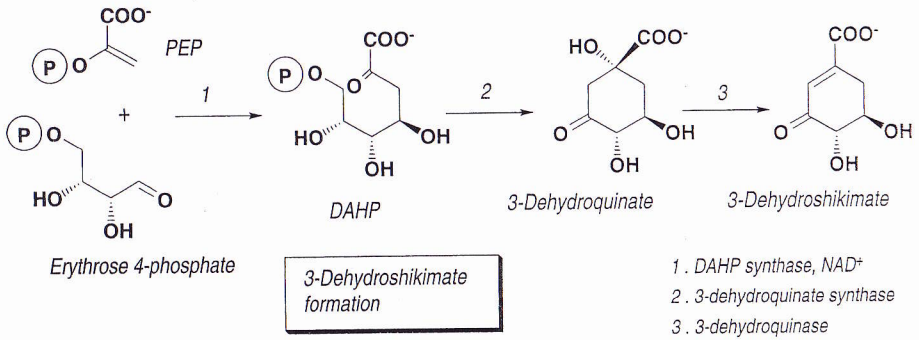
QUERCUS ROBUR L.

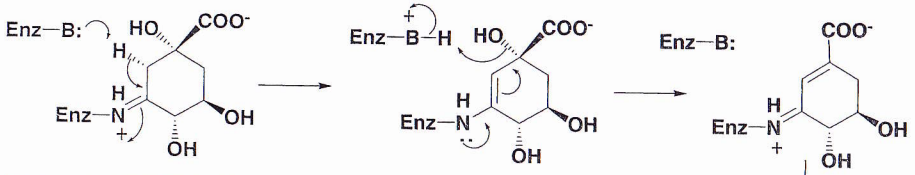
SHIKIMATES
Phenylpropane Derivative-Containing Drugs

1. BIOSYNTHETIC ORIGIN OF THE AROMATIC RING (Shikimic Acid Pathway)

Since numerous works and reviews are devoted to this reaction sequence and to the mechanisms involved, we shall only present here a succinct summary of the pathway leading from the products of glycolysis and of the Calvin cycle to aromatic amino acids (phenylalanine and tyrosine) and to cinnamic acids.

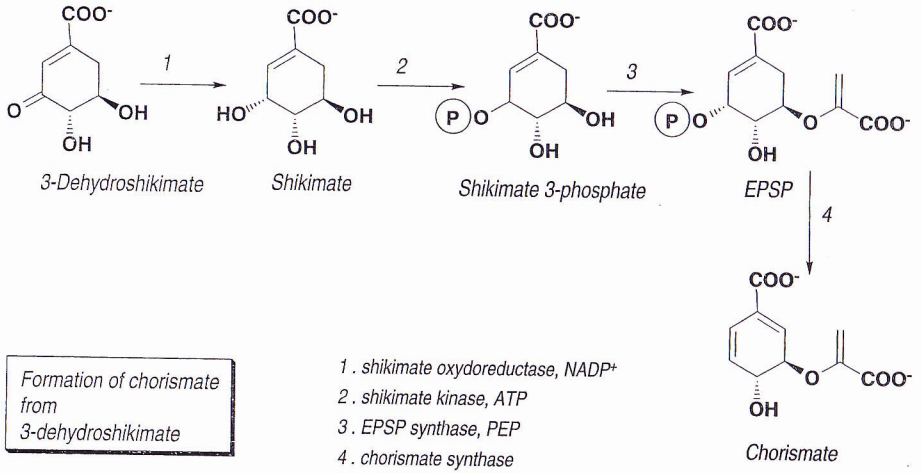


The first reaction is the condensation of phosphoenolpyruvate (= PEP) with erythrose-4-phosphate which yields a C_7 compound, 3-deoxy-D-arabinoheptulosonate-7-phosphate (= DAHP). The cyclization of DAHP to 3-dehydroquinate is a complex reaction which involves an intramolecular aldol condensation subsequent



Conversion of 3-dehydroquinate to 3-dehydroshikimate (enzyme: 3-dehydroquinate dehydratase)

catalyzed by an enzyme which forms a transient Schiff base between a lysine residue and the carbonyl group of 3-dehydroquinate, and induces a stereospecific *cis* elimination of a water molecule. Following the reduction of 3-dehydroshikimate and shikimate phosphorylation, condensation with another molecule of PEP yields an enol ether, 5-enolpyruvylshikimate 3-phosphate (= EPSP). This leads, *via* an unusual *trans* 1,4-elimination, to chorismate.



