512. *The Absolute Configuration of the Leucoanthocyanidin, Peltogynol*

By C. H. Hassall and J. Weatherston

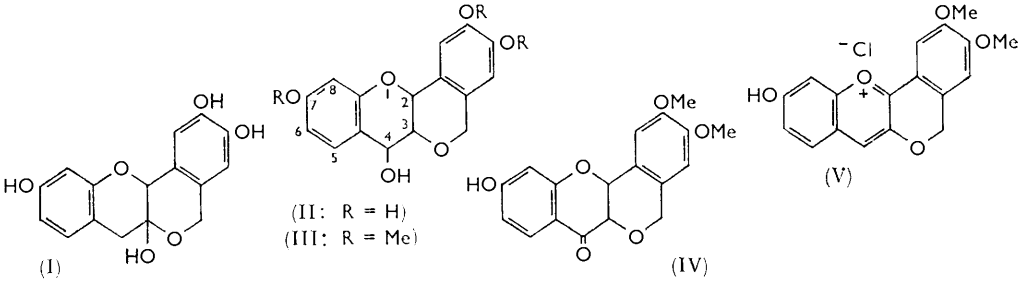
The relative configurations at positions 2, 3, and 4 in peltogynol (I) have been established by means of n.m.r. spectroscopy and degradation. The absolute configuration at position 3 is defined by comparison of (+)-2-methoxy-1-(2,4-dimethoxyphenyl)-3-(4,5-dimethoxy-2-methylphenyl)propane (VIII), obtained from tri-*O*-methyl-4-deoxypeltogynol (VI), with the related compound derived from (+)-catechin. This established the absolute configurations of peltogynol and peltogynol B as 2*S*,3*R*,4*S* and 2*S*,3*R*,4*R*, respectively. The conformation of peltogynol is discussed.

Peltogynol was first isolated by Robinson and Robinson [1] in connection with their investigations of the natural, colourless precursors of anthocyanidins. It was assigned the structure (I) but this was later revised to (II) when it was shown that oxidation of the methylation product (III) with manganese dioxide produced the compound (IV).[2,3] Additional support for the structure of peltogynol has been obtained through the synthesis of tri-*O*-methylpeltogynidin chloride (V).[4] Clearly, peltogynol is related to other natural

[1] G. M. Robinson and R. Robinson, *J.*, 1935, 744.
[2] W. R. Chan, W. G. C. Forsyth, and C. H. Hassall, *Chem. and Ind.*, 1957, 264.
[3] W. R. Chan, W. G. C. Forsyth, and C. H. Hassall, *J.*, 1958, 3174.
[4] R. Bryant, C. H. Hassall, and J. Weatherston, *J.* 1964, 4941.

leucoanthocyanidins that are now known to be flavan-3,4-diols.[5] We have undertaken the determination of the absolute configuration of peltogynol to allow further consideration of its relationship to these compounds.

The earlier studies of the degradation of peltogynol and the natural diastereoisomer, peltogynol B, have provided evidence of the relative configurations at positions 3 and 4 in these compounds.[2,6] Oxidation of the tri-*O*-methyl-derivatives of both compounds gave tri-*O*-methylpeltogynone (IV); evidently the two isomers differed only in the mode of attachment of the 4-hydroxyl group. As tri-*O*-methylpeltogynol was formed exclusively when tri-*O*-methylpeltogynone, with a relatively unhindered carbonyl group, was reduced with sodium borohydride, peltogynol and peltogynol B have been formulated with an

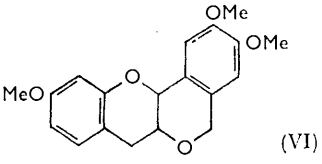


equatorial and an axial 4-hydroxyl group, respectively. Peltogynol B, unlike peltogynol, formed the anthocyanidin peltogynidin when heated in air at the relatively low temperature of 130°. This reaction involved elimination of the 4-hydroxyl group and the 3-hydrogen atom; it would occur most readily when this hydrogen atom had an axial conformation. This led to the assignment of the configurations 3H(*ax*),4H(*ax*)-*trans* and 3H(*ax*),4H(*eq*)-*cis* to peltogynol and peltogynol B, respectively. Degradative studies of tri-*O*-methyl-4-deoxypeltogynol (VI) have provided further evidence of this configuration at position 3.

