Synthesis of Condensed Tannins. Part 12. Direct Access to [4,6]- and [4,8]-all-2,3-*cis*-Procyanidin Derivatives from (−)-Epicatechin: Assessment of Bonding Positions in Oligomeric Analogues from *Crataegus oxyacantha* L.

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Synthesis of methyl ether acetates of [4,6]- and [4,8]-all-2,3-*cis*-procyanidin biflavanoids is effected by oxidative functionalization of (−)-epicatechin tetramethyl ether with lead tetra-acetate, and condensation of the resultant 2,3-*cis*-flavan-3,4-diol derivative with (−)-epicatechin. Their natural phenolic counterparts in *Crataegus oxyacantha* are associated with exclusively [4,8]-linked 2,3-*cis*-tri- and tetra-flavanoid procyanidin analogues. Bonding positions on each of the phenolic nuclei are established by chemical shift differences ($\Delta\delta_{6\text{-H},8\text{-H}}$) based on 6- and 8-bromo-(−)-epicatechin methyl ether acetates as reference compounds, supported by associated ^{1}H n.m.r. shift parameters.

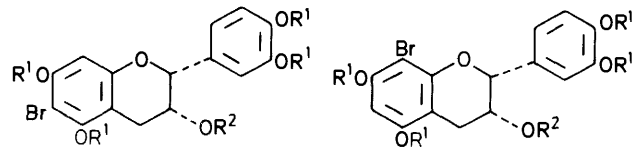
The exclusive 2,3-*cis*-configuration of constituent [(−)-epicatechin] units representing one of the variants (designated B_2) in a series of then presumed [4,8]-linked procyanidin biflavanoids isolated from the fruit of *Crataegus oxyacantha* L. (≡ *C. monogyna* Jacq.) was established initially by Weinges and co-workers.[1,2] Other analogues of this type including the [4,6]-isomer (B_5) were subsequently isolated by Haslam and co-workers,[3-5] the relative configuration of their 'upper' units being readily defined also as 3,4-*trans* by ^{13}C n.m.r. spectroscopy. Such studies were extended to higher oligomers[6-8] (*e.g.* all-2,3-*cis* triflavanoid C_1), but in no instance at this level was unequivocal spectrometric distinction generally available between the alternatives of interflavanoid bonding to either the C-6 or C-8 positions in the phloroglucinol ring systems of each of the constituent units. This was due in part to spectral complexity resulting from the high activation energy ($\Delta G_{rot.}^{\ddagger}$) required to overcome the effects of rotational isomerism in the free phenols and particularly in their acetates, hitherto widely used for ^{13}C and ^{1}H n.m.r. spectroscopy of procyanidin oligomers, thus necessitating assignment of resonances characteristic of major rotational isomers (*e.g. cf.* ref. 7). However, contributory factors were the lack of suitable 6- and 8-substituted (−)-epicatechins as reference compounds (*cf.* ref. 9) and absence of direct synthetic access (*cf.* ref. 4) to bi- and tri-flavanoid procyanidins with 2,3-*cis*-stereochemistry, and hence simple direct assessment of their absolute configurations. These problems are partly overcome by the selective use of oligomeric methyl ether acetates; by synthesis of the corresponding derivatives of 6- and 8-bromo-(−)-epicatechins; and by the limited application of Brown's[10,11] oxidative 4-functionalization of (−)-epicatechin tetramethyl ether to synthesis of 2,3-*cis*-procyanidins.

In order to place the absolute chemical shift parameters of 6-H and 8-H in (−)-epicatechin units beyond doubt, and also to determine the relative merits of shift differences ($\Delta\delta_{6\text{-H},8\text{-H}}$) of residual aromatic protons in the peracetate and methyl ether acetate derivatives, 6- and 8-bromo-(−)-epicatechin and (+)-catechin were synthesised by direct bromination of the parent phenols with pyridinium hydrobromide–perbromide using a simplified variation of Hemingway's[12] procedure. The 6- and 8-bromo derivatives were isolated in the free phenolic form in 14 and 16% and 17 and 20% yields respectively under optimised conditions in addition to 6,8-dibromo derivatives (16 and 7% respectively). Direct bromination thus obviates the need for selective debromination of 6,8-dibromo tetramethyl ether derivatives.[9] These 6- and 8-bromo derivatives [(1), (4), (7), and (10)] were converted into their respective peracetates [(2), (5), (8), and (11)] and tetramethyl ether acetates [(3), (6), (9), and (12) respectively].

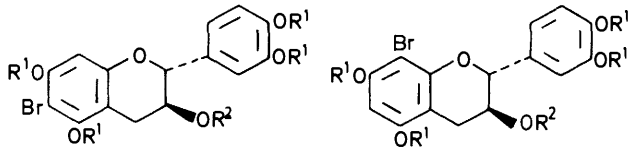
Table 1. Chemical shifts of 2-H, 3-H, 6-H, and 8-H of tetramethyl ether acetates and penta-acetates of (−)-epicatechin and (+)-catechin in $CDCl_3$

	δ			
Derivatives	2-H	3-H	6-H	8-H
(−)-Epicatechin				
Me_4Ac				
6,8-Br_2	5.17	5.53	—	—
6-Br (3)	5.06	5.45	—	6.45
8-Br (6)	5.12	5.53	6.19	—
Ac_5				
6,8-Br_2	5.20	5.43	—	—
6-Br (2)	5.10	5.39	—	6.77
8-Br (5)	5.20	5.46	6.68	—
(+)-Catechin				
Me_4Ac				
6,8-Br_2	5.34	5.46	—	—
6-Br (9)	5.06	5.37	—	6.41
8-Br (12)	5.32	5.45	6.17	—
Ac_5				
6,8-Br_2	5.27	5.28	—	—
6-Br (8)	5.13	5.25	—	6.75
8-Br (11)	5.25	5.27	6.69	—

The desired distinction between 6- and 8-bromo-(−)-epicatechin tetramethyl ether acetates [(3) and (6) respectively] by *X*-ray methods (*cf.* ref. 13) was unfortunately not possible due to their micro-crystallinity. However, comparison of their ^{1}H n.m.r. spectra in $CDCl_3$ (Table 1) showed that the effect of 8-substitution in both mono- and di-brominated derivatives relative to 6-substitution in catechins causes con-



(1) $R^1 = R^2 = H$ (4)
(2) $R^1 = R^2 = Ac$ (5)
(3) $R^1 = Me, R^2 = Ac$ (6)



(7) $R^1 = R^2 = H$ (10)
(8) $R^1 = R^2 = Ac$ (11)
(9) $R^1 = Me, R^2 = Ac$ (12)

sistent deshielding of 2-H. On this basis the shift of residual A-ring protons in monobrominated derivatives was also consistent, 8-H always resonating to lower field than 6-H as previously established for a variety of tetramethyl ether derivatives of (+)-catechin. With the identity of the 6- and 8-bromo-(−)-epicatechin methyl ether acetates and peracetates established with reasonable certainty, the relative shift differences ($\Delta\delta_{6\text{-H}.\,8\text{-H}}$) for the acetates of (−)-epicatechin and (+)-catechin [(2), (5): 0.09, 0.07 respectively] were observed to be relatively small compared with those of their methyl ether acetates [(3), (6): 0.26, 0.25 respectively]; acetylation of aromatic functionality therefore narrows these parameters. The small margin of difference for the acetates based on absolute shift values endorses our earlier selection of methyl ether acetate derivatives [9] for distinguishing between points of aromatic bonding in oligomers, apart from other advantages discussed below.

