X-Ray Structure, Conformation, and Absolute Configuration of 8-Bromotetra-O-methyl-(+)-catechin

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Summary The X-ray structure of 8-bromotetra-O-methyl-(+)-catechin confirms the substitution position of the bromine atom and the 2R,3S absolute configuration of the parent compound (+)-catechin; in the heterocyclic ring both the heteroatom and C-4 are marginally above the mean plane of the adjoining benzene ring, and its conformation is midway between half-chair and sofa arrangements.

BROMINATION of tetra-O-methyl-(+)-catechin (2) was presumed by Weinges et al.¹ to occur at C-8 on the premise that it represents a more reactive nucleophilic centre than C-6 and is sterically less hindered. Weinges¹ used an 8bromo derivative (4) for the synthesis of 4,8-linked biflavonoids via the 8-lithio intermediate. Considering that (+)-catechin (1) units constitute the 'lower' terminal units of most biflavonoids present in commercially important wattle ('Mimosa')² and guebracho³ extracts, and in other condensed tannins,⁴ and that their point of linkage (either 4,6 or 4,8) to the mono- or polyflavonoid residues is still a matter of conjecture, an unambiguous basis is required for their synthesis by similar means from 8- (4) and 6-bromo-3-O-benzyltetra-O-methyl-(+)-catechin (5),⁵ or for their differentiation through the chemical shifts of residual 6- or 8-protons.⁶ Assignments of the relative and absolute configuration of (+)-catechin have hitherto been based on chemical,⁷ n.m.r.,⁸ and optical rotation data,⁷ and attempted definition of the conformation of the heterocyclic ring could draw no distinction between the sofa and half-chair arrangements⁸ when in solution.

The 8-bromo derivative (3), m.p. 172-174 °C, was prepared by direct bromination of tetra-O-methyl-(+)-



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catechin (2) with 1 mol. equiv. of pyridinium hydrobromide perbromide in 95% ethanol from which it crystallizes. Suitable crystals were formed by crystallization from dibutyl ether at ambient temperatures. The resultant product, $C_{19}H_{21}BrO_6$ (3), was orthorhombic, space group $P2_12_12_1$, with a = 28.679(20), b = 12.967(10), c = 5.053(10)Å, $D_{\rm m} = 1.499$, $D_{\rm c} = 1.503$ g cm⁻³, Z = 4. Intensities of 1071 independent reflections were measured on a Philips 1100 X-ray diffractometer using graphite-monochromated Mo- K_{α} ($\lambda = 0.7017$ Å) radiation. The structure was solved by the heavy atom method using successive Fourier syntheses and refined anisotropically by least squares to a residual R of 0.046.[†] Hydrogen atoms were included in the calculation at expected positions, but not refined. The absolute configuration was determined by comparing R-values for the two enantiomeric structures, at an early stage of the refinement, yielding R-values of 0.102 and 0.112. The structure corresponding to the higher *R*-value may be rejected at high (> 99.9%) significance.⁹

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.



Structure of (6). Dihedral angles in degrees. Distances out of the mean plane of the adjacent benzenoid ring in pm.

The structure determination¹⁰ confirmed that bromine substitutes more readily at C-8 than at C-6 in the tetra-Omethyl-(+)-catechin (2), and that the phenyl and hydroxy groups at positions 2 and 3 in the puckered ring of the 8-bromo derivative (6) are in the trans-diequatorial position.

Both the heterocyclic oxygen and 4-carbon atom lie slightly above the mean plane of the adjacent benzene ring [cf. (6)], but this may be simply an effect of crystal packing. The conformation of the puckered ring is between a C-2-sofa and a C-2,C-3-half-chair conformation in the crystal. Formula (6) shows the dihedral angles in the ring. In the ideal C-2-sofa the C-3,C-4,C-10,C-9 dihedral angle would be zero, and in the C-2,C-3-half-chair it would be equal to the C-2,O,C-9,C-10 value. From the positions of the C and O atoms of the molecular skeleton the calculated dihedral angles of the hydrogen atoms attached to the heterocyclic ring are: between H_{2ax} and H_{3ax} 180°; between H_{3ax} and H_{4eq} and H_{4ax} 42 and 162°, respectively (all $\pm 4^{\circ}$).

The solid-state conformation thus confirms the absolute configuration of (+)-catechin as 2R,3S and defines the nature of the heterocyclic ring, free of the effects of conformational equilibrium as when in solution. Confirmation of the position of bromination at C-8 also defines the structure of 6-bromotetra-O-methyl-(+)-catechin (5), when considered in conjunction with its ¹H-n.m.r. spectrum.⁵

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