# Condensed Tannins: Quinone Methide Intermediates in Procyanidin Synthesis

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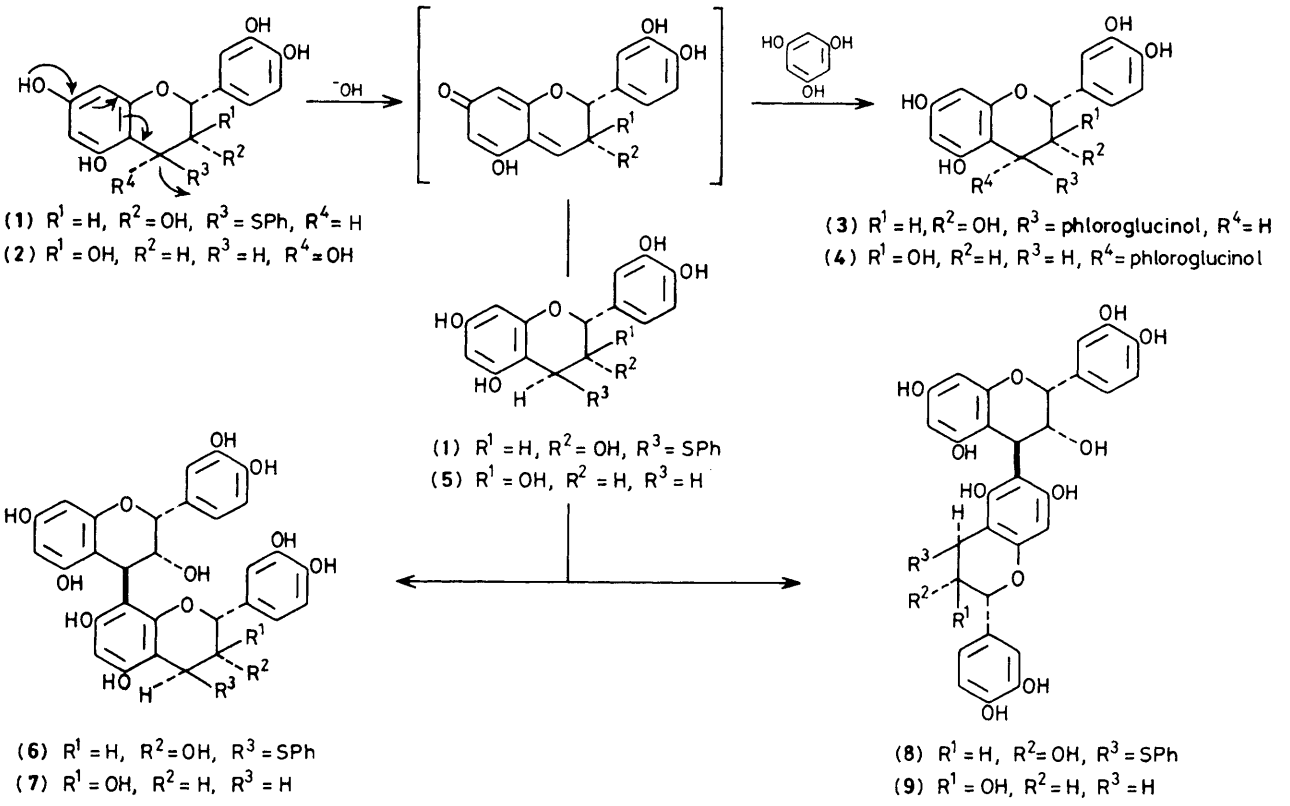
Comparisons of acid- and base-catalysed reactions of epicatechin-(4$\beta$)-phenyl sulphide and leucocyanidin show that condensations proceed more rapidly at alkaline than at acidic pH so the biosynthesis of condensed tannins may occur through a quinone methide rather than a carbocation intermediate.

Proanthocyanidins (condensed tannins) are widely distributed in plants[1,2] and are found in sufficiently high concentration in some tree barks to encourage their industrial utilization.[3] These polymers consist of flavanoid units linked through the C-4 of the pyran ring to the C-6 or C-8 carbons of the aromatic A-ring.[1,4] Recent advances in the chemistry of condensed tannins are due largely to the successful synthesis of many proanthocyanidin isomers by acid-catalysed condensations.[5–9] These facile acid-catalysed condensations have prompted the use of the term 'biomimetic synthesis' and hypotheses on polymer biosynthesis that involve protonation of a flavan-3,4-diol[8] or a flav-3-en-3-ol[10] to produce dimers and oligomers. While proanthocyanidins can be readily synthesized *in vitro* by protonation of flavan-3,4-diols, it seems equally plausible that the route to their biosynthesis could be through a quinone methide intermediate. Acid- and base-catalysed reactions of flavan derivatives containing good leaving groups at C-4 were compared to examine this hypothesis.

Rapid base-catalysed condensation of these compounds was first demonstrated through reactions of epicatechin-(4$\beta$)-phenyl sulphide (**1**). When (**1**) was dissolved in acetone–water (1 : 1, v/v) and the pH adjusted to 9.0 with sodium hydrogen carbonate–sodium carbonate buffer, epicatechin-(4$\beta$→8)-epicatechin-(4$\beta$)-phenyl sulphide (**6**), epicatechin-(4$\beta$→6)-epicatechin-(4$\beta$)-phenyl sulphide (**8**), and polymeric materials were produced after only 30 min at ambient temperature (Scheme 1). Epicatechin-(4$\beta$→2)-phloroglucinol (**3**) was the major reaction product of (**1**) and phloroglucinol after 45 min at pH 9.0. Similarly, the dimeric procyanidins epicatechin-(4$\beta$→8)-catechin (**7**) and epicatechin-(4$\beta$→6)-catechin (**9**) were produced after 30 min of reaction of (**1**) with (+)-catechin (**5**). Parallel reactions of (**1**) at pH 3 in acetone–water with phloroglucinol or (+)-catechin yielded no condensation products even after 8 h at ambient temperature. These results clearly demonstrate that, in reactions of epicatechin-(4$\beta$)-phenyl sulphide, condensation proceeds much more rapidly through




**Scheme 1**

a quinone methide reacting with a phenolic anion than through acid-catalysed condensations involving carbocations.

A similar comparison of acid- and base-catalysed condensations of (2*R*,3*S*,4*R*)-flavan-3,3′,4,4′,5,7-hexaol or leucocyanidin (**2**) prepared according to the method of Porter and Foo[11] showed that polymerization occurred more rapidly at pH 9.0 than 3.0. Additionally, base-catalysed reactions of (**2**) in the presence of excess of phloroglucinol gave catechin-(4α→2)-phloroglucinol (**4**) more rapidly than did the acid-catalysed reaction.

Although epimerization at C-2 is known to occur in alkaline solutions, (+)-catechin was unaffected after several hours at pH 9.0 and ambient temperature. No epimerization at C-2 was noted in the reaction products of epicatechin-(4β)-phenyl sulphide after 1 h at pH 9.0 either. The identity and stereochemistry of these products were confirmed by $^1$H and $^{13}$C n.m.r. spectra as well as by chromatographic comparisons with authentic compounds.[12] As observed in the above products, the stereochemistry of natural procyanidins at C-4 has been shown to be invariably *trans* to the C-3 hydroxy group. Preservation of the stereochemistry at C-4 rules out an $S_N2$ reaction. The quinone methide intermediate is fully consistent with such stereospecificity since the addition of a bulky flavanoid substituent at C-4 is most favoured from the less-hindered side, or *trans* to the C-3 hydroxy group.

The procyanidin dimers (**7**) and (**9**) did not react with phloroglucinol after several hours at pH 9.0 and ambient temperature indicating that the lower flavanoid unit is not a good leaving group in base-catalysed reactions. The lower phloroglucinol ring should be ionized just as readily as the upper unit, thus inhibiting interflavanoid bond cleavage and formation of a quinone methide. This stabilization of the interflavanoid bond would facilitate further reaction of oligomers with quinone methide intermediates enabling the oligomers to accumulate and propagate in molecular weight. Consideration of all the preceding factors leads to the conclusion that quinone methides are more likely to be involved in the biosynthesis of these polymers than carbocation intermediates.

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