Direct synthesis of the corresponding derivatives [(14), (16) respectively] of the [4,6]- and [4,8]-2,3-*cis*-procyanidins (B_5 and B_2) was available by convenient 4-functionalization of (−)-epicatechin tetramethyl ether with lead tetra-acetate using the method of Brown and co-workers.[11] However, in our hands this led directly to the 2,3-*cis*-flavan-3,4-*trans*-diol in *ca.* 20% yield (33% on starting material consumed) instead of the expected 4-acetate, without the necessity for an intermediate hydrolytic step. Condensation of the synthetic diol with a 2 : 1 molar excess of (−)-epicatechin gave the desired [4,6]- and [4,8]-procyanidin octamethyl ether diacetates [(14), (16)] in significant yields (10.3, 8.4% respectively on the basis of flavan-3,4-diol consumed) after methylation and acetylation of the intermediate products (13), (15). Initial distinction between these derivatives was on the basis of chemical shifts [(14), $\delta_{8\text{-H}}$ 6.38; (16) $\delta_{6\text{-H}}$ 6.20] in $CDCl_3$ at 100 °C (*cf.* Table 1).

The lack of regioselectivity in this condensation [(−)-2,3-*cis*-leucocyanidin tetramethyl ether + (−)-epicatechin], and the progressively increasing regioselectivity in the synthesis of [4,6]- and [4,8]-profisetinidins [*ex.* (+)-mollisacacidin + (+)-catechin] (*ca.* 1 : 6) under similar conditions,* and of [4,6]- and [4,8]-2,3-*trans*-procyanidins [ex. (+)-2,3-*trans*-leucocyanidin + (+)-catechin] (*ca.* 1 : 10) at pH 5 [15] in favour of the sterically less hindered 8-position on (+)-catechin as common nucleophile, presumably reflects amongst other factors also the increasing stability of the electrophilic intermediates [(22) ⟶ (23) ⟶ (24)] generated from the respective flavan-3,4-diols. Once formed, the reaction of the least stable of these [(22), due to methylation], assisted by neighbouring group participation, proceeds very rapidly with resultant lack of selectivity between the C-8 and C-6 positions on (−)-epicatechin. Conversely the carbenium ion (24) derived from the free phenolic (+)-leucocyanidin should form with exceptional rapidity due to its great stability, but having formed reacts more slowly for the same reason; hence its highly preferential attack at the sterically less hindered C-8 position. The stability of the free phenolic resorcinol analogue (23) should be intermediate between these extremes in line with its reduced degree of regioselectivity.

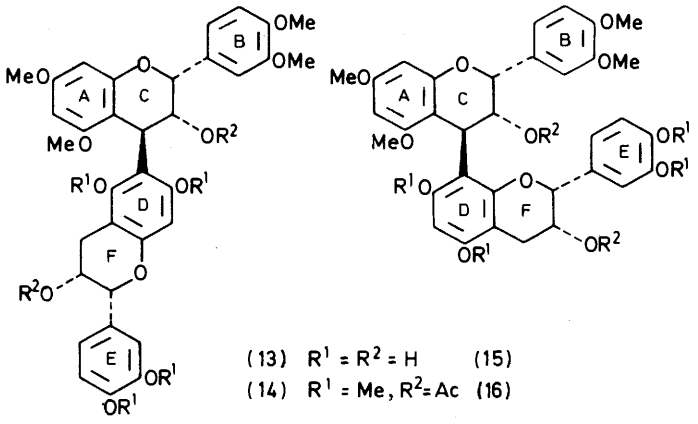
This hypothesis † accordingly rationalises the exceptional selectivity of the 4-carbenium ions [(24) and (21)] derived from free phenolic 2,3-*trans*- [15] and 2,3-*cis*-leucocyanidins for electrophilic substitution at C-8 of their flavan-3-ol analogues, (+)-catechin and (−)-epicatechin, as evinced by the relative natural abundance of the products and the relative proportions of biflavanoids obtained from synthesis. The same inference is applicable to the observed stereospecificity during condensations involving the 2,3-*trans*-carbenium ion (24) [15] which leads to procyanidin oligomers with 2,3-*trans*-3,4-*trans* configuration of individual units; attack by the nucleophile from the less hindered ' lower ' side of the carbenium ion (*cf.* refs. 15 and 16) presumably proceeding to the exclusion of the less favoured (mainly through 1,3-interaction with the *axial* 2-proton) approach from the ' upper ' side of the electrophile. Our previous proposal [15] in this regard of a predominantly S_N2 condensation mechanism under conditions (pH 5) approaching neutrality based on a thermodynamically more stable 2,3-*trans*-3,4-*cis*-leucocyanidin should be discarded in favour of the above, also since Porter and Foo [17] have recently found the unstable reduction product of (+)-taxifolin to be a (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-leucocyanidin.

The presence of the natural [4,6]- and [4,8]-bi-[(−)-epicatechin] biflavanoids B_5 and B_2 [(13) and (15) respectively] in the fruit of *Crataegus oxyacantha* L. (*cf.* ref. 3) was shown by the identity of their methyl ether acetates [(14) and (16) respectively; isolated in the ratio of 1 : 14], with their synthetic equivalents. They are accompanied in the same source by [4,8:4,8]-tri- (C_1) [3,7] and [4,8:4,8:4,8]-tetra-flavanoid oligomers [(17) and (19) respectively] which were isolated as methyl ether acetates in the proportions of 6.6 : 1.2 relative to those of the biflavanoid analogues. These compounds gave sharp ^1H n.m.r. spectra (*cf.* Figure 1) at 100 °C, which obviated the necessity of selecting shifts representative of ' predominant ' rotamers and a resultant arbitrary basis of comparison as, for example, in the case of procyanidin peracetates.[7] The sharply defined spectra also provide unequivocal proof of the optical purity of the products and hence the absence of diastereoisomers which could result from inversions (or racemization) at any stage during the course of synthesis.

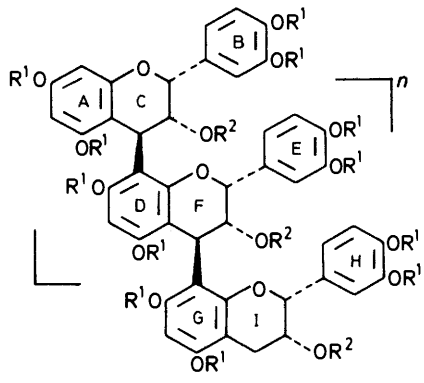
The heterocyclic regions of the ^1H n.m.r. spectra of these derivatives of 2,3-*cis*-3,4-*trans*-procyanidin oligomers are relatively poorly defined compared with those of their 2,3-*trans*-3,4-*trans* isomers (*cf.* Figure 1 and Figure 1, ref. 15), due to small couplings ($J_{2,3}$ *ca.* 1.6, $J_{3,4}$ *ca.* 2.3 Hz), secondary long-range coupling over four bonds (2-H, 4-H) or benzylic

* Refinement of isolation procedures used previously [14] has led to both pairs of 3,4-*trans* and 3,4-*cis* [4,6]- and [4,8]-profisetinidin diastereoisomers expected from the synthesis with regioselectivity in the proportions indicated.

† Designated as the ' selectivity-reactivity relationship ' in electrophilic aromatic substitution, *cf.* G. W. Klumpp, ' Reactivity in Organic Chemistry,' Wiley-Interscience, New York, 1982, pp. 219, 352.

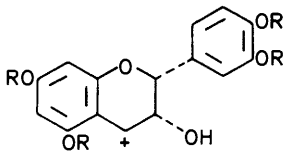


(13) $R^1 = R^2 = H$ (15)
(14) $R^1 = Me, R^2 = Ac$ (16)

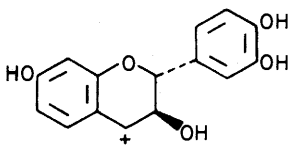


$n = 1$ $n = 2$

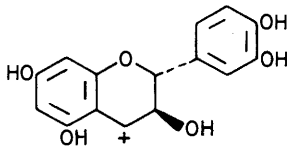
(17) $R^1 = R^2 = H$ (19)
(18) $R^1 = Me, R^2 = Ac$ (20)



(21) R = H
(22) R = Me



(23)



(24)

coupling (2-H) of doublets and multiplets, and their overlap. The spectra nevertheless provide useful ' fingerprints ' for identification of these ubiquitous compounds. Allocations are assisted by direct comparison of the high-field aromatic and especially heterocyclic resonances of the oligomers B_2, B_5, and C_1 and the all-[4,8]-linked tetraflavanoid, with those of (−)-2,3-*cis*-3,4-*trans*-4-(2,4,6-trihydroxyphenyl)-3,3′,4′,5,7-pentahydroxyflavan [18] as representative of an ' upper ' unit, and also by means of low-power decoupling (*cf.* Figure 1). Noteworthy is the consistent shielding of resonances, due to both 6-H and 8-H (A-ring) of the ' upper ' unit in the methyl ether acetates of [4,8]-bi- [(16), δ 5.83, 5.94 respectively], [4,8:4,8]-tri- [(18), δ 5.85, 6.02 respectively] and [4,8:4,8:4,8]-tetraflavanoid homologues (δ 5.76, 5.96 respectively) relative to those of the 4-arylflavan-3-ol (δ 6.12, 6.39 respectively) and [4,6]-isomer [(14), δ 6.06, 6.30 respectively] (*cf.* Figure 1 and Table 2). The suggested use of this shift effect, previously recorded by Hemingway and co-workers [7] for procyanidin peracetates, in differentiating between [4,8] and [4,6] isomers is mainly restricted to the ' upper ' terminal units of 2,3-*cis*-3,4-*trans* configuration, since it is much less obvious for their 2,3-*trans*-3,4-*trans* analogues (*cf.* Figure 1, ref. 15). Furthermore these shifts, which are thus linked to the stereochemistry at C-4 (quasi-*axial* orientation of the 4-flavanyl substituent), are considered attributable to shielding induced by the aromatic E-ring of the next 2,3-*cis*-3,4-*trans* ' lower ' unit, as judged from Dreiding models.

An associated phenomenon is the selective and pronounced broadening of 6-H (A-ring) doublets attributable to all [4,8]-linked ' upper ' terminal units of the methyl ether acetates of the bi- (16), tri- (18) and tetra-flavanoid (20) analogues (*cf.* Figure 1). From extensive spin-decoupling it was evident that, under the experimental conditions ($CDCl_3$, 100 °C), long-range benzylic coupling with 4-H (C) is to a very limited degree responsible for this effect, rather than the n.O.e. between these protons claimed by Outtrup and Schaumberg,[19] of which we found no evidence. The main cause of differential line-broadening is due to a phenomenon associated with temperature-dependent dynamic rotational isomerism, since resonances due to 6-H (A) of the [4,8]-procyanidin sharpen at 140 °C in $(CD_3)_2SO$ to the equivalent of those of its *meta*-coupled 8-H (A) counterpart, compared with broad absorptions exhibited only by the former at 100 °C in the same

