Synthesis of Condensed Tannins. Part 8.† The First ' Branched ' [4,6 : 4,8 : 4,6]-Tetraflavanoid. Coupling Sequence and Absolute Configuration

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Condensation of (+)-(2*R*)-2,3-*trans*-3,4-*trans*-flavan-3,3',4,4',7-pentaol [(+)-mollisacacidin] ‡ with excess of (−)-(2*R*)-2,3-*trans*-flavan-3,3',4',7-tetraol [(−)-fisetinidol] proceeds beyond the expected biflavanoid range to generate significant yields of both the ' linear ' [4,6 : 4,6]-2,3-*trans*-3,4-*cis* : 2',3'-*trans*-3',4'-*trans* : 2'',3''-*trans*-trifisetinidol and the first ' branched ' [4,6 : 4,8 : 4,6]-2,3-*trans*-3,4-*cis* : 2',3'-*trans*-3',4'-*trans* : 2'',3''-*trans*-3'',4''-*trans* : 2''',3'''-*trans*-tetrafisetinidol.

The products indicate a selective condensation sequence due to differing steric constraints, operative at competing nucleophilic centres in each intermediate substrate, assisted by hyperconjugative effects.

The sequential nature of the initial steps in natural condensed tannin formation culminating in ' angular ' triflavanoids and involving (+)-catechin or (+)-gallocatechin as bifunctional phloroglucinol-type nucleophiles has been adequately demonstrated by biomimetic syntheses, with substitution at C-8 on the catechin unit preceding that at C-6.[1,2] Structural elaboration of the triflavanoids can be attained by biogenetic condensation at accessible nucleophilic centres of the upper and lower ' terminal ' resorcinol-type flavanyl units introduced in these initial steps[3,4] [*cf.* formula (9)] as typified in black wattle bark (*Acacia mearnsii*) and quebracho tannins (*Schinopsis* spp.).

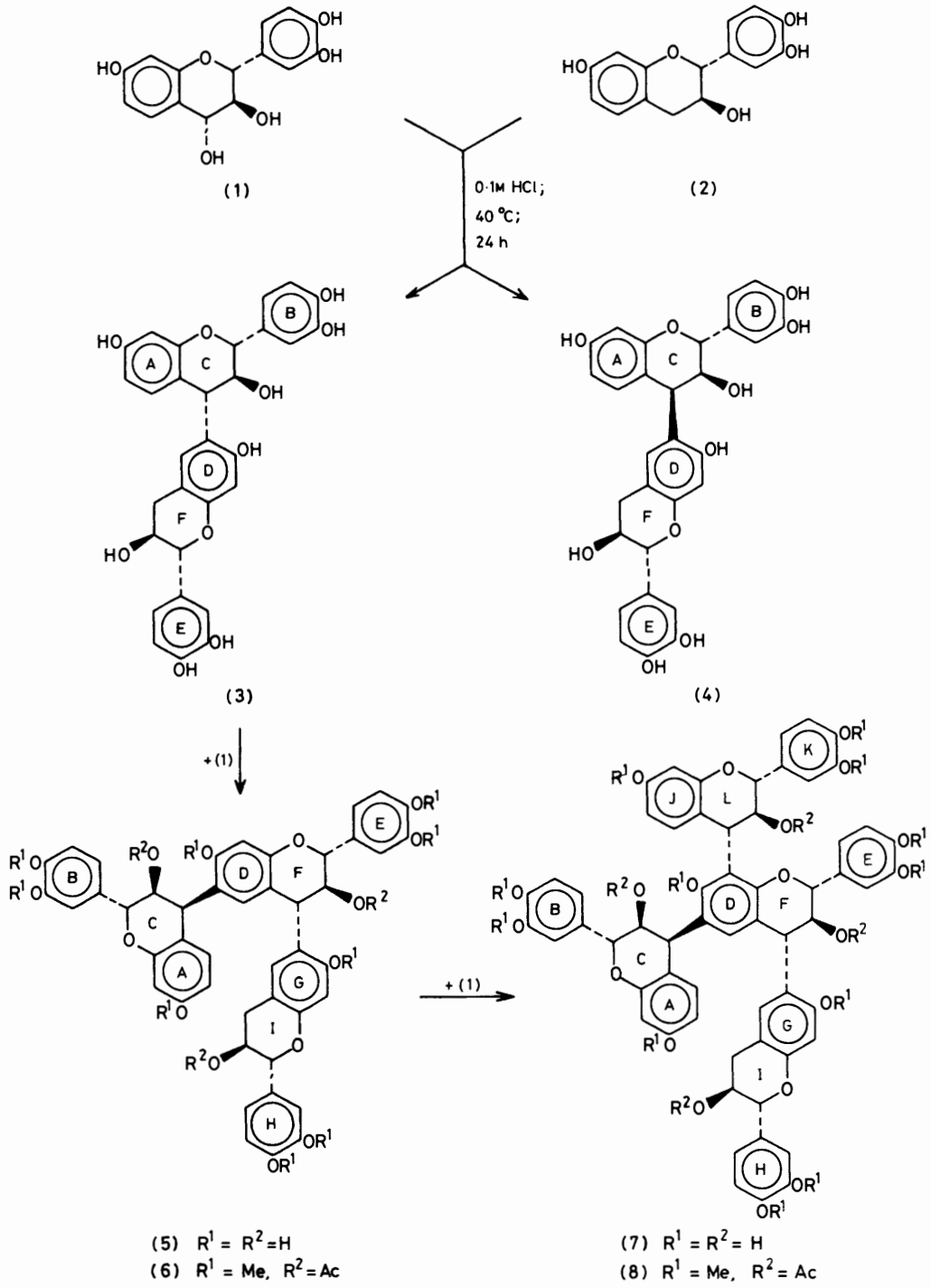
In order to chart the likely course of such natural condensations to higher oligomeric levels which exclusively involve resorcinol-type flavanoid species, the flavan-3,4-diol (+)-mollisacacidin (1) was condensed with its flavan-3-ol analogue (−)-fisetinidol (2) under those relatively mild conditions (0.1M HCl; 40 °C; 24 h) which provide adequate yields while ensuring selectivity. The use of an excess of (−)-fisetinidol as competitive nucleophile with an accessible nucleophilic 6-position [initial 1 : 3 molar ratio (1) : (2)] similarly ensured selectivity during successive condensation steps. In addition to the expected[5] all-*trans*-biflavanoid (3) and its 3,4-*cis*-isomer (4), a novel ' linear ' triflavanoid (5) and the first ' branched ' tetraflavanoid (7) were formed in the proportions 1.5 : 7 : 5 : 2, respectively, based on yields of their methyl ether acetates. The structures and stereochemistry of the [4,6]-biflavanoids [(3) and (4)] are known,[5] although the ratio in which they are formed (1.5 : 7, respectively) represents the reverse of that expected (3 : 2) from previous syntheses,[5] where the formation of higher oligomers was overlooked.

