Synthesis of Condensed Tannins. Part 3.† Chemical Shifts for Determining the 6- and 8-Bonding Positions of 'Terminal' (+)-Catechin Units

By **Hans K. L. Hundt** and **David G. Roux,*** Department of Chemistry, University of the Orange Free State, P.O. Box 339, Bloemfontein, 9300 Republic of South Africa

Pairs of 8- and 6-functionalized (Br, OH, OAc, CO_2Me, and CH_2Me groups) 3',4',5,7-tetra-*O*-methyl-(+)-catechins available through selective bromination and debromination reactions and hence *via* lithio-analogues, provide diagnostic chemical shifts of their residual 6- and 8-protons. These fall within narrow ranges [$\delta(CDCl_3)$ 6.07—6.24 and 6.30—6.47 respectively] devoid of overlap, which are useful for differentiating between 4,6- and 4,8-linked biflavanoids. Supplementary ^1H-shift parameters are also available.

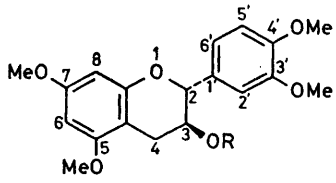
The mechanism of a newly observed acid-catalysed migration of bromine from the 6- to the 8-position is examined. Direct carboxylation of (+)-catechin proceeds regiospecifically at the 6-position.

Our earlier recognition of the limitations inherent in a predominantly analytical approach to condensed tannin chemistry prompted the initiation of studies based almost entirely on synthesis some six years ago.[1] As a starting-point one of the more important, but then unresolved problems, was differentiation between the alternatives of C^4–$C^{6''}$ and C^4–$C^{8''}$ interflavanoid links in those instances where the 'lower' or 'terminal' tannin unit is composed of substituted (+)-catechin or (−)-epicatechin. Lack of suitable ^1H n.m.r. spectrometric parameters led to the previous use of an indirect method based on the progressive shielding of methoxy-proton resonances with change of solvent composition.[2]

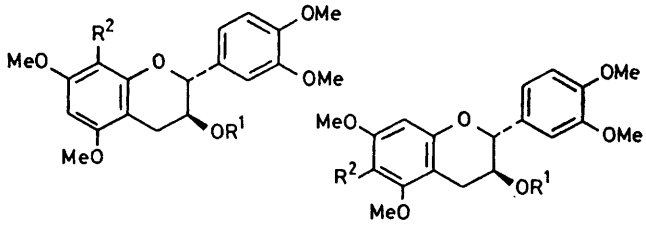
RESULTS AND DISCUSSION

Our approach to the problem of interflavanoid linkages particularly in biflavanoids devolves around the unambiguous synthesis of a range of 6- and 8-substituted (+)-catechin derivatives [(4)—(14) and (15)—(27), respectively] in order to obtain absolute values for the chemical shifts of the residual A-ring protons (H-8 and H-6, respectively) while incorporating the effects of both electron-withdrawing and electron-releasing substituents.[3] Synthesis of 6- and 8-bromo-3-*O*-benzyl-3',4',5,7-tetra-*O*-methyl-(+)catechins ([6) and (17) respectively] as key intermediates was established as the most suitable point of departure. Preparation of the 8-bromo-compound followed from direct bromination of the methyl ether (1) with pyridinium hydrobromide perbromide (PHPB), and subsequent benzylation of the 3-hydroxy-function. Weinges [4] postulated the occurrence of selective 8-bromination on the premise that this position in (+)-catechin is the more reactive nucleophilic centre, and sterically less hindered than C-6. Since hitherto no absolute proof existed, the product (6) was subjected to *X*-ray diffraction analysis.[5,‡] The results confirmed previous predictions, a related type of bromination having been established by Van Soest [6] for the bromohepta-*O*-methyl derivative of dehydrodicatechin A.

Examination of the Bromination of (+)-*Catechin and its Tetramethyl Ether by G.L.C. and T.L.C.*—As an initial approach to the synthesis of the isomeric 6-bromo-derivative, direct bromination of tetra-*O*-methyl-(+)-catechin and its derivatives under various conditions was attempted. The reaction products were analysed in each instance by gas-liquid chromatography (g.l.c.) and by



(1) R = H
(2) R = Ac
(3) R = CH_2Ph

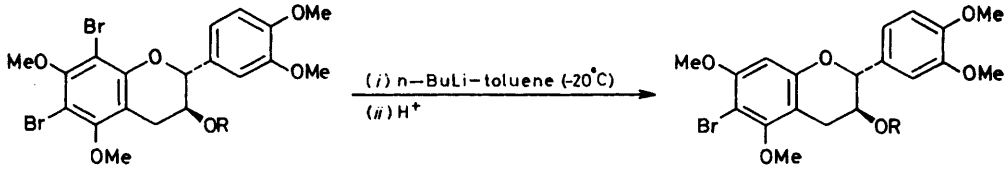


δ(H-6)				δ(H-8)
6.21	(4)	R^1 = H; R^2 = Br	(15)	6.40
6.20	(5)	R^1 = Ac; R^2 = Br	(16)	6.47
6.22	(6)	R^1 = CH_2Ph; R^2 = Br	(17)	6.41
6.22	(7)	R^1 = H; R^2 = OH	(18)	6.32
6.18	(8)	R^1 = CH_2Ph; R^2 = OH	(19)	6.32
6.18	(9)	R^1 = H; R^2 = OAc	(20)	6.36
6.19	(10)	R^1 = Ac; R^2 = OAc	(21)	6.40
6.15	(11)	R^1 = CH_2Ph; R^2 = OAc	(22)	6.34
6.10	(12)	R^1 = H; R^2 = CO_2Me	(23)	6.32
6.11	(13)	R^1 = Ac; R^2 = CO_2Me	(24)	6.32
6.10	(14)	R^1 = CH_2Ph; R^2 = CO_2Me	(25)	6.32
		R^1 = OAc; R^2 = CH_2OMe	(26)	6.37
		R^1 = OAc; R^2 = CH_2OAc	(27)	6.40

† Part 2, J. H. van der Westhuizen, D. Ferreira, and D. G. Roux, preceding paper.

‡ An error made in the signs of the torsion angles reported by Engel *et al.*[5] necessitates their reversal in the figure.

thin layer chromatography (t.l.c.), methods which separate 6- and 8-bromo-derivatives of 3',4',5,7-tetra-*O*-methyl-(+)-catechin [(4) and (15) respectively] remarkably well. The 3-*O*-acetates and 3-benzyl ethers of the 6-bromo-derivatives were more mobile than the 8-bromo-compounds, exhibiting higher R_F values on t.l.c. and shorter retention times on g.l.c. For 3-hydroxy-derivatives, however, the relative mobilities on t.l.c. were dependent on the solvent system.



