Synthesis of Condensed Tannins. Part 20. Cycloconformations and Conformational Stability Among Derivatives of 'Angular' Tetraflavanoid Profisetinidins

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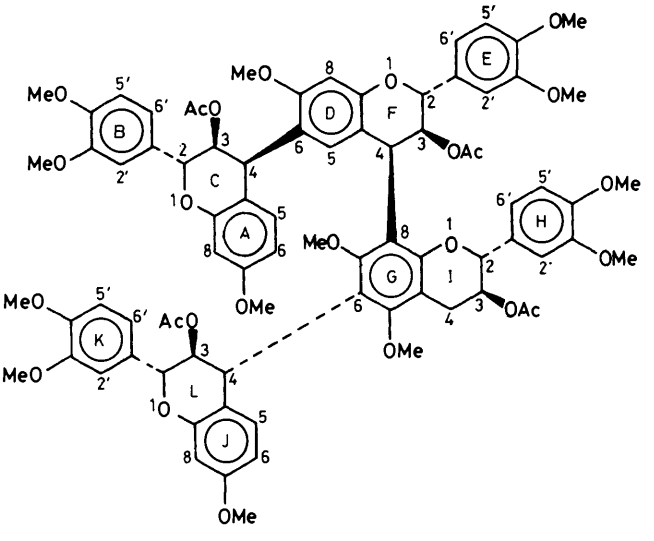
Conformational analysis of tridecamethyl ether tetra-acetates of two natural and three synthetic 'tetrameric' profisetinidin condensed tannins based on nuclear Overhauser effect difference spectroscopy reveals overall 'cyclic' arrangements of flavanyl units in each despite mutual stereochemical and structural differences. The unique thermodynamic stability of their dominant (85—90% abundance) conformers is attributed to the combined effects of the relative configurations of constituent flavanyl units, to steric repulsion by functional groups *ortho* to interflavanyl bonds, and to steric inhibition of mobility about interflavanyl bonds due to partial overlap of terminal units.

'Mimosa' (*Acacia mearnsii*) and 'quebracho' (*Schinopsis* spp.) extracts, long known for their extensive use in industrial applications, particularly in the tanning industry, each contain in excess of 70% condensed tannins. The phenolic mixtures represent molecular mass gradations ranging from 300 to 3 000,[1,2] the individual relative affinities of lower-range units (*M* 300—900) for collagen, modified collagens and cellulose in aqueous medium, being proportionate to their mass.[3,4] Enhanced affinity of the more highly 'astringent' condensed tannin units (*M* 1 100—3 000) for the same substrates could, apart from mass, be contingent upon either conformational stability or molecular mobility. Combinations of these factors should affect solubility and hence movement within plant tissues. Similar considerations apply to the rate of penetration into hides and skins during commercial tannage, and to tannin mobility within, and desorption from, finished leather under moist conditions. Related phenomena of industrial import concern the 'pot-life' and 'curing-time' characteristics of thermosetting tannin-based adhesives which depend on the availability and distribution of strong nucleophilic centres on the periphery of constituent flavanyl units during cross-linking with formaldehyde.

Tannins from the aforementioned extracts are typified by 'angular'† triflavanoids comprised of flavanyl substituents at the 6- and 8-positions of (+)-catechin (2,3-*trans*-3′,4′,5,7-tetrahydroxyflavan-3-ol), or more rarely (+)-gallocatechin [5′-hydroxy-(+)-catechin].[5–7] The decamethyl ether triacetates of representative diastereoisomeric [4,6:4,8]-bis-[(−)- or (+)-fisetinidol]-(+)-catechins,[6,7] for example, all exhibit dynamic rotational isomerism‡ about the interflavanoid bonds at ambient temperatures irrespective of stereochemical differences at the 4-C bonding positions of the (−)- or (+)-fisetinidol (2,3-*trans*-3′,4′,7-trihydroxyflavan-3-ol) substituents. However, regio- and stereo-specific substitution by an additional (−)- or (+)-fisetinidol unit at 6-C of the upper unit of these 'trimers', a process subject to asymmetric induction,[8,9] leads to predominant (85—90% abundance) 'stable' conformations for the tridecamethyl ether tetra-acetates of only two of the known eight tetrameric profisetinidin tannins present in the heartwoods of *A. mearnsii* (black wattle) and *Rhus lancea*§ (karree).[8,9] For these diastereoisomers the sequence of flavanyl units, their bonding positions, and absolute stereochemistry at 11 of the 14 chiral centres were established by synthesis in conjunction with high resolution ^{1}H n.m.r.[8,9,12] using significant shift parameters derived from lower oligomers.[7] Hitherto undefined chirality, therefore, relates to stereochemistry about three interflavanyl bonds in each isomeric tannin. The present work indicates that thermodynamic properties are responsible for the conformational stability of 'angular' tetramers, with the relative stereochemistry of constituent flavanyl units and their steric interactions, including cyclic arrangements,[13] as the main contributors. Supporting evidence is available from three synthetic profisetinidin isomers[14] which lack natural counterparts.

The respective isomers (**1**) and (**2**) derived from *A. mearnsii*

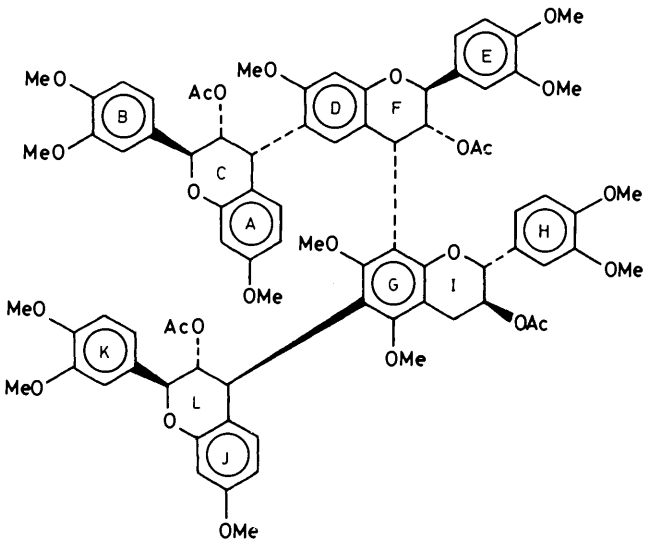


(**1**) [4,6:4,8]-2,3-*trans*-3,4-*cis*:2,3-*trans*-3,4-*cis*, [4,6]-2,3-*trans*-3,4-*trans* and (2*R*) configurations of flavanyl substituents on the (+)-catechin (GHI) moiety

† The term 'branched' is reserved for those tetraflavanoids with flavanyl substituents at the 4, 6, and 8 positions of a 'central' flavan-3-ol unit (*cf.* refs. 9,10).