Formation of chorismate from 3-dehydroshikimate

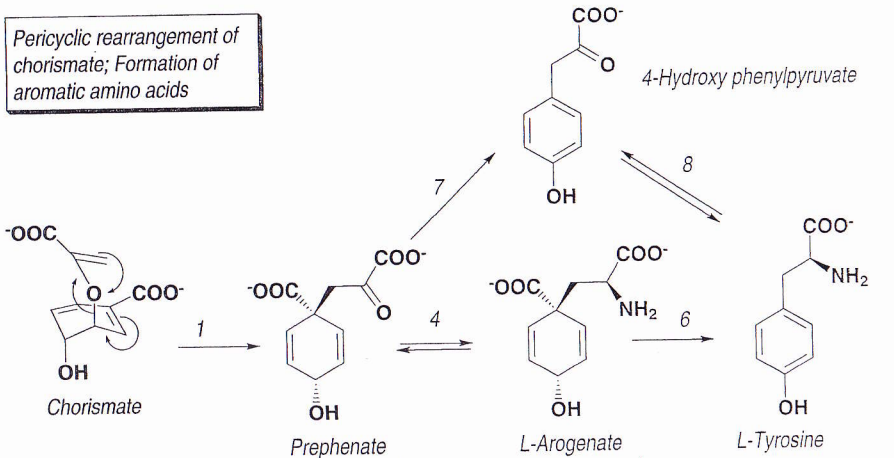
1. shikimate oxydoreductase, NADP+
2. shikimate kinase, ATP
3. EPSP synthase, PEP
4. chorismate synthase

Chorismic acid holds a key position in metabolism and has multiple fates:

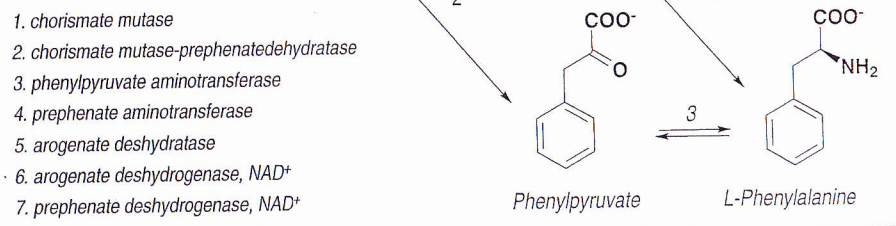
• Claisen-type pericyclic rearrangement to prephenate. This pathway leads, *via* phenylpyruvate, to phenylalanine and tyrosine. This rearrangement is catalyzed by an enzyme, chorismate mutase, which transfers the side chain derived from PEP to the carbocycle, and thereby generates the skeleton of phenylpropanes. The enzyme is thought to control the conformation by favoring a chair transition state with pseudoaxial substituents;

