949. *The Synthesis of Tri-O-methylpeltogynidin Chloride.*

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The structure of peltogynol has been confirmed by synthesis of tri-*O*-methylpeltogynidin chloride (IV).

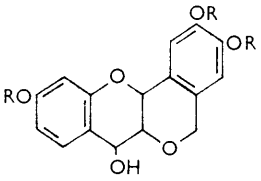
Peltogynol, the first naturally occurring leucoanthocyanidin to be investigated, has been assigned the molecular structure (I) as a result of degradative studies.[1-3] Further evidence of the isochroman ring in this structure, and in that of the corresponding anthocyanidin-[peltogynidin chloride (III)], has been obtained through the synthesis of tri-*O*-methylpeltogynidin chloride (IV).

Robinson and Robinson [3] reported that when tri-*O*-methylfisetinidin chloride was heated in the presence of formaldehyde, the reaction mixture gave colour reactions similar to those of tri-*O*-methylpeltogynidin salts, but the products were not isolated. We have been unsuccessful in attempts to prepare the tri-*O*-methylpeltogynidin chloride by similar means.

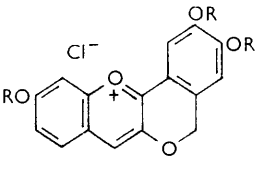
When 2′-hydroxy-4,4′,5-trimethoxychalcone-2-carboxylic acid (V) was treated with hydrogen peroxide and sodium hydroxide under conditions similar to those used by Algar and Flynn [4] for the synthesis of flavanols, a neutral product $C_{16}H_5O_4(OMe)_3$, m. p. 323—325°, was obtained. It was evident from the method of synthesis and from its properties that this was 6,7,7′-trimethoxychromono(3′,2′:3,4)isocoumarin (VI). The lactone band at 1740 cm.$^{-1}$ in the infrared absorption spectrum and the very close similarity of the ultraviolet absorption spectrum in 10% sodium hydroxide solution to that of 7,3′,4′-trimethoxyflavonol provided further evidence of the structure of this compound. Reduction of the flavonol derivative (VI) with lithium aluminium hydride gave a good yield of a compound $C_{16}H_{11}O_3(OMe)_3$, m. p. 201—202°. This has been assigned the same structure as tri-*O*-methylpeltogynol (II). The ultraviolet absorption spectra of tri-*O*-methylpeltogynol and the synthetic isomer are identical, and the small differences in the infrared and nuclear magnetic resonance (n.m.r.) spectra are attributable to stereochemical differences. Evidently reduction of both the lactