Crystal Structure and Absolute Configuration of (−)-3-*O*-Acetyl-6-bromo-3′,4′,5,7-tetra-*O*-methylepicatechin, a Reference Compound for the Aromatic Bonding Positions of 2,3-*cis*-Procyanidins†

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Determination of the structure of (−)-(2*R*,3*R*)-3-*O*-acetyl-6-bromo-3′,4′,5,7-tetra-*O*-methylepicatechin in the crystalline state confirmed the position of bromination and hence that of its 8-bromo isomer; both are key reference compounds for assessing the aromatic bonding positions in 2,3-*cis*-procyanidins. The half-chair conformation of the heterocyclic ring is shown to be in close agreement with the published structure of (−)-epicatechin. Determination of the absolute configuration of the derivative, in accord with earlier chemical evidence, is shown to hinge on detailed refinement of an extended data set.

Procyanidin condensed tannins, commonly encountered in plants, are constituted jointly and severally of 6- or 8-substituted (−)-2,3-*cis*-epicatechin and (+)-2,3-*trans*-catechin units.[1] As the result of restricted rotation about the interflavanyl bonds of oligomeric tannins,[2] various factors are likely to contribute jointly to the conformation of the higher procyanidin oligomers as exemplified by the 'tetrameric' profisetinidins.[3,4] They include variation in the interflavanyl aromatic substitution positions; in the conformations of heterocyclic ring systems of constituent flavanyl units; in their absolute configurations; and in their aromatic functionality.

Our earlier assessment of aromatic substitution positions on units of the (+)-2,3-*trans*-catechin type by n.m.r. chemical shift differences ($\Delta\delta_{6\text{-H},8\text{-H}}$) was dependent on the relative and absolute shift values of residual ring *A* protons in a range of 6- and 8-functionalised (+)-catechin tetramethyl ether derivatives in $CDCl_3$.[5] In turn, distinction between them required unambiguous structural assignment of (+)-3-*O*-acetyl-8-bromo-3′,4′,5,7-tetra-*O*-methylcatechin.[6] Our present provision of rigid proof of structure of (−)-3-*O*-acetyl-6-bromo-3′,4′,5,7-tetra-*O*-methylepicatechin serves to differentiate between 6- and 8-substituted (−)-epicatechin units in procyanidin oligomers on a similar basis.[7]

Simultaneous determination of the conformation of the heterocyclic ring of the (−)-6-bromoepicatechin derivative was of interest on account of considerable differences between the conformations reported recently for free phenolic (−)-epicatechin[8] and its 8-bromo-3′,4′,5,7-tetra-*O*-methyl derivative[9] (*cf.* ref. 8).

In the present work the absolute configuration of a (−)-epicatechin unit was attempted for the first time by direct physical means, as opposed to chemical methods previously adopted. This latter work may be summarised as follows. After the early accurate deductions by Freudenberg[10] based on a number of chemical analogies, Birch, Clark-Lewis, and Robinson,[11] through application of Prelog's atrolactic method[12] to (−)-epicatechin tetramethyl ether, proved beyond doubt the designation of the parent compound as (2*R*,3*R*)-3′,4′,5,7-tetrahydroxyflavan-3-ol. Next, Zust, Lohse, and Hardegger[13] applied the technically difficult method of exhaustive ozonolysis to both (−)-epicatechin and (+)-catechin. Selective destruction of the aromatic rings of the former, for example, gave 2-deoxy-D-xylitol of known absolute configuration in support of the foregoing assignment. We show here that determination of the absolute configuration of the crystalline 6-bromo derivative[7] hinges on detailed refinement of an extended data set.

Experimental

The title compound,[7] $C_{21}H_{23}BrO_7$ (M_r = 467.3), crystallises in the orthorhombic space group $P2_12_12_1$ (Z = 4) which is uniquely defined by the systematic absence of *h*00, 0*k*0, and 00*l*, reflections for $h,k,l \neq 2n$. The unit-cell constants a = 17.964(7), b = 13.167(3), and c = 9.127(8) Å (V = 2 158.8 Å^3) were determined from the accurate measurement of the 2θ-values of 25 reflections in the range $15 \leqslant \theta \leqslant 20°$. Intensity data were measured at room temperature in the range $2 \leqslant \theta \leqslant 30°$ with a Nonius CAD4 single-crystal diffractometer, with an incident beam graphite-crystal monochromator [λ(Mo-K_α) = 0.7017 Å]. For the structure solution all reflections with $0 \leqslant h \leqslant 25$, $0 \leqslant k \leqslant 18$, $0 \leqslant l \leqslant 12$ were recorded, and in order to determine the absolute configuration the Friedel-opposite reflections at negative *hkl* were measured directly after each reflection of positive index. A variable scan speed in ω—2θ mode, adjusted in terms of the intensity during pre-scan, but not exceeding 5.5° min^{-1} and not less than 1 min per reflection, was used. Data reduction consisted of correction for background, Lorentz polarisation, and absorption; μ = 18.7 cm^{-1}. Absorption corrections were determined empirically[14] from scans of 9 suitable reflections at $\chi \simeq 90°$, in 37 different orientations, 10° apart.

Results and Discussion

The structure was solved by Patterson methods and refined by the full-matrix least-squares technique, using the program SHELX.[15] In view of the fairly widespread practice[16] of basing enantiomer refinement on data sets not containing Friedel opposites, without applying absorption corrections and using unit weights, the importance of these factors was reiterated

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† *Supplementary data available* (SUP 56421, 2 pp.); anisotropic thermal paramaters. For details of Supplementary Publications see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, Issue 1, 1986. Structure factor tables are available from the editorial office on request.

Table 1. *R* Indices

	(2*S*,3*S*)	(2*R*,3*R*)
$R = \Sigma\lvert F_0 - F_c\rvert/\Sigma\lvert F_0\rvert$	0.084	0.062
$R_w = \Sigma w^{\frac{1}{2}}(\lvert F_0 - F_c\rvert)/\Sigma w^{\frac{1}{2}}(\lvert F_0\rvert)$	0.057	0.036
$R_g = [\Sigma w(\lvert F_0 - F_c\rvert)^2\Sigma w(\lvert F_0\rvert)^2]^{\frac{1}{2}}$	0.049	0.029

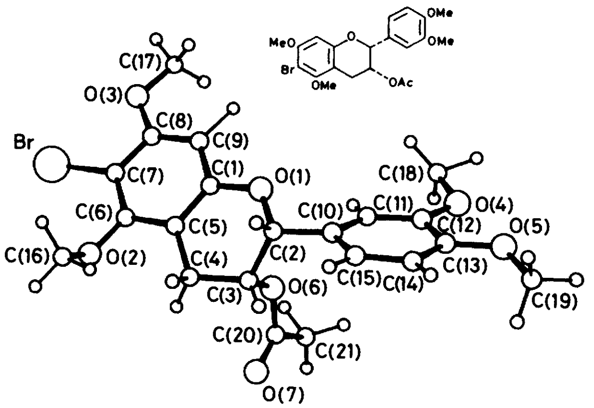

Figure 1. Perspective drawing of the molecule, defining the crystallographic numbering scheme for non-hydrogen atoms

Table 2. Refined fractional atomic co-ordinates (× 10^4) with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
Br	−198.7(4)	−2 332.5(5)	−2 433.3(11)
O(1)	1 887(2)	1 205(3)	−2 748(5)
O(2)	933(3)	−1 879(3)	−4 811(5)
O(3)	−44(3)	−604(3)	−364(5)
O(4)	2 563(3)	4 915(4)	−3 001(6)
O(5)	3 916(3)	4 997(4)	−3 875(5)
O(6)	1 634(2)	1 626(3)	−5 641(5)
O(7)	1 770(3)	1 277(4)	−8 024(5)
C(1)	1 422(3)	378(4)	−2 730(9)
C(2)	2 491(4)	1 193(4)	−3 780(7)
C(3)	2 194(4)	871(5)	−5 250(8)
C(4)	1 895(3)	−192(4)	−5 214(7)
C(5)	1 429(3)	−329(5)	−3 873(7)
C(6)	960(3)	−1 160(5)	−3 741(7)
C(7)	475(3)	−1 233(4)	−2 561(9)
C(8)	472(3)	−483(5)	−1 482(8)
C(9)	954(4)	323(5)	−1 542(7)
C(10)	2 869(3)	2 193(5)	−3 738(6)
C(11)	2 517(4)	3 078(6)	−3 374(9)
C(12)	2 878(4)	4 001(5)	−3 374(8)
C(13)	3 596(4)	4 050(5)	−3 854(7)
C(14)	3 957(4)	3 188(6)	−4 236(9)
C(15)	3 599(4)	2 254(7)	−4 177(8)
C(16)	1 510(5)	−2 614(6)	−4 713(9)
C(17)	−114(6)	200(7)	602(11)
C(18)	1 878(5)	4 898(7)	−2 278(12)
C(19)	4 609(5)	5 114(7)	−4 560(11)
C(20)	1 502(5)	1 787(6)	−7 059(10)
C(21)	1 007(4)	2 683(7)	−7 325(11)
H(2)	2 911(4)*	650(4)	−3 458(7)
H(3)	2 594(21)	901(29)	−5 850(42)
H(4,1)	1 556(3)	−311(4)	−6 175(7)
H(4,2)	2 350(3)	−729(4)	−5 213(7)
H(9)	985(20)	1 009(26)	−588(44)
H(11)	2 097(22)	3 013(33)	−3 152(49)
H(14)	4 550(4)	3 187(6)	−4 436(9)
H(15)	3 829(23)	1 632(30)	−4 401(50)
H(16,1)	1 362(5)	−3 108(6)	−5 611(9)
H(16,2)	1 558(5)	−3 054(6)	−3 720(9)
H(16,3)	2 036(5)	−2 250(6)	−4 945(9)
H(17,1)	−557(6)	−34(7)	1 328(11)
H(17,2)	−260(6)	913(7)	93(11)
H(17,3)	394(6)	290(7)	1 219(11)
H(18,1)	2 122(5)	5 574(7)	−1 811(12)
H(18,2)	1 613(5)	4 460(7)	−1 424(12)
H(18,3)	1 469(5)	5 109(7)	−3 090(12)
H(19,1)	4 709(5)	5 923(7)	−4 551(11)
H(19,2)	4 657(5)	4 832(7)	−5 667(11)
H(19,3)	5 013(5)	4 740(7)	−3 871(11)
H(21,1)	752(4)	2 864(7)	−8 365(11)
H(21,2)	1 271(4)	3 354(7)	−6 884(11)
H(21,3)	585(4)	2 420(7)	−6 572(11)

* Hydrogen atoms with low e.s.d. are riding on the corresponding carbon atoms.

during refinement of this structure. It was found that two modes of refinement indicated different enantiomers as the most likely absolute configuration. A standard data set, consisting of 1 025 reflections, not including Friedel opposites and not corrected for absorption, refined to unit weight *R* indices of 0.07 and 0.08 for the (2*S*,3*S*)- and (2*R*,3*R*)-conformations, respectively. This difference is highly significant in terms of a Hamilton test.[17] The *R* indices in refinement with the full data set of 2 410 reflections corrected for absorption and using a weighting scheme based on counting statistics, are shown in Table 1. There is an even more significant difference, but now favouring the opposite (2*R*,3*R*)-isomer. We accept the more detailed refinement as conclusive and as dramatic vindication of the cautionary measures advocated by Jones[16] for the refinement of absolute structure.

Some of the methyl hydrogen atoms that could not be located by difference synthesis were placed in calculated positions and the methyl groups were refined as rotating tetrahedra, using a common isotropic temperature factor for all hydrogen atoms. Anisotropic thermal parameters were refined for all non-hydrogen atoms. The refined co-ordinates are in Table 2, listed in terms of the atomic numbering scheme defined in Figure 1. The numbering of hydrogen atoms follows the carbon atom numbers.

Refinement was considered complete when all parameter shifts were less than 0.5σ and residual electron density nowhere exceeded 0.7 e Å^{-3}. All calculated bond lengths and angles compared well with accepted literature standards,[18] and the molecular conformation is firmly established in an absolute sense. A stereoscopic drawing of the molecule is shown in Figure 2. The aromatic ring *A* is flat; the largest deviation of a ring carbon atom from the best least-squares plane is 0.004 Å. The deviations of all ring *A* and ring *C* atoms from this plane are shown in Figure 3(A) together with the endocyclic torsion angles in these rings. The puckered ring has the symmetrical half-chair conformation $^2H_3$, in terms of the crystallographic C-atom numbering and as specified by its co-ordinates of pucker:[19] φ = 270°, θ = 126°, and amplitude *a* = 0.5 Å.