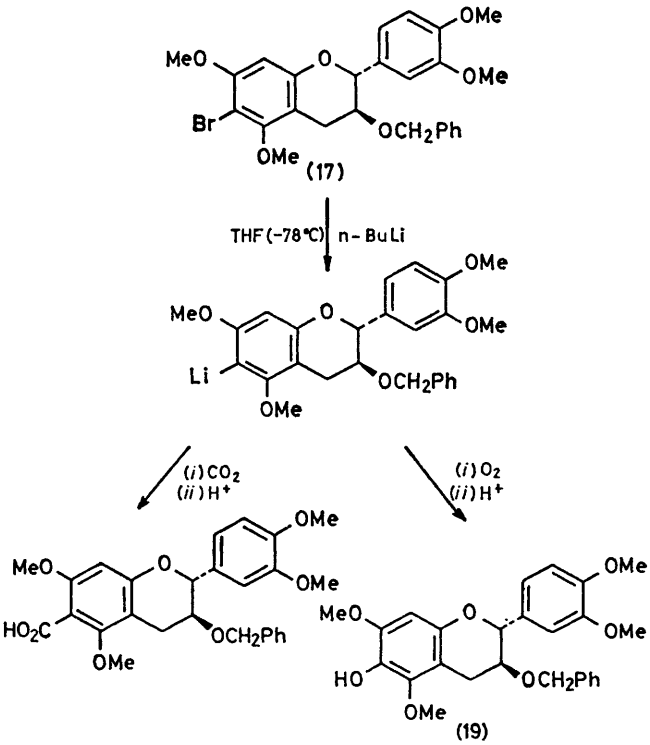
(28) R = H (15)
(29) R = Ac (16)
(30) R = CH_2Ph (17)

For brominations under a range of conditions it is evident that initial reaction occurs exclusively at the 8-position; that subsequent bromination at the 6-position leading to a 6,8-dibromo-derivative follows at a much slower rate; and that prolonged bromination leads to substitution at C-6' on the B-ring with formation of a 2',6,8-tribromo-derivative. The results indicate that the 6-bromo-derivative cannot be obtained by direct reaction with 3',4',5,7-tetra-*O*-methyl-(+)-catechin and its 3-*O*-acetyl and 3-*O*-benzyl derivatives (1)—(3).

Since steric factors obviously play a dominant role, bromination of free phenolic (+)-catechin in pyridine was examined on a 1 : 1 molar basis using PHPB. The products were either trimethylsilylated or methylated and their composition examined by g.l.c. Trimethylsilyl products correspond to unbrominated (40%), monobrominated (40%), and dibrominated derivatives (20%), reflecting (see below) inability to separate the trimethylsilyl ethers of 6- and 8-bromo-(+)-catechin. Methylated reaction products represent unbrominated (35%), 6-bromo- (11%), 8-bromo- (28%), and 6,8-dibromo-tetra-*O*-methyl-(+)-catechin (27%). This indicates that reduced steric congestion with bromination of the free-phenolic (+)-catechin is responsible for the direct formation of the 6-bromo-derivative, whereas a significant steric factor favouring 8-bromination must operate for the methyl ether and its derivatives. These indications are supported by evidence that no bromination occurs with 3,3',4',5,7-pentakis-*O*-trimethylsilyl-(+)-catechin under far more vigorous conditions.

Synthesis of 6 *and* 8-*Substituted Carboxy- and Hydroxy-*(+)-*catechin Derivatives.*—Considering that 3-*O*-benzyl-6-bromo-3',4',5,7-tetra-*O*-methyl-(+)-catechin (17) could not be obtained in reasonable yields by direct bromination of (+)-catechin, the ease with which the 6,8-dibromo-derivative of the methyl ether (28) could be obtained suggested a possible route to the 6-bromo-compound by partial debromination. This was based on the premise that, since the 8-position of 3',4',5,7-tetra-*O*-methyl-(+)catechin is attacked more readily than in the 6-position, the former should be removed more readily. A g.l.c. study of the debromination of various 6,8-dibromo-derivatives resulted in a high yield (74%) of the 6-bromo-isomer (17) from 3-*O*-benzyl-6,8-dibromo-3',4',5,7-tetra-*O*-methyl-(+)-catechin (30) by partial debromination with n-butyl-lithium. The reaction (30) ⟶ (17) represents the first unambiguous synthesis of a 6-substituted (+)-catechin derivative,[3] the product serving as key intermediate for the production of other 6-substituted derivatives.

The 6- and 8-bromo-3-*O*-benzyl-3',4',5,7-tetra-*O*-methyl-(+)-catechins [(17) and (6) respectively], obtained as above, were used for synthesising the following 6- and 8-substituted (+)-catechin derivatives (18)—(27)



and (7)—(14), respectively. Access to the carboxy- and hydroxy-derivatives was by the action of CO_2 and O_2, respectively, on the 6- and 8-lithio-derivatives of 3-*O*-benzyl-3',4',5,7-tetra-*O*-methyl-(+)-catechin as illustrated for the 6-derivatives (17). The remainder were obtained by debenzylation (hydrogenation with Pd–C),

acetylation, and methylation (diazomethane) in the usual way.

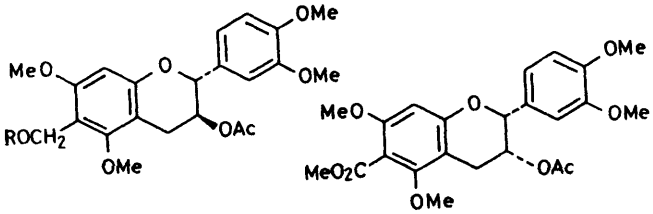
Relative and Absolute Values of Chemical Shifts of Residual A-*Ring and Heterocyclic Protons for* 6- *and* 8-*Bromo-, Carboxy-, and Hydroxy-*(+)-*catechin Derivatives.*—Comparison of ^{1}H n.m.r. spectra of the 6- and 8-substituted (+)-catechin derivatives reveals a remarkable consistency within the range of absolute values of the chemical shifts of H-8 and H-6 (in $CDCl_3$) almost irrespective of the type of substituent on the A-ring, although resonances associated with ester substituents (12)—(14) and (23)—(25) are slightly to high field in each instance [*cf.* δ values tabulated for compounds (4)—(27)]. The values for H-6 fall within the range δ 6.10—6.22 (mean 6.17) and those for H-8 within the range δ 6.32—6.47 (mean 6.37). The lack of overlap of these two ranges despite relatively small shift differences permits their possible adoption as a diagnostic basis for differentiating between C^4–$C^{6''}$ and C^4–$C^{8''}$ linked biflavanoids.