‡ Indicated by line-broadening of resonances in their ^{1}H n.m.r. spectra at *ca.* 20 °C.[11]

§ *Rhus lancea* and *Schinopsis balansae*/*S. lorentzii* (Anacardiaceae) are closely related species with similar, if not identical, heartwood content.[7]



(2) [4,6:4,8]-2,3-*trans*-3,4-*cis*:2,3-*trans*-3,4-*cis*, [4,6]-2,3-*trans*-3,4-*trans* and (2*S*) configurations

and *R. lancea* possess identical relative configurations, but enantiomeric [(2*R*,3*S*) and (2*S*,3*R*)] [4,6:4,8]-bis-(2,3-*trans*-3,4-*cis*-fisetinidol) (ABC-DEF units) and [4,6]-2,3-*trans*-3,4-*trans*-fisetinidol (JKL) substituents on (+)-catechin(GHI) as mutual 'nucleophile'. The unusual stability * of the dominant conformer of each of the two diastereoisomers is evident from sharp ^{1}H n.m.r. spectra, devoid of line-broadening over a wide temperature range (−50 °C to >80 °C) apart from a degree of loss of resolution at low temperatures. The probable co-existence also in the static domain of at least two minor conformers of each under ambient conditions at *ca.* 3.9 and 10.7% relative abundances for the (2*R*)-isomer (**1**) and *ca.* 1.9 and 9.6 for (2*S*) (**2**) was estimated by integration of sharp acetyl proton resonances, after repeated purification of the compounds to ensure the complete absence of isomeric compounds as impurities. The preponderance (85—88% abundance; *cf.* Table 1) of one 'stable' conformer at ambient temperatures permitted the first conformational analysis of derivatives of high-molecular condensed tannins, and hence assessment of absolute configurations about each of the sp^2–sp^3 C–C interflavanoid bonds.

Conformational analysis of the (2*R*,3*S*)-profisetinidin 'tetramer'[8] derivative (**1**) by nuclear Overhauser effect (n.O.e.) difference spectroscopy at 300 MHz ($CDCl_3$, 25 °C) is also feasible because of sufficiently large shift differences (in Hz) between significant highfield methoxy resonances (*cf.* Table 2) and excellent resolution of aromatic and heterocyclic proton resonances. The analysis of (**1**) (n.O.e. data indicated in Table 3) is primarily and most conveniently based on interactions of 7-OMe(G) and 5-OMe(G) of the (+)-catechin(GHI) moiety and also of 5-H(D) of the [4,8]-(−)-fisetinidol unit (*cf.* Figure 1 and Table 3). These n.O.e. associations indicate the close proximity of 7-OMe(G) to 5-H(D), 4-H(F), 5-H(J), and 4-H(L), and of 5-H(D) to 2-H(C), permitted by a single arrangement of flavanyl units as in Figure 1. In this conformation the respective C–H bonds of the sp^3-hybridized 4-carbons of the heterocyclic C, F, and L ring systems bisect the plane of the aromatic D, G and again G rings respectively, with 4-H(C) directed at the 7-OMe (D) group and both 4-H(F) and 4-H(L) directed at the 7-OMe(G) group. The (−)-fisetinidol(JKL) unit, therefore, appears to be inverted relative to its DEF counterpart from the perspective of

* On the n.m.r. time-scale.

Table 1. Stable conformers of the tetraflavanoid profisetinidin derivatives (**1**)—(**5**) at 20 °C

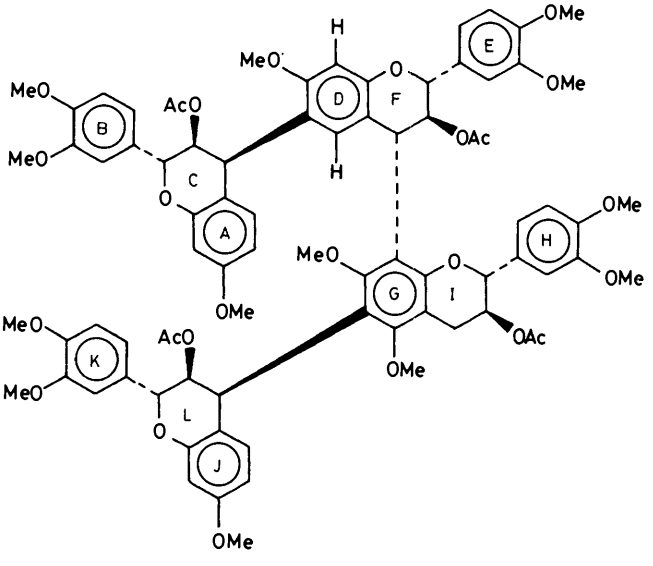
	%* Stable conformers		
		Minor	
Compd.	Major		
(**1**)	85.4	10.7	3.9
(**2**)	88.5	9.6	1.9
(**3**)	86	14	—
(**4**)	86	14	—
(**5**)	90	10	—

* Relative abundance.

the observer. Conformational analysis of this dominant conformer with the aid of Dreiding models indicates that in order to satisfy n.O.e. associations, the DEF and JKL (−)-fisetinidol units are at right angles to the general plane of the GHI (+)-catechin unit (*cf.* Figure 1), and that the ABC (−)-fisetinidol unit occupies a general plane at right angles to its DEF counterpart. The general conformation of the tetraflavanoid molecule is, therefore, cyclic with the pyrocatechol B-ring abutting on the resorcinol J-ring, and the remaining pyrocatechol E, H, and K rings radiating out in three differing directions.