The structure of the ' linear ' triflavanoid (5) was derived from analysis of its nonamethyl ether triacetate (6), $C_{60}H_{62}O_{18}$, by mass spectrometry (M^+ 1 070) and 500 MHz ^{1}H n.m.r. spectroscopy in $(CD_3)_2SO$ recorded at a sufficiently high temperature (363 K) to ensure sharpness of all resonances. The latter technique showed the compound to be the 4''-deoxy-analogue of the first ' linear ' [4,6 : 4,6]-triflavanoid with a terminal 3,4-diol function, recently isolated from the heartwood of *Acacia mearnsii*.[6] Three sharply defined acetoxy- and nine methoxy-proton resonances are evident. The high-field aromatic region of the trifisetinidol derivative (6) is almost identical with that of its 4''-hydroxy-analogue,[6] apart from significant shielding (Δδ −0.1) of the 5-H(G) resonance in the former relative to the latter instance (*cf.* Figure 1 and Figure 2 of reference 6), four aromatic singlets, and a single aromatic ABC spin system correlating with [4,6 : 4,6] bonding between resorcinol-type flavanoid units. By means of spin-decoupling of heterocyclic protons, two AMX systems with both large ($J_{2,3} = J_{3,4} = 9.5$ Hz) and small couplings ($J_{2,3}$ 6.0, $J_{3,4}$ 4.5 Hz), were identified, and also a single ABMX system ($J_{2,3}$ 7.0, $J_{3,4eq}$ 5.5, $J_{3,4ax}$ 8.0 Hz). The former pair represents units with all-*trans* and 2,3-*trans*-3,4-*cis* configurations respectively, while the latter, which incorporates a 4-methylene function ($J_{4eq,4ax}$ 16.0 Hz; δ 2.68, 2.84) and also a 3-H multiplet (δ 5.16), distinguishes the ' lower ' terminal 2,3-*trans*-flavan-3-ol system. Assignment of the 3,4-*cis* and 3,4-*trans* configurations to the ' upper ' and ' middle ' units, respectively, was possible by means of spin-decoupling techniques involving the interaction between the 4- and line-broadened 5-protons as before,[6] thus establishing the sequence of units as 2,3-*trans*-3,4-*cis* : 2',3'-*trans*-3',4'-*trans* : 2'',3''-*trans*. Spin-decoupling of the 2- and 6-protons of the aromatic B-, E-, and H-rings by irradiation of the heterocyclic 2-protons of the respective C-, F-, and I-ring systems permits assignment of all aromatic resonances (Figure 1). The trifisetinidol (5) accordingly represents both a structural and stereochemical analogue of the first known natural triflavanoid with a terminal diol function[6] and hence the similar 2*R*,3*S*,4*S* : 2'*R*,3'*S*,4'*R* : 2''*R*,3''*S* absolute configuration.

The oligomeric tetraflavanoid analogue (7), resulting from the same condensation, is structurally related to the triflavanoid (5) as is evident from a comparison of the 500 MHz ^{1}H n.m.r. spectrum of its dodecamethyl ether tetra-acetate derivative (8), $C_{80}H_{82}O_{24}$ (Figure 2) with that of the nonamethyl ether triacetate (6) of the triflavanoid (Figure 1). Chemical shifts in the aromatic and heterocyclic regions are temperature-dependent to varying degrees and so our comparison (Experimental section) was accordingly performed under the same conditions of solvent [$(CD_3)_2SO$] and temperature (363 K), although spin-decoupling was repeated at 328 K (Figure 2) due to reduced overlap of benzenoid resonances at this lower temperature.