However, various chemical-shift differences between the heterocyclic protons H-2, H-4a, and H-4b, together with those for the aromatic protons H-6 and H-8 for all compounds (see Tables 1 and 2 of SUP 22965 *) provide other parameters which may be of potential value for differentiating between C-6 and C-8 substituted (+)-catechin derivatives. Thus, while the H-8 resonances of C-6 substituted derivatives are on an average 0.2 p.p.m. downfield from the H-6 resonances of the C-8 substituted series, their H-2 resonances occur 0.1—0.2 p.p.m. upfield. Thus Δδ(H-2,H-8) for the C-6 functionalized derivatives (1.60—1.71) is always larger than the equivalent Δδ(H-2,H-6) parameter for C-8 substituted analogues (1.28—1.47). This provides for distinction between the two types of compounds without resorting to accurate determination of the absolute chemical shift of a given proton.

Similarly the resonances of H-4a and H-4b in C-8 substituted derivatives tend to lie at slightly higher field strengths than those of the corresponding protons in the C-6 substituted series, Δδ(H-2,H-4a) and Δδ(H-2,H-4b) being larger for C-8 than for C-6 substituted analogues (see Tables 1 and 2 of SUP 22965). The ratios Δδ(H-2,H-4a)/Δδ(H-2,H-6), Δδ(H-2,H-4b)/Δδ(H-2,H-6), Δδ(H-2,H-4a)/(Δδ(H-2,H-8), and Δδ(H-2,H-4b)/Δδ(H-2,H-8) are accordingly expected to furnish even better distinction between C-6 and C-8 substituted derivatives. These ratios are summarized (see Table 3 of SUP 22965), and it is notable that the ranges of ratios calculated do not overlap for the relevant C-6 and C-8 substituted derivatives.

An indication of the relevant degree of differentiation of the three methods may be obtained by determining the *t* statistic for the average of two samples, where for instance, the samples represent the values δ(H-8) and δ(H-6) for the various C-6 and C-8 substituted (+)-catechin compounds of a given derivative of the 3-hydroxy-function (see Table 4 of SUP 22965). From these results it is apparent that the most reliable allocation of C-6 or C-8 substitution is available from assessment of Δδ(H-2,H-6 or 8) for the free hydroxy-derivative. However, the results of the analysis also imply that the three methods are essentially comparable in their powers of differentiation. Hence there is no special advantage in calculating the ratios indicated, but assessment of Δδ(H-2,H-6 or 8) has the advantage that it is independent of absolute values of chemical shifts. This is, therefore, the method of choice when dealing with C-6 or C-8 substituted (+)-catechin derivatives, where electronic effects of the substituent are confined mainly to the benzene ring. Where the attached group exerts anisotropic effects (*e.g.* another flavanoid unit) which may influence the chemical shift of H-2, preference is given to the chemical shifts of H-6 and H-8 as diagnostic criteria.

Carboxylation of (+)-*Catechin.*—The above criteria were applied to the acetoxymethyl derivative of 3′,4′,5,7-tetra-*O*-methyl-(+)-catechin previously synthesised by Ferreira,[7] by direct carboxylation of the free phenol followed by methylation and reduction. These compounds [(26) and (27)] were postulated as being C-8 substituted [7] by virtue of the relative shifts of methoxy-group resonances on progressive change of solvent composition from $CDCl_3$ to [$^2H_6$]benzene.[2] The chemical shifts for the A-ring singlet for the methoxymethyl (26) and acetoxymethyl (27) derivatives (δ 6.37 and 6.40, respectively) are by contrast well within the range for H-8 protons (6.32—6.47). Values of Δδ(H-2,H-6) calculated for the same compounds (1.27 and 1.30, respectively) were similarly within the range calculated for C-6 substitution (1.24—1.38). Likewise values for the ratio Δδ(H-2,H-4ab)/Δδ(H-2,H-6) calculated at 1.76 and 1.70, respectively, are within the range calculated for C-6 substitution.



Comparison of the ^{1}H n.m.r. spectrum of the immediate synthetic precursor of the hydroxymethyl derivatives (26) and (27) with that of the authentic 3-*O*-acetyl-6-methoxycarbonyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (24), obtained *via* 6-bromo- and 6-lithio-derivatives as described earlier, showed these compounds to be identical. The above test case provides proof of the diagnostic value of the criteria as outlined above, and indicates

* Tables of chemical shifts, chemical-shift differences, and *t* statistics are deposited as Supplementary Publication No SUP 22965 (5 pp.). For details see Notice to Authors No. 7, *J. Chem. Chem. Soc., Perkin Trans. I*, 1980, Index issue.

that interpretations based on the relative shift of methoxy-resonances on progressively changing solvent from $CDCl_3$ to C_6D_6 [2] can be in error.

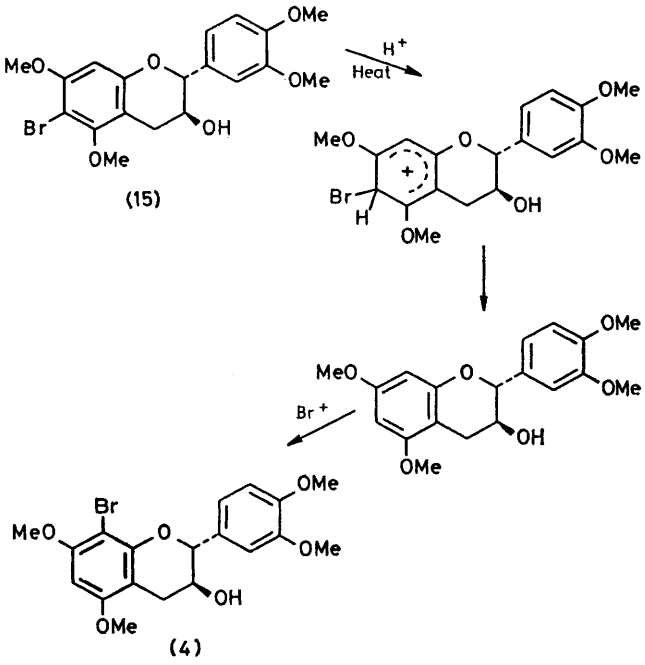
In view of the results obtained from the bromination of (+)-catechin in which both 8- (predominantly) and 6-bromo-derivatives are formed, the regiospecific 6-carboxylation of (+)-catechin is at first surprising. Conditions employed by Ferreira [7] were accordingly repeated and the products subjected to g.l.c. and t.l.c. after methylation (diazomethane). No 8-methoxycarbonyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin could be demonstrated amongst the reaction products, but after further acetylation 3-*O*-acetyl-6-methoxycarbonyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (24) and -(+)-epicatechin [(31) H-8 at δ 6.35] were obtained in 20% combined yield; the latter presumably formed by epimerization.