Similar n.O.e. difference associatons were established for the (2*S*,3*R*)-profisetinidin tannin derivative (**2**),[9] partial overlap of some of the significant resonances in $CDCl_3$ necessitating examination also in C_6D_6 solution (*cf.* Table 3). From Dreiding models it is evident that the conformations of the ABC-DEF-G-JKL systems in (**1**) and (**2**) are enantiomeric (*cf.* Figures 1 and 2), the mutual GHI system of the (+)-catechin moiety which projects outwards offering no significant steric interaction in either instance. This correlates with the observation that the two tetraflavanoids (**1**) and (**2**) with identical relative configurations of constituent units exhibit similar conformational stabilities. However, a single point of difference between them is the abnormal coupling constants of the heterocyclic protons of the 2,3-*trans*-3,4-*cis* DEF unit of (**2**) ($J_{2,3}$ 10.2, $J_{3,4}$ 9.2 Hz)[9] at ambient temperatures, compared with their equivalent in (**1**) ($J_{2,3} = J_{3,4} = 8.0$ Hz).[8] This may indicate a considerable degree of steric strain connected with a twisted boat conformation in the former.

The (2*R*,3*S*)-profisetinidin tetraflavanoid isomers (**3**) and (**4**),



(**3**) [4,6:4,8]-2,3-*trans*-3,4-*cis*:2,3-*trans*-3,4-*trans*, [4,6]-2,3-*trans*-3,4-*cis* and (2*R*) configurations