Twelve methoxy and four acetoxy resonances are clearly defined in the spectrum at 328 K, in agreement with the proposed structure (8). The chemical shifts and coupling constants of the heterocyclic protons of the methyl ether acetates of the tri- and tetra-flavanoids are similar (*cf.* Figures 1 and 2), but differ in respect of an additional AMX system in

† Part 7 is reference 2.
‡ In the preceding paper, (+)-mollisacacidin (1) is called (+)-leucofisetinidin.



Scheme

the latter ($J_{2,3}$ 9.8, $J_{3,4}$ 10.2 Hz) at δ 5.00 (2-H, doublet), 6.083 (3-H, triplet), and 4.725 (4-H, doublet) indicative of a 2,3-*trans*-3,4-*trans*-flavan. The high-field doublet [4-H(L)] attributed to this unit is subject to pronounced benzylic coupling (J 1.0 Hz), which finds its counterpart in the aromatic region (see below). The low-field position of the 3-H(L) triplet, δ 6.083, is characteristic of 3-axial protons geminal to an acetoxy-function where this arrangement is present in 4-linked flavanyl units which are flanked at the point of their attachment to aryl rings by *ortho* oxygen substituents. Such deshielding of 3-H(L) in conjunction with the high-field position of 4-H(L) implies a [4,8] linkage of the introduced unit to a resorcinol-type flavanoid moiety.

Similarly, extensive spin-decoupling in the aromatic region established the presence of six additional protons, represented by ABC- and AMX-systems located mainly to low and high fields, respectively. The X-portion, 5-H(J) (δ 6.729) of the latter reflects the same secondary benzylic coupling as observed for 4-H(L), while the remaining two protons in the system, 6-H(J) (δ 6.561) and 8-H(J) (δ 6.410) resonate at higher field, as expected from their presence in a resorcinol-type ring system. Spin-decoupling also established the relation-

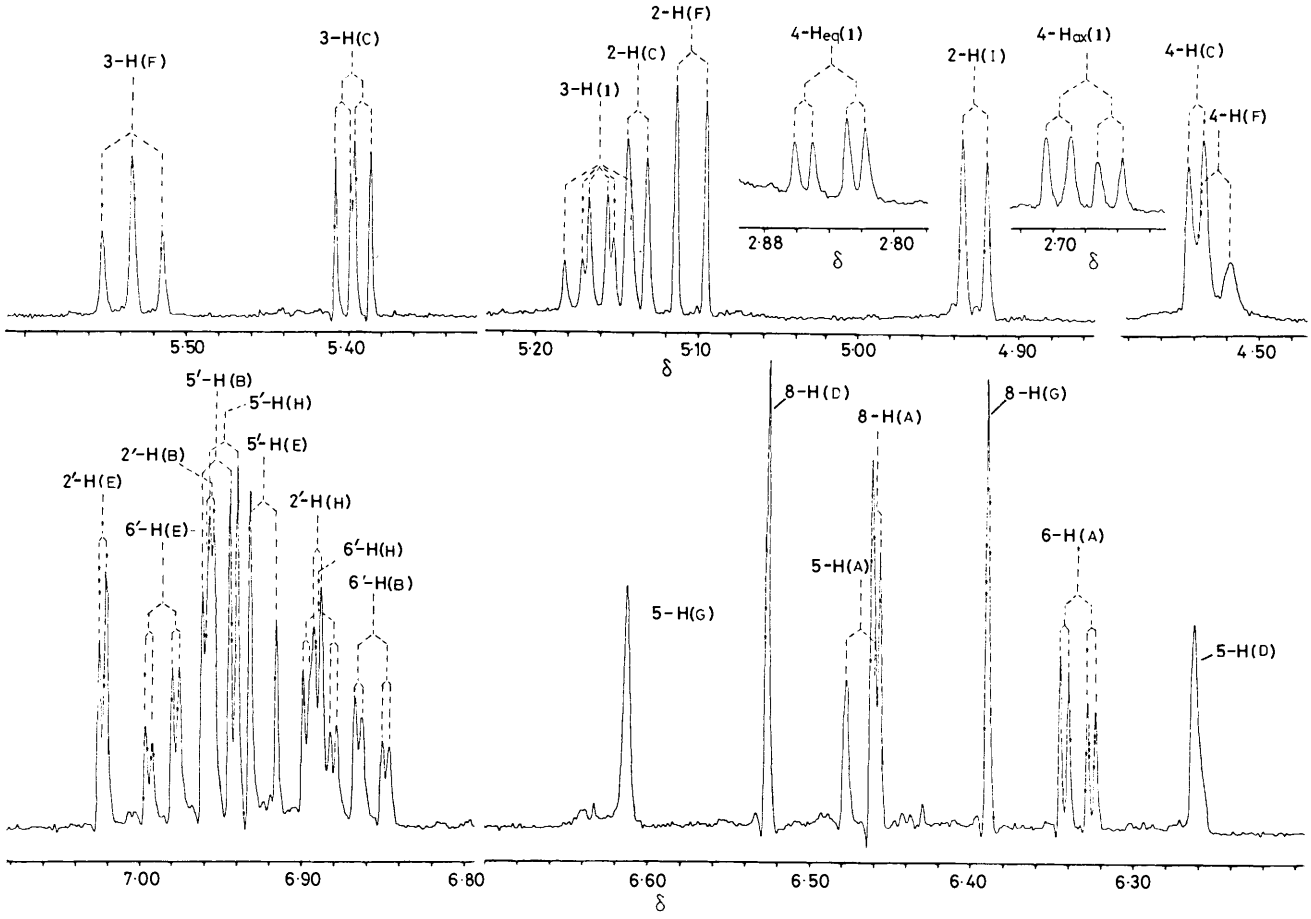


Figure 1. Heterocyclic and aromatic regions from the 500 MHz ^{1}H n.m.r. spectrum of [4,6:4,6]-2,3-*trans*-3,4-*cis*:2′,3′-*trans*-3′,4′-*trans*:2″,3″-*trans*-trifisetinidol nonamethyl ether triacetate (6) (363 K)

