Phlobatannins *via* Facile Ring Isomerizations of Profisetinidin and Prorobinetinidin Condensed Tannin Units

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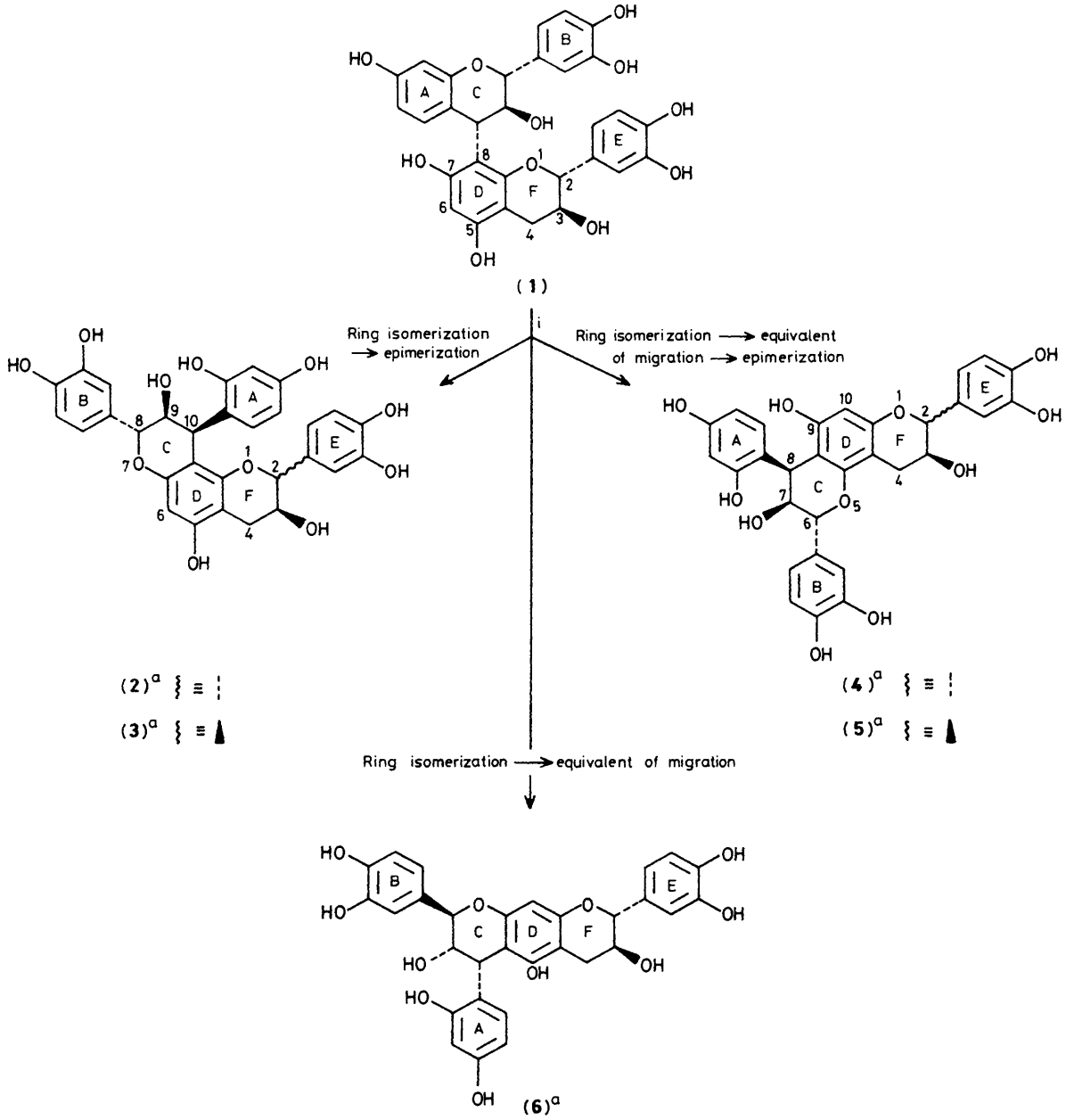
[4,8]-2,3-*trans*-3,4-*trans*-(−)-Fisetinidol-2,3-*trans*-(+)-catechin and its (−)-robinetinidol homologue are to a varying degree subject to facile ring isomerizations (also when preceded by induced positional isomerization) in $NaHCO_3$–Na_2CO_3 buffer solution under nitrogen, with liberation of reactive nucleophilic resorcinol units to form a range of bifunctional phlobatannins.

The natural occurrence of the novel class of ring-isomerized condensed tannin units, termed 'phlobatannins,'[1] prompted our present investigation of efficient methods of inducing ring isomerization in biflavanoid units present in commercially-available condensed tannins, our ultimate aim being their activation for use in 'cold-set' adhesive applications through 'liberation' of reactive nucleophilic resorcinol units.[1] The obvious choice of conditions was those applied by Freuden-



Scheme 1. *Reagents and conditions:* i, $NaHCO_3$–Na_2CO_3, 50 °C, 5 h, N_2. [a] The relative stereochemistry of the C-rings ($J_{2,3}$ 10.0, $J_{3,4}$ 5.5—5.9 Hz) and F-rings ($J_{2,3}$ 6.0—7.5 Hz and $J_{2,3}$ <1 Hz) is reflected in the coupling constants of the heptamethyl ether acetates of the phlobatannins (**2**)—(**6**).