The results indicate that under the reaction conditions (CO_2 atmosphere, hydrogencarbonate solution, 97 °C) the sterically less hindered 8-carboxylation is reversible leaving the more stable 6-carboxy-derivative as the main product, together with its epimer; and also that formation of 6-substituted derivatives of (+)-catechin during biflavanoid formation (*i.e.* C^4–$C^{6''}$ linked biflavanoids) cannot be ruled out.

Application of Chemical-shift Criteria to Biflavanoids.— Closer analogues are obviously required in order to confirm the above ranges of chemical shifts for 6- and 8-flavanyl derivatives of (+)-catechin. However, it is interesting to note that Drewes *et al.*[8] in earlier work, drew attention to the possible diagnostic value of chemical shifts of H-6″ and H-8″ in the natural biflavanoids present in the bark of *Acacia mearnsii* which are comprised of (+)-catechin and (+)-gallocatechin units as 'lower terminal' moieties.[9] The range of observed chemical shifts of high-field aromatic singlets (δ 6.11—6.31) indicates that these compounds are most likely 4,8-linked, an observation which was recently confirmed by their synthesis.[10] Similarly leucoguibourtinidin-(+)-catechins and -(−)-epicatechins from *A. luederitzii* [11] (δ 6.16—6.25) represent 4,8-linked biflavanoids, previous assignments being based on solvent-induced chemical shifts [2] of methoxy-resonances.

Acid-catalysed C-6 ⟶ C-8 *Migration of Bromine in* 6-*Bromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin*.— Treatment of 6-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (15) in isopropyl alcohol–concentrated HCl (8 : 1 v/v) showed that the compound exhibits a half-life of *ca.* 10 min under these conditions, being converted almost quantitatively into the 8-isomer in a pseudo-first-order reaction (*cf.* Experimental section). On treating the 8-bromo-derivative (4) under identical conditions, *ca.* 4% of the 6-isomer appears to be formed (g.l.c.).

Considering that migration occurs in a compound in which all the phenolic methoxy-groups remain intact during the process, a possible Wessely–Moser rearrangement [12] is excluded. A plausible mechanism for this novel migration involves debromination of the 6-bromo-derivative, followed by re-bromination at C-8 as outlined [*cf.* Scheme, (15) ⟶ (4)]. Similar isomerizations through migration of the functional group of arylsulphonic acids in sulphuric acid [13] are to be expected since the lability of sulphonate groups when attached to the aromatic ring is well known.



SCHEME

Indirect proof of the above mechanism was provided by treating an equimolar mixture of the 6-bromo-isomer and radio-labelled 3′,4′,5,7-tetra-*O*-methyl-(+)-catechin under the conditions described above to give the pure 8-bromo-isomer with a specific activity of 44.4% of that of synthetic radio-labelled 8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin. This compares with 36.8% specific activity of an 8-bromo-isomer obtained when using the 8- in place of the 6-bromo-isomer as above. Both reactions indicate that intermolecular bromine exchange occurs, migration from the 6-position being more rapid. Preference for 8-bromination in these reactions probably reflects the extent of steric compression in the 6-bromo- relative to the 8-bromo-derivative. The significance of the C-6 ⟶ C-8 migration of bromine will become evident from bromine-induced degradations of certain biflavanoids (4-flavanylflavan-3,4-diols).[3]

EXPERIMENTAL

Thin layer chromatography (t.l.c.) was performed on DC-Plastikfolin, and Kieselgel 60 F_{254} (0.25 mm) and the plates sprayed with H_2SO_4–HCHO (50 : 1 w/v) after development. Colours are those obtained with this reagent. Preparative plates (20 × 20 cm) [Kieselgel PF_{254} (1.0 mm)] were air-dried and used without prior activation. Gas-liquid chromatography (g.l.c.) was on a Varian 2000 instrument using a flame-ionization detector. The column, 3 mm × 180 cm, glass, was packed with 3% OV-17 on Chromosorb W (AW-DMCS, 100—200 mesh). Nitrogen was used as carrier gas with a flow rate of 60 ml min^{-1}, and with tem-

peratures at 270 °C (injection port), 250 or 270 °C (column), and 280 °C (detector). Retention times (s) and peak areas (μV s) were obtained with a Hewlett–Packard 3370B integrator.

^{1}H Nuclear magnetic resonance (n.m.r.) spectra were recorded on Varian XL-100 or Bruker WP-80 spectrometers for $CDCl_3$ solutions with $SiMe_4$ as internal standard. Mass-spectral data were registered on a Varian CH-5 instrument. The C and H analyses were by Analytische Laboratorien, Fritz-Pregl-Strasse 24, 5270 Gummersbach 1 Elbach, Germany. Melting points (uncorrected) were determined on a Kofler hot-stage microscope.

Methylations were with dimethyl sulphate and anhydrous Na_2SO_4 in dry acetone under reflux, while acetylations were carried out in acetic anhydride–pyridine (1 : 1 v/v) at ambient temperature overnight. Benzylation was by addition of freshly-prepared benzyl iodide to the compound (20 ml g^{-1}) in freshly distilled dimethylformamide over freshly prepared silver oxide (*ca.* 5 mol Ag_2O per mol material) with stirring. The progress of these reactions was monitored by t.l.c.

G.L.C. and T.L.C. Study of the Course of Bromination of (+)-*Catechin and its* 3′,4′,5,7,*Tetra*-O-*methyl Derivative*

Bromination Procedures.—0.02M Solutions of each of pyridinium hydrobromide perbromide [15] (PHPB), (+)-catechin, and 3′,4′, 5,7-tetra-*O*-methyl-(+)-catechin and its 3-*O*-acetyl and 3-*O*-benzyl derivatives were prepared in anhydrous pyridine, and also of the first three compounds in methanol.

To a solution containing (+)-catechin or one of its derivatives in a reaction vial equipped with a Teflon screw-cap was added the brominating agent (PHPB) (0.1 or 0.2 ml) in pyridine, depending on whether a 1 : 1 or 1 : 2 molar bromination was being undertaken. Reaction proceeded at room temperature for 10 min, after which a 10% solution of ' Powersil ' silylating reagent (Applied Science Laboratories) (0.5 ml) in pyridine was added for those solutions which originally contained (+)-catechin or its tetramethyl ether. The tightly capped vial was heated at 100 °C for 10 min, when 1 μl of the resultant solution was analysed by g.l.c.

The same reaction in methanol was completed by addition of pyridine (1 drop) after the initial 10-min heating period, and the methanol evaporated at the boil in a stream of filtered air. Silylation as above was followed by g.l.c.

Trimethylsilyl derivatives of (+)-catechin and its tetramethyl ether were prepared by treating 0.1-ml solutions with 10% ' Powersil ' (5 ml) in pyridine at 100 °C for 10 min.

