement with those reported by Leete. Battersby et al. reported that acetate is *not* incorporated in a specific manner into the alkaloid.

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