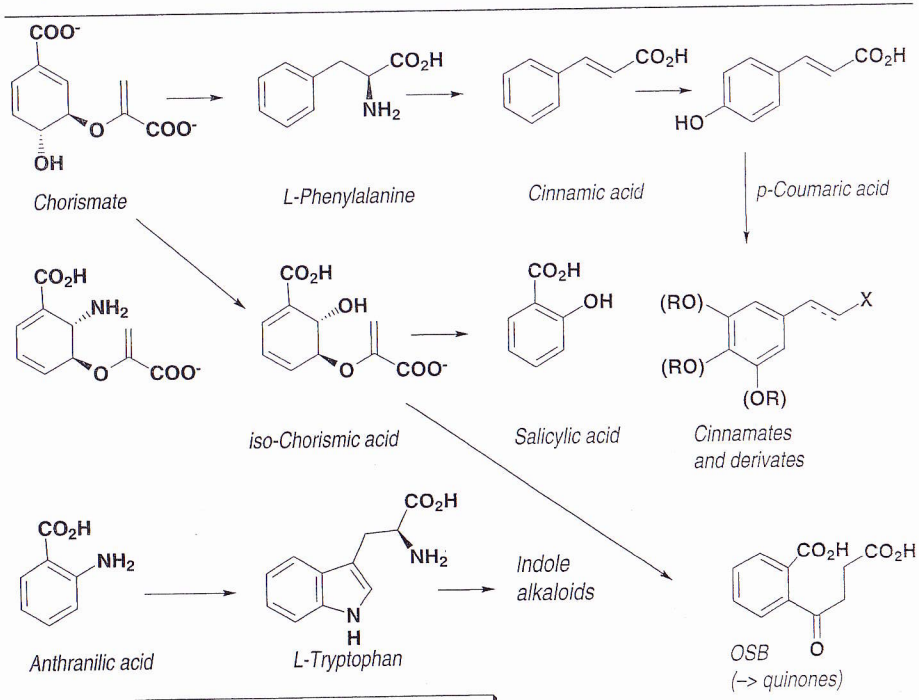
• amination and anthranilate (= 2-aminobenzoate) formation. Anthranilate is the required intermediate of the biosynthesis of tryptophan, which is the starting point of the formation of all indole alkaloids. It is also the (direct) precursor of most

Pericyclic rearrangement of chorismate; Formation of aromatic amino acids



1. chorismate mutase
2. chorismate mutase-prephenatedehydratase
3. phenylpyruvate aminotransferase
4. prephenate aminotransferase
5. arogenate deshydratase
6. arogenate deshydrogenase, NAD+
7. prephenate deshydrogenase, NAD+





Fate of chorismic acid (main pathways)

• hydroxylation and dehydration to isochorismate, from which arise phenol acids in C_6-C_1 (e.g., salicylic acid), and *via* *o*-succinylbenzoic acid (= OSB), certain naphthoquinones.

Prephenate decarboxylation, aromatization, and reductive deamination yield L-phenylalanine. If the hydroxyl in the C-4 position is conserved (formation of 4-hydroxy-phenylpyruvate by prephenate dehydrogenase), then the reductive amination yields L-tyrosine. Another biogenetic pathway to aromatic amino acids is also known, in which the initial step is the reductive amination of the α-ketoacid; the resulting amino acid (L-arogenate) is subsequently decarboxylated and aromatized to L-phenyl-alanine (by arogenate dehydratase) or else to L-tyrosine (by arogenate dehydrogenase).

2. ORIGIN AND FATE OF CINNAMIC ACIDS

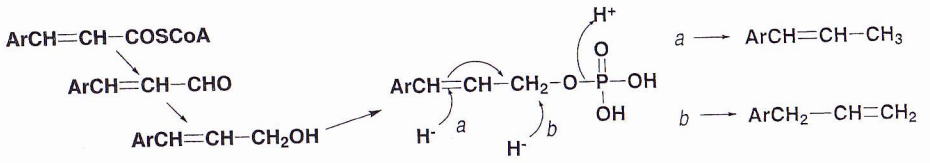
Compounds with a C_6-C_3 unit, often collectively referred to as phenylpropanoids, are the most common of all shikimic acid metabolites. No matter the degree of oxidation of their side chain (alcohol, aldehyde, propene, or other), they arise from cinnamic acids. These are virtually universal and may occur in the free or combined state (as esters, amides, or glycosides); they frequently acylate the most diverse metabolites. Furthermore, the phenylpropanoid moiety may cyclize (coumarins), dimerize (lignans), polymerize (lignins), or undergo side chain elongation (stilbenes, flavonoids).

The stereospecific elimination of ammonia from phenylalanine yields (*E*)-cinnamic (= *trans*-cinnamic) acid. The reaction is catalyzed by phenyl ammonia lyase (PAL), and the elimination of ammonia is facilitated by the reaction between the NH_2 function and a dehydroalanine residue on the prosthetic group of the enzyme. In the majority of cases, 4-mono- and 4,5-dihydroxylated cinnamic acids (e.g.,4-coumaric and caffeic acids, respectively) arise from cinnamic acid hydroxylation. Thus, cinnamate 4-hydroxylase (a cytochrome P450-dependent monooxygenase) catalyzes cinnamic acid hydroxylation.