The relationship of the configurations at positions 2 and 3 has been defined by n.m.r. spectroscopy. The ABC system of positions 2, 3, and 4 in tri-*O*-methylpeltogynol produced a complex series of bands in the region τ 4·5—6. It was not possible to distinguish particular spin–spin multiplets sufficiently to allow the assignment of reliable values to the coupling constants $J_{2,3}$ and $J_{3,4}$ in this case. However, the resonances arising from the 2- and 3-protons in tri-*O*-methylpeltogynone appeared as a well-defined pair of doublets (τ 4·8, 5·7), characteristic of such an AB system. The value of the coupling constant $J_{2,3}$ was 12·4 c./sec. This is in good agreement with values observed for various 3-substituted flavanones with 2,3-*trans* configurations whereas the coupling constants of *cis*-isomers of this and related AB series have very much lower values.[7]

With the knowledge of the relative configurations at positions 2, 3, and 4 it became possible to determine the absolute configuration of peltogynol by defining the stereochemistry at one of these centres. Tri-*O*-methyl-4-deoxypeltogynol (VI), which was obtained from tri-*O*-methylpeltogynol by hydrogenolysis, was reduced with sodium and ethanol in liquid ammonia. It is to be expected that hydrogenolysis with cleavage of the oxygen–carbon bonds involving carbon atoms at positions 2 and 7′ should occur under these conditions. After methylation, two major products were characterised. The compound, $C_{16}H_{12}O(OMe)_4$, m. p. 143°, was formed in greater yield. The n.m.r. spectrum showed signals at τ 2·7—3·6 (ar. *H*, 5), 5·25 (CH_2·O, 2), 6·21 (O·CH_3, 12), and 6·3—8·0 (ar. CH_2 and O·CH:, 5). The assignments are in good agreement with closely related cases [8]

[5] J. W. Clark-Lewis in " The Chemistry of the Flavonoid Compounds," ed. T. Geissman, Pergamon, London, 1962, p. 217.
[6] W. G. C. Forsyth, C. H. Hassall, and J. B. Roberts, *Chem. and Ind.*, 1958, 656.
[7] J. W. Clark-Lewis, L. M. Jackman, and T. M. Spotswood, *Austral. J. Chem.*, 1964, **17**, 632.
[8] L. M. Jackman, " Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, London, 1959.



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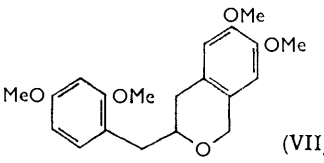
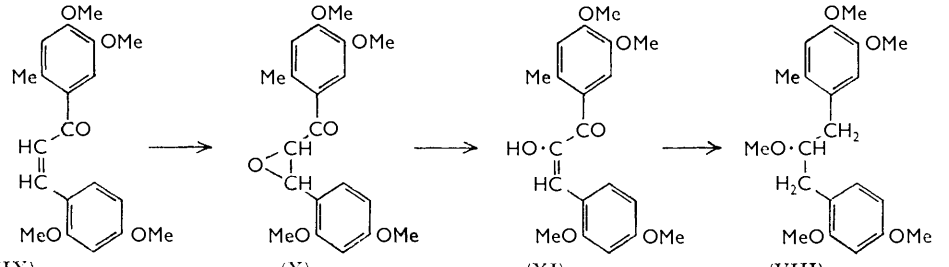


(VII)

and indicate the structure (VII). The second product of hydrogenolysis, $C_{16}H_{13}(OMe)_5$, $[\alpha]_D^{22}$ +86°, was identified as the (+)-compound (VIII), by its infrared and n.m.r. spectra and by comparison with the corresponding racemic compound. This was synthesised, unambiguously, from the chalcone (IX). The epoxide (X) was converted by sodium hydroxide into the dione (XI) which gave the methyl ether (VIII) through hydrogenation, followed by methylation. The infrared spectra of the degradation product and the synthetic compound showed the very small differences to be expected when comparing an optical isomer with the corresponding racemic form.



