

Condensed Tannins: Synthesis of the First 'Branched' Procyanidin Trimer

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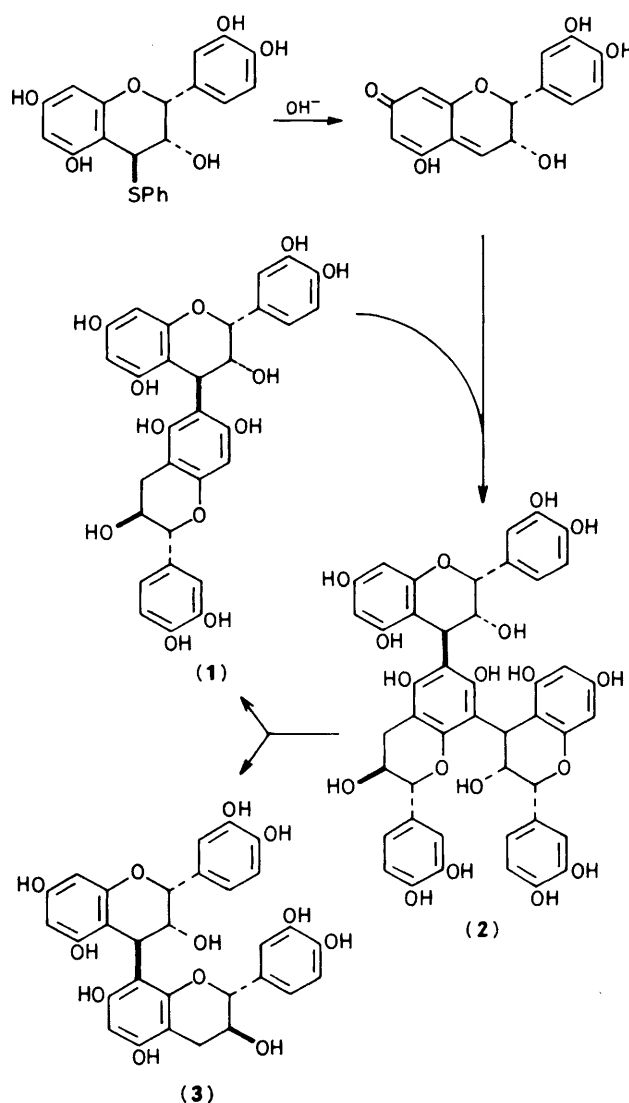
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Synthesis of the branched procyanidin trimer, epicatechin-(4 β →8)-catechin-(6→4 β)-epicatechin has been accomplished and in higher yield than the linear analogues, suggesting that procyanidin polymers may be highly branched.

Condensation of mollisacacidin with catechin under acidic conditions resulted in a 'branched' or angular (fisetinidin)₂-catechin trimer where both fisetinidin units were substituted on the catechin moiety.^{1,2} The corresponding branched procyanidin trimers have hitherto not been synthesized and analogous acid-catalysed condensation of leucocyanidins³ or procyanidins⁴ with catechin have given only 'linear' procyanidin oligomers. This difference in interflavanoid bonding between the profisetinidins and procyanidins is attributed to the higher reactivity of the phloroglucinol A ring over a resorcinol system which, in the case of fisetinidin-catechin reactions, favours condensation at the catechin A ring over the resorcinol ring of the fisetinidin unit. These observations have provided support for the view that the condensed tannins of black wattle (*Acacia mearnsii*) are angular in shape^{2,5} while the more common condensed tannins of the procyanidin class are linear⁶ and linked by either C(4)-C(8) or C(4)-C(6) interflavanoid bonds.^{4,7}

Procyanidin synthesis *via* the quinone-methide route has yielded dimers and related derivatives more cleanly and efficiently than the acid-catalysed condensation reactions.⁸ Extension of this synthesis by treating the quinone-methide generated from (4 β)-epicatechin phenyl sulphide with epicatechin-(4 β →6)-catechin (**1**) resulted in stereospecific and regioselective condensation to yield the first branched procyanidin trimer, epicatechin-(4 β →8)-catechin-(6→4 β)-epicatechin (**2**), [α] +73°, and the linear trimer epicatechin-(4 β →8)-epicatechin-(4 β →6)-catechin in a ratio of 8:1, respectively (Scheme 1). The constitution of the branched trimer was readily evident from the products of partial degradation with phenylmethanethiol. In contrast to the linear procyanidins which rapidly yield the terminal catechin unit,⁹ the product (**2**) generated catechin much more slowly, supporting the thesis that the catechin was doubly substituted with two epicatechin units. Additionally, no procyanidin dimer thioethers were detected during the course of the reaction. Production of the two dimers epicatechin-(4 β →6)-catechin (**1**) and epicatechin-(4 β →8)-catechin (**3**) unambiguously verified the branched structure of (**2**).

The structure of (**2**) is also supported by the ¹³C n.m.r. spectral data. The ratios of the areas of the C(2) and C(3) resonances of catechin to epicatechin units are 1 to 2 in both instances, thereby confirming the (epicatechin)₂-catechin trimeric constitution.¹⁰⁻¹² The chemical shifts of both C(3) carbon atoms of the two epicatechin units are coincident occurring at δ 72.5 p.p.m., consistent with the C(3) chemical shifts of the top epicatechin units in linear trimers.¹⁰⁻¹² The coincident resonance of both epicatechin units is in contrast to the situation encountered in linear trimers where the C(3) chemical shift for the middle epicatechin moieties are found 0.5 to 1.3 p.p.m. upfield of those for the corresponding carbon atom of the top epicatechin unit.^{4,11} The most diagnostic feature of the ¹³C n.m.r. spectrum of (**2**) is the unsubstituted A ring carbon shifts. Two signals, of comparable intensity, are observed at δ 96.6 and 96.1 p.p.m. which are attributable to the C(6) and C(8) carbons atoms, respectively.^{4,11} Both of



Scheme 1

these resonances display *meta-meta* coupling in the gated decoupling experiment, thus confirming the absence of substitution on the epicatechin A rings.

The ¹H n.m.r. data are also fully consistent with a branched (epicatechin)₂-catechin trimer structure. Complete assignment of all the heterocyclic ring and A ring protons is possible. The most distinctive feature is the coincidence of the protons attached to C(2) of the two epicatechin units at δ 4.87. In the linear trimers, the chemical shifts of the top and middle epicatechin units are distinctly different.¹⁰ The A ring protons

occur at δ 6.06 in the shape of an unresolved triplet resulting from a superimposed double doublet of the two similar AB systems.

The stereochemistry at the two C(4) positions of the epicatechin units is evident from the epicatechin C(2) chemical shifts. Again, these two chemical shifts are coincident at δ 76.8 p.p.m. showing that the appending catechin unit is *trans* to the 3-hydroxy group since, in both instances, the C(2) carbon resonances are shifted upfield by 2.3 p.p.m. from the C(2) epicatechin chemical shift due to the γ -gauche effect between the axial protons at C(2) and the catechin unit at both C(4) positions.

The branched trimer (2) is the major product of the reaction and the ease by which the compound is formed in comparison with linear analogues clearly shows that disubstitution of the A ring is not sterically inhibited and that branching may be a significant feature of natural proanthocyanidin polymers.

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