Condensed Tannins: Direct Synthesis, Structure, and Absolute Configuration of Four Biflavonoids from Black Wattle Bark ('Mimosa') Extract

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Summary Optically pure (+)-2,3-*trans*-3,4-*trans*-flavan-3,3′,4,4′,7-pentaol [(+)-mollisacacidin] and (+)-2,3-*trans*-flavan-3,3′,4′,5,7-pentaol [(+)-catechin] condense rapidly in 0·1 M HCl to give good yields of 4,8-linked diastereoisomeric biflavonoid proanthocyanidins of all-*trans* and 2,3-*trans*-3,4-*cis*-2,3-*trans* configurations, and also the 4,6-linked all-*trans* isomer; c.d. comparison thus enables confirmation of the absolute configurations of three known 4,8-linked all-*trans* biflavonoids from black wattle bark as 2*R*,3*S*,4*S*–2*R*,3*S*, and also identification of a fourth as 2*R*,3*S*,4*R*–2*R*,3*S*.

The relative configurations of derivatives of six biflavonoid proanthocyanidins from the black wattle (*Acacia mearnsii*) comprised of both flavan-3-ol and flavan-3,4-diol 'terminal' (lower) units were determined for the first time more than 10 years ago,[1,2] leaving their absolute configurations and point of linkage in the former group[1] open to doubt. With the latter issue now open to diagnostic interpretation from chemical shifts of 6- and 8-protons,[3] the absolute configuration of the all-*trans* (−)-fisetinidol–(+)-catechin (**1**), (−)-robinetinidol–(+)-catechin (**2**), and (−)-robinetinidol–(+)-gallocatechin (**3**) units required confirmation.

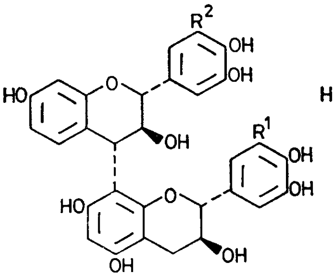
Thus, treatment of (2*R*,3*S*,4*R*)-flavan-3,3′,4,4′,7-pentaol [(+)-mollisacacidin] (**6**) and (2*R*,3*S*)-flavan-3,3′,4′,5,7-pentaol [(+)-catechin] (**7**) with 0·1 M HCl at ambient temperatures for 2 h gave a mixture of three biflavonoids (**1**), (**4**), and (**5**) in 28, 16·5, and 5·5% yield, respectively. The same reaction also proceeds, albeit more slowly, in the presence of organic acids. Among these the predominant 4,8-linked all-*trans* isomer (**1**) could be separated by t.l.c. (benzene–acetone, 1 : 1 v/v), R_F 0·33. The remainder (**4**) and (**5**) migrated as a mixture (R_F 0·42) separable by paper chromatography.

TABLE. Chemical shifts and coupling constants (in parentheses; Hz) of heterocyclic ring protons of 4-aryl- and 4-flavanyl-3′,4′,7-trimethoxy-2,3-*trans*-flavan-3-ol derivatives.[a]

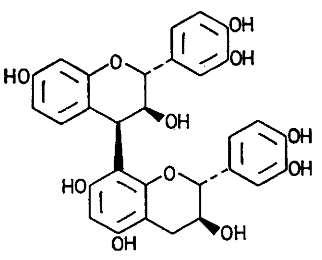
	Chemical shift (τ)						
	C-Ring				F-Ring		
	2-H	3-H	4-H	3-OAc	2-H	3-H	3-OAc
4-Substituent: 2,4-Dimethoxyaryl							
2,3-*t*-3,4-*t*	5·00(d) ($J_{2,3}$ 10·0)	4·23(t) (Σ*J*'s 19·0)	5·38(d) ($J_{3,4}$ 9·0)	8·42	—	—	—
2,3-*t*-3,4-*c*	4·87(d;8·0)	4·47(dd; 13·0)	5·18(d;5·0)	8·24	—	—	—
2,4,6-Trimethoxyaryl							
2,3-*t*-3,4-*t*	5·10(d; 10·0)	3·98(t; 19·8)	5·15(d; 9·8)	8·43	—	—	—
2,3-*t*-3,4-*c*[b]	5·06(d; 10·0)	4·55(dd; 16·3)	4·96(d; 6·3)	8·32	—	—	—
3′,4′,5,7-Tetra-*O*-methyl-(+)-catechin (4-flavanyl substituent) 4,8-Coupled:							
2,3-*t*-3,4-*t*	5·22(d; 10·0)	3·97(t; 19·0)	5·23(d; 9·0)	8·44	*ca.* 5·22	*ca.* 5·22	8·16
2,3-*t*-3,4-*c*	4·74(d; 9·0)	4·46(dd; 15·5)	5·10(d; 6·5)	8·29	5·93(d) ($J_{2,3}$ 8·5)	4·94(m)	8·20
4,6-Coupled:							
2,3-*t*-3,4-*t*	5·33(d; 10·0)	3·92(dd; 18·8)	5·11(d; 8·8)	8·39	5·09(d; 7·5)	4·72(m)	8·10

[a] *t* = *trans*, *c* = *cis*. [b] Synthetic racemate.