Bromination Study of (+)-*Catechin.*—A 1 : 1 molar ratio of (+)-catechin and the brominating agent (PHPB) gave three products with retention times of 300 [3,3′,4′,5,7-pentakis-*O*-trimethylsilyl-(+)-catechin], 498 (monobromosilyl ether) and 796 s (6,8-dibromosilyl ether), whereas a 1 : 2 molar ratio gave a single product with retention time 796 s (6,8-dibromo-derivative), together with traces of unbrominated and 8-bromo-derivatives. Identical results were obtained in MeOH. The 6,8-dibromo-pentakis-*O*-trimethylsilyl-(+)-catechin exhibits mass-fragmentation spectra consistent with the structure (M^+ 806/808/810).

Bromination of (+)-catechin [177 mg (0.60 mmol)] dissolved in methanol (10 ml) to which pyridine (0.1 ml) followed by PHPB (200 mg, 0.62 mmol) had been added gave a product after 5 min, which was methylated with dimethyl sulphate. G.l.c. of the resultant mixture gave four products with retention times 162 [3′,4′,5,7-tetra-*O*-methyl-(+)-catechin], 261 (6-bromo-derivative), 290 (8-bromo-derivative), and 403 s (6,8-dibromo-derivative) in the ratio 34.9 : 10.8 : 27.6 : 26.8, respectively.

Bromination of 3′,4′,5,7-*Tetra*-O-*methyl*-(+)-*catechin and Derivatives.*—Bromination of this compound with one molar equivalent of PHPB gave a major component, the 8-bromo-derivative (290 s) and a trace of unchanged material (162 s). With two molar equivalents two major components, the 8-bromo- (290 s) and 6,8-dibromo- (403 s) derivatives, were obtained in *ca.* equal amounts. The same results were obtained in methanol, and also by using bromine vapour in anhydrous benzene. Irrespective of the solvent used, monobromination occurs exclusively in the 8-position and dibromination is not as rapid as with (+)-catechin.

Bromination of the 3-*O*-acetyl- and 3-*O*-benzyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechins proceeded as above to give 8-bromo- and 6,8-dibromo-derivatives with retention times 268 and 350 s (acetate) and 781 and 1 047 s (benzyl ether).

3,3′,4′,5,7-Pentakis-*O*-trimethylsilyl-(+)-catechin (retention time 300 s; column temperature 250 °C) was unreactive under more drastic conditions (100 °C; 10 min) of bromination.

Partial Debromination of 6,8-*Dibromo*-3′,4′,5,7-*Tetra*-O-*methyl*-(+)-*catechin, and the* 3-O-*Acetyl and* 3-O-*Benzyl Derivatives.*—Partial debromination of the three 6,8-dibromo-derivatives using n-butyl-lithium was examined in order to ascertain which compound lends itself best to this reaction. To 0.01 mmol of each one dissolved in anhydrous benzene (0.2 ml) was added 5 μl of a 20% solution of n-butyl-lithium in n-pentane (0.015 mmol). After allowing 10 min for reaction, a 5% solution of aqueous acetic acid (1 ml) was added to each reaction solution. Then chloroform (1 ml) was added; after shaking, 5 μl of the chloroform phase was analysed by g.l.c. under the conditions described earlier.

From the debromination of the 3-*O*-benzyl derivative four sharply defined products were obtained with retention times 454 [3-*O*-benzyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin], 733 (6-bromo), 787 (8-bromo), and 1 043 s (6,8-dibromo) with the ratio of their peak areas being 1 : 12 : 7.5 : 9.4, respectively, indicating the availability of the 6-bromo-derivative in relatively good yield. Poor debromination of the methyl ether derivative, and a multiplicity of products from the 3-*O*-acetyl derivative, casts doubt on their suitability for synthetic use.

6- *and* 8-*Brominated* (+)-*Catechin Derivatives*

8-*Bromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (4).—To 3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (1) (3.5 g, 10 mmol) in 96% ethanol (50 ml), heated until the solid had just dissolved, was added solid PHPB (3.2 g, 10 mmol) in small portions over 10 min. Crystallization commenced after final addition of the brominating agent. Recrystallization from 95% ethanol (150 ml) gave colourless needles (2.85 g, 66% yield), m.p. 172—174 °C (lit.,[4] 174 °C); *m/e* 424/426 (M^+).

3-O-*Benzyl*-8-*bromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (6).—The above 8-brominated compound (4) was benzylated as described by Weinges *et al.*[4] giving colourless needles, m.p. 138—140 °C (lit.,[4] 139—140 °C); *m/e* 514/516 (M^+).

3-O-*Acetyl*-8-*bromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (5).—Acetylation of the above 8-bromo-derivative (4) (100 mg) gave a quantitative yield of an *amorphous solid*; *m/e* 466/468 (M^+).

6,8-*Dibromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (28).—To 3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (1) (100 mg) dissolved in a mixture of methanol (2 ml) and benzene (1 ml) was added PHPB (200 mg) dissolved in methanol (3 ml). After 3 h at room temperature two drops of pyridine were added and the solution taken to dryness at 50 °C under reduced pressure. The crystalline residue, recrystallized twice from 96% ethanol (2 ml), yielded *colourless needles* (81 mg, 55%), m.p. 184—187 °C (decomp.) (Found: C, 45.5; H, 4.0. $C_{19}H_{20}Br_2O_6$ requires C, 45.3; H, 4.0%); *m/e* 502/504/506 (M^+).

3-O-*Acetyl*-6,8-*dibromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (29).—Acetylation of the 6,8-dibromo-derivative (28) (50 mg) yielded *colourless plates* (35 mg), m.p. 154—156 °C, from glacial acetic acid; *m/e* 544/546/548 (M^+).

3-O-*Benzyl*-6,8-*dibromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (30).—3-*O*-Benzyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (3) (5 g) and acetamide (2 g) were dissolved in ethyl acetate (100 ml) and the solution warmed to 55 °C. While stirring, a solution of bromine in ethyl acetate (14.6 ml of a 0.3 g ml^{-1}) was added during 5 min and the reaction left at 55 °C for 1 h. The red solution was treated with water (100 ml) and SO_2 bubbled through the mixture, leaving a red deposit and the ethyl acetate phase almost colourless. The ethyl acetate phase was washed with 5% $NaHCO_3$ (4 × 25 ml) solution and dried (anhydrous Na_2SO_4). The residue obtained from evaporation of the solvent crystallized from 96% ethanol as *colourless needles* (5 g, 73%), m.p. 118—119 °C (Found: C, 52.4; H, 4.6. $C_{26}H_{26}Br_2O_6$ requires C, 52.6; H, 4.4%); *m/e* 592/594/596 (M^+).

Benzylation of 6,8-dibromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (28) yields the same compound.