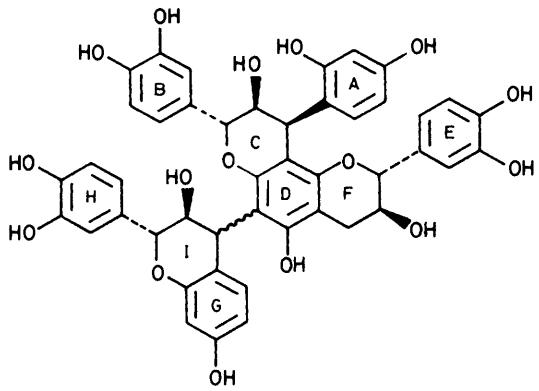
berg and Purrmann[2] for epimerization at C-2 of (+)-catechin *via* intermediate fission of the heterocyclic ring.

Treatment of the model compound [4,8]-2,3-*trans*-3,4-*trans*-(−)-fisetinidol-2,3-*trans*-(+)-catechin (**1**)[3] with 0.025 M $NaHCO_3$–0.025 M Na_2CO_3 buffer[4] (pH 10) for 5 h at 50 °C under nitrogen gave significant (75%) conversion into five products of stereospecific ring isomerization (**2**)—(**6**). These comprise the anticipated phlobatannin (**2**) as a product of ring isomerization of the C-ring of the parent compound; its C-2 (F-ring) epimer (**3**) representing conversion of the (+)-catechin moiety of (**2**) into (+)-epicatechin; the corresponding isomeric pair (**4**) and (**5**), their formation implying the equivalent of positional isomerization of the (−)-fisetinidol unit to the 6-position of the (+)-catechin moiety, ring isomerization with its 5-OH function, and also epimerization at C-2 (F) as before; also their structural isomer (**6**) indicative of the alternative mode of cyclization with the 7-OH (*cf.* mechanistic discussion below).

The structures of products (**2**)—(**6**) were established by application of nuclear Overhauser effect (n.O.e.) difference spectroscopy to their heptamethyl ether diacetates as previously demonstrated for 'phlobatannins.'[1] In each instance n.O.e. associations of 2-OMe (A) with 3-H (A), and of 4-OMe (A) with both 3-H (A) and 5-H (A) indicated the disassociation of resorcinol moieties from heterocyclic C-rings, compared with involvement in the parent compound (**1**). In addition, the ^1H n.m.r. spectra of the derivatives were characterized by the typical[1] absence of the effects of dynamic rotational isomerism at ambient temperatures, and also by the significant reversals[1] of chemical shifts of 2-H (C)† (δ 4.95—4.98) and 4-H (C) (5.04—5.17) of their 2,3-*trans*-3,4-*cis* heterocyclic C-rings, compared with those of 'conventional' [4,6]- and [4,8]-isomers of both 2,3-*trans*-3,4-*cis* and -3,4-*trans* stereochemistry (*cf.* ref. 5).

Differentiation of the heptamethyl ether diacetates of the various isomeric phlobatannins (**2**)—(**6**) presented problems in the sense that absolute values of chemical shifts of 8-H (D) resonances of derivatives corresponding to (**4**) and (**5**) (δ 6.083, 6.170 respectively) differ‡ from the reliable parameters established for [4,6]-biflavanoids (δ 6.32—6.47),[6] although 6-H (D) shifts of the derivatives of (**2**) and (**3**) (δ 6.165, 6.185 respectively) were in line with those of [4,8]-biflavanoids (δ 6.10—6.22).[6] However, the heptamethyl ether diacetate of (**2**) proved identical to the product derived from acid-induced isomerization,[3] while the pairs (**2**) and (**3**), and (**4**) and (**5**) followed from the general congruence of the chemical shifts of heterocyclic C-ring proton resonances [(**2**) and (**3**): δ 4.965, 4.960 (2-H), 5.503, 5.503 (3-H), 5.075, 5.043 (4-H); (**4**) and (**5**): δ 4.953, 4.952 (2-H), 5.303, 5.343 (3-H), 5.062, 5.078 (4-H)]. In addition 2-H (F) is shielded (δ 4.630) in the heptamethyl ether diacetate of (**2**) relative to the same protons in the corresponding derivatives of (**4**) (δ 4.957) and (**6**) (δ 5.070), presumably reflecting the anisotropic effect of its A-ring. Finally, for the derivatives of (**2**) and (**3**) n.O.e. difference spectroscopy also reflects the selective association of 5-OMe (D) with 6-H (D); for the derivatives of (**4**) and (**5**) of 9-OMe (D) with 10-H (D); whereas similarly for (**6**) n.O.e. associations of 5-OMe (D) are conspicuously absent. Collectively the above evidence supports the structures indicated.