Comparison of the qualitative features of the aromatic ring *A* and heterocyclic ring *C* or the (−)-6-bromoepicatechin derivative [Figure 3(A)] with published values for (−)-epicatechin[8] [Figure 3(B)] shows that the distances (pm) of the heterocyclic atoms (1—4, 9, and 10; chemical numbering) from the mean plane of the aromatic ring are similar. However, a significant difference is the position of C(4) below this plane (−15 pm) in the derivative as compared with its position slightly above (+4.3 pm) in the free phenol. The torsion angles of heterocyclic bonds of the two compounds are similarly in agreement, with the exception that the angles at C(10)–C(4) differ by 6.2°. The puckered heterocyclic ring systems of both

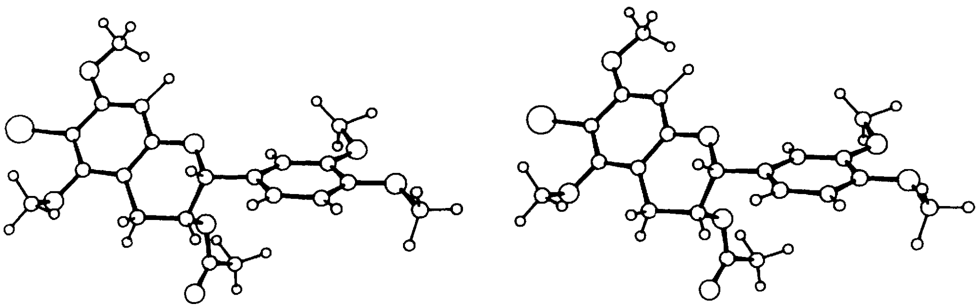

Figure 2. Stereoscopic drawing of the molecule

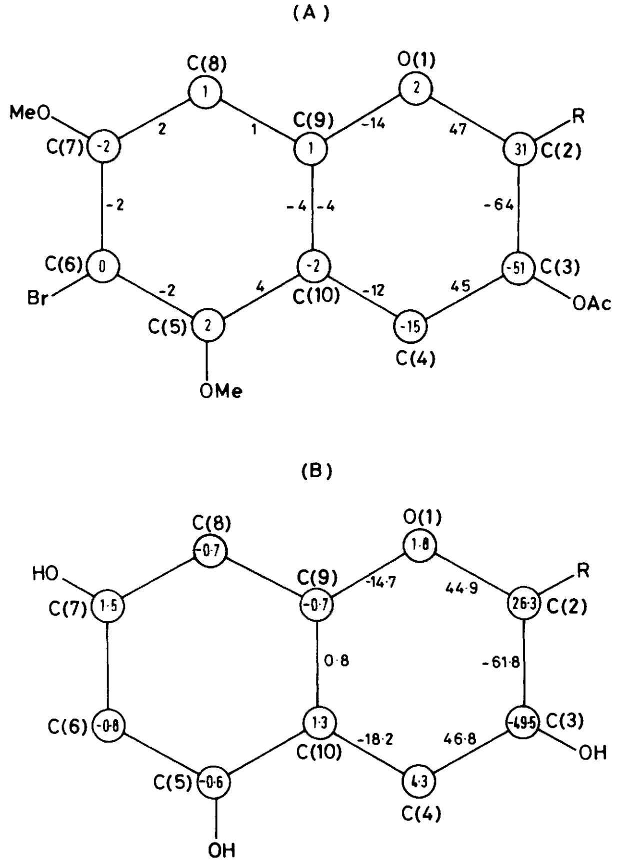

Figure 3. Schematic drawing using chemical numbering to show deviations of the ring *A* and ring *C* atoms from the mean plane through ring *A* in pm, and endocyclic torsion angles in degrees for (−)-3-*O*-acetyl-6-bromo-3′,4′,5,7-tetra-*O*-methylepicatechin (A) in comparison with published data[8] for (−)-epicatechin (B)

(−)-epicatechin and its 6-bromo methyl ether acetate correspond to half-chair conformations, both differing somewhat from that of (+)-8-bromo-3′,4′,5,7-tetra-*O*-methylcatechin, which lies somewhere between a C(2)-'sofa' and a C(2),C(3)-half-chair conformation.[6] The conformational similarity* between (−)-epicatechin and its derivative could prove to be significant in the conformational analysis of procyanidin oligomers, now preferably characterised as methyl ether acetates.[20]

Confirmation of the predicted 6-position of bromine in the (−)-epicatechin derivative also validates the structure of its 8-bromo isomer,[7] thus providing an essential basis for differentiating points of flavanyl substitution on 2,3-*cis*-3,4-*trans*-flavan-3-ol units in procyanidin homologues by means of ^{1}H n.m.r. shift differences.[7,20,21]

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* However, Begley, Whiting, and Haslam[9] describe (−)-8-bromotetra-*O*-methylepicatechin as having an 'envelope' heterocyclic ring conformation.