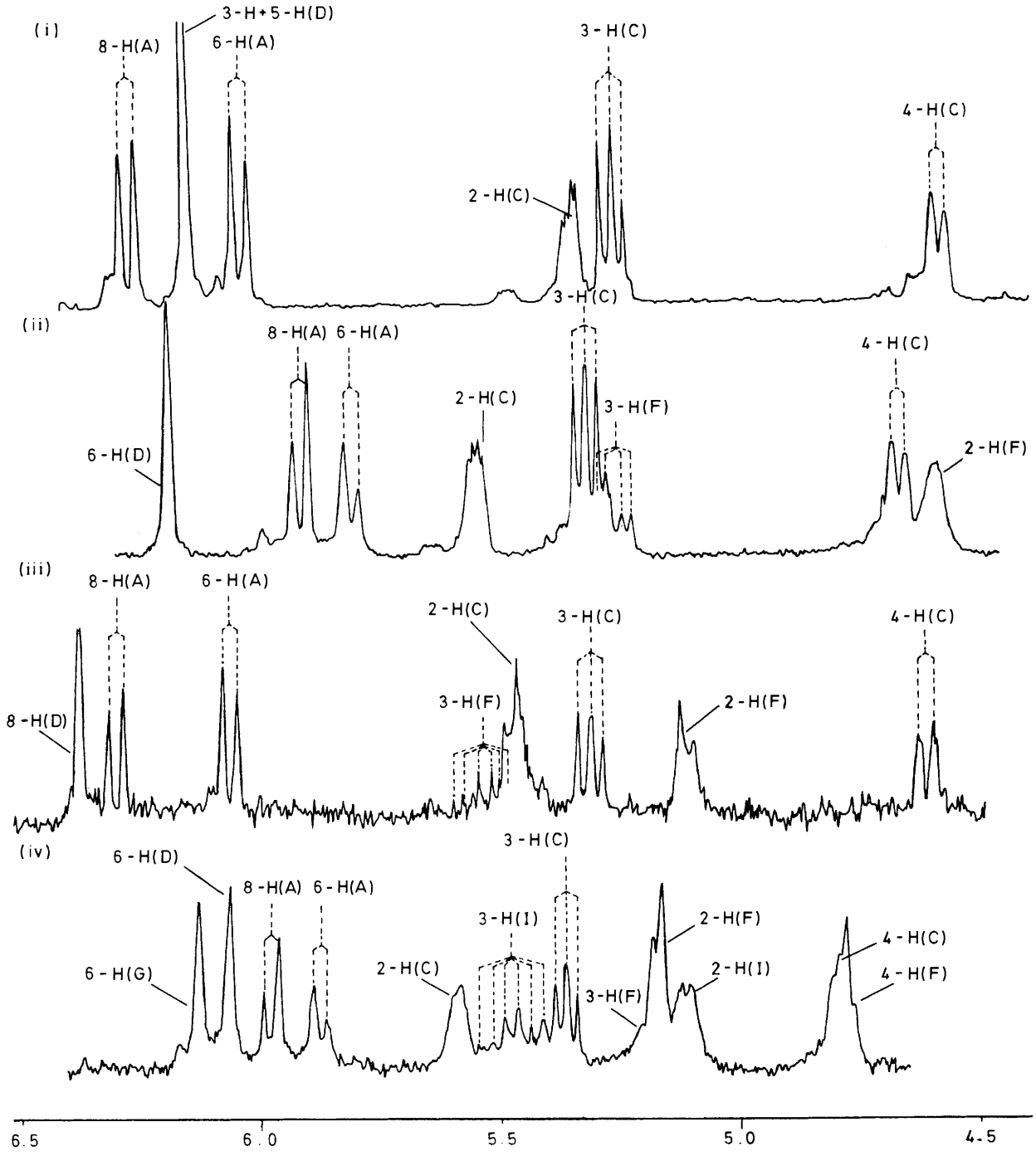


Figure 1. ^{1}H N.m.r. spectra of the methyl ether acetates of (i) 2,3-*cis*-3,4-*trans*-4-(2′,4′,6′-trihydroxyphenyl)-3,3′,4′,5,7-pentahydroxyflavan, and procyanidins (ii) B_2, (iii) B_5, and (iv) C_1 in $CDCl_3$ at 100 °C

solvent. The contrasting absence of line-broadening of 6-H (A) in the [4,6]-procyanidin derivative (14) and its 4-arylflavan-3-ol analogue at 100 °C (*cf.* Figure 1) is indicative of a lower activation energy for ' fast ' rotation about their interflavanoid bonds.* This behavioural difference, in conjunction with the above shielding phenomena, may be taken to confirm [4,8]-bonding of ' upper ' 2,3-*cis*-3,4-*trans* terminal units in oligomers under specific ($CDCl_3$, 100 °C) experimental conditions.

From the above, also augmented shielding and line-broadening of 6-H resonances contributed by ' central ' units [D-ring in ' trimeric ' derivative (18); D- and G-rings in tetrameric derivative (20)] relative to their counterparts in ' lower ' terminal units (G- and J-rings respectively) would be anticipated as rationalised in Table 2.

Despite otherwise sharply defined ^{1}H n.m.r. spectra at 80

* A sensitive relative index of ' fast ' rotation is temperature dependence in achieving equivalent sharpness of 3-$COCH_3$ (F) and 3-$COCH_3$ (C) resonances of each isomer; the [4,6]- and [4,8]-procyanidins requiring *ca.* 110 °C and *ca.* 140 °C respectively, almost irrespective of the solvents used.

Table 2. Comparison of chemical shifts of 6-H and 8-H of 2,3-*cis*-flavan-3-ol and procyanidin methyl ether acetates

Compound	δ ($CDCl_3$, 100 °C) 6-H	8-H
Monoflavanoids		
[(−)-Epicatechin derivatives]		
4-Ar [18]	6.12d	6.39d
6-Br (3)	—	6.45s
8-Br (6)	6.19s	—
Biflavanoids		
[4,6]-Procyanidin (B_5) (14)	6.06d (A)	6.30d (A)
	—	6.38s (D)
[4,8]-Procyanidin (B_2) (16)	5.83d (A)	5.94d (A)
	6.20s (D)	—
Triflavanoid		
[4,8:4,8]-Procyanidin (C_1) (18)	5.85d (A)	6.02d (A)
	6.02s (D) *	—
	6.13s (G) *	—
Tetraflavanoid		
[4,8:4,8:4,8]-Procyanidin (20)	5.76d (A)	5.96d (A)
	6.03s (D or G) *	—
	6.09s (G or D) *	—
	6.16s (J) *	

* Tentative assignments.

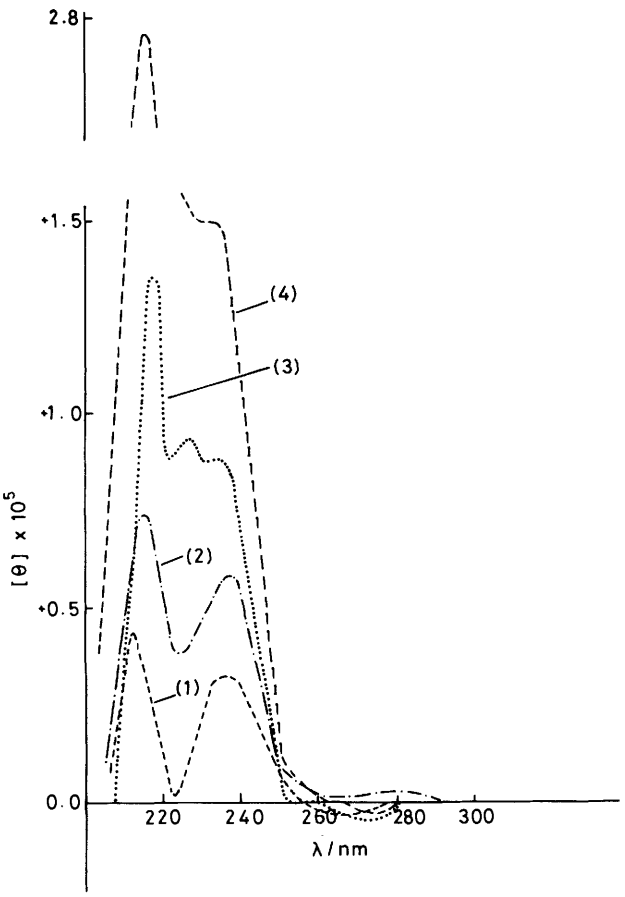


Figure 2. C.d. spectra of the methyl ether acetates of the procyanidins: (1) [4,8]-' dimer,' B_2; (2) [4,6]-' dimer,' B_5; (3) [4,8:4,8]-' trimer,' C_1; and (4) [4,8:4,8:4,8]-' tetramer '

MHz ($CDCl_3$, 100 °C) in which diagnostic contribution to heterocyclic resonances by ' upper ' units as typified by 2,3-*cis*-3,4-*trans*-4-arylflavan-3-ol analogue persists in the higher oligomers (Figure 1), relatively poor definition of heterocyclic couplings of the remaining units leads to considerable spectral complexity with increasing mass at this frequency. This necessitates work at high magnetic field strengths (*cf.* ref. 20), methyl ether acetates being more suited to such study at upper temperature limits since they exhibit lower activation energies for ' fast ' rotation than peracetates, while also permitting critical assessment of the purity of diastereoisomers. However, for the compounds under examination low-power decoupling at 80 MHz is sufficient for satisfactory assignment of heterocyclic protons of procyanidin ' dimers ' and ' trimers ' (Figure 1), while positive Cotton effects of increasing amplitude with mass at low wavelengths as reflected in their c.d. spectra (Figure 2), provide confirmation of homogeneous 2,3-*cis*-3,4-*trans* configurations of constituent units of the oligomers.[16]

The synthetic potential of the condensation of 2,3-*cis*-3,4-*trans*-leucocyanidin tetramethyl ether [11] with free phenolic catechins is limited to the production of ' angular ' [4,6:4,8]-linked (*cf.* ref. 21) rather than ' linear ' [4,8:4,8]-procyanidin ' trimers ' when using 2 : 1 molar equivalents respectively. Coupling of the leucocyanidin derivative with (+)-catechin should also result in the selective formation of derivatives of the stereochemically ' mixed ' procyanidins B_1 and B_7 (*cf.* ref. 3).

Experimental

^1H N.m.r. spectra were recorded on a Bruker WP-80 spectrometer in $CDCl_3$ at 100 °C with Me_4Si as internal standard. Mass spectra were obtained with a Varian CH-5 instrument. C.d. spectra were recorded in methanol on a Jasco J-20 spectropolarimeter. Analyses (C, H, and Br) were performed by Analytical Laboratories, Postfach 1249, D-5250 Engels-

kirchen, West Germany. Thin-layer chromatography (t.l.c.) was done on DC-Plastikfolin Kieselgel 60 PF_{254} (0.25 mm) and the plates were sprayed with H_2SO_4–HCHO (40 : 1, v/v) after development. Preparative plates [20 × 20 cm; Kieselgel PF_{254} (1.0 mm)] were air-dried and used without prior activation. Column chromatography (2 × 60 cm) on Sephadex LH-20 in ethanol was performed at a flow rate of *ca.* 0.75 ml min^{-1}. Methylations were at −15 °C with an excess of diazomethane in methanol–diethyl ether over 48 h, and acetylations were performed in acetic anhydride–pyridine. Evaporations were done under reduced pressure at 50 °C in a rotary evaporator.

Bromination of (+)-*Catechin and* (−)-*Epicatechin.*—(+)-Catechin hydrate (1 g, 2.75 mmol) was dissolved in dioxane (10 ml) and pyridinium hydrobromide perbromide (882 mg, 2.75 mmol) added. The reaction mixture was stirred under nitrogen for 10 min at ambient temperature, diluted with water (30 ml), and the solution extracted with ethyl acetate (3 × 50 ml). The ethyl acetate extract was concentrated and dried *in vacuo* yielding a brown solid. P.l.c. separation of the crude product [chloroform–methanol–acetic acid–water (85 : 15 : 10 : 3, v/v × 2)] gave four fractions at R_F 0.55, 0.46, 0.38, and 0.33. The fractions were eluted with acetone, the volumes of each of the acetone eluates being then reduced, each treated with 50 ml water, and then evaporated to remove residual acetone. Each aqueous phase was extracted (3 × 50 ml) with ethyl acetate. The above treatment with water was necessary to obviate a degree of autocondensation during concentration of extracts to dryness. The products (73, 167, 175, and 98 mg respectively) obtained on removal of the solvent showed single spots on t.l.c. plates, the R_F 0.33 fraction consisting of unchanged (+)-catechin.

6-*Bromo*-3,3′,4′,5,7-*penta*-O-*acetyl*-(+)-*catechin* (8).—Acetylation of fraction R_F 0.46 (143 mg) and p.l.c. separation [benzene–acetone (8 : 2, v/v)] gave small needles, m.p. 148—150 °C, from ethanol (lit.,[12] 149—151 °C), R_F 0.66 (135 mg), δ ($CDCl_3$) 7.25—7.09 [m, 3 × arom. H(B)], 6.75 [s, 8-H(A)], 5.26 [t, 3-H (C)], 5.13 [d, 2-H(C)], 2.78 (m, CH_2), 2.30 (×2), 2.25 (×2) (s, 4 × $COCH_3$), and 1.97 [s, 3-$COCH_3$(C)].

8-*Bromo*-3,3′,4′,5,7-*penta*-O-*acetyl*-(+)-*catechin* (11).—Acetylation of fraction R_F 0.38 (148 mg) and p.l.c. separation [benzene–acetone (8 : 2, v/v)] gave fine needles from ethanol, m.p. 123—124 °C (lit.,[12] 123—125 °C), R_F 0.64 (121 mg), δ ($CDCl_3$) 7.25—7.09 [m, 3 × arom. H(B)], 6.69 [s, 6-H(A)], 5.31 [m, 3-H (C)], 5.26 [d, 3-H(C)], 2.88—2.69 (m, CH_2), 2.35, 2.27 (×2), 2.25 (s, 4 × $COCH_3$), and 2.00 [s, 3-$COCH_3$(C)].

6,8-*Dibromo*-3,3′,4′,5,7-*penta*-O-*acetyl*-(+)-*catechin.*—Acetylation of fraction R_F 0.55 (67 mg) and p.l.c. separation [benzene–acetone (8 : 2, v/v)] gave long needles from ethanol, m.p. 171—173 °C (lit.,[12] 173—175 °C), R_F 0.68 (44 mg), δ ($CDCl_3$) 7.25—7.11 [m, 3 × arom. H(B)], 5.33 [m, 3-H(C)], 5.27 [d, 2-H(C)], 2.91—2.70 (m, CH_2), 2.41, 2.33, 2.28 (×2) (s, 4 × $COCH_3$), and 2.03 [s, 3-$COCH_3$(C)].

