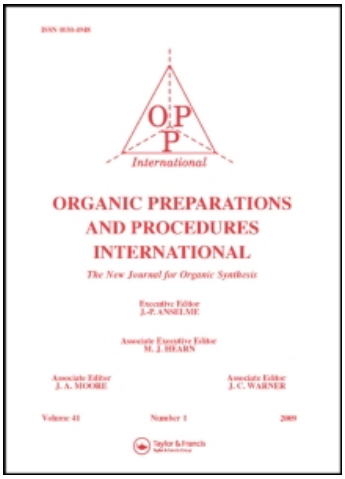

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SYNTHESIS OF 6-BROMO-, 8-BROMO- AND 6, 8-DIBROMOCATECHIN

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SYNTHESIS OF 6-BROMO-, 8-BROMO- AND 6,8-DIBROMOCATECHIN

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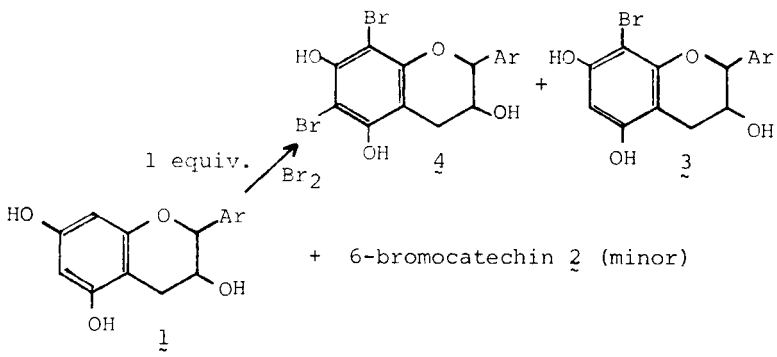
Unambiguous determination of the position of inter-flavanoid coupling in condensed tannins remains an unresolved problem although several empirical NMR criteria have been proposed to distinguish between C-6/C-4" and C-8/C-4" linked procyanidin dimers.[1-3] The introduction of an easily removable protecting group at C-6 (or C-8) of (+)-catechin ((2R-trans)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3,5,7-triol (1)) would permit regiospecific coupling of a second flavanoid unit (electrophilic center at C-4") at C-8 (or C-6). With this goal in mind, we investigated procedures for the preparation and debromination of 6-bromocatechin (2), 8-bromo-catechin (3) and 6,8-dibromocatechin (4).

In agreement with the results obtained recently by McGraw et al.[4] under similar reaction conditions, we found that bromination of (+)-catechin with one molar equivalent of bromine in acetonitrile in the presence of excess sodium bicarbonate gives a mixture containing 3 and 4 as major products together with unreacted starting material and a small quantity of 2.

Similar results were obtained with other brominating agents, viz., pyridinium bromide perbromide (PBP)[2] in methanol, N-bromosuccinimide (NBS) in dimethylformamide (DMF)[5] or acetonitrile, and bromine in dichloromethane. In all cases, tlc monitoring revealed the rapid formation of both 3 and 4 during the early stages of the reaction, e. g., after the addition of only 0.03 molar equivalents of NBS in DMF, which is attributed to the intermediacy of a highly reactive quinonoid "ketobromide".[6] All attempts to stop the reaction at the monobromination stage by varying reaction time, temperature and solvent failed.

Ar = 3,4-$(HO)_2C_6H_3$



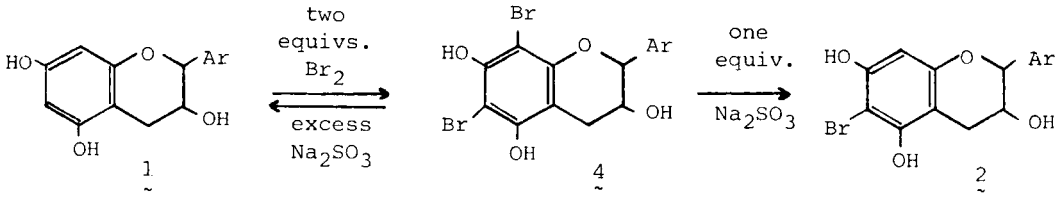
Catechin and 4 were readily separated from the monobromocatechins by hplc, and the separation of 2 and 3 was achieved by subsequent column chromatography on silica. The three bromocatechins which have never been characterized before are amorphous white solids, readily distinguishable from each other by pmr (chemical shifts in ppm. for H-2, H-4(axial), H-4(equatorial), H-6 and H-8, measured in acetone-d_6): 2 (4.61,2.60, 2.91, -, 6.11), 3 (4.77, 2.60, 2.84, 6.23, -) and 4 (4.86, 2.69, 2.86, -, -). Satisfactory microanalytical data were obtained for all three compounds. Since the pmr parameters

