Phlobatannins, A Novel Class of Ring-isomerized Condensed Tannins

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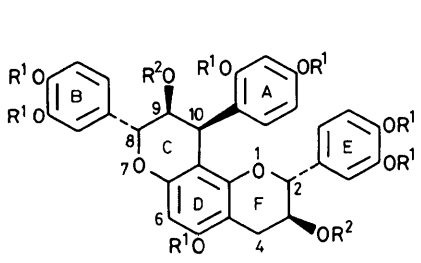
Four members of a novel class of natural 'phlobaphene' condensed tannins, representing the products of stereospecific ring-isomerization of those 2,3-*trans*-3,4-*trans*-(−)-fisetinidol units present in 'conventional' [4,8]-bi- and [4,6 : 4,8]-tri-flavanoid profisetinidins, are defined as functionalized 8,9-*trans*-9,10-*cis*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromene (**1**) and the homologous hexahydrodipyrano[2,3-*f*,2′,3′-*h*]chromene (**5**) by nuclear Overhauser effect difference spectrometry.

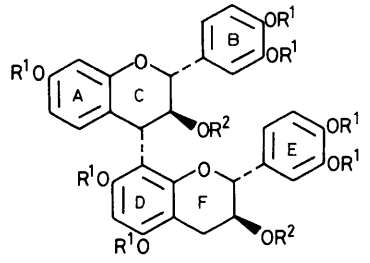
The term 'phlobatannins' in tannery parlance has long been associated with the insoluble phenolic fractions which accompany condensed tannins, and probably owes its origin to the insolubility induced in commercial tanning extracts during addition of strong mineral acid, resulting in so-called 'phlobaphenes' or 'tanner's reds.' Possible transformations associated with this phenomenon were recently examined by us.[1] Acid treatment of the model compound [4,8]-2,3-*trans*-3,4-*trans*-(−)-fisetinidol-2,3-*trans*-(+)-catechin (**3**) as representative of commercially used condensed tannins[2—4] gave, among others, low yields of the 8,9-*trans*-9,10-*cis*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromene (**1**) and its 8,9-*cis*-isomer.[1] These two compounds represent products of heterocyclic ring isomerization of the 'upper' (−)-fisetinidol unit.[1] The natural occurrence of several units of this type in two closely related species of the Caesalpiniodeae is now established by nuclear Overhauser effect (n.O.e.) difference spectrometry.

Superficially, perceptible differences between the ^{1}H n.m.r.

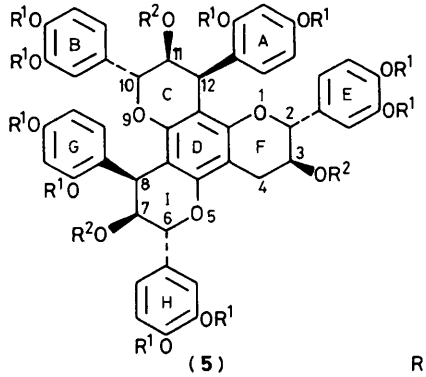


(**1**)
(**2**)

$R^1 = R^2 = H$
$R^1 = Me,\ R^2 = Ac$

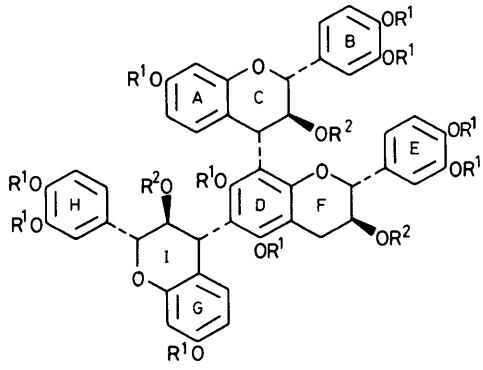


(**3**)
(**4**)

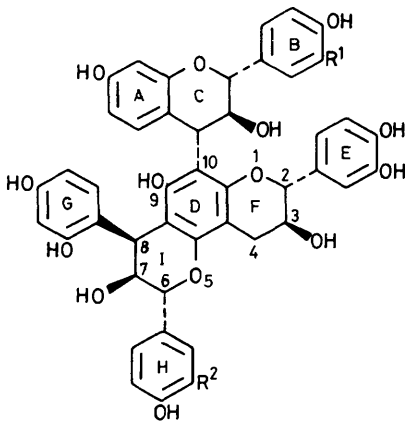


(**5**)
(**6**)

$R^1 = R^2 = H$
$R^1 = Me,\ R^2 = Ac$



(**7**)
(**8**)



(**9**) R^1 = H, R^2 = OH

(**10**) R^1 = OH, R^2 = H

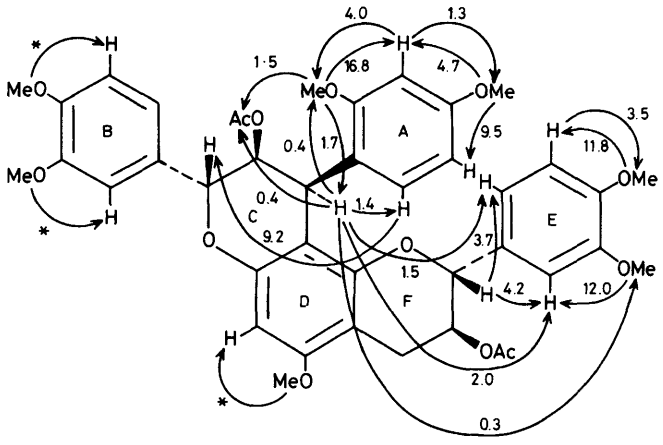


Figure 1. * Percentage n.O.e. enhancement not available owing to signal overlap.