6-*Bromo*-3-O-*acetyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (9.)—Methylation of the phenolic fraction R_F 0.46 (167 mg) gave the tetramethyl ether (183 mg), which when acetylated and the product purified by p.l.c. [benzene–acetone (9 : 1, v/v)] gave a white solid, R_F 0.53 (119 mg), δ ($CDCl_3$) 6.88 [s, 3 × arom. H(B)], 6.41 [s, 8-H(A)], 5.38 [q, 3-H(C)], 5.08 [d, 2-H(C)], 3.88, 3.85, 3.84, 3.79 (s, 4 × OMe), 3.00 (dd, 4-$H_{eq.}$), 2.81 (dd, 4-$H_{ax.}$), and 1.96 [s, 3-$COCH_3$(C)].

8-*Bromo*-3-O-*acetyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (12).—The R_F 0.38 phenolic fraction (175 mg) treated as above gave a white solid, R_F 0.53 (136 mg), δ ($CDCl_3$) 6.93 [d, 2′-H(B)], 6.88 [dd, 6′-H(B)], 6.78 [d, 3′-H(B)], 6.17 [s, 6-H(A)], 5.46 [q, 3-H(C)], 5.32 [d, 2-H(C)], 3.89, 3.83, 3.81, 3.78 (s, 4 × OMe), 2.76 (d, CH_2), and 2.00 [s, 3-$COCH_3$(C)].

6,8-*Dibromo*-3-O-*acetyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin.*—The R_F 0.55 phenolic fraction (73 mg), treated as above gave a white solid, R_F 0.53 (44 mg), δ ($CDCl_3$) 6.83br [s, 3 × arom. H(B)], 5.46 [q, 3-H(C)], 5.34 [d, 2-H(C)], 3.88, 3.86, 3.83, 3.76 (s, 4 × OCH_3), 2.90 (d, CH_2), and 2.03 [s, 3-$COCH_3$(C)].

Bromination of (−)-epicatechin (1 g) was performed according to the procedure for (+)-catechin, giving 1.515 g crude solid. The mixture was resolved by p.l.c. [$CHCl_3$–MeOH–HOAc–H_2O (85 : 15 : 10 : 3, v/v)] giving four fractions at R_F 0.39, 0.31, 0.23, and 0.18. Re-separation in the same system (×2) gave fractions at R_F 0.49 (161 mg), 0.36 (148 mg), 0.28 (206 mg), and 0.19 (343 mg), the last-mentioned representing unchanged (−)-epicatechin.

6-*Bromo*-3,3′,4′,5,7-*penta*-O-*acetyl*-(−)-*epicatechin* (2).—Acetylation of 20 mg of the R_F 0.36 fraction yielded the crude acetate (27 mg), which when purified by p.l.c. [benzene–acetone (9 : 1, v/v)] gave long *needles* from ethanol, m.p. 162—165 °C, R_F 0.32 (20 mg) (Found: C, 51.8; H, 4.0; Br, 14.0. $C_{25}H_{23}BrO_{11}$ requires C, 51.8; H, 4.1; Br, 13.8%); *m/z* 578 (M^+, 62.5%), 580 (M^+ +2, 67.5); δ ($CDCl_3$) 7.39—7.20 [m, 3 × arom. H(B)], 6.77 [s, 8-H(A)], 5.39 [m, 3-H(C)], 5.12 br [s, 2-H(C)], 2.95 (m, CH_2), 2.36, 2.34, 2.26 (×2) (s, 4 × $COCH_3$), and 1.93 [s, 3-$COCH_3$(C)].

8-*Bromo*-3,3′,4′,5,7-*penta*-O-*acetyl*-(−)-*epicatechin* (5).—Acetylation of 20 mg of the R_F 0.28 fraction yielded the crude acetate (29 mg), which when purified by p.l.c. [benzene–acetone (9 : 1, v/v)] gave *needles* from ethanol, m.p. 169—171 °C, R_F 0.33 (22 mg) (Found: C, 52.0; H, 4.2; Br, 14.0. $C_{25}H_{23}BrO_{11}$ requires C, 51.8; H, 4.1; Br, 13.8%); *m/z* 578 (M^+, 29.6%) and 580 (M^+ +2, 33.1); δ($CDCl_3$) 7.44—7.23 [m, 3 × arom. H(B)], 6.68 [s, 6-H(A)], 5.46 [m, 3-H(C)], 5.21br [s, 2-H(C)], 2.98 (m, CH_2), 2.34, 2.29 (× 3) (s, 4 × $COCH_3$), and 1.91 [s, 3-$COCH_3$(C)].

6,8-*Dibromo*-3,3′,4′,5,7-*penta*-O-*acetyl*-(−)-*epicatechin.*—Acetylation of 20 mg of the R_F 0.49 fraction gave the crude acetate (29 mg), which when purified by p.l.c. [benzene–acetone (9 : 1, v/v)] gave long *needles* from ethanol, m.p. 192—196 °C, R_F 0.37 (20 mg) (Found: C, 46.4; H, 3.6. $C_{25}H_{23}Br_2O_{11}$ requires C, 45.6; H, 3.4%); *m/z* 656 (M^+, 9.7%), 658 (M^+ +2, 23.6), 660 (M^+ +4, 8.9); δ ($CDCl_3$) 7.45—7.24 [m, 3 × arom. H(B)], 5.54 [m, 3-H(C)], 5.21br [s, 2-H(C)], 2.99 (m, CH_2), 2.41, 2.36, 2.29 (×2) (s, 4 × $COCH_3$), and 1.91 [s, 3-$COCH_3$(C)].

6-*Bromo*-3-O-*acetyl*-3′,4′,5,7-*tetra*-O-*methyl*-(−)-*epicatechin* (3).—Successive methylation and acetylation of the R_F 0.36 (128 mg) fraction yielded the crude methyl ether (102 mg) and methyl ether acetate (113 mg) respectively. The latter when purified by p.l.c. [benzene–acetone (9 : 1, v/v)] gave small *prisms* from absolute ethanol, m.p. 182—183 °C, R_F 0.56 (50 mg) (Found: C, 54.0; H, 5.0; Br, 17.2. $C_{21}H_{23}BrO_7$ requires C, 54.0; H, 5.0; Br, 17.2%); *m/z* 466 (M^+, 42.9%), 468 (M^+ +2, 42.2); δ ($CDCl_3$) 7.03 [d, 2′-H(B)], 6.99 [dd, 6′-H(B)], 6.86 [d, 5′-H(B)], 6.45 [s, 8-H(A)], 5.45 [m, 3-H(C)], 5.06br [s, 2-H(C)], 3.89, 3.88, 3.86, 3.81 (s, 4 × OMe), 3.09 (d, CH_2), and 1.92 [s, 3-$COCH_3$(A)].