3-O-*Benzyl*-6-*bromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (17).—3-*O*-Benzyl-6,8-dibromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (30) (5 g) was dissolved in toluene (110 ml) and then toluene (10 ml) distilled off to remove moisture azeotropically. The solution was cooled to −20 °C under dry nitrogen and a 20% solution of n-butyl-lithium in n-pentane (4 ml) added dropwise during 10 min with magnetic stirring. 10% Acetic acid (100 ml) was then immediately added while stirring vigorously. The toluene phase was washed (4×) with 5% $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. The residue obtained after removal of the toluene was dissolved in chloroform and adsorbed on silica gel (25 g) (Merck, Silicagel 60, 230—400 mesh). The dry powder was added to a silica gel dry column (250 g) which was eluted successively with: chloroform–light petroleum (60—80 °C)–ether 1 : 5 : 4 (250 ml); 1 : 4 : 5 (250 ml); 1 : 3 : 6 (250 ml); 1 : 2 : 7 (250 ml); 1 : 1 : 8 (250 ml); and then chloroform–ether 1 : 9 (250 ml). 50-ml Fractions were collected, the 3-*O*-benzyl-6-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin eluting in fractions 7—12: these were combined and evaporated to give a residue which was crystallized from hot 96% ethyl alcohol (50 ml) yielding *colourless plates* (2.38 g, 55%), m.p. 115—117 °C (Found: C, 60.4; H, 5.3. $C_{26}H_{27}BrO_6$ requires C, 60.6; H, 5.3%); *m/e* 514/516 (M^+).

6-*Bromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (15).—A solution of the benzyl ether (17) (3g) in ethyl acetate (10 ml) was hydrogenated over 10% Pd–C (50 mg) until hydrogen uptake ceased. The resultant residue in 96% ethyl alcohol (2 ml) yielded *colourless needles* (330 mg, 80%), m.p. 130—132 °C (Found: C, 53.6; H, 5.0. $C_{19}H_{21}BrO_6$ requires C, 53.7; H, 5.0%); *m/e* 424/426 (M^+).

3-O-*Acetyl*-6-*bromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (16).—Acetylation of the 6-bromo-ether (100 mg) (15) yielded an *amorphous solid*; *m/e* 466/468 (M^+).

6- *and* 8-*Substituted Carboxy- and Hydroxy*-(+)-*catechin Derivatives*

3-O-*Benzyl*-8-*hydroxy*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (8).—To 3-*O*-benzyl-8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (6) (100 mg) dissolved in anhydrous tetrahydrofuran (4 ml) at − 78 °C was added 15% n-butyl-lithium in n-pentane (0.2 ml); 2 min after completion of the addition, oxygen was bubbled through the reaction solution for 3 min, after which a 1% aqueous HOAc (10 ml) solution was added and the products extracted (3 × 20 ml) with ether. T.l.c. separation [chloroform–ethyl acetate (9 : 1)] gave two fractions of R_F 0.50 and 0.93, the lower R_F fraction being the 8-*hydroxy-derivative* (52 mg) which yielded *colourless needles* (26 mg, 30%) from 96% ethanol, m.p. 132—134 °C (Found: C, 69.0; H, 6.3. $C_{26}H_{28}O_7$ requires C, 69.0; H, 6.2%); *m/e* 452 (M^+).

8-*Acetoxy*-3-O-*benzyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (11).—Acetylation of the 8-hydroxy-derivative (8) (20 mg) and t.l.c. purification [chloroform–ethyl acetate (9 : 1)] yielded an *amorphous solid* (20 mg); *m/e* 494 (M^+); R_F 0.77.

3-O-*Benzyl*-6-*hydroxy*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (19).—3-*O*-Benzyl-6-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (17) (100 mg) was treated with n-butyl-lithium as described for the 8-bromo-3-*O*-benzyl ether (6). T.l.c. separation [chloroform–ethyl acetate (9 : 1)] yielded two fractions of R_F 0.61 and 0.93, the lower R_F product being the 6-hydroxy-derivative obtained as an *amorphous solid* (44 mg, 50%) (Found: C, 68.9; H, 6.3. $C_{26}H_{28}O_7$ requires C, 69.0; H, 6.2%); *m/e* 452 (M^+).

6-*Acetoxy*-3-O-*benzyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (22).—Acetylation of the 3-*O*-benzyl-6-hydroxy-derivative (19) (20 mg) and t.l.c. purification [ether–hexane (3 : 1)] yielded an *amorphous solid* (20 mg); *m/e* 494 (M^+); R_F 0.57.

8-*Acetoxy*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (9).—The 8-acetoxy-3-*O*-benzyl derivative (11) (50 mg) dissolved in 96% ethanol–acetic acid (9 : 1) (10 ml), was hydrogenated to completion over 10% Pd–C. T.l.c. purification [chloroform–ethyl acetate (9 : 1)] yielded an *amorphous solid* (40 mg, 98%), R_F 0.21 (Found: C, 62.2; H, 5.9. $C_{21}H_{24}O_8$ requires C, 62.4; H, 6.0%); *m/e* 404 (M^+).

6-*Acetoxy*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (20).—The 6-acetoxy-3-*O*-benzyl derivative (22) (70 mg) hydrogenated as described above gave, after t.l.c. purification [chloroform–ethyl acetate (9 : 1)], an *amorphous solid* (56 mg, 98%), R_F 0.18 (Found: C, 62.4; H, 6.0. $C_{21}H_{24}O_8$ requires C, 62.4; H, 6.0%); *m/e* 404 (M^+).

8-*Hydroxy*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (7).—The 8-hydroxy-3-*O*-benzyl derivative (8) (50 mg) dissolved in 96% ethanol–acetic acid (9 : 1) (10 ml) was hydrogenated as above. T.l.c. purification [dichloromethane–acetone (19 : 1)] yielded an *amorphous solid* (34 mg, 85%), R_F 0.12 (Found: C, 62.9; H, 6.0. $C_{19}H_{22}O_7$ requires C, 63.0; H, 6.1%); *m/e* 362 (M^+).

6-*Hydroxy*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (18).—3-*O*-Benzyl-6-hydroxy-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (50 mg) (19) hydrogenated as above yielded after t.l.c. purification [dichloromethane–acetone (19 : 1)] an *amorphous solid* (35 mg, 87%), R_F 0.10 (Found: C, 62.9; H, 6.2. $C_{19}H_{22}O_7$ requires C, 63.0; H, 6.1%); *m/e* 362 (M^+).

8-*Acetoxy*-3-O-*acetyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (10).—Acetylation of 8-hydroxy-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (7) (25 mg) and t.l.c. purification [ether–

hexane (3 : 1)] yielded an *amorphous solid* (26 mg), R_F 0.31 (Found: C, 61.9; H, 6.0. $C_{23}H_{26}O_9$ requires C, 61.9; H, 5.9%); *m/e* 446 (M^+).