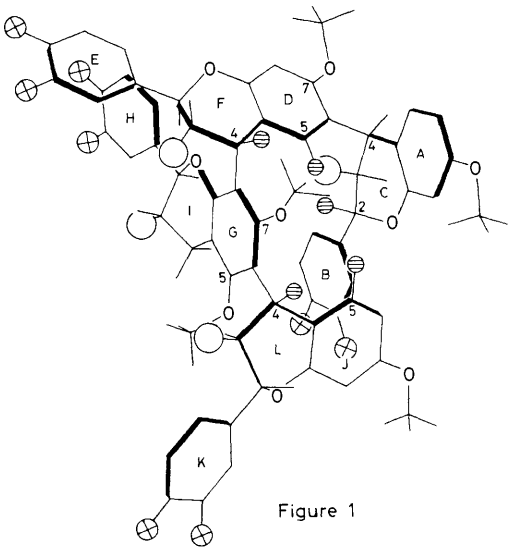


Figure 1

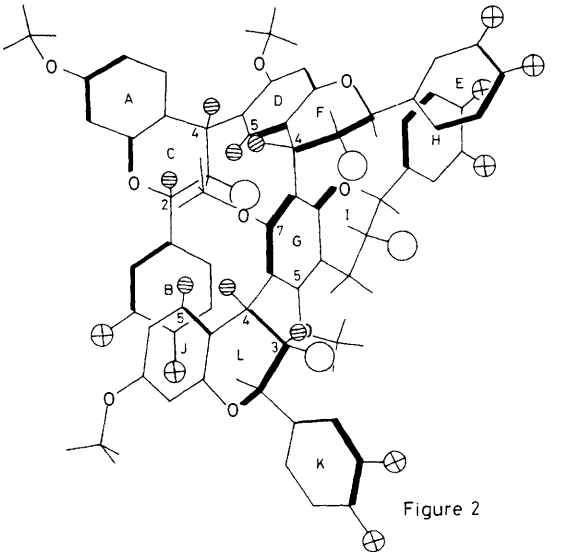


Figure 2

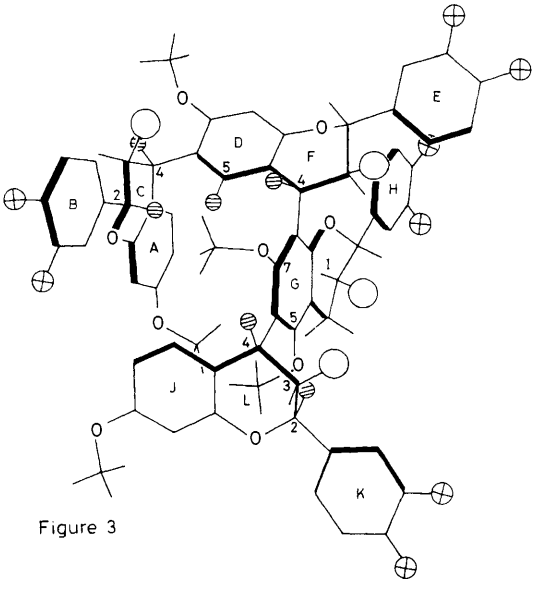


Figure 3

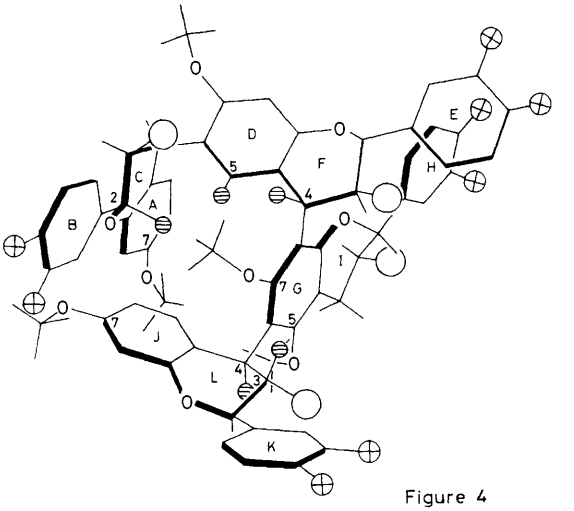


Figure 4

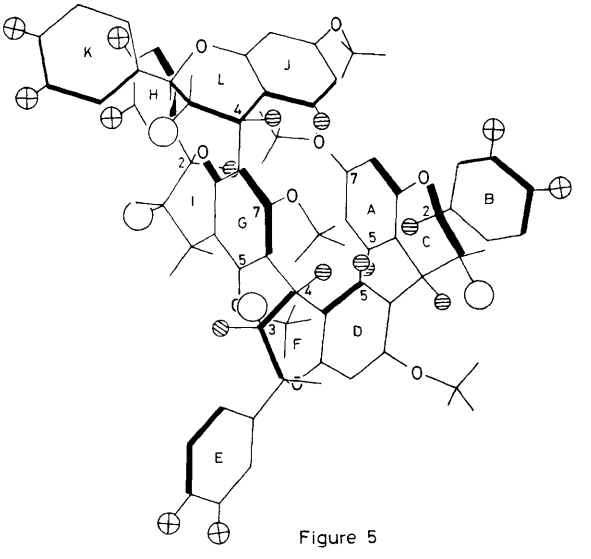


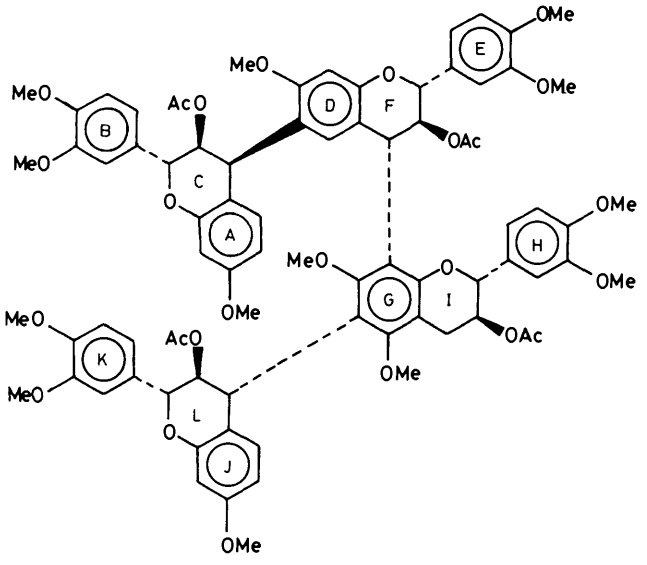
Figure 5

Figures 1—5. The cycloconformations of the tridecamethyl ether tetra-acetates of 'angular' profisetinidin tetramers (**1**)—(**5**) with ⊜ representing protons involved in n.O.e. difference interactions with methoxy function, and ○ and ⊕ respectively indicative of 3-acetoxy and 3′,4′-methoxy functions on pyrocatechol units. In order to avoid serious overlap of features during representation the structures were viewed from the best vantage point with the H-ring of the (+)-catechin moiety directed away from the viewer as constant factor. The figures illustrate the proximity of 7-OMe(G) to the relevant D, F, J, and L ring protons, and of 5-H(D) to 2-H(C) for each major conformer of compounds (**1**)—(**5**)

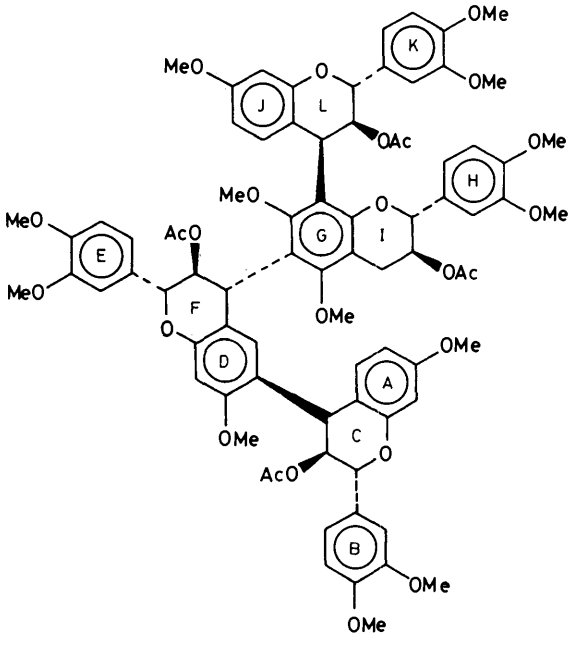
Table 2. Chemical shifts of highfield methoxy resonances of the tetraflavanoids (**1**)—(**5**) at 20 °C

(**1**) (2*R*) *tc,tc/tt* δ($CDCl_3$)	(**2**) (2*S*) *tc,tc/tt* δ($CDCl_3$)	(**3**) (2*R*) *tt,tt/tc* δ($(CD_3)_2CO$)	(**4**) (2*R*) *tc,tt/tt* δ(C_6D_6)	(**5**) (2*R*) *tc/tc,tt* δ($CDCl_3$)
3.752 (7A)	3.664 (7D)	3.843 (7D)	3.770 (5G)	3.757 (7D)
3.723 (7J)	3.636 (7A)	3.798 (7G)	3.646 (7A)	3.735 (7G)
3.692 (7G)	3.506 (7G)	3.024 (5G)	3.326 (7G)	3.700 (7A)
3.341 (7D)	3.056 (5G)		3.196 (7D)	3.490 (7J)
2.924 (5G)			3.100 (7J)	2.795 (5G)
	δ(C_6D_6)		δ($CDCl_3$)	
	3.673 (7G)		3.060 (7G)	

The relative configurations of (−)-fisetinidol units attached to (+)-catechin, or similarly their succession in bis-(−)-fisetinidol substituents, are indicated as either *tt* ≡ 2,3-*trans*-3,4-*trans* or *tc* ≡ 2,3-*trans*-3,4-*cis*.



(**4**) [4,6:4,8]-2,3-*trans*-3,4-*cis*:2,3-*trans*-3,4-*trans*, [4,6)-2,3-*trans*-3,4-*trans* and (2*R*) configurations



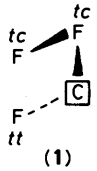
(**5**) [4,8]-2,3-*trans*-3,4-*cis*, [4,6:4,6]-2,3-*trans*-3,4-*cis*:2,3-*trans*-3,4-*trans* and (2*R*) configurations

stereochemically related (2*R*-series) to (**1**), were synthesized by condensing the [4,6]-biflavan-3,4-diol hexamethyl ether triacetate of 2,3-*trans*-3,4-*cis*:2,3-*trans*-3,4-*trans* or -*cis* configuration corresponding to the units ABC-DEF, with the free-phenolic [4,6]-2,3-*trans*-3,4-*cis*-and [4,6]-2,3-*trans*-3,4-*trans*-(−)-fisetinidol-(+)-catechins (GHI-JKL equivalent) respectively; while (**5**), a positional isomer of (**3**), originated by similar means using [4,8]-2,3-*trans*-3,4-*cis*-(−)-fisetinidol-(+)-catechin as substrate.[14] All condensations involving the [4,6]-biflavan-3,4-diol derivatives with 3,4-*cis* configuration at the point of interflavanyl junction, gave products with 3,4-*trans* configuration at the point of condensation. The reactions are again subject to asymmetric induction.[14] After full substitution none of the products of biflavanoid-biflavanoid condensations correspond to derivatives of natural profisetinidin tetraflavanoids isolated hitherto, but each of the three tridecamethyl ether tetra-acetates (**3**), (**4**), and (**5**) exists as a major stable conformer at ambient temperatures (*cf.* Table 1).