ship between 2-H(L) and the ABC-system of ring K, thus completing the assignment of the additional 4-linked and 3,3′,4′,7-substituted 2,3-*trans*-3,4-*trans*-flavanyl moiety.

Bonding of this JKL all-*trans*-flavanyl unit does not occur at the nucleophilic 6- or 8-positions of the benzenoid A-ring of the triflavanoid [from consideration of the intact high-field AMX-system of the 2,3-*trans*-3,4-*cis* 'upper' terminal flavanyl unit] and must accordingly be attached to the remaining nucleophilic C-8(D) or C-8(G) positions of the 'middle' and 'lower' units, respectively. This deduction is supported by comparison of the aromatic resonances of the triflavanoid and tetraflavanoid derivatives (Figures 1 and 2, respectively), from which the disappearance of one of the four singlets which characterize the former, *i.e.* the sharp low-field singlet (δ 6.528) corresponding in chemical shift to 8-H(D), is evident. However, in view of the variable temperature-dependence of chemical shifts in these compounds, confirmation was sought by double irradiation of 8-H(G) (δ 6.406) of the tetraflavanoid derivative which sharpens the signal due to 5-H(G) (δ 6.638), thus establishing the relationships between the three residual aromatic singlets. The remaining broad singlet δ 6.418 [5-H(D)], characterized by its known * temperature-dependence in terms of deshielding [313 K: δ 6.342; 333 K, 6.374; 363 K, 6.417], is sharpened in the spectrum of the tetraflavanoid derivative relative to its counterpart in the triflavanoid spectrum (*cf.* Figures 1 and 2), possibly as a result of relief from *para*-coupling, while retaining sharp benzylic coupling (*J ca.* 1.0 Hz). On this basis the all-*trans* flavanyl unit JKL is placed at C-8(D) of the 'central' flavanoid unit. The resultant 'branched' arrangement of the tetraflavanoid, with three flavanyl units attached to the 4-, 6-, and 8-positions of the 'central' DEF flavan-3-ol, appears to be supported by the observation that resonances of the substituent units are sharp over a wide temperature range (313—363 K), whereas substantial line-broadening particularly of all the heterocyclic protons of the central unit, persists (Figure 2) presumably as a consequence of the cumulative effect of dynamic rotational isomerism about three interflavanoid bonds. Finally, structural analysis of the triflavanoid (5) with the aid of Dreiding models indicates position C-8(D) to be more accessible than the competing nucleophilic centre C-8(G) in potential tetraflavanoid formation, with due consideration of interflavanoid rotameric forms and hydrogen bonding.

Circular dichroism (c.d.) of the trifisetinidol derivative (6) (Figure 3) showed positive low-wavelength Cotton effects reminiscent of the 'abnormal' spectrum of its 4-oxy-(I-ring) analogue [6] in terms of the aromatic quadrant rule.[7] Apart from the possibility of the dominance of the effects of the 3,4-*cis* stereochemistry [8] of the 'upper' terminal unit at C-4, these unusual phenomena may be due to the as yet unknown contributions of rotational isomerism about the interflavanoid bond since c.d. spectra are recorded only at ambient temperatures. However, the negative low-wavelength Cotton

* Strong deshielding of 5-H(G) with increasing temperature has been observed in a number of resorcinol-type polyflavanoids including the triflavanoid analogue with a terminal diol function.[6]