spectra of the methyl ether acetates of the associated isomeric pairs (**1**) and (**3**) and (**5**) and (**7**) from these sources are the reversal of the relative chemical shifts of the equivalent of 2-H and 4-H (C- and I-ring) resonances, dissimilar coupling constants for C- and I-ring signals, and the contrasting absence of rotational isomerism[5] in the mono- and di-pyranochromene derivatives (**2**) and (**6**). However, n.O.e. difference spectra in C_6D_6 solution of the heptamethyl ether diacetate (**2**) and decamethyl ether triacetate (**6**) indicate unequivocally that the resorcinol (A- and G-ring) moieties are 'free' in the respective phenols (**1**) and (**5**) derived from the heartwoods of *Guibourtia coleosperma* (false mopane) and *Colophospermum mopane* (mopane) respectively.

Thus for the heptamethyl ether diacetate (**2**) (Figure 1) the arrow heads show enhanced signals with percentage n.O.e. calculated by comparing the size ratio of the positive (enhanced) and negative (irradiated) resonances in each difference spectrum. Association of the 2-OMe (A-ring) resonance with those of 3-H(A) and 10-H(C); 4-OMe (A) with both 3-H(A) and 5-H(A); and 6-H(A) with 10-H(C) shows that in the parent 8,9-*trans*-9,10-*cis*-2,8,10-triphenyl-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromene (**1**) both hydroxy groups of the resorcinol A-ring are available for methylation compared with involvement of the equivalent of one of these in the heterocyclic C-ring of the 'conventional' [4,8]-(−)-fisetinidol-(+)-catechin (**3**). The association of 6-H(A) with 8-H(C) is in line with the 'sofa' (envelope) conformation of the C-ring of (**2**) based on proton–proton coupling constants ($J_{8,9}$ 10.5, $J_{9,10}$ 6.0 Hz) and hence with the proximate *axial* and quasi-*axial* orientations of 8-H(C) and resorcinol A-ring respectively. The same associations apply to the protons of the resorcinol A- and G-rings of the more complex derivative (**6**), the phenol (**5**) thus corresponding to a functionalized 2,6,8,10,12-pentaphenyl-3,4,7,8,11,12-hexahydro-2*H*,6*H*, 10*H*-dipyrano[2,3-*f*,2′,3′-*h*]chromene.

The novel functionalized mono- and di-pyranochromene homologues (**1**) and (**5**) accompany [4,8]-(−)-fisetinidol-(+)-catechin (**3**) and [4,6:4,8]-bi-[(−)-fisetinidol]-(+)-catechin (**7**) respectively, in the respective heartwoods of *G. coleosperma* and *C. mopane*. The implied heterocyclic ring fissions of (−)-fisetinidol units and stereospecific recyclizations (*cf.* the phlobaphene reaction[1]) required for the conversions (**3**) ⟶ (**1**) and (**7**) ⟶ (**5**) embrace rotation about the 3,4-C–C bond, retention of configuration at 2-C, and hence conversion from 2,3-*trans*-3,4-*trans* ($J_{2,3} = J_{3,4} = 9.5$ Hz) to the equivalent of 2,3-*trans*-3,4-*cis* (J 10.5 and 6.0 Hz) configurations.

Conjecture regarding these *in vivo* conversions finds support in the isolation of two 'isomerization-intermediates' (**9**) and (**10**) from *C. mopane*. These functional isomers represent products of selective ring-isomerization involving [4,6]-(−)-fisetinidol and [4,6]-3′-deoxy-(−)-fisetinidol substituents *via* cyclization with the 5-hydroxy group of the (+)-catechin 'substrate' in each instance to give isomeric 3,4,7,8-tetrahydro-2*H*,6*H*-pyrano[2,3-*f*]chromenes (**9**) and (**10**) respectively. On this assumption, the 5,6-dihydroxy function of the D-ring of the (+)-catechin unit appears to be a prerequisite for ring-isomerization. Differentiation of (**9**) and (**10**) as nonamethyl ether triacetates, similarly free of dynamic rotational isomerism, was possible only through application of the same n.O.e. difference methods as above. The c.d. spectra of the methyl ether acetates of compounds (**1**) and (**5**) show intense positive Cotton effects at 240 nm corresponding to 10*S*- and 8*S*,12*S*-configurations (*cf.* ref. 6) respectively as indicated, in agreement with application of the aromatic quadrant rule.[7]

The apparent conformational stability of the new group of compounds and also the relative planarity of the central 'core' after dual isomerization [*e.g.* the CDFI tetracyclic system of (**5**)] leads to the postulate that these factors contribute to reduced solubility in aqueous media and thus enhancement of their affinity for collagen substrates. This, in addition to our known acid-catalysed isomerization,[1] prompts assignment of the term 'phlobatannins' to the new group of flavanoids.

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