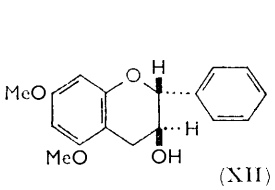
(IX) (X) (XI) (VIII)

The absolute configuration of the (+)-compound (VIII) has been established by comparing its optical rotatory dispersion curve with that of the (−)-compound (XIII) which was prepared from the tetra-*O*-methyl derivative of (+)-catechin (XII) by reduction with sodium and ethanol in liquid ammonia.[9] The optical rotatory dispersion (o.r.d.) curve of this substituted (−)-propan-2-ol (XIII) was measured by Djerassi [10] for the region 300—450 mμ. We obtained a similar curve for this region but, as a result of extending the measurement to 240 mμ, also observed a negative aromatic Cotton effect with a peak at 268 mμ. In the case of the (+)-compound (VIII) the o.r.d. curve was similar in form but opposite in sign. It follows that peltogynol has the same configuration at position 3 as (−)-catechin, which is known to have the absolute configuration, 2*R*,3*R*.[9] This, taken with the previous evidence of the 2H,3H,4H-*trans,trans* relationship, establishes the absolute configuration of peltogynol as 2*S*,3*R*,4*S*, represented by the formula (XIV). Peltogynol B, which differs from peltogynol only in the configuration at position 4, has the absolute configuration 2*S*,3*R*,4*R* (XV).

Although the evidence establishes the absolute configuration of peltogynol, it is not possible to define the conformation of this compound with the same certainty. Several investigators have discussed possible preferred conformations of the heterocyclic ring in flavans. Two alternatives have been favoured. In one case it has been proposed that five atoms in the heterocyclic ring are coplanar with the fused aromatic nucleus; [11] in the other, the heterocyclic ring is postulated as a " half-chair " [12] similar to that suggested for cyclohexene.[13] In the case of peltogynone, spectroscopic evidence favours the first alternative, represented in structure (XVI). The carbonyl frequency at 1687 cm.$^{-1}$ indicates that the 4-keto-group is conjugated and coplanar with the adjacent benzene

[9] A. J. Birch, J. W. Clark-Lewis, and A. V. Robertson, *J.*, 1957, 3586.
[10] C. Djerassi, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), 1959, **20**, 138.
[11] E. M. Philbin and T. S. Wheeler, *Proc. Chem. Soc.*, 1958, 167.
[12] E. A. H. Roberts, *Chem. and Ind.*, 1955, 631.
[13] D. H. R. Barton, R. C. Cookson, W. Klyne, and C. W. Shoppee, *Chem. and Ind.*, 1952, 21.

nucleus.[14] The value of the 2,3-coupling constant ($J_{2,3}$ = 12·4 c./sec.) is near the upper limit observed for the interaction of 1,2-diaxial protons.[15] This is attributed to the fact that the dihedral angle of these substituents is close to 180°.[7,16] The conformation of ring D is also represented in the " five-point-coplanar " form; this is preferred when ring C has similar geometry. However, we can offer no evidence to confirm that the conformations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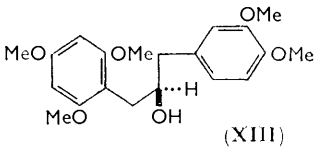
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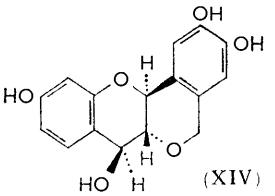
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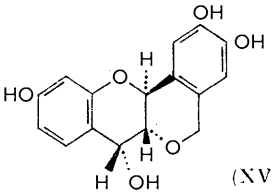
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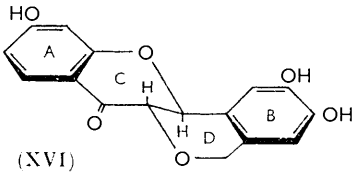
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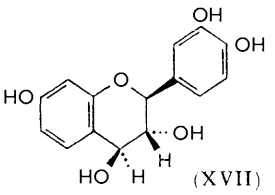
(XVII)