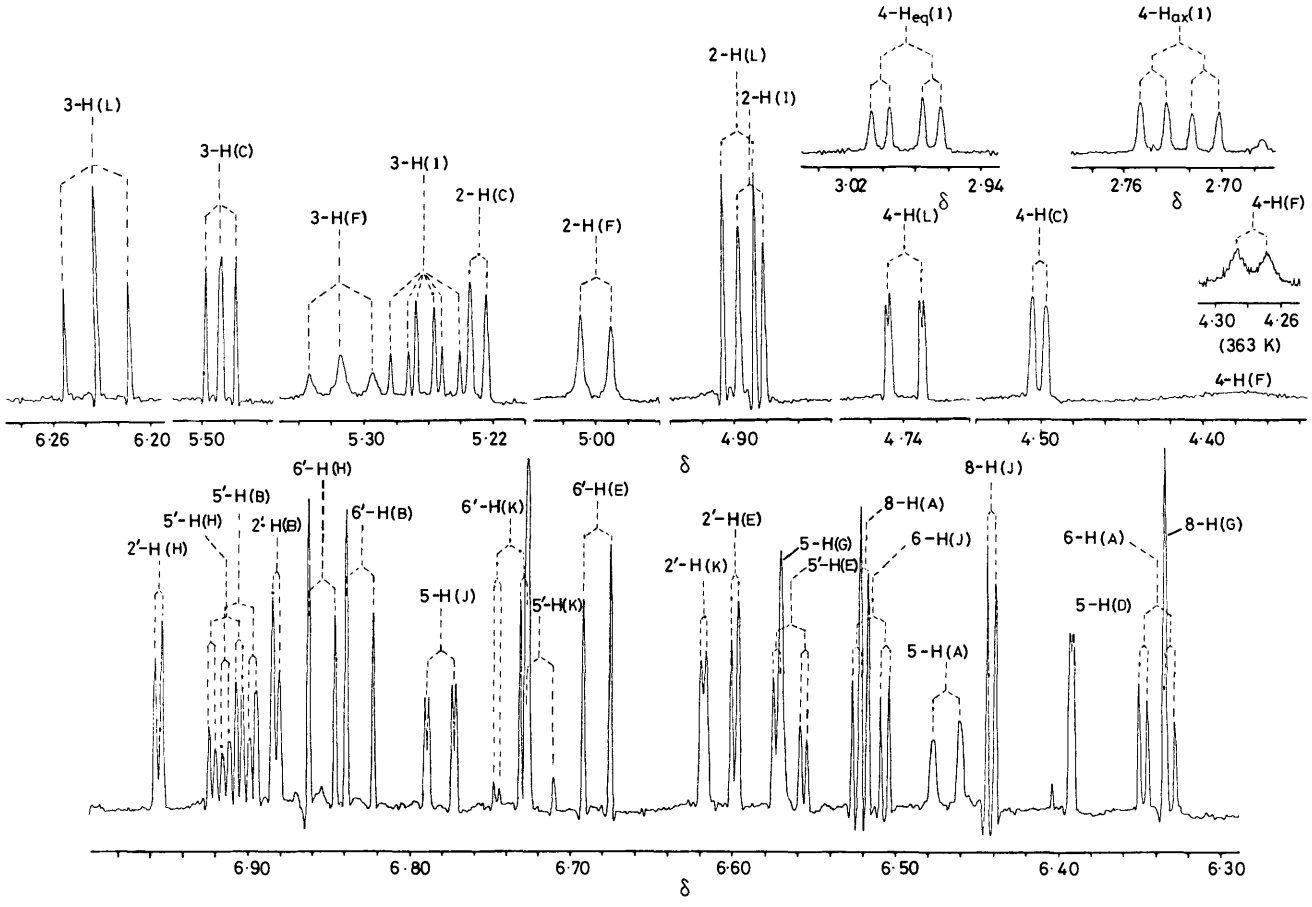


Figure 2. Heterocyclic and aromatic regions from the 500 MHz ^{1}H n.m.r. spectrum of [4,6:4,8:4,6]-2,3-*trans*-3,4-*cis*:2′,3′-*trans*-3′,4′-*trans*:2″,3″-*trans*-3″,4″-*trans*:2‴,3‴-*trans*-tetrafisetinidol dodecamethyl ether tetra-acetate (8) (328 K)

effects exhibited by the tetrafisetinidol derivative (8) reflect the dominance of the 3,4-*trans* stereochemistry of constituent units but without any indication of contributions by the 3,4-*cis* arrangement of the 4,6-linked ABC flavanyl unit. Thus, at the current state of our knowledge, application of c.d. to the assignment of absolute configurations at C-4 in higher oligomers is limited. Nevertheless, from synthesis employing compounds of known absolute configuration, and from a knowledge of 3,4-*cis*- and -*trans*-stereochemistry as defined by ^{1}H n.m.r. spectroscopy, the absolute configuration of the [4,6 : 4,8 : 4,6]-tetrafisetinidol (7) may be specified as 2*R*,3*S*,-4*S* : 2′*R*,3′*S*,4′*R* : 2″*R*,3″*S*,4″*R* : 2‴*R*,3‴*S* as illustrated.

The generation of four main products (3)—(5) and (7) in significant yield * [biflavanoids (3) and (4) *ca.* 20%; triflavanoid (5) 5.6%, and tetraflavanoid (7) 3.0%] from the condensation of (+)-mollisacacidin (1) with an assured excess (throughout the reaction) of nucleophilic (−)-fisetinidol indicates the following reaction sequence. Steric constraints

$$(1) + (2) \longrightarrow (4) + (3) \xrightarrow{+(1)} (5) \xrightarrow{+(1)} (7), \text{ (Scheme)}$$

are presumably responsible for inhibition of continued ' linear ' condensation at C-6(A) in those oligomeric intermediates [*i.e.* (4) and (5)] which embody 3,4-*cis* configurations in their ' upper ' terminal flavanyl units. This is reflected in the unusual 7 : 1.5 excess † of the 3,4-*cis*-bifisetinidol (4) [over its *trans*-isomer (3)] isolated from the biflavanoid fraction, due in part to selective participation of the all-*trans*-isomer (3) in further condensation, as substantiated by the all-*trans* biflavanoid core of the higher oligomers (5) and (7). On this basis C-8(D) of the all-*trans* ' middle ' unit of the triflavanoid represents the least hindered of the nucleophilic centres, thus allowing the formation of the ' branched ' tetraflavanoid.