8-*Bromo*-3-O-*acetyl*-3′,4′,5,7-*tetra*-O-*methyl*-(−)-*epicatechin* (6).—Successive methylation and acetylation of the R_F

0.28 fraction (184 mg) gave the crude tetramethyl ether (164 mg) and methyl ether acetate (182 mg) respectively. The latter when purified by p.l.c. [benzene–acetone (9 : 1, v/v)] gave fine *needles* from absolute ethanol, m.p. 188—189 °C, R_F 0.50 (91 mg) (Found: C, 54.1; H, 5.1. $C_{21}H_{23}BrO_7$ requires C, 54.0; H, 5.0%); *m/z* 466 (M^+, 37.7%), 468 (M^+ +2, 38.7); δ ($CDCl_3$) 7.14 [d, 2′-H(B)], 7.03 [dd, 6′-H(B)], 6.86 [d, 5′-H(B)], 6.19 [s, 6-H(A)], 5.54 [m, 3-H(C)], 5.12br [s, 2-H(C)], 3.88 (×2), 3.86, 3.83 (s, 4 × OCH_3), 2.95 (d, CH_2), and 1.87 [s, 3-$COCH_3$ (C)].

6,8-*Dibromo*-3-O-*acetyl*-3′,4′,5,7-*tetra*-O-*methyl*-(−)-*epicatechin*.—Successive methylation and acetylation of the R_F 0.49 fraction (141 mg) gave the crude methyl ether (108 mg) and methyl ether acetate (125 mg). The latter when purified by p.l.c. [benzene–acetone (9 : 1, v/v)] gave *needles* from ethanol, m.p. 164—167 °C, R_F 0.47 (50 mg) (Found: C, 46.3; H, 4.2; Br, 29.2. $C_{21}H_{22}Br_2O_7$ requires C, 46.4; H, 4.1; Br, 29.3%); *m/z* 544 (M^+, 36.8%), 546 (M^+ +2, 41.5), 548 (M^+ +4, 37.5); δ ($CDCl_3$) 7.09br [s, 2′-H(B)], 7.03 [dd, 6′-H(B)], 6.87 [d, 5′-H(B)], 5.45 [m, 3-H(C)], 5.16br [s, 2-H(C)], 3.89 (×3), 3.88 (s, 4 × OMe), and 1.88 [s, 3-$COCH_3$ (C)].

Synthesis of [4,6]- *and* [4,8]-*Di*-O-*acetyl*-*octa*-O-*methyl*-2,3-cis-3,4-trans:2′,3′-cis-*Procyanidins* (B_5, B_2)

(2R,3R,4S)-2,3-cis-3,4-trans-3′,4′,5,7-*Tetramethoxyflavan*-3,4-*diol*.—(2*R*,3*R*)-3′,4′,5,7-Tetramethoxyflavan-3-ol (1.6 g) dissolved in dry benzene (30 ml) was treated with $Pb(OAc)_4$ (1 g) and the mixture stirred at ambient temperatures. After 24 h a further portion of $Pb(OAc)_4$ (1 g) was added and the mixture stirred for a further 4 h to complete the reaction as monitored by t.l.c. [benzene–acetone (8 : 2, v/v)]. After addition of water (30 ml) the benzene phase was separated and the aqueous phase re-extracted with benzene (20 ml). The solid (1.65 g) obtained on evaporation of the organic solvent was separated by p.l.c. [benzene–acetone (8 : 2, v/v)] into three fractions at R_F 0.64 (235 mg), 0.54 (550 mg), and 0.46 (310 mg). The R_F 0.54 fraction proved to be unchanged (−)-epicatechin tetramethyl ether, while fraction R_F 0.46 isolated as a white solid, which crystallised from benzene as needles, m.p. 120 °C, $[\alpha]_{589}^{20}$ −32.2° (*c*, 1 in $CHCl_3$) {lit.,[11] m.p. 120—121 °C), $[\alpha]_{589}^{20}$ −33.7°}, proved to be the 2,3-*cis*-3,4-*trans*-3′,4′,5,7-tetramethoxyflavan-3,4-diol, δ ($CDCl_3$) 7.12—6.84 [m, 3 × arom. H(B)], 6.20 [d, *J* 2.5 Hz, 8-H(A)], 6.12 [d, *J* 2.5 Hz, 6-H(A)], 5.09 [s, 2-H (C)], 4.84 [d, *J* 2.5 Hz, 4-H(C)], 4.00 [m, 3-H(C)], 3.89, 3.87, 3.82, 3.76 (s, 4 × OCH_3), 2.95br (s, 4-OH), and 1.81 (s, 3-OH); *m/z* 362 (M^+, 13.4%), 3.44 (M^+ −18, 35), 316 (48), 301 (26), 180 (100), 167 (38), 165 (54), 151 (57), and 137 (33).

Condensation of (2R,3R,4S)-2,3-cis-3,4-trans-3′,4′,5,7-*tetramethoxyflavan*-3,4-*diol with* (−)-*Epicatechin*.—The flavan-3,4-diol (310 mg, 0.85 mmol) was dissolved in ethanol (40 ml) followed by addition of 0.1 M-HCl (100 ml). (−)-Epicatechin (497 mg, 1.7 mmol) was then added and the reaction mixture stirred under nitrogen for 24 h. Extraction with EtOAc (4 × 100 ml) and concentration of the extract gave a solid (1.16 g) which was methylated and separated by p.l.c. [benzene–acetone (8 : 2, v/v)] to give three fractions at R_F 0.54 (183 mg), 0.34 (57 mg), and 0.28 (48 mg).

(2R,3R)-2,3-cis-3-*Acetoxy*-6-[(2R,3R,4R)-2,3-cis-3,4-trans-3-*acetoxy*-3′,4′,5,7-*tetramethoxyflavan*-4-*yl*]-3′,4′,5,7-*tetramethoxyflavan* [(14), B_5 *Derivative*].—The R_F 0.28 octamethyl ether was purified by p.l.c. in benzene–acetone (8 : 2, v/v) to give a colourless solid, R_F 0.62 (32 mg), δ ($CDCl_3$, 100 °C) 7.06—6.69 (m, 6 × arom. H), 6.38 [s, 8-H (D)], 6,30 [d, 8-H-(A)], 6.06 [d, 6-H(A)], 5.53 [m, 3-H(F)], 5.47br [s, 2-H(C)], 5.31 [t, $J_{2,3}$ 1.5 and $J_{3,4}$ 2.2 Hz, 3-H(C)], 5.11br [d, 2-H(F)], 4.59 [d, $J_{3,4}$ 2.2 Hz, 4-H(C)], 3.83, 3.81 (×2), 3.80, 3.78, 3.57, 3.53br, 3.44br, (s, 8 × OCH_3), 2.69 (m, CH_2), 1.91 [s, 3-$COCH_3$(F)], and 1.78 [s, 3-$COCH_3$(C)]; c.d. spectrum (Figure 2).