of the heterocyclic rings in peltogynol are the same as those in peltogynone. As the energy barrier between the " half-chair " and the " five-point-coplanar " conformation is small,[17] it is possible that the latter form in peltogynone is determined by the conjugation of the 4-keto group with ring A.

Absolute configurations of natural flavan-3,4-diols

Trivial name	$[\alpha]_D$	Substituents	Configuration	Ref.
Melacacidin	(−)	3′,4′,7,8-Tetrahydroxy-	2*R*,3*R*,4*R*	18
Teracacidin	(−)	4′,7,8-Trihydroxy-	2*R*,3*R*,4*R*	19
Leucorobinetinidin	(+)	3′,4′,5′,7-Tetrahydroxy-	2*R*,3*S*,4*R*	20
Mollisacacidin	(+)	3′,4′,7-Trihydroxy-	2*R*,3*S*,4*R*	19, 20
Leucofisetinidin	(−)	3′,4′,7-Trihydroxy-	2*S*,3*R*,4*S*	21, 22
	(−)	,, ,,	2*R*,3*R*,4*R*	23
		,, ,,	2*R*,3*R*,4*S*	23
Peltogynol	(+)	—	2*S*,3*R*,4*S*	—
Peltogynol B	(+)	—	2*S*,3*R*,4*R*	—

The absolute configurations of various natural flavan-3,4-diols have been determined (Table). In only one case, (−)-leucofisetinidin, has the 2*S*,3*R*,4*S* configuration of peltogynol been found. This relates to our earlier suggestion [3] that the biogenesis of peltogynol could involve condensation of formaldehyde, or its equivalent, with the corresponding flavan-3,4-diol, now identified as (−)-leucofisetinidin (XVII).

Experimental

Melting points were determined on a Kofler hot-stage. Ultraviolet absorption spectra were measured in ethanol on a Unicam S.P. 500 and infrared absorption spectra for solutions in chloroform on a Perkin-Elmer Infracord. N.m.r. spectra were determined with a Perkin-Elmer 40 Mc./sec. spectrometer in deuterated chloroform using tetramethylsilane as an internal

[14] T. H. Simpson and B. L. Shaw, *J.*, 1955, 655.
[15] K. L. Williams and W. S. Johnson, *J. Amer. Chem. Soc.*, 1961, **83**, 4625.
[16] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.
[17] W. B. Whalley, Symposium on Vegetable Tannis, Cambridge (1956), Society of Leather Trades' Chemists, Croydon, 1956, p. 151.
[18] J. W. Clark-Lewis and G. F. Katekar, *Proc. Chem. Soc.*, 1960, 345.
[19] J. W. Clark-Lewis and G. F. Katekar, *J.*, 1962, 4502.
[20] C. P. Lillya, S. E. Drewes, and D. G. Roux, *Chem. and Ind.*, 1963, 783.
[21] J. W. Clark-Lewis, *Rev. Pure Appl. Chem. (Australia)*, 1963, **12**, 96.
[22] S. E. Drewes and D. G. Roux, *Chem. and Ind.*, 1963, 532.
[23] S. E. Drewes and D. G. Roux, *Chem. and Ind.*, 1964, 1799.

standard. Alumina for chromatography was Spence type H, washed with ethyl acetate and activated at 110° for 48 hr. Thin-layer chromatography was on Kieselgel G (Merck) using the system benzene–dioxan–acetic acid (90 : 25 : 4), unless stated otherwise.