of the two monobromo-compounds are too close to permit unambiguous structure assignments, 2 and 3 (also 4) were converted by standard methods[7] to their respective 3',4',5,7-tetra-O-methyl derivatives 5 and 6 whose melting points (128-130° and 172-174°, respectively) and spectral characteristics (pmr) were found to be identical to those of authentic samples.[1,4,8] It is noteworthy that the values of the chemical shift difference D = Δδ(H-8, H-2) - Δδ(H-6, H-2) and of the ratio difference R = Δδ(H-2, H-4e)/Δδ(H-6, H-2) - Δδ(H-2, H-4e)/Δδ(H-8, H-2) are considerably lower for 2 and 3 (D = 0.04 p.p.m., R = 0.19) in acetone-d_6 than for 5 and 6 (D = 0.40 p.p.m., R = 0.62) in $CDCl_3$ thus rendering these previously proposed criteria[1,2] much less useful for the distinction between 6- and 8-substituted catechins in their free phenolic forms than in their methylated forms.

In view of the known tendency of halogenated phenols to rearrange by intermolecular halogen transfer, we tested the stability of 2, 3 and 4 toward acid under conditions most favorable for interflavanoid coupling. In the event, no isomerization was observed on treatment of pure 2 with 0.1 N hydrochloric acid at ambient temperature for 29 hours, nor did bromine migrate from 4 to 1 when a mixture of these two compounds was subjected to the same reaction conditions. Therefore, 6- and 8-bromocatechin would appear to be suitable substrates for regiospecific interflavanoid coupling (at C-8 and C-6, respectively) if convenient procedures could be developed for their large-scale preparation and debromination.

This goal was partially achieved by reductive removal of one bromine atom from 4 with sodium sulfite, a reagent which

is known to sulfonate catechin[9] at 170° and pH 5.9 and to debrominate bromoresorcinols[10] at 20° and pH >7. 6,8-Dibromocatechin (4), prepared in high yield from two molar equivalents of bromine and catechin in acetonitrile solution, underwent regiospecific debromination at C-8 on treatment with an equimolar amount of sodium sulfite in aqueous methanol in the presence of excess sodium bicarbonate.



Without bicarbonate, 2 and 4 were found in approximately equal quantities in the crude product mixture indicating that sulfite functions not only as reducing agent but also as base to neutralize the originally formed bisulfate and that it has considerably greater reducing power (at pH >7) than sodium bisulfite (at pH 5-6). Sodium dithionite exhibited the same regiospecificity. Complete debromination of 4 and 2 to 1 was readily accomplished with excess sodium sulfite at room temperature which demonstrates the feasibility of using bromine as protecting group at C-6 of catechin when regiospecific coupling is desired at C-8. The mild reaction conditions required for both selective and total debromination of 4 and the presence of small quantities of 4 and 1 in all crude monodebromination products show that the reactivity difference between the Br-C6 and the Br-C8 bond is relatively small. All attempts to change the regioselectivity of the reaction by using zinc as reducing agent[11] in acidic or basic medium

failed. Research on the synthesis of pure 8-bromocatechin is in progress.

EXPERIMENTAL SECTION

6,8-Dibromocatechin (4).- To a solution of 2.90 g (10.0 mmol) of (+)-catechin in 250 mL acetonitrile containing 2.52 g (30 mmol) sodium bicarbonate was added, dropwise with magnetic stirring (25°, 1 h) 200 mL of a 0.100 M solution of bromine in acetonitrile (standardized by iodometric titration with 0.100 M aqueous sodium thiosulfate). The beige solid residue left after solvent evaporation was dissolved in 125 mL ether and 50 mL water, the layers were separated, and the organic layer was washed with 40 mL water. Drying ($MgSO_4$), filtration and ether evaporation gave 3.92 g (82.5%) 6,8-dibromocatechin as a white, fluffy solid. The crude product (2.45 g) was dissolved in 70 mL ether and precipitated with 300 mL petroleum ether (40-60°) yielding pure 4 (1.81 g), mp 160-165° (decomp.), $[\alpha]_D^{32}$-53.1° (c 9.0, acetone). Traces of 8-bromocatechin were removed from smaller product samples by preparative tlc on Kieselgel PF_{254} ($CHCl_3$/MeOH/HOAc/H_2O 28:5:3:1 by volume).