6-*Acetoxy*-3-O-*acetyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (21).—Acetylation of 6-hydroxy-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (18) (25 mg) and t.l.c. purification [ether–hexane (3 : 1)] yielded an *amorphous solid* (24 mg), R_F 0.36 (Found: C, 61.8; H, 5.9. $C_{23}H_{26}O_9$ requires C, 61.9; H, 5.9%); *m/e* 446 (M^+).

3-O-*Benzyl*-8-*methoxycarbonyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (14).—To 3-*O*-benzyl-8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (6) (300 mg) dissolved in anhydrous tetrahydrofuran (10 ml) at −78 °C was added 15% n-butyl-lithium in n-pentane (0.5 ml); 2 min after addition of n-butyl-lithium, carbon dioxide was bubbled through the solution for 3 min while being allowed to warm to room temperature. 1.5% Aqueous HOAc (20 ml) was then added and the products extracted (3 × 20 ml) with ether. The ether phase was re-extracted with 5% aqueous NaOH (3 × 10 ml). To the basic aqueous extract was added crushed ice (20 g) followed by 6M HCl (10 ml). The pink solid which precipitated was dried (148 mg), then dissolved in ether and methylated with an excess of diazomethane overnight. Purification by t.l.c. [dichloromethane–acetone (49 : 1)] yielded as major product [R_F 0.79; chloroform–ethyl acetate (9 : 1)] the required methoxycarbonyl derivative as an *amorphous solid* (126 mg, 44%) (Found: C, 67.9; H, 6.1. $C_{28}H_{30}O_8$ requires C, 68.0; H, 6.1%); *m/e* 494 (M^+).

3-O-*Benzyl*-6-*methoxycarbonyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (25).—3-*O*-Benzyl-6-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (17) (300 mg) was treated with n-butyl-lithium as described above. No solid was obtained on acidification of the basic extract. The acidified mixture was, therefore, extracted with ether (3 × 20 ml) (70 mg). The product was methylated with an excess of diazomethane overnight as before and purification by t.l.c. [dichloromethane–acetone (49 : 1)] yielded as major product [R_F 0.84; chloroform–ethyl acetate (9 : 1)] the required methoxycarbonyl derivative as an *amorphous solid* (47 mg, 16%) (Found: C, 68.0; H, 6.1. $C_{28}H_{30}O_8$ requires C, 68.0; H, 6.1%); *m/e* 494 (M^+).

8-*Methoxycarbonyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (12).— 3-*O*-Benzyl-8-methoxycarbonyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (14) (50 mg) dissolved in methanol–acetic acid (9 : 1) (4 ml) was hydrogenated to completion over 10% Pd–C. T.l.c. purification (ether) yielded an *amorphous solid* (35 mg, 86%), R_F 0.41 (Found: C, 62.3; H, 6.0. $C_{21}H_{24}O_8$ requires C, 62.4; H, 6.0%); *m/e* 404 (M^+).

6-*Methoxycarbonyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (23).— 3-*O*-Benzyl-6-methoxycarbonyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (25) (42 mg) was hydrogenated as above. T.l.c. purification (ether) under the same conditions yielded an *amorphous solid* (30 mg, 87%), R_F 0.47 (Found: C, 62.2; H, 6.0. $C_{21}H_{24}O_8$ requires C, 62.4; H, 6.0%); *m/e* 404 (M^+).

3-O-*Acetyl*-8-*methoxycarbonyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (13).—Acetylation of 8-methoxycarbonyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (12) (30 mg) yielded a light yellow *amorphous solid* (quantitative); *m/e* 446 (M^+).

3-O-*Acetyl*-6-*methoxycarbonyl*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (24).—Acetylation of 6-methoxycarbonyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (23) (28 mg) yielded a light yellow *amorphous solid* (quantitative), with an n.m.r. spectrum identical to that obtained by Ferreira[7]; *m/e* 446 (M^+).

Acid-catalysed Bromine Migration in 6-*Bromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (15).—The 6-bromo-derivative (15) (3 mg) was dissolved in isopropyl alcohol (4 ml); 0.1 ml of the solution was evaporated on a rotary evaporator at 30 °C, redissolved in chloroform (0.1 ml) and 5 μl of this solution investigated by g.l.c. Concentrated HCl (0.5 ml) was added to the remaining 3.9 ml solution which was left at room temperature (25 °C) while 0.1-ml aliquots of the reaction solution were removed after 5 and 35 min, evaporated, and redissolved in $CHCl_3$ for g.l.c. investigation as described above. The remaining reaction solution in a well stoppered flask was placed in a boiling water-bath and again 0.1-ml aliquots sampled and prepared for g.l.c. as described above after 5, 15, 30, and 60 min. The results of the g.l.c. analysis are presented in the Table.

Peak area of individual peaks expressed as a percentage of the total peak area of the gas chromatogram

Reaction time/min	Reaction temperature (°C)	Retention time/s				
		358	535	625	704	783
0	25	0.50	0	0	99.50	0
5	25	0.55	0	0	99.45	0
35	25	0.43	0	0	99.57	0
5	95	1.12	0.54	0	68.56	29.77
15	95	3.49	0.89	1.40	31.52	62.59
30	95	5.54	0.36	0.97	11.29	81.85
60	95	5.40	1.61	2.05	4.83	86.12

The retention times correspond to the following products: 3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (1) (358s), unknowns (535 and 625 s), 6-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (15) (704 s), and 8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (4) (783 s).

An equation [$y = 96.069 \exp^{-0.072t}$] for the curve obtained for the decrease of 6-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin *vs.* reaction time at 95 °C was calculated by regression analysis employing the method of least squares, and was shown to fit the first four experimental points (up to 30 min) with a correlation coefficient of 0.999 indicating that the conversion of 6-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin into the isomeric 8-bromo-derivative is a first-order process, the half-life of the 6-bromo-derivative being 9.63 min under these conditions. *Ca.* 3% conversion to the 6-bromo-derivative was obtained when the same experiment was carried out with 8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (3 mg).

Acid-catalysed Conversion of 6-*Bromo*-3′,4′,5,7-*tetra*-O-*methyl*-(+)-*catechin* (15) *into the* 8-*Bromo-isomer* (4).—6-Bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (15) (48 mg) dissolved in isopropyl alcohol (20 ml) + concentrated HCl (2.5 ml) was heated in a tightly stoppered flask in a boiling water-bath for 40 min and the solvent then evaporated on a rotary evaporator at 40 °C. After purification by t.l.c. [dichloromethane–acetone (49 : 1)] the major product obtained (35 mg) was recrystallized twice from 96% ethanol as colourless needles (24 mg, 50%), m.p. 171—173 °C. No m.p. depression was observed on admixture with authentic 8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (4), and the n.m.r. spectra were also identical.

