Condensed Tannins: Determination of the Point of Linkage in 'Terminal' (+)-Catechin Units and Degradative Bromination of 4-Flavanylflavan-3,4-diols

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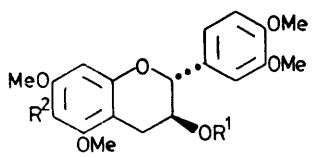
Summary Data for a variety of 8- and 6-substituted 3′,4′,5,7-tetra-*O*-methyl-(+)-catechins show that the chemical shifts for the residual A-ring protons at C-6 and C-8 fall into narrow ranges without overlap [τ ($CDCl_3$) 3·76—3·93; 3·51—3·70, respectively]; degradative bromination of novel flavanyl[6,4]- and -[8,4]flavan-3,4-diols, in which bromine serves as 'marker' for the point of attachment of the 'lower' flavanyl unit, also provides a method for determining the absolute configurations of both constituent flavonoids at C-2 and C-3.

ONE of the unresolved problems of condensed tannin chemistry is that of differentiating between the alternatives of C-4—C-6″ and C-4—C-8″ links, where the 'lower' terminal unit, as typified amongst others by (+)-catechin, possesses a phloroglucinol A-ring.[1] The unambiguous synthesis of both 6- (**1b**) and 8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechins (**2b**) was accordingly undertaken in order to obtain specific ^{1}H-n.m.r. data. The 8-bromo-derivative was obtained as previously indicated,[2] while the 6-bromo-compound was synthesised by partial debromination of 6,8-dibromo-3′,4′,5,7-tetra-*O*-methyl-3-*O*-benzyl-(+)-catechin with n-butyl-lithium. This reaction sequence starting with (+)-catechin represents the first unambiguous synthesis of a 6-substituted (+)-catechin derivative.[2,3] Thus the 6- and 8-bromo-3′,4′,5,7-tetra-*O*-

methyl-3-*O*-benzyl-(+)-catechins were used for the synthesis of the 6- and 8-substituted compounds (**1a—k** and **2a—k**). The carboxy and hydroxy analogues were obtained by the action of CO_2 and O_2, respectively, on the 6- and 8-lithio derivatives, and the remainder by debenzylation (hydrogenation over Pd/C), acetylation, and methylation (diazomethane) in the usual way.[3]

Chemical shift data for these compounds show that the residual A-ring protons at C-6 and C-8 fall into narrow ranges which are devoid of overlap [τ ($CDCl_3$) 3·78—3·90 and 3·53—3·68, respectively]. Comparative values for a variety (20) of 4,6- and 4,8- coupled biflavonoid derivatives comprised mainly of 4-flavanylflavan-3,4-diol and 4-flavanylflavan derivatives, cover similar ranges [τ ($CDCl_3$): 6-H, 3·76—3·93; 8-H, 3·51—3·70; $\Delta\tau$ (6-H, 8-H) 0·10—0·27]. These parameters are useful for determining the points of linkage of 'terminal' (+)-catechin units in biflavonoids,[4] and possibly also in condensed tannins.

Conditions for the first synthesis of 4-flavanyl-2,3-*trans*-flavan-3,4-diols were essentially those employed by Weinges *et al.*[5] for the preparation of biflavonoids, involving in this instance Grignard-type addition reactions between 6- and 8-lithio-3′,4′,5,7-tetra-*O*-methyl-3-*O*-benzyl-(+)-catechin on



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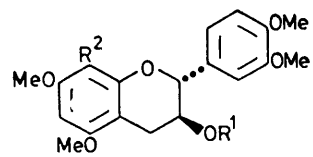


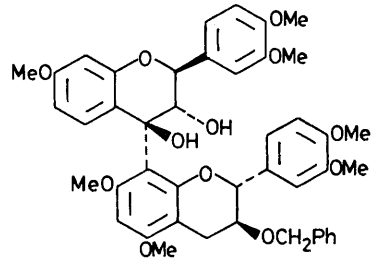
(2)