However, steric effects are inadequate to explain both the selectivity and regiospecificity observed in the successive condensations of the flavan-3,4-diol with the all-*trans* biflavanoid (3) and the triflavanoid (5) since these steps, which dictate the general course of progressive condensation, occur despite competing nucleophilic centres on these and other potential substrates (4), and also despite the sustained excess of the parent nucleophile, (−)-fisetinidol (2), throughout the reaction. Under mild conditions, both the bi- (3) and tri-flavanoid (5) apparently behave as activated nucleophiles, and consideration must be given to the effects of substituents other than hydroxy and alkoxy on those rings which are subject to preferential electrophilic aromatic substitution. Since hyperconjugation in benzylic cations [9] and the hyperconjugative angu-

* Yields indicated are of the free phenolic form and are based on complete consumption of (+)-mollisacacidin.

† At 40 °C this condensation is presumed to be under stereochemical rather than thermodynamic control (*cf.* reference 8). Such conjecture is also supported by evidence of the relative stability with respect to inversion at C-4 of the all-*trans*-bifisetinidol (3) under the same experimental conditions.

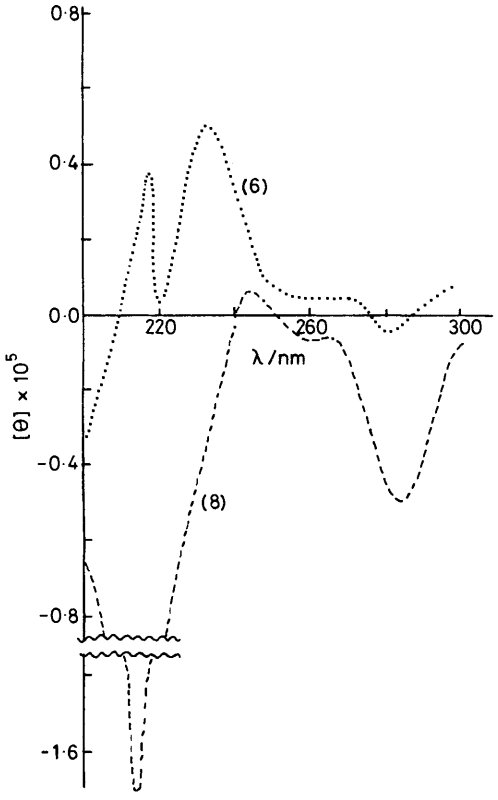
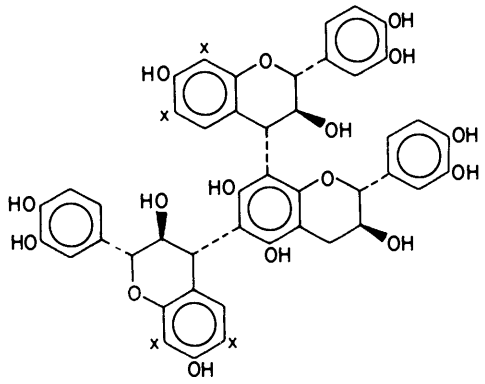


Figure 3. C.d. spectra of the nonamethyl ether triacetate of trifisetinidol, (6), and the dodecamethyl ether tetra-acetate of tetrafisetinidol, (8)

lar dependence between the C–H bond and cations [10,11,12] are firmly established for both intrinsic and kinetic isotope effects they are now considered with regard to the present condensation reaction (*cf.* reference 13). Electrophilic attack by the flavan-4-yl carbocation at C-6 (A-ring) of the all-*trans* biflavanoid (3) and at C-8 (D-ring) of the triflavanoid (5) leads plausibly to electron demand at C-4 of the C-ring (half-chair conformation) of the former, and at both C-4 positions (C- and F-rings) (boat and half-chair conformations, respectively) of the latter. All methine protons at these positions are doubly benzylic, and also favourably [11] *axial* to the rings undergoing substitution. Considering likely arenium-ion charge distributions,[14] both factors could combine to induce significant hyperconjugative effects despite location of methine groups *meta* to the point of attack. By contrast, substitution at C-6 or -8 (A-ring) of the non-reactive 3,4-*cis*-biflavanoid (4), where the methine proton at C-4 of the C-ring (half-chair) is orientated quasi-equatorial relative to the A-ring, would be less subject to contributory hyperconjugative stabilization of the delocalized charge. Thus both steric and conformationally dependent hyperconjugative effects apparently determine the course of condensations leading to higher oligomers.

Both the penultimate and final steps in this condensation sequence between resorcinol-type flavanoids provide predictions regarding steric control operative during further structural elaboration of 'angular' triflavanoids [*e.g.* compound (9)] of varying stereochemistry [1-4] present in black wattle bark and quebracho tanning extracts since this occurs by similar means through condensation of resorcinol-type flavan-4-yl carbocations at nucleophilic C-6 or C-8 centres of resorcinol-based flavanyl substituents on the 'central' (+)-catechin or (+)-gallocatechin units [*cf.* structure (9)].



(9)

[x] indicates residual reactive nucleophilic centres

Experimental

^{1}H N.m.r. spectra were recorded on Bruker WP-80 and WM-500 spectrometers in $CDCl_3$ and $(CD_3)_2SO$, respectively, with Me_4Si as internal standard. Determination of coupling constants and spin-decoupling at 500 MHz both required suitable scale expansion. All spectra at this frequency were subject to Gaussian enhancement. Mass spectra were obtained with a Varian CH-5 instrument using suitable reference compounds for calibration at high mass values. C.d. data were obtained in methanol on a Jasco J-20 spectropolarimeter. Analyses (C and H) were performed by Analytische Laboratorien, Postfach 1249, D-5250 Engelskirchen, West Germany. Preparative layer chromatography (p.l.c.) was done on Kieselgel 60 PF_{254} (1.0 mm) 20 × 20 cm plates which were air-dried and used without prior activation. Methylations were performed with an excess of diazomethane in methanol–diethyl ether at −15 °C over 48 h, while acetylations were in acetic anhydride–pyridine. Evaporations were done under reduced pressure at 50 °C in a rotary evaporator.

