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Facile Self-condensation of Melacacidin: a Demonstration of the Reactivity of the Pyrogallol A-Ring

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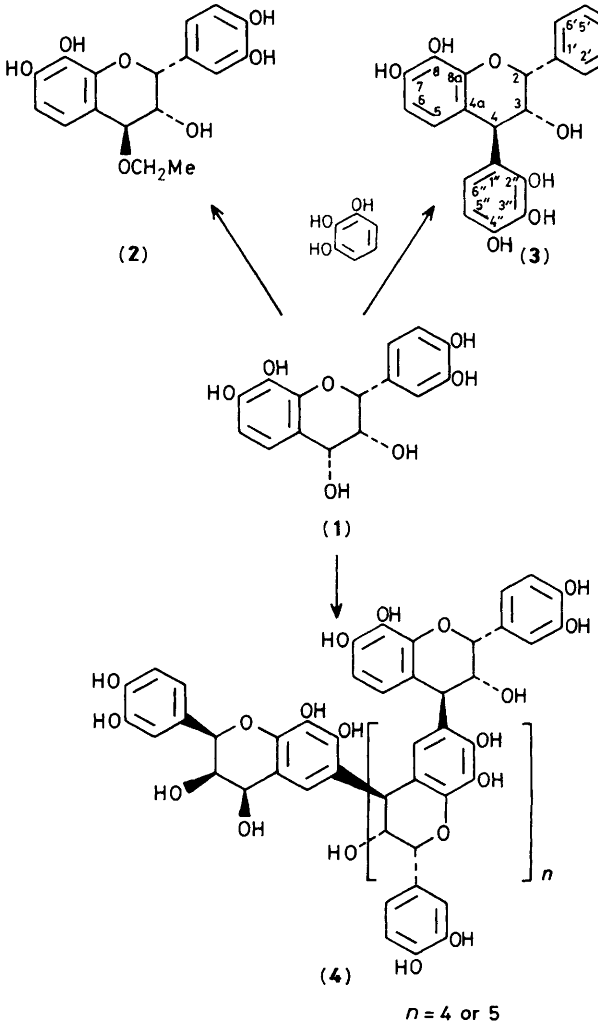
(−)-2,3-*cis*-3,4-*cis*-Flavan-3,3′,4,4′,7,8-hexaol [(−)-melacacidin] reacted rapidly with itself or with pyrogallol under mild acidic conditions to yield stereospecific condensation products, suggesting that the formation of natural proanthocyanidins of the 7,8-dihydroxyflavanoid pattern is not chemically prohibited.

The presently known polymeric proanthocyanidins may be divided into two groups according to their flavanoid A-ring substitution pattern; those with a phloroglucinol ring such as the procyanidins and the prodelphinidins, and those with a resorcinol nucleus which include the profisetinidins and prorobinetinidins. These *meta* oxidation patterns impart reactivity to the flavans by increasing the nucleophilicity of the A-ring and, in the case of the flavan-3,4-diols, by promoting the formation of reactive intermediates such as the flavan C-4 carbocations[1,2] or quinone methides[3] which can be readily stabilised by electron delocalization. The formation of these biopolymers in nature is believed to occur by nucleophilic condensation of the flavans with the reactive intermediates and such reactions have been demonstrated to occur readily in biomimetic syntheses.[1—4]

Although flavanoids with a pyrogallol A-ring (7,8-dihydroxy substitution) commonly occur in many *Acacia* species,[5—7] only the resorcinol type polymers are known.[8,9] 2,3-*cis*-3,4-*cis*-Flavan-3,3′,4,4′,7,8-hexaol [(−)-melacacidin] (**1**) is believed to be unreactive because the electronic effect of the 7-hydroxy group is substantially negated by the presence of the neighbouring 8-substituent.[8] Consequently Roux and co-workers[8,9] suggested that on electronic grounds polymers consisting of the pyrogallol A-ring flavanoids such as melacacidin and teracacidin units are unlikely to exist and that the polymers that co-occur with these flavan-3,4-diols are probably oxidation products.

The production of 4-*O*-ethylisomelacacidin (**2**) on treatment of melacacidin with 0.7% HCl in EtOH as reported by Clark-Lewis and Williams[10] was confirmed by both t.l.c. and ^{13}C n.m.r. data. However, when the reaction mixture was concentrated under a stream of N_2 at ambient temperatures, a polymer, $[\alpha]_D$ −17° (*c* 0.03, MeOH), $\bar{M}_n$ 1841 (by vapour phase osmometry) was obtained in almost quantitative yield. When the reaction of melacacidin was repeated in the presence of an excess of pyrogallol, a stereo- and regio-specific condensation resulted to give a product (**3**), $[\alpha]_D$ + 10° (*c* 0.02, MeOH), in 70% yield. The constitution of this product was readily apparent from its ^{13}C n.m.r. spectrum and