Anal. Calcd. for $C_{15}H_{12}Br_2O_6$: C, 40.21; H, 2.70.

Found: C, 39.92, H, 2.96.

Mass spectrum (15 eV): Molecular ion at m/e 446(9.1), 448(15.3) and 450(8.6); ring A fragment ($C_7H_5Br_2O_3$) at 295(4.7), 297(10.2) and 299(4.6); ring B fragments at 152(25.0), 124(7.2) and 123(5.8); HBr at 80(93.5) and 82(100).

Monobromination of Catechin.- To a solution of 2.90 g (10.0 mmol) catechin in 250 mL acetonitrile were added 1.26 g (15 mmol) sodium bicarbonate and, dropwise with stirring (25°,

30 min), a solution of 1.60 g (10 mmol) bromine in 100 mL acetonitrile. The solvent was evaporated under reduced pressure and the residue dissolved in 250 mL ether and 60 mL water. Separation of the layers, washing with 50 mL water, drying ($MgSO_4$) and ether evaporation gave 2.84 g of a mixture of catechin (1), 6-bromocatechin (2), 8-bromocatechin (3) and 6,8-dibromocatechin (4) from which 1.34 g of a mixture of 2 and 3 (approximate molar ratio 1:2) was separated by preparative hplc (Bondapak C-18; elution with 20% and 80% aqueous MeOH). Analytical samples of pure 2 and 3 were obtained by subsequent dry column chromatography on Kieselgel 60 ($CHCl_3$/MeOH/HOAc 90:10:0.2 by volume). 8-Bromocatechin melts at 120-126° (decomp.); $[\alpha]_D^{32}$-65.6° (c 0.56, acetone).

Anal. Calcd. for $C_{15}H_{13}BrO_6$: C, 48.80; H, 3.55.

Found for 2: C, 48.96; H, 4.13.

Found for 3: C, 48.30; H, 4.19.

Mass spectra (15 eV): Molecular ions at m/e 368(34.3) and 370(36.8); ring A fragments ($C_7H_6BrO_3$) at 217(34.6) and 219(29.7); ring B fragments at 152(48.8), 153(17.5), 123(26.5) and 124(26.2); HBr at 80(91.6) and 82(100).

Partial Debromination of 6,8-Dibromocatechin.- A solution of 0.84 g (10 mmol) sodium bicarbonate in 50 mL water was added to a solution of 4.48 g (10 mmol) 6,8-dibromocatechin in 100 mL methanol; 1.26 g sodium sulfite (10 mmol) dissolved in 50 mL water was then dropped into the rapidly stirred mixture (15 min, 25°). After stirring for an additional ten minutes the methanol was evaporated (40°, rotavac), and the remaining aqueous solution extracted with six equal volumes of ether. Drying of the combined ether extracts ($MgSO_4$) and solvent evaporation gave 2.58 g (70%) crude product which was

chromatographically purified (see above) on a small scale yielding 6-bromocatechin (60 mg), mp 128-133° (decomp.), $[\alpha]_D^{32}$+7.0° (c 1.0, acetone).

Total Debromination of 6,8-Dibromocatechin. - A solution of 76 mg (0.60 mmol) sodium sulfite in 2 mL water was added to a solution of 45 mg (0.10 mmol) 6,8-dibromocatechin in 3 mL methanol at room temperature. After shaking the mixture for a few minutes, the methanol was evaporated (40°, rotavac), sodium chloride was added, and the aqueous solution was extracted with ether (7 × 4 mL). Drying ($MgSO_4$) and evaporation of the solvent gave 34 mg of a white, solid residue which was purified by precipitation from ether solution with five volumes of petroleum ether (40-60°), filtration and air-drying (40°). The product (26 mg) was shown to be identical to catechin by tlc analysis, pmr and mixed melting point (170-172°).

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