Tri-O-methylpeltogynone (IV).—Tri-*O*-methylpeltogynol was oxidised [3] with active manganese dioxide, to give needles, m. p. 210—215° (Found: C, 66·4; H, 5·4. Calc. for $C_{19}H_{18}O_6$: C, 66·6; H, 5·3%). N.m.r. spectrum (with number of protons in parentheses): τ 2·0—3·5 (multiplet, ar. *H*, 5); 4·8, 5·75 (pair of doublets, 2*H*,3*H*, 2; $J_{2,3}$ = 12·4 c./sec. using 40 Mc./sec. instrument, 12·7 c./sec. using 60 Mc./sec. instrument); 5·1 (singlet, aryl-CH_2, 2); 6·1—6·3 (multiplet, O·CH_3, 9).

6,7,7′-*Trimethoxychromano*(3′,2′:3,4)*isochroman* [*Tri*-O-*methyl*-4-*deoxypeltogynol* (VI)].—Tri-*O*-methylpeltogynol (7·3 g.), in dioxan (200 ml.), was added to reduced palladium prepared by shaking palladium chloride (2·61 g.) in methanol (100 ml.) under hydrogen. After the uptake was complete (18 hr.), the mixture was filtered to remove catalyst, and evaporated to give a gum which crystallised from methanol–chloroform as colourless *needles* (5·24 g.), m. p. 164—165°, $[\alpha]_D^{28}$ +258° (*c* 1·79 in tetrachloroethane), $\lambda_{max.}$ 282 mμ (log ε 3·76) (Found: C, 69·2; H, 6·2. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%).

(+)-2-*Methoxy*-1-(2,4-*dimethoxyphenyl*)-3-(4,5-*dimethoxy*-2-*methylphenyl*)*propane* (VIII).—Finely divided sodium (3·0 g.) was added to the isochroman (VI) (2·5 g.) in liquid ammonia (1·6 l.) and ethanol (400 ml.) during 30 min. After ammonium chloride (4 g.) had been added, the solvent was allowed to evaporate during 24 hr. An aqueous solution of the product was acidified with 2N-hydrochloric acid. Evaporation of the chloroform extract of the solution gave a yellow gum which was separated into neutral (850 mg. starting material) and phenolic fractions. The latter fraction, in 2N-sodium hydroxide (200 ml.) was methylated with dimethyl sulphate (6 ml.) during 3 hr. The mixture was extracted with chloroform which gave, on evaporation, a neutral gum (753 mg.). Acidification of the alkaline solution followed by extraction with chloroform gave crystalline, phenolic material (1·1 g.).

Thin-layer chromatography showed that the neutral gum was a mixture. The major component was obtained by chromatography of the gum (753 mg.) on an alumina column (32 g.). Elution with benzene, followed by repeated recrystallisation of the major fraction, from ethanol, gave colourless needles (157 mg.), m. p. 143—144°, $[\alpha]_D^{25}$ +100° (*c* 0·86 in chloroform), $\lambda_{max.}$ 282 mμ (log ε 3·83) [Found: C, 69·6; H, 7·04; OMe, 34·3. $C_{16}H_{12}O_5(OMe)_4$ requires C, 69·8; H, 7·02; OMe, 36·0%]. The compound gave no coloration with ferric chloride. It was identified as (+)-3-(2,4-*dimethoxybenzyl*)-6,7-*dimethoxychroman* (VII) by means of the n.m.r. evidence given above.