For the diastereoisomer (**3**) with [4,6:4,8]-2,3-*trans*-3,4-*cis*:2,3-*trans*-3,4-*trans*-bis-[(−)-fisetinidol] (ABC-DEF) and [4,6]-2,3-*trans*-3,4-*cis*-(−)-fisetinidol(JKL) substituents on the (+)-catechin(GHI) moiety, stability of the major conformer and suitable chemical shifts at high resolution permitted n.O.e. difference spectroscopy (*cf.* Table 2 and ref. 14). As before, the multiple n.O.e. difference associatons of 7-OMe(G) with 4-H(F), 5-H(D) and 4-H(L), and of 5-OMe(G) with 2-H(L) and 3-$COCH_3$(L) establish the stereochemical relationship between constituent DEF-GHI-JKL flavanoid units, while the single associaton of 5-H(D) with 2-H(C) indicates the orientation of ABC-DEF units. Thus, assuming half-chair conformations for the heterocyclic systems from coupling constants, conformational analysis (Dreiding models) again indicates a 'cyclic' conformation of flavanoid units (Figure 3) rather similar to that of the (2*S*)-type tetraflavanoid derivative (*cf.* Figure 2). Conformational stability in this instance apparently results from A-ring–J-ring interaction in contrast to (**1**) and (**2**) where B-ring–J-ring steric effects operate.

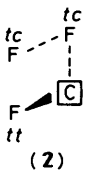
N.O.e. difference spectroscopy of (**4**), a [4,6]-3,4-*trans*(JKL) epimer of (**3**), shows multiple associations of 7-OMe(G) with 4-H(F), 5-H(D) and 3-H(L), and of 5-OMe(G) with 4-H(L). These establish the relative spatial positions of the DEF-GHI-JKL system, while association of 5-H(D) with 2-H(C) determines the ABC-DEF relationship (*cf.* Figure 4). Inversion at 4-C(L) in (**4**) relative to (**3**) is supported by significant associations of 5-OMe(G) with 4-H(L) and of 7-OMe(G) with 3-H(L) in the former (**4**), compared with the pairs 5-OMe(G)/2-H(L) and 7-OMe(G)/4-H(L) in the latter (**3**). However, in spite of this single stereochemical difference, A-ring–J-ring interaction as for (**3**) is indicated from conformational analysis.

Table 3. Signal enhancements based on n.O.e. difference spectroscopy of tridecamethyl ether tetra-acetates of profisetinidin condensed tannins.*



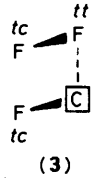
(1)

($CDCl_3$)	%†
5-OMe(G) ⟶ 3-H(L)	1.2
7-OMe(G) ⟶ 5-H(D)	0.8
⟶ 4-H(L)	1.9
⟶ 4-H(F)	2.3
⟶ 5-H(J)	1.7
7-OMe(D) ⟶ 8-H(D)	4.0
4-H(C) ⟶ 5-H(A)	2.4
4-H(F) ⟶ 5-H(D)	2.9
⟶ 7-OMe(G)	1.9
2-H(C) ⟶ 5-H(D)	1.0
8-H(D) ⟶ 7-OMe(D)	0.7
5-H(D) ⟶ 2-H(C)	1.0
⟶ 4-H(F)	1.0



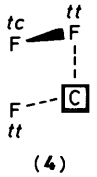
(2)

($CDCl_3$)	%†
5-OMe(G) ⟶ 3-H(L)	2.3
7-OMe(G) ⟶ 5-H(D)	1.2
⟶ 4-H(L)	2.7
⟶ 4-H(F)	2.2
⟶ 5-H(J)	0.7
7-OMe(D) ⟶ 8-H(D)	4.0
(C_6D_6)	
4-H(F) ⟶ 5-H(D)	0.9
⟶ 7-OMe(G)	0.5
2-H(C) ⟶ 5-H(D)	1.6
5-H(D) ⟶ 2-H(C)	1.9
⟶ 4-H(F)	1.6



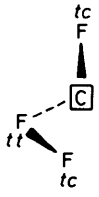
(3)

($CDCl_3$)	%†
7-OMe(D) ⟶ 8-H(D)	12.5
8-H(D) ⟶ 7-OMe(D)	3.7
5-H(D) ⟶ 4-H(F)	4.5
⟶ 2-H(C)	5.9
7-OMe(G) ⟶ 4-H(F)	9.5
⟶ 4-H(L)	8.9
⟶ 5-H(D)	4.7
5-OMe(G) ⟶ 2-H(L)	7.2
⟶ 3-OAc(L)	0.9



(4)

($CDCl_3$)	%†
5-OMe(G) ⟶ 4-H(L)	3.4
7-OMe(G) ⟶ 4-H(F)	2.1
⟶ 3-H(L)	1.7
⟶ 5-H(D)	1.5
5-H(D) ⟶ 2-H(C)	2.1
7-OMe(D) ⟶ 8-H(D)	5.3
8-H(D) ⟶ 7-OMe(D)	1.0
7-OMe(A) ⟶ 6-H(A)	3.7
⟶ 8-H(A)	2.6
7-OMe(J) ⟶ 6-H(J)	2.6
⟶ 8-H(J)	3.8



(5)