The Carboxylation of (+)-*Catechin with* CO_2 *in Sodium Hydrogencarbonate Solution*.—(+)-Catechin (200 mg) dissolved in saturated $NaHCO_3$ solution (10 ml) was heated on a boiling water-bath, while CO_2 was bubbled through the solution for 30 min.[7] Water was removed in a rotary evaporator. The dried residue was methylated with di-

methyl sulphate in anhydrous acetone–K_2CO_3. T.l.c. (ether) indicated products with R_F 0.85, 0.78, 0.74, 0.50, 0.47, 0.39, 0.29, 0.21, and 0.09. By using reference compounds, that product with R_F 0.74 was tentatively identified as 3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (1) and that with R_F 0.50 as 6-methoxycarbonyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (23). No 8-methoxycarbonyl isomer (12) could be identified. For further proof of identity the reaction mixture was acetylated. T.l.c. [ether–hexane (3 : 1)] revealed major products with R_F 0.66, 0.43, 0.34, 0.18, 0.13, and 0.08. With the aid of reference compounds that product with R_F 0.66 was identified as 3-*O*-acetyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (2) and that with R_F 0.43 as 3-*O*-acetyl-6-methoxycarbonyl-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (24). Small amounts of each of these products were isolated in chromatographically pure form by t.l.c. [ether–hexane (3 : 1)], and mass spectrometry showed them to have molecular weights 388, 446, 446, 404, 374, and 374 respectively, confirming the identity of the products with R_F 0.66 and 0.43. Mass and n.m.r. spectra of the product with R_F 0.34 identified it as 3-*O*-acetyl-6-methoxycarbonyl-3′,4′,5,7-tetra-*O*-methylepicatechin (31). The acetates with R_F 0.13 and 0.08, which represented *ca.* 80% of the reaction products, are under investigation.

Radio-labelled 3′,4′,5,7-Tetra-O-methyl-(+)-catechin.— A solution of (*U*-^{14}C)-(+)-catechin (specific activity 8.845 μCi mg^{-1}, Ciba-Geigy, Basel) (50 μCi, 10 μl) in absolute ethanol (2 ml) was added to (+)-catechin (1 g). The mixture was methylated with dimethyl sulphate in anhydrous acetone–K_2CO_3 giving an 85% yield of the methyl ether (from 95% ethanol), m.p. 149—151 °C. The specific activity of the product was determined by dissolving 1.45 mg in scintillation cocktail (10 ml) in a scintillation vial and counting for 20 min (Found: 286 030 counts min^{-1} mmol^{-1}).

Radio-labelled 8-Bromo-3′,4′,5,7-tetra-O-methyl-(+)-catechin.—Bromination of labelled 3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (346 mg, 1 mmol) with PHPB gave colourless needles (246 mg) (from 95% ethanol), m.p. 172—174 °C. The specific activity was determined by dissolving 1.569 mg of the product in scintillation cocktail (10 ml) in a scintillation vial and counting for 20 min (Found: 297 418 counts min^{-1} mmol^{-1}).

Bromine Migration.—6-Bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (15) (42.5 mg) and the radio-labelled 3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (1) (34.6 mg) were dissolved in isopropyl alcohol (20 ml) and concentrated HCl (2.5 ml) and heated on a boiling water-bath (95 °C) for 40 min. The solvent was evaporated at 40 °C on a rotary evaporator. The residue, dissolved in ether, was mixed with silica gel (3 g) (Merck, silica gel 60 230–400 mesh) and the solvent allowed to evaporate to yield a dry powder. The residue was chromatographed on a dry silica gel column (50 g) which was eluted with the following mixtures, 10-ml fractions being collected. ether–hexane (1 : 1), 50 ml; (3 : 1), 100 ml; and (4 : 1), until all products had eluted. Fractions 21—23, containing almost pure 8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (4), were combined (19 mg); recrystallization from methanol (1 ml) yielded colourless needles (12 mg), m.p. 173—174 °C. The specific activity was determined by dissolving the product (1.415 mg) in scintillation cocktail (10 ml) in a scintillation vial and counting for 20 min [Found: 132 155 counts min^{-1} mmol^{-1} = 44.43% of the specific activity of the synthetic radio-labelled 8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)catechin (4)].

The experiment was repeated with the exception that 8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (4) was used instead of the 6-bromo-compound (15). The specific activity of the 8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin isolated from the reaction was found to be 109 595 counts min^{-1} mmol^{-1} = 36.84% of the specific activity of the synthetic radio-labelled 8-bromo-3′,4′,5,7-tetra-*O*-methyl-(+)-catechin (4). These experiments show clearly that both C-6 ⟶ C-8 and C-8 ⟶ C-8 intermolecular bromine exchange takes place.

We thank the Council of Scientific and Industrial Research, Pretoria, the Sentrale Navorsingsfonds of this University, and the Wattle Bark Industry of South Africa Marketing Committee for financial support.

[0/797 *Received*, 27*th May*, 1980]

REFERENCES

[1] H. K. L. Hundt, Doctoral Thesis, University of the Orange Free State, Bloemfontein, November 1977.
[2] A. Pelter and P. I. Amenechi, *J. Chem. Soc.* (*C*), 1969, 887; A. Pelter, P. I. Amenechi, R. Warren, and S. H. Harper, *ibid.*, 1969, 2572.
[3] H. K. L. Hundt and D. G. Roux, *J. Chem. Soc., Chem. Commun.*, 1978, 696.
[4] K. Weinges, J. Perner and H.-D. Marx, *Chem. Ber.*, 1970, 2344.
[5] D. W. Engel, M. Hattingh, H. K. L. Hundt and D. G. Roux, *J. Chem. Soc., Chem. Commun.*, 1978, 695.
[6] T. C. van Soest, *Liebigs Ann. Chem.*, 1971, **754**, 137.
[7] D. Ferreira, Doctoral Thesis, University of the Orange Free State, Bloemfontein, January 1973.
[8] S. E. Drewes, D. G. Roux, H. M. Saayman, J. Feeney, and S. H. Eggers, *Chem. Commun.*, 1966, 370.
[9] S. E. Drewes, D. G. Roux, H. M. Saayman, S. H. Eggers, and J. Feeney, *J. Chem. Soc.* (*C*), 1967, 1302.
[10] J. J. Botha, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Chem. Commun.*, 1978, 700.
[11] I. C. du Preez, A. C. Rowan, and D. G. Roux, *Chem. Commun.*, 1970, 492.
[12] F. Wessely and G. H. Moser, *Monatsh. Chem.*, 1930, **56**, 97.
[13] H. Cerfontain, ' Mechanistic Aspects of Aromatic Sulphonation and Desulphonation.' Interscience, New York, 1968, p. 205.