'Liberation' of nucleophilic A-rings as in the phlobatannins (**2**)—(**6**) and concomitant involvement of a functional group of



(**7**) { ≡ ¦

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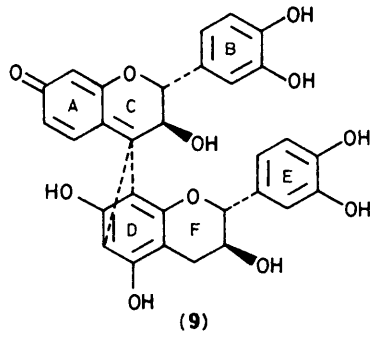
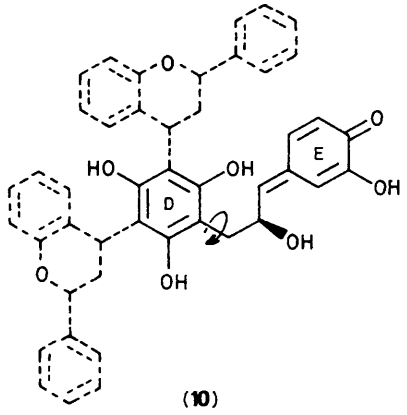


(**9**)



(**10**)

the (+)-catechin moiety during ring isomerization led to an examination of the relative nucleophilicity of the A- and D-rings. Coupling of a molar equivalent of (+)-mollisacacidin [(+)-2,3-*trans*-3′,4′,7-trihydroxyflavan-3,4-*trans*-3,4-diol] with the tetrahydropyrano[5,6-*h*]chromene (**2**) resulted in two products (**7**) and (**8**) only [$J_{2,3} = J_{3,4}$ 9.9 Hz; δ 4.747 (4-H), 4.943 (2-H), 6.288 (3-H) and $J_{2,3}$ 8.0, $J_{3,4}$ 7.0 Hz; δ ~4.90 (4-H), 5.187 (2-H), 5.535 (3-H) for I-ring systems of the methyl ether acetates] representing 3,4-*trans* and 3,4-*cis* stereochemistry respectively of the introduced units, and also elimination of the high-field aromatic singlet [δ 6.165, 6-H (D)] of the corresponding derivative of (**2**). Coupling, therefore, occurs preferentially in each instance at C-6 (D), the remaining nucleophilic centre on the phloroglucinol ring system of the (+)-catechin moiety of (**2**), despite involvement of two of its three functional groups as heteroatoms in pyran ring systems.

† In order to permit direct ^1H n.m.r. comparisons between the phlobatannins (**2**)—(**6**), flavanoid numbering for their respective C-rings is retained.

‡ By contrast the shift for 8-H (D) of the derivative of (**6**) is in agreement (δ 6.449) with established[6] parameters.

From this result we venture the prediction that, barring steric inhibition of condensation with ring A, bifunctionality of the ring-isomerized products in adhesive applications involving formaldehyde is ensured by potent nucleophilicity at both C-5 (A) and C-6 or -10 (D).

A parallel ring isomerization reaction§ on [4,8]-2,3-*trans*-3,4-*trans*-(−)-robinetinidol-2,3-*trans*-(+)-catechin, a homologue of (**1**) possessing a pyrogallol (in place of catechol) B-ring, proceeded to completion under much milder conditions (20 °C, 5 h), and hence without epimerization at C-2 (F) of the (+)-catechin moiety. However, inversion at C-2 (C-ring) of the homologue of (**2**) was in evidence to give the 2,3-*cis*-3,4-*cis* diastereoisomer (*cf.* ref. 3), and also the equivalent of 8 → 6 migration of the (−)-robinetinidol moiety followed by ring-isomerization with 5-OH (D) to afford the homologue of (**4**). The aforementioned phenomena are attributable to the enhanced ionization and hence electron-release from the pyrogallol compared with the catechol B-ring. This should contribute not only to facile ring-opening, but also to inversion at C-2 (C-ring) of the ring-isomerized product [homologue of (**2**)] under conditions sufficiently mild so as to preclude epimerization at C-2 (F) of the (+)-catechin moiety.

Under the prescribed conditions ring isomerization probably proceeds *via* a quinone–methide mechanism involving the B-ring,[7] and positional isomerization *via* the same mechanism, but involving migration of a mollisacacidin quinone methide intermediate (**9**) derived from the A-ring as initially postulated by Whalley[8] in the biosynthesis of dracorubins, and latterly by Hemingway *et al.*[9] for interflavanyl condensations under alkaline conditions.

Alternatively, a quinone methide intermediate (**10**) derived from the E-ring could undergo rotation and recyclization, thereby simultaneously achieving the observed positional and configurational isomerizations.

In potential commercial adhesive applications activation of condensed tannins *via* the ring-isomerization procedure, oxidative conditions should be avoided since we have established that pyrogallol moieties are involved in facile condensation reactions with nucleophilic centres.

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§ Particularly significant as regards the predominantly pyrogallol-based 'Mimosa' (wattle) extract from *Acacia mearnsii*.

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