($CDCl_3$)	%†
5-OMe(G) ⟶ 5-H(A)	1.5
⟶ 5-H(D)	1.1
⟶ 3-H(F)	1.5
7-OMe(J) ⟶ 8-H(J)	1.0
⟶ 6-H(J)	1.7
7-OMe(A) ⟶ 8-H(A)	3.9
⟶ 6-H(A)	3.5
⟶ 2-H(I)	1.2
7-OMe(G) ⟶ 4-H(L)	2.1
⟶ 4-H(F)	2.2
⟶ 2-H(C)	1.6
⟶ 5-H(D)	2.0
7-OMe(D) ⟶ 8-H(D)	5.1
5-H(D) ⟶ 2-H(C)	2.1
4-H(F) ⟶ 5-H(D)	2.3
8-H(D) ⟶ 7-OMe(D)	1.0

* The abbreviated formulae (**1**)—(**5**) indicate 3,4-configurations (absolute) only, all units being 2,3-*trans*, with F ≡ (+)-or (−)-fisetinidols and C ≡ (+)-catechin. Relative configurations are indicated as either *tt* ≡ 2,3-*trans*-3,4-*trans* or *tc* ≡ 2,3-*trans*-3,4-*cis*.

† Only those significant n.O.e. difference effects which could be quantified are indicated; others confirm the various structural and conformational assignments.

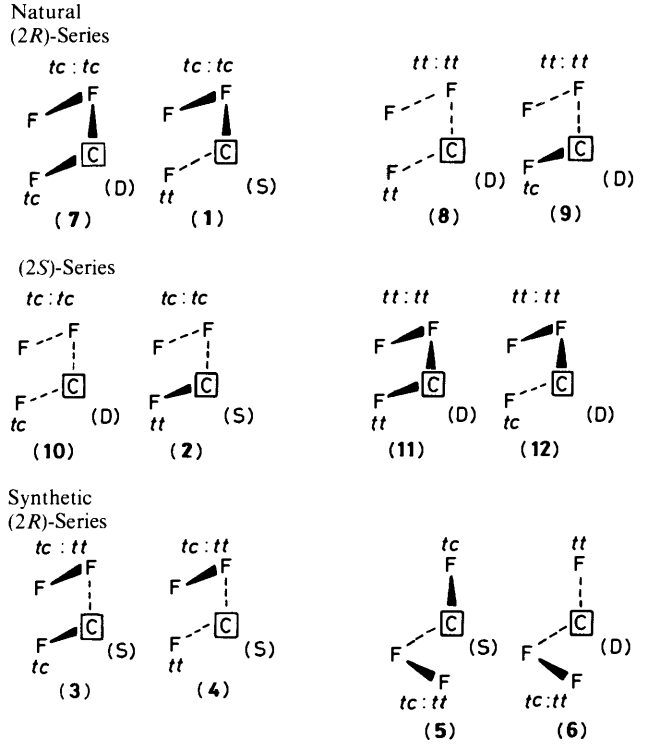
The synthetic tetraflavanoid isomer (**5**) differs structurally from both (**3**) and (**4**) due to the reversed positions of the bi- and mono-fisetinidol substituents on the (+)-catechin(GHI) moiety.[14] Nevertheless, diagnostic n.O.e. difference associations of 7-OMe(G) with 4-H(L), 4-H(F), 2-H(C), and 5-H(D), supported by those of 5-OMe(G) with 5-H(A), 7-OMe(A) with 2-H(I) and 5-H(D) with 2-H(C) elegantly define the ABC-DEF-G-JKL conformation. The significant 7-OMe(A)/2-H(I) association establishes the relative proximity of the ABC and GHI flavanoid units. Once again conformational analysis indicates a cyclic conformation with J-ring–A-ring interaction as in (**3**) and (**4**).

The indicated conformations of the profisetinidin 'tetramers' (**1**)—(**5**) (*cf.* Figures 1—5) all satisfy minimum steric energy requirements in the sense that the general plane of the [4,8]-linked DEF (−)-fisetinidol unit of compounds (**1**)—(**4**) is preferentially orientated away from the 7-OMe(G) function of the (+)-catechin, but inclined towards its heterocyclic oxygen (I-ring) due presumably to greater steric repulsion of the former. Similarly in the same group the general plane of the [4,6]-linked JKL (−)-fisetinidol unit is inclined away from 7-OMe(G) but towards 5-OMe(G);* a preferential effect plausibly attributable to the 'buttressing effect' of the 8-flavanyl(DEF) substituent on the 7-OMe(G) group. Also, within the same group [(**1**)—(**4**)] the general plane of the remaining [4,6]-linked ABC 'terminal' (−)-fisetinidol unit adopts an inclination removed from 7-OMe(D) due to steric repulsion. Identical repulsive effects by functional groups *ortho* to interflavanyl bonds apparently also apply to the positional isomer (**5**). The favoured torsional positions are valid despite stereochemical differences at 4-C (3,4-*cis vs.* 3,4-*trans*) in each of the (−)-fisetinidol units under discussion.

Thus, among the tridecamethyl ether tetra-acetates of eight natural[8,9] and four synthetic[14] tetrameric profisetinidins, five exhibit predominant 'stable' conformations (n.m.r. time-scale) at ambient temperatures (*cf.* Scheme). These may be regarded as undergoing 'slow' exchange with their minor conformers (*cf.* Table 1). The remaining seven isomers (**6**)—(**12**) show varying degrees of line-broadening under similar conditions indicative of 'intermediate' rates of rotation about their interflavanyl bonds, since 'fast' torsional oscillation of flavanyl units and 'fast' exchange between conformers of individual flavanyl heterocyclic rings as in 'monomers' do not apparently contribute to broadening. In this connection the consistently large coupling constants of heterocyclic protons ($J_{2,3} = J_{3,4ax.} = 9.5$ Hz) of the (+)-catechin units in the 'stable' isomers (**1**)—(**5**) compared with those of the corresponding derivative of the 'monomer' ($J_{2,3} = J_{3,4ax.} = 7.0$ Hz), both in $CDCl_3$ at 20 °C, indicate a higher degree of conformational stability in the former, probably resulting from partial restriction of H-ring (B-ring equivalent) mobility. The same considerations also apply to the consistently large couplings observed for all-*trans* heterocyclic F- and C-rings ($J_{2,3}$ 9.5—10.0, $J_{3,4}$ 9.75—10.3 Hz) of substituent fisetinidol units† of these 'tetramers'.