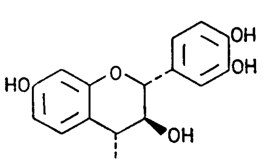
The compounds were identified by methylation with diazomethane and the heptamethyl ethers acetylated to give their diacetates. 4,8-Linked derivatives of the diastereoisomers (**1**) and (**4**) were readily distinguished[3] from the 4,6-linked geometrical isomer (**5**) by the chemical shifts of the high-field singlet in the aromatic region (τ 3·85, 3·87, and 3·74, respectively) and their relative chemical shifts [Δτ (6-H, 8-H) 0·11] in the latter instance. Their relative stereochemistry was deduced by comparing their coupling constants with those of synthetic 4-arylflavan-3-ol analogues[4] (Table). The absolute configurations of the compounds at C-4 are accordingly self-evident. Chemical shifts of C- and F-ring heterocyclic protons were also in close agreement (Table).



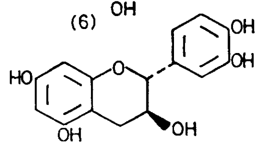
(1) R¹ = R² = H
(2) R¹ = H, R² = OH
(3) R¹ = R² = OH



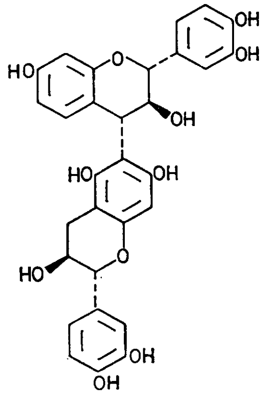
(4)



(6)



(7)



(5)

The above condensation led to re-examination of the natural biflavonoids (A), (B), and (D) [(**1**), (**2**), and (**3**)] which are major components of the commercially important black wattle bark ('Mimosa') extract.[1] The fraction A of the extract[1] yielded two components, (**1**) and (**4**), with heptamethylether diacetates identical to those of the synthetic products by n.m.r. spectroscopy, m.s., and c.d.; differences in the Cotton effects at *ca.* 220 nm are significant

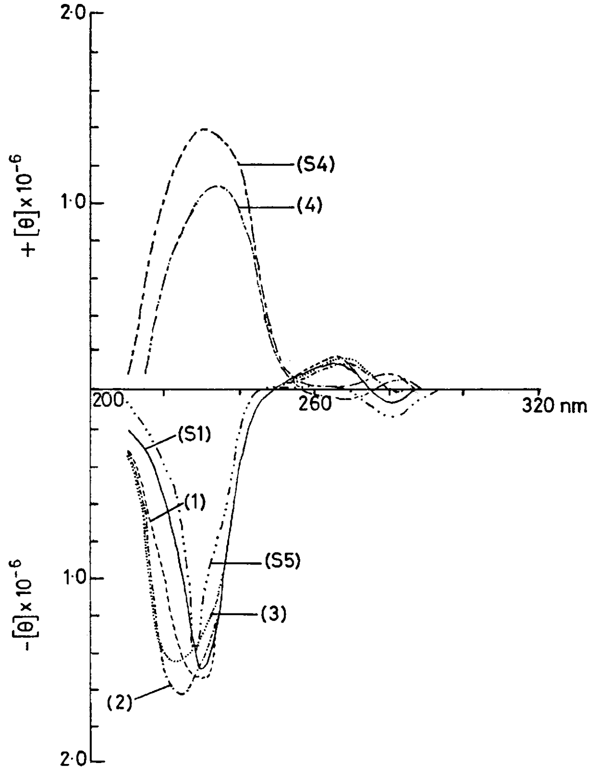


FIGURE. C.d spectra of methyl ether diacetates of natural and synthetic biflavonoids (**1**)—(**5**) (synthetic compounds are designated by the prefix S).

and highly diagnostic[4] (*cf.* Figure). The natural 4,8-linked 2,3-*trans*-3,4-*cis*-2,3-*trans*-biflavonoid (**4**), previously overlooked, represents the major component in fraction A of the extract, whereas the all-*trans*-diastereoisomer (**1**) predominates amongst the products of synthesis. The 4,6-linked structural isomer (**5**) was not observed in fraction A of the extract. The related 4,8-linked (−)-robinetinidol–(+)-catechin (**2**, component B) and (−)-robinetinidol–(+)-gallocatechin (**3**, component D) (6-H singlets at τ 3·87 and 3·83) were not accompanied by 3,4-*cis*-diastereoisomers, and both possess the same 2*R*,3*S*,4*S*–2*R*,3*S* configuration as (**1**) (*cf.* c.d. curves of their methyl ether diacetates in Figure).

The above supports the long-held hypothesis[1,5] that flavan-3,4-diols, *via* their 4-carbocations, and nucleophilic flavan-3-ols, represent the direct precursors of biflavonoids and of related polyflavonoid tannins, all of which typically coexist in natural extracts.

Financial assistance by the Wattle Bark Industry of South Africa Marketing Committee, the Leather Industries Research Institute, Grahamstown, the Sentrale Navorsingsfonds of this University, and the South African Council of Scientific and Industrial Research is acknowledged.

(*Received*, 19*th December* 1977; *Com.* 1283.)

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