(2R,3R)-2,3-cis-3-*Acetoxy*-8-[(2R,3R,4R)-2,3-cis-3,4-trans-3-*acetoxy*-3′,4′,5,7-*tetramethoxyflavan*-4-*yl*]-3′,4′,5,7-*tetramethoxyflavan* [(16), B_2 *Derivative*].—The R_F 0.34 octamethyl ether was purified by p.l.c. in benzene–acetone (8 : 2, v/v) to give a colourless solid, R_F 0.56 (26 mg), δ ($CDCl_3$, 100 °C) 7.06—6.67 (m, 6 × arom. H), 6.20 [s, 6-H(D)], 5.94 [d, *J* 2.5 Hz, 8-H(A)], 5.83br [d, *J* 2.5 Hz, 6-H(A)], 5.54br [s, 2-H(C)], 5.34 [t, $J_{2,3}$ 1.7 and $J_{3,4}$ 2.2 Hz, 3-H(C)], 5.28 [m, 3-H(F)], 4.68 [d, $J_{3,4}$ 2.2 Hz, 4-H (C)], 4.60br [s, 2-H(F)], 3.82 (×4), 3.70 (×2), 3.58, 3.53 (s, 8 × OCH_3), 1.86 [s, 3-$COCH_3$(F)], and 1.72 [s, 3-$COCH_3$ (C)]; c.d. spectrum (Figure 2).

The R_F 0.54 (183 mg) fraction from the condensation proved to be (−)-epicatechin tetramethyl ether, representing unused starting material.

Isolation of Oligomeric 2,3-cis-*Procyanidins from the Fruits of* Crataegus oxyacantha *L.* (≡ C. monogyna *Jacq.*)

The crude phenolic fraction (3.0 g) obtained by aqueous extraction of the fruits of *C. oxyacantha* (hawthorn) was subjected to chromatography on Sephadex LH-20 columns (60 × 2.0 cm) using ethanol as eluant. Fractions (15 ml each) were collected and grouped after monitoring by p.l.c. [EtOAc–HCO_2H–H_2O (90 : 5 : 5, v/v)].

[4,8]-2,3-cis-3,4-trans:2′,3′-cis-*Procyanidin* (B_2) *Octamethyl Ether Diacetate* (16).—Fractions 75—105 (280 mg) were methylated and the product purified by p.l.c. [benzene–acetone (9 : 1, v/v)], R_F 0.17 (163 mg). Acetylation and purification by p.l.c. [benzene–acetone (8 : 2, v/v)] gave the octamethyl ether diacetate, R_F 0.67 (119 mg) identical with the synthetic product by ^1H n.m.r. and c.d. spectrometry.

[4,6]-2,3-cis-3,4-trans:2′,3′-cis-*Procyanidin* (B_5) *Octamethyl Ether Diacetate* (14).—Fractions 127—161 (250 mg) were methylated and the product subjected to p.l.c. in benzene–acetone (8 : 2, v/v) to give two fractions, R_F 0.30 (29 mg) and 0.21 (46 mg).

The former fraction, R_F 0.30 (29 mg), was acetylated and the product purified by p.l.c. [benzene–acetone (9 : 1, v/v)] affording the octamethyl ether diacetate, R_F 0.40 (5 mg), identical with the synthetic product by ^1H n.m.r., mass and c.d. spectrometry.

[4,8:4,8]-2,3-cis-3,4-trans:2′,3′-cis-3′,4′-trans:2″,3″-cis-*Procyanidin* (C_1) *Dodecamethyl Ether Triacetate* (18).—The latter fraction, R_F 0.21 (46 mg), was acetylated and the product purified by p.l.c. [benzene–acetone (8 : 2, v/v)] to give the dodecamethyl ether diacetate as a white solid, R_F 0.51 (33 mg), δ ($CDCl_3$, 100 °C) 7.09—6.84 (m, 9 × arom. H), 6.13 [s, 6-H(D or G)], 6.04 [s, 6-H(G or D)], 6.02 [d, *J* 2.5 Hz, 8-H(A)], 5.85br [d, *J* 2.5 Hz, 6-H(A)], 5.59br [s, 2-H(C)], 5.45 [m, 3-H(I)], 5.38 [t, 3-H(C)], 5.21 [m, 3-H(F)], 5.18 [d, 2-H-(F)], 5.13 [d, 2-H (I)], 4.81br [s, 4-H(C)], 4.79br [s, 4-H(F)], 3.80 (×3), 3.79, 3.78, 3.76, 3.72, 3.63, 3.62, 3.59 (×2), 3.41 (s, 12 × OCH_3), 2.95 (m, CH_2), 1.86 [s, 3-$COCH_3$(I)], 1.73 [s, 3-$COCH_3$(C)], and 1.63 [s, 3-$COCH_3$(F)]; c.d. (Figure 2).

[4,8:4,8:4,8]-2,3-cis-3,4-trans:2′,3′-cis-3′,4′-trans:2″,3″-cis-3″,4″-trans:2‴,3‴-cis-*Procyanidin Hexadecamethyl Ether*

Tetra-acetate (20).—Fractions 207—236 (260 mg) were methylated and the product purified by p.l.c. [benzene–acetone (7 : 3, v/v)], R_F 0.40 (20 mg). The methyl ether was acetylated and the methyl ether acetate subjected to p.l.c. [benzene–acetone (8 : 2, v/v)] to give a white solid, R_F 0.39 (6 mg), δ ($CDCl_3$, 100 °C) 7.19—6.56 (m, 12 × arom. H), 6.16, 6.09, 6.03 [s, 3 × 6-H(D, G, and J)], 5.96 [d, *J* 2.5 Hz, 8-H-(A)], 5.76br [d, *J* 2.5 Hz, 6-H(A)], 5.63br (s), 5.54—5.20 (m, × 6), 5.03br (s), 4.92br (s), 4.82 (d), 4.48br (d) [11 × heterocyclic H], 3.97—3.22 (s, 15 × OCH_3), 2.97 (s, OCH_3), 3.11—2.82 (m, CH_2), 1.86 [s, 3-$COCH_3$(L)], 1.73 [s, 3-$COCH_3$ (C)], and 1.69, 1.62 [s, 2 × 3-$COCH_3$(F and I)], c.d. (Figure 2).

Acknowledgements

Tenure by one of us (H. K.) of a South African C.S.I.R. Research Fellowship and support by the Sentrale Navorsingsfonds of the University of the Orange Free State is acknowledged. The crude phenolic extract of *C. oxyacantha* was kindly supplied by Dr. H. Jaggy, Firma Schwabe, Karlsruhe. Spin-decoupling experiments were performed in part by Dr. E. V. Brandt, University of the Orange Free State.

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Received 13*th June* 1983; *Paper* 3/979