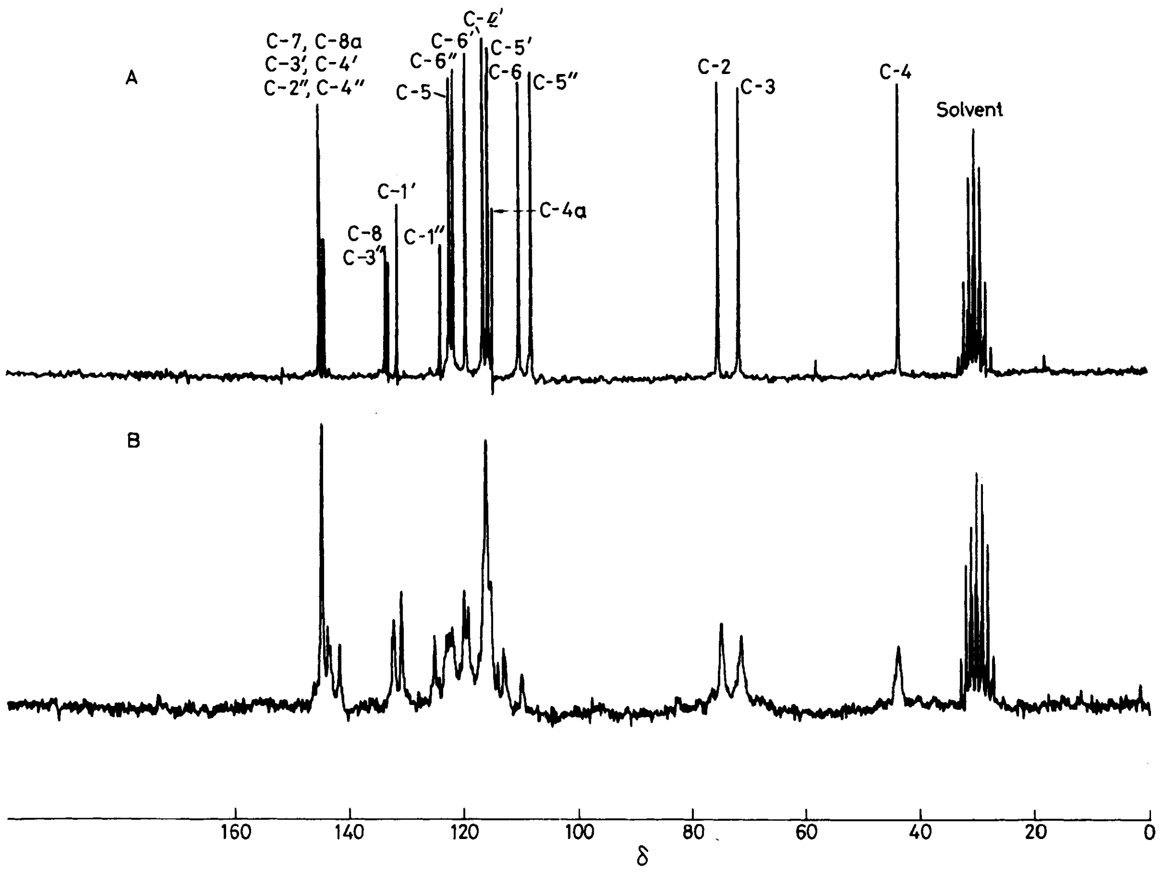


Figure 1. ^{13}C (20 MHz) N.m.r. spectra of (A) melacacidin–pyrogallol condensation product (**3**) and (B) polymer (**4**).

the elemental analysis of its octa-acetate derivative. The chemical shift for C-4 at δ 43.8 is consistent with an aryl substituent at that site, and the upfield shift position of C-2 at δ 75.2 is characteristic of the γ-shielding effect of a quasi-axial pyrogallol substituent at C-4 and the 2,3-*cis*-3,4-*trans* stereochemistry of the substituents on the heterocyclic ring.[1,11] A consideration of mesomeric effects suggests that the positions *ortho* to either the 1- or 3-hydroxy groups of the pyrogallol ring would be favoured for condensation and this was confirmed by ^{13}C n.m.r. data which show the presence of aromatic carbon chemical shifts at δ 107.8 and 121.6 attributable to C-5'' and C-6'' of the pyrogallol ring. The relatively upfield position of the substituted quaternary carbon at δ 123.9 (C-1'') is, as expected, due to the substituent effect of the neighbouring hydroxy group. The structure of (**3**) is also confirmed from an examination of its ^{1}H and ^{13}C n.m.r. spectra which compare well with those of epicatechin (4β→2) phloroglucinol particularly in the heterocyclic region.

Comparison of the ^{13}C n.m.r. spectra of (**3**) and the polymer (Figure 1) shows a close relationship thus confirming the stereochemistry and points of linkage between the melacacidin units. The molecular weight value suggests that the polymer consists of an average of between 6 and 7 flavan units. The observation of a chemical shift at δ 110.0 is attributed to the unsubstituted C-6 carbon of the upper proanthocyanidin unit and suggests an open chain polymer as in (**4**), rather than a cyclic polymer which could be formed by head-to-tail condensations of the open-chain polymer. These results, contrary to previous suggestions in the literature,[8,9] show that flavanoids with a pyrogallol A-ring are capable of undergoing self-condensations analogous to those of the phloroglucinol and resorcinol counterparts which give rise to the corresponding polymeric proanthocyanidins.

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