Acid-catalysed Condensation of (2R,3S,4R)-*Flavan*-3,3′,4,4′,7-*pentaol* [(+)-*Mollisacacidin*] *with* (2R,3S)-*Flavan*-3,3′,4′,7-*tetraol* [(−)-*Fisetinidol*].—(−)-Fisetinidol (2) (5.5 g, 0.02 mol) was partialy dissolved in 0.1M HCl (800 cm^3). (+)-Mollisacacidin (1) (2.0 g, 0.007 mol) was then added in small quantities over 1 h to the stirred suspension kept at 40 °C. The reaction mixture was kept at the same temperature for 24 h and the reaction was then terminated by the addition of saturated $NaHCO_3$ solution (400 cm^3). The reaction products were extracted with ethyl acetate (3 × 400 cm^3) and the combined extracts were dried (anhydrous Na_2SO_4). After evaporation of the solvent the recovered solids were separated by p.l.c. [benzene–acetone–methanol (7 : 2 : 1 v/v/v) as developer] to yield three fractions at R_F 0.38 (800 mg), 0.27 (340 mg), and 0.19 (230 mg), as well as some unchanged (−)-fisetinidol.

Fraction 1–*the biflavanoids* (2R,3S,4R)-3-*acetoxy*-4-[(2R,3S)-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-6-*yl*]-3′,4′,7-*trimethoxyflavan and its* (2R,3S,4S)-isomer. The R_F 0.38 fraction (250 mg), after methylation with diazomethane and p.l.c. separation with benzene–acetone (8 : 2 v/v), gave two bands at R_F 0.25 and 0.22. These were acetylated, and subsequent p.l.c. separation of the acetates [1,2-dichloroethane–acetone (9 : 1 v/v) as developer] gave the hexamethyl ether diacetates of the (4*S*)-(4) (22 mg) and 4(*R*)-(3) (5 mg) bifisetinidols, respectively. Their ^{1}H n.m.r., c.d., and mass spectra were identical with those previously obtained from the same condensation but under different conditions.[8]

Fraction 2—*the triflavanoid* (2R,3S,4R)-3[*acetoxy*-6-[(2R,-3S,4S)-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-4-*yl*]-4-[(2R,3S)-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-6-*yl*]-3′,4′,7-*trimethoxyflavan* (6). Methylation of the R_F 0.27 fraction with diazomethane, followed by p.l.c. of the product [1,2-dichloroethane–acetone (8 : 2 v/v) as developer], gave the nonamethyl ether of compound (5), R_F 0.31. Subsequent acetylation, followed by p.l.c. [benzene–acetone (9 : 1 v/v)] gave the *nonamethyl ether triacetate* (6), R_F 0.40, as a solid (54 mg) (Found: C, 67.2; H, 5.9. $C_{60}H_{62}O_{18}$ requires C, 67.3; H, 5.8%); δ [500 MHz; $(CD_3)_2SO$; 90 °C] 7.023 [d, *J* 2.0 Hz, 2-H(E)-ring], 6.985 [dd, *J* 2.0 and 8.0 Hz, 6-H(E)], 6.954 [d, *J* 2.0 Hz, 2-H(B)], 6.957 [d, *J* 8.5 Hz, 5-H(B)], 6.949 [d, *J* 8.0 Hz, 5-H(H)], 6.922 [d, *J* 8.0 Hz, 5-H(E)], 6.890 [d, *J* 2.0 Hz, 2-H(H)], 6.889 [dd, *J* 2.0 and 8.0 Hz, 6-H(H)], 6.856 [dd, *J* 2.0 and 8.5 Hz, 6-H(B)], 6.614br s, 5-H(G)], 6.528 [s, 8-H(D)], 6.478 [d, *J* 8.5 Hz 5-H(A)], 6.460 [d, *J* 2.0 Hz, 8-H (A)], 6.390 [s, 8-H(G)], 6.336 [dd, *J* 2.0 and 8.5 Hz, 6-H(A)], 6.262br [s, 5-H(D)], 5.534 [t, $J_{2,3} = J_{3,4} = 9.5$ Hz, 3-H(F)], 5.399 [dd, $J_{2,3}$ 6.0, $J_{3,4}$ 4.5 Hz, 3-H(C)], 5.163 [m, 3-H(I)], 5.139 [d, $J_{2,3}$ 6.0 Hz, 2-H(C)], 5.105 [d, $J_{2,3}$ 9.3 Hz, 2-H (F)], 4.928 [d, $J_{2,3}$ 7.0 Hz, 2-H(I)], 4.540 [d, $J_{3,4}$ 4.5 Hz, 4-H(C)], 4.526br [d, $J_{3,4}$ 9.5 Hz, 4-H(F)], 3.787, 3.772 3.750, 3.738, 3.724, 3.710, and 3.645 (integrals 1:3:1:1:1:1:1) (7 × s, 9 × OMe), 2.840 [dd, $J_{3,4eq}$ 5.5, $J_{4ax,4eq}$ 16.0 Hz, 4-H_{eq}(I)], 2.682 [dd, $J_{3,4ax}$ 8.0, $J_{4ax,4eq}$ 16.0 Hz, 4-H_{ax}(I)], 1.881 [s, 3-OAc(C)], 1.745 [s, 3-OAc(F)], and 1.620 [s, 3-OAc(I)]; *m/z* 1 070 (M^+), 1 010 [$(M - 60)^+$, 78%], 980 [$M - 90)^+$, 25], 979 [$(M - 91)^+$, 29], 951 [$(M - 119)^+$, 8.4], 919 [$(M - 151)^+$, 8.5], 891 [$(M - 179)^+$, 2.6], 817 (33), 803 (17.4), 758 (16.3), 757 (27), 716 (34), 715 (3.9), 697 (6.9), 653 (21), 595 (6.2), 504 (3.8), 475 (5.0), 417 (4.4), 297 (16.8), 222 (7.1), 180 (97), and 151 (100); c.d.; see Figure 3.