τ (8-H)		R^1	R^2	τ (6-H)
3·59	**a**	$PhCH_2$	Br	3·78
3·60	**b**	H	Br	3·79
3·53	**c**	Ac	Br	3·80
3·68	**d**	$PhCH_2$	OH	3·82
3·68	**e**	H	OH	3·78
3·66	**f**	$PhCH_2$	OAc	3·85
3·64	**g**	H	OAc	3·82
3·60	**h**	Ac	OAc	3·81
3·68	**i**	$PhCH_2$	CO_2Me	3·90
3·68	**j**	H	CO_2Me	3·90
3·68	**k**	Ac	CO_2Me	3·89

the one hand, and 2,3-*trans*-dihydroflavonol derivatives such as 3′,4′,5,7-tetra-*O*-methyl-(+)-taxifolin and 3′,4′,7-tri-*O*-methyl-(±)-fustin on the other.

In order to illustrate the synthetic, degradative, and stereochemical implications of this work, only the addition of 6- and 8-lithio-3′,4′,5,7-tetra-*O*-methyl-3-*O*-benzyl-(+)-catechin (2*R*;3*S*), to 3′,4′,7-tri-*O*-methyl-(±)-fustin (2*R*,3*R* and 2*S*,3*S*) is discussed, with structural indication [(**3**)—(**6**)] limited only to the expected products of 4,8″-coupling.

All four of the expected diol products were obtained for each of the C-4—C-6″ and C-4—C-8″ coupling reactions, 3,4-*trans*-diols from C-4—C-8″ coupling being separable, for example, by t.l.c. in dichloromethane–acetone (9:1 v/v) [(**3**), (**4**); R_F 0·44, 0·38], while the 3,4-*cis*-diols [(**5**), (**6**); R_F 0·35] required separation as their 3-*O*-acetyl derivatives in dichloromethane–ethyl acetate (9:1 v/v) [(**3**), R_F 0·23; (**4**), 0·21; (**5**), 0·38; (**6**), 0·49]. The 3,4-*trans*- and 3,4-*cis* allocations were based on the observation of rapid conversion of low R_F 3,4-*trans*-diols in dry acetone with anhydrous copper(II) sulphate into higher R_F 3,4-*cis*-isomers, which were then slowly converted by *trans*-elimination of the elements of water into flav-3-en-3-ols,[3] whereas the 3,4-*cis*-diols went directly to the flav-3-en-3-ols. The four diastereoisomers (**3**)—(**6**) were isolated in the ratio *ca.* 8:8:1:1.



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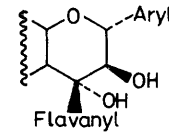

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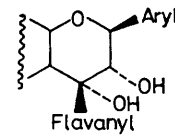

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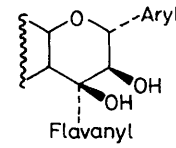
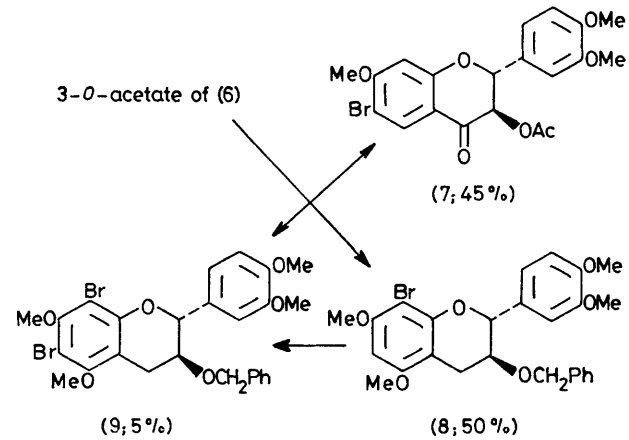


(6)