Subsequent reactions of cinnamic acids, especially ester formation, require their preliminary activation, either as esters of coenzyme A, or as esters of glucose, with the latter functioning as acylating reagent as well as acylation substrate.

Cinnamic aldehydes and alcohols arise from stepwise enzymatic reduction of the esters of cinnamic acids and of coenzyme A.

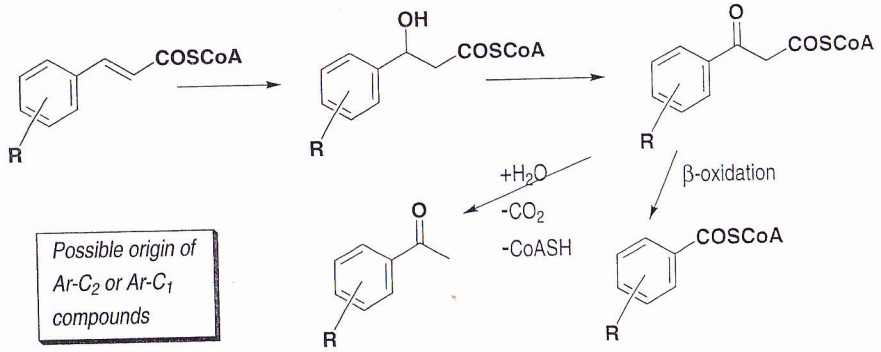
Among the most important cinnamic acid metabolites are phenylpropanoids, especially allyl- and propenylphenols. Their formation mechanisms remain



Likely origin of allyl- and propenylphenols

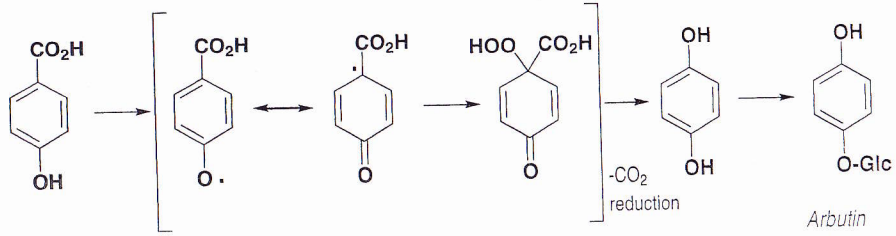
Shortening of the side chain yields benzoic acids and their derivatives or simple phenols.

• Benzoic acids and their derivatives. Ar-C_1-type compounds (e.g., vanillin, benzoic acid) can arise directly from 3-dehydroshikimic acid (like gallic acid) or from chorismic acid (like salicylic acid), but as a general rule, they result from side chain degradation of the corresponding cinnamic acids. Although some Ar-C_2-type compounds are formed from cinnamates, most benzophenones arise from the metabolism of acetate and malonate.



Possible origin of Ar-C_2 or Ar-C_1 compounds

• Simple phenols. These seldom occur naturally. In all likelihood, they arise from benzoic acid decarboxylation (oxidative or not). For example, arbutin may arise from the decarboxylation of peroxidized 4-hydroxybenzoic acid.



Arbutin

Chief drugs containing phenylpropanoids include sources of essential oils whose major constituents are allyl- and propenylphenols (e.g., essential oils of clove, sassafras or Apiaceae): their structures and the biological properties that some of them impart to the drugs containing them will be indicated in the corresponding chapter (see essential oil-containing drugs). In addition, esters of gallic acid and glucose (i.e., hydrolyzable tannins), since they have physico-chemical and biological properties similar to those of condensed tannins, will be studied together (see tannin-containing drugs).

Accordingly we shall cover: first, simple phenols and phenolic acids, then balsams, coumarins, and lignans; and second, chain elongation products of phenylpropane.

3. BIBLIOGRAPHY

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Phenols and Phenolic Acids