Fraction 3—*the tetraflavanoid* (2R,3S,4R)-3-*acetoxy*-8-[(2R,-3S,4R)-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-4-*yl*-6-[(2R,3S,4S)-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-4-*yl*]-4-[(2R,3S)-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-6-*yl*]-3′,4′,7-*trimethoxyflavan* (8). The R_F 0.19 fraction (230 mg) gave the dodecamethyl ether as a single, prominent fraction, R_F 0.21, after methylation with diazomethane and purification by p.l.c. [1,2-dichloroethane–acetone (7 : 3 v/v)]. Acetylation of the methyl ether and purification [p.l.c.; benzene–acetone (9 : 1 v/v] gave the *dodecamethyl ether tetra-acetate* as a pale, buff solid (19 mg) (Found: C, 67.1; H, 5.8. $C_{80}H_{82}O_{24}$ requires C, 67.3; H, 5.8%); δ[500 MHz; $(CD_3)_2SO$; 90 °C] 6.992 [d, *J* 8.3 Hz, 5-H(B)], 6.954 [d, *J* 2.0 Hz, 2-H(H)], 6.926 [d, *J* 8.3 Hz, 5-H(H)], 6.897 [d, *J* 2.0 Hz, 2-H(B)], 6.870 [dd, *J* 2.0 and 8.3 Hz, 6-H(B)], 6.853 [dd, *J* 2.0 and 8.0 Hz, 6-H(H)], 6.800 [d, *J* 8.3 Hz, 5-H(K)], 6.767 [d, *J* 8.3 Hz, 5-H(E)], 6.729 [dd, *J* 1.5 and 8.5 Hz, 5-H(J)], 6.725 [dd, *J* 2.0 and 8.0 Hz, 6-H(K)], 6.638br [s, 5-H(G)], 6.631 [d, *J* 2.0 Hz, 2-H(K)], 6.571 [d, *J* 2.5 Hz, 2-H(E)], 6.561 [dd, *J* 2.5 and 8.5 Hz, 6-H(J)], 6.536 [d, *J* 2.5 Hz, 8-H(A)], 6.488 [dd, *J* 2.0 and 8.0 Hz, 6-H(E)], 6.451 [d, *J* 8.5 Hz, 5-H(A)], 6.418br [s, *J ca.* 1.0 Hz, 5-H(D)], 6.410 [d, *J* 2.5 Hz, 8-H(J)], 6.406 [s, 8-H(G)], 6.351 [dd, *J* 2.3 and 8.5 Hz, 6-H(E)], 6.083 [t, $J_{2,3} = J_{3,4} = 10.0$ Hz, 3-H(L)], 5.429 [t, $J_{2,3} = J_{3,4} = 4.0$ Hz, 3-H-(C)], 5.313 [d, $J_{2,3}$ 4.0 Hz, 2-H(C)], 5.177 [m, 3-H(I)], 5.142 [t, $J_{2,3} = J_{3,4} = 9.0$ Hz, 3-H(F)], 5.000 [d, $J_{2,3}$ 9.8 Hz, 2-H(L)], 4.978 [d, $J_{2,3}$ 7.2 Hz, 2-H(F)], 4.896 [d, $J_{2,3}$ 9.3 Hz, 2-H(I)], 4.725 [sec. split d, *J* 10.2 and 1.0 Hz, 4-H(L)], 4.420 [d, $J_{3,4}$ 4.0 Hz, 4-H(C)], 4.277 [d, $J_{3,4}$ 9.0 Hz, 4-H(F)], 3.872, 3.860, 3.845, 3.825, 3.820, 3.785, 2.780, 3.758, 3.710, 3.630, 3.620, and 3.545 (12 × s, 12 × OMe), 2.860 [dd $J_{3,4eq}$ 5.5, $J_{4ax,4eq}$ 16.0 Hz, 4-H_{eq}(I)], 2.730 [dd, $J_{3,4ax}$ 8.0, $J_{4ax,4eq}$ 16.0 Hz, 4-H_{ax}-(I)], and 1.892, 1.840, 1.632, and 1.585 (4 × s, 4 × 3-OAc); *m/z* 1 427.2 ± 0.6 (M^+); c.d.; see Figure 3.

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