As no pure constituent of the alkali-soluble fraction could be obtained by recrystallisation alone, a portion (320 mg.) was methylated with dimethyl sulphate (0·5 ml.) and anhydrous potassium carbonate (550 mg.) in anhydrous acetone (30 ml.) during 9 hr. The brown gum obtained by working up in the usual way was purified by chromatography on alumina. Elution with benzene gave the (+)-*compound* (VIII) (60 mg.) as colourless needles, m. p. 92—93°, $[\alpha]_D^{27}$ (86° (*c* 1·5 in chloroform), $\lambda_{max.}$ 282 mμ (log ε 3·94) [Found: C, 70·1; H, 7·5; OMe, 43·4. $C_{16}H_{13}O_5(OMe)_5$ requires C, 69·9; H, 7·8; OMe, 43·3%].

2,4,4′,5′-*Tetramethoxy*-2′-*methylchalcone Epoxide* (X).—4,5-Dimethoxy-2-methylacetophenone (1·94 g.), 2,4-dimethoxybenzaldehyde (1·66 g.), 60% potassium hydroxide (4 ml.), and methanol (4 ml.) were heated under reflux for 2 hr. The mixture solidified on standing; 2,4,4′,5′-*tetramethoxy*-2′-*methylchalcone* (3·18 g.) was obtained as pale yellow plates, m. p. 119—120° (from methanol), $\lambda_{max.}$ 211, 247, 353 mμ (log ε 4·42, 4·17, 4·24), $\nu_{max.}$ 1668 cm.$^{-1}$ (C=O, unsat.) (Found: C, 67·0; H, 6·5. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%).

The chalcone (13 g.) was dissolved in methanol (98 ml.) and acetone (33 ml.) at 40°. 4N-Sodium hydroxide (9 ml.) and 30% hydrogen peroxide (13 ml.) were added. After 24 hr. at 0° the *epoxide* (10·2 g.) separated. It crystallised from ethyl acetate, m. p. 130—134°, $\lambda_{max.}$ 210, 233, 284 mμ (log ε 4·48, 4·40, 4·12), $\nu_{max.}$ 1675 cm.$^{-1}$ (CO) (Found: C, 67·0; H, 6·5. $C_{22}H_{22}O_6$ requires C, 67·0; H, 6·2%).

(±)-2-*Methoxy*-1-(2,4-*dimethoxyphenyl*)-3-(4,5-*dimethoxy*-2-*methylphenyl*)*propane* (VIII).—The epoxide (4 g.) in N-potassium hydroxide (24 ml.) and ethanol (50 ml.) was heated under reflux for 30 min. After removal of ethanol and acidification, the *dione* (XI) (3 g.) separated as crystals (from methanol), m. p. 143—146°, $\lambda_{max.}$ 209, 235 (infl.), 252, and 366 mμ (log ε 4·24, 392, 3·95, 4·15), $\nu_{max.}$ 3330 (OH), 1700 cm.$^{-1}$ (CO) (Found: C, 67·1; H, 6·4. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%).

The dione (1 g.) in ethanol (100 ml.) was hydrogenated in the presence of Adams catalyst during 3 days. The product was shown by thin-layer chromatography to contain several compounds. The mixture (627 mg.) was methylated by shaking in *NN*-dimethylformamide (6 ml.) with methyl iodide (1 ml.) and silver oxide (1 g.) for 20 hr. The required (±)-*derivative* (VIII) was obtained as a colourless gum by preparative thin-layer chromatography using Kieselgel G (Merck) and the solvent system: benzene–ether (7 : 3). The synthetic product (Found: C, 69·5; H, 7·7. $C_{21}H_{28}O_5$ requires C, 69·9; H, 7·8%) and the optically active isomer derived from peltogynol had infrared spectra which were almost identical; the very small differences, which were in the regions 1250—1266 and 1110—1125 cm.$^{-1}$, were to be expected when comparing an optical isomer with a racemic form. The synthetic compound and the (+)-isomer had identical R_F values for thin-layer chromatograms on Kieselgel using either the system benzene–dioxan–acetic acid (90 : 25 : 4) or benzene–ether (7 : 3).

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