Comparison of the relatively limited number of pairs of 'tetramers' which differ at a single chiral centre (*cf.* Scheme) indicates that conformational stability is conferred on derivatives by [4,6:4,8]-bis-[(−)-fisetinidol] substituents of 2,3-*trans*-3,4-*cis*:2,3-*trans*-3,4-*trans* configuration irrespective of stereochemical differences in the remaining [4,6]-(−)-fisetinidol substituent [*cf.* (**3**) and (**4**)]. This contrasts with the dynamic behaviour of all those with all-*trans*-bis-[(−)-fisetinidol] substituents [*cf.* (**8**), (**9**), (**11**), and (**12**)]. Between these behavioural extremes are partial effects introduced by [4,6:4,8]-bis-[2,3-*trans*-3,4-*cis*-(−)-fisetinidol] [*cf.* (**1**) *vs.* (**7**), and (**2**) *vs.* (**10**)] and [4,6:4,6]-2,3-*trans*-3,4-*cis*:2,3-*trans*-3,4-*trans*-bis-[(−)-fisetinidol] substituents [*cf.* (**5**) *vs.* (**6**)] in stabilizing conformations of the respective tetramers, where the effects also depend on the relative configurations of the remaining [4,6]- or [4,8]-(−)-fisetinidol substituents respectively. From these examples it is also apparent that final introduction of 2,3-*trans*-3,4-*cis*-(−)-fisetinidol units (in contrast to those with 2,3-*trans*-3,4-*trans* configurations) into 'angular' 'trimers', all of which exist in the dynamic domain,[5,7] promotes conformational stability in the resultant 'angular' tetramers.‡ This observation correlates with our general finding that temperature (entropy) requirements for 'fast' rotation (n.m.r. time-scale), in order to obtain sharply defined spectra, is consistently higher for bi- and tri-flavanoid analogues with 2,3-*trans*-3,4-*cis* substituents compared with those with 2,3-*trans*-3,4-*trans*-(−)-fisetinidol substituents. However, in the case of the tetraflavanoids the requirements are obviously more complex considering that the all-2,3-*trans*-3,4-*cis*-biflavanoid configuration of substituents does not necessarily confer stability [*cf.* (**7**) *vs.* (**1**), and (**10**) *vs.* (**2**)], although in 8-linked monoflavanoid units this arrangement is apparently effective in a single instance [*cf.* (**5**) *vs.* (**6**)].

Progressive temperature elevation of each 'stable' derivative over the range 20—170 °C induces 'rapid' dynamic rotational isomerism as evinced by the progressive broadening of resonances initially, followed by their resharpening in the upper range (*cf.* 170 °C), but each reverts to the same dominant conformation on return to ambient conditions. Such behaviour is presumably attributable to the thermodynamic stability of



Scheme. 'Tetrameric' profisetinidin derivatives (**1**)—(**5**) represent units with predominant (85—90%) and 'stable' conformations (S) at ambient temperatures. All others exist in a dynamic domain (D) over a wide temperature range (−50 °C to +170 °C). The conventions adopted for abbreviated formulae are defined in Table 3

* Compound (**4**) is an apparent exception with the JKL (−)-fisetinidol unit placed midway between 7-OMe(G) and 5-OMe(G) and its interflavanyl bond *equatorial* relative to the heterocyclic L-ring.

† However, in this instance conformational stability is partly, if not predominantly, attributable to bulky 2- and 4-aryl substituents on each heterocyclic ring.

‡ 4-Arylflavan-3-ols (and flavan-3,4-diols) of 2,3-*trans*-3,4-*cis* configuration are also known to be thermodynamically more stable than their 2,3-*trans*-3,4-*trans* isomers.[15]

each conformer, *i.e.* significant low enthalpy and high entropy differences[16] between these and other possible rotamers. Conformational comparisons between pairs of isomers, which individually exhibit either 'static' or 'dynamic' behaviour while differing at a single 4-C chiral centre [*e.g.* (**2**) *vs.* (**10**) and (**5**) *vs.* (**6**)] show relatively small differences between overlap of 'terminal' flavanyl units in cyclic arrangements, thus supporting the concept of thermodynamic stability of derivatives (**1**)—(**5**) of 'angular' profisetinidin 'tetramers', to which the relative configurations of individual flavanoid units and terminal overlap apparently contribute. Recent theoretical attempts at deriving conformations of polymeric condensed tannins *via* a minimum total energy approach by Pizzi *et al.*[17] was without the necessary foreknowledge of the structure of 'angular' 'tetramers'. Their conclusions regarding the relative dominance of Van der Waals forces and contributory hydrogen bonding energies could be misleading considering the limitations of the program employed, and validity of the initial assumptions.

The varying stereochemistry and irregular aromatic substitution rule out considerations of a regular helix, but the overall 'stable' conformation of (**1**) is of right-handed screwness [(P)-helicity, *cf.* Figure 1], with the reverse for (**2**)—(**5**) [(M)-helicity, *cf.* Figures (2)—(5)].

We speculate that the phenolic forms of condensed tannins of natural origin[8,9] corresponding to the derivatives (**1**) and (**2**) exist as stable 'cyclic' conformations judging by evidence of conformational stability and non-bonded intramolecular steric interactions of the functionalized aromatic B and J rings which may be attractive rather than repulsive due to strong hydrogen bonding and weaker Van der Waals forces. Similarly free phenols representative of the remaining group of natural profisetinidin diastereoisomers (**7**)—(**12**)[8,9] (*cf.* Scheme) may adopt cycloconformations under aqueous conditions, considering the hydration sphere which will be associated with, among others, their 'terminal' ABC and JKL units, despite the indicated mobility of their tridecamethyl ether tetra-acetates. This notion is supported by an examination of Dreiding models.* 'Angular' tetraflavanoid condensed tannins may be regarded as the key prototypes of higher oligomers present in 'mimosa' and 'quebracho' extracts (and in other members of the Leguminoseae and Anacardiaceae) as regards their conformations and dynamic behaviour.

Synthetic evidence[9] of the extension of condensation from 'tetramers' to 'pentamers' by flavanyl substitution at 8-C (D-ring) of the free phenolic form of the (2*S*,3*R*)-profisetinidin 'tetramer' (**12**) is in agreement with the steric availability of this nucleophilic centre, presuming existence of the 'tetramer' in a stable cycloconformation. However, judging from peripheral 'nucleophilic' positions on the established conformation of its diastereoisomer (**2**) (*cf.* Figure 2), 6-C (A-ring) appears an equally strong candidate, while 6-C(J) on a 'terminal' unit is apparently subject to steric hindrance.

Similar speculative arguments apply to the availability of nucleophilic centres for cross-linking reactions at ambient temperatures during adhesive applications (*cf.* Introduction). Radiating pyrocatechol function of low reactivity may partially inhibit condensation *via* methylene bridges with the commonly used formaldehyde as cross-linking agent. It may also be significant that, apart from viscosity considerations, rapid penetration of condensed tannins into hides is traditionally effected by using warm liquors; conditions which are likely to promote molecular mobility.

* The specific attractive interaction of intramolecular hydrogen bonding of 7-OH(D), 5-OH(G), and 7-OH(G) groups, for example, is likely to be more important than their steric repulsion (*cf.* previous discussion on the repulsive effects of methoxy groups in these positions).

Experimental

The natural 'tetrameric' profisetinidin condensed tannins of the (2*R*) and (2*S*) series from the heartwoods of *Acacia mearnsii* (black wattle) and *Rhus lancea* (karree) respectively (*cf.* Scheme) were isolated as their tridecamethyl ether tetra-acetates by methods outlined previously.[8,9] The composition of the phenolic mixture from *R. lancea* is almost identical with those from the heartwoods of *Schinopsis balansae* and *S. lorentzii* (quebracho).[7] The same 'tetramers' were also synthesized by condensation of (+)-mollisacacidin trimethyl ether with [4,8]-2,3-*trans*-3,4-*trans*- and [4,8]-2,3-*trans*-3,4-*cis*-(−)-fisetinidol-(+)-catechin synthons,[12] and similarly by condensation of (−)-leucofisetinidin [(−)-mollisacacidin] trimethyl ether with [4,8]-(+)-fisetinidol-(+)-catechins of similar configuration, followed by full methylation with diazomethane and subsequent acetylation.

Synthetic 'angular' (2*R*)-profisetinidin isomers which have no natural counterparts (*cf.* Scheme) were obtained by condensation of the hexamethyl ether tri-acetates of [4,6]-2,3-*trans*-3,4-*cis*:2,3-*trans*-3,4-*trans* or -*cis*-(−)-fisetinidol-(+)-mollisacacidins with appropriate [4,6]- and [4,8]-(−)-fisetinidol-(+)-catechins.[14]

The ^{1}H n.m.r. spectra of the derivatives of the 'tetramers' were recorded on a 300 MHz Bruker AM spectrometer in $CDCl_3$, $(CD_3)_2CO$, or C_6D_6 at 19 or 20 °C. Methoxy resonances of A-, D-, J-, and G-rings (*cf.* Table 2) were distinguished by their n.O.e. (difference) associations with known aromatic protons in *ortho*-positions[8,9,14] or with others on adjacent flavanyl units (*cf.* Table 3). The n.O.e. difference spectra were recorded by methods outlined in the literature.[18–20]

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References

1 S. R. Evelyn, *J. Soc. Leather Trades' Chem.*, 1954, **38**, 142, 309; S. R. Evelyn, D. R. Cooper, and P. C. van Berge, *J. Polym. Sci.*, 1958, **33**, 53.
2 D. G. Roux and S. R. Evelyn, *Biochem. J.*, 1958, **69**, 530; *ibid.*, 1958, **70**, 344; *ibid.*, 1960, **76**, 17; D. G. Roux and E. Paulus, *Biochem. J.*, 1962, **82**, 320.
3 D. G. Roux, *J. Soc. Leather Trades. Chem.*, 1955, **39**, 80, 153, 321; *Nature* (*London*), 1958, **181**, 1793.
4 R. L. Sykes and D. G. Roux, *J. Soc. Leather Trades' Chem.*, 1957, **41**, 14.
5 P. M. Viviers, J. J. Botha, D. Ferreira, D. G. Roux, and H. M. Saayman, *J. Chem. Soc., Perkin Trans. 1*, 1983, 17.
6 J. J. Botha, P. M. Viviers, D. A. Young, I. C. du Preez, D. Ferreira, D. G. Roux, and W. E. Hull, *J. Chem. Soc., Perkin Trans. 1*, 1982, 527.
7 P. M. Viviers, H. Kolodziej, D. A. Young, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2555.
8 D. A. Young, D. Ferreira, D. G. Roux, and W. E. Hull, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2529.
9 D. A. Young, H. Kolodziej, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2537.
10 J. A. Steenkamp, D. Ferreira, D. G. Roux, and W. E. Hull, *J. Chem. Soc., Perkin Trans. 1*, 1983, 23.
11 I. C. du Preez, A. C. Rowan, D. G. Roux, and J. Feeney, *J. Chem. Soc., Chem. Commun.*, 1971, 315.
12 D. A. Young, A. Cronjé, A. Botes, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2521.
13 E. V. Brandt, D. A. Young, H. Kolodziej, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Chem. Commun.*, 1986, 913.
14 D. A. Young, D. Ferreira, and D. G. Roux, *J. Polym. Sci., Polym. Chem. Ed.*, 1986, **24**, 835.

15 J. H. van der Westhuizen, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1220.
16 J. March, 'Advanced Organic Chemistry,' McGraw-Hill Kogakusha, Tokyo, 1977, 2 edn., p. 190.
17 A. Pizzi, F. A. Cameron, and N. J. Eaton, *J. Macromol. Sci. Chem.*, 1986, **23**, 515.
18 L. D. Hall and J. M. K. Sanders, *J. Am. Chem. Soc.*, 1980, **102**, 5704.
19 W. E. Hull, 'Aspect 2000 Application Note No. 1,' *Bruker Reports*, 1978, **1**, 4.
20 E. G. Chapman, D. B. Abercrombie, P. D. Cary, and E. M. Bradbury, *J. Magn. Reson.*, 1978, **31**, 459.

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