Selective degradation of these biflavonoids was achieved by differential bromination. The 3-*O*-acetate of the 3,4-*trans*-diol (**4**) was dissolved in methanol, treated with a slight excess of bromine at room temperature for 2 min, and the products were isolated by t.l.c. Instead of the expected brominated dimer, three monomeric products: 6,8-dibromo- (**9**) and 8-bromo-3′,4′,5,7-tetra-*O*-methyl-3-*O*-benzyl-(+)-catechin (**8**) and 6-bromo-3′,4′,7-tri-*O*-methyl-3-*O*-acetyl-(+)-fustin (**7**) were isolated in exceptionally high yields in the proportions indicated, and identified by t.l.c., n.m.r. spectroscopy, c.d., and m.s. in comparison with brominated reference compounds.

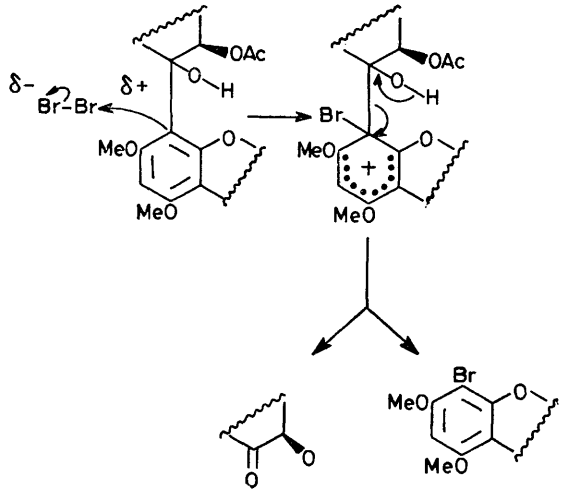


The isolation of products (**7**) and (**8**) is significant since it shows that bromination proceeds with fission of the inter-flavonoid bond, bromine entering that position on the A-ring of the 'lower' unit to which the 'upper' flavonoid unit was attached. Some dibromination of the 'lower' unit also takes place. However, while only a small quantity of the

dibromo-derivative (**9**) was obtained, (**7**) and (**8**) were formed almost quantitatively.

Similarly the 3-*O*-acetate of the diastereoisomeric 3,4-*trans*-diol (**3**) gave the 6,8-dibromo- (**9**) and 8-bromo-(+)-catechin derivatives (**8**) (5 and 50%) and the enantiomer of (**7**), 6-bromo-3′,4′,7-tri-*O*-methyl-3-*O*-acetyl-(−)-fustin (45%).

The mechanism in the Scheme is advanced for the products obtained, the primary driving force of the reaction being electrophilic attack by Br^+ at the sp^2-carbon involved in linkage between flavonoid units.



SCHEME

Formation of 6-bromo-3′,4′,5,7-tetra-*O*-methyl-3-*O*-benzyl-(+)-catechin (20% yield) during bromination of the C-4—C-6″ linked analogue of (**3**) is highly significant, since it supports the proposed mechanism especially with respect to the position of bromination on the A-ring of the 'lower' flavonoid unit. The corresponding dibromo derivative (**9**) is formed in higher (20%) yield, probably reflecting lower steric hindrance at the 8-position of the 6-bromo-(+)-catechin derivative than at the 6-position of the 8-bromo analogue. Likewise isolation of the (−)-fustin derivative [enantiomer of (**7**), 50%] establishes the absolute stereochemistry at C-2 and C-3 of the 'upper' unit of the biflavonoid. Similar results were obtained for the 4,6-linked analogue of (**4**), as well as for synthetic 4-flavanyl-flavan-3,4-diol analogues derived from tetra-*O*-methyl-(+)-taxifolin.

The foregoing indicates that degradative bromination of biflavonoids could possibly be developed into an elegant and powerful procedure for determining both the position of linkage between two constituent flavonoids as well as their absolute stereochemistry, in a single experiment. This is needed especially in those instances where interflavonoid bonds between resorcinol–resorcinol and resorcinol–phloroglucinol type flavonoid units are resistant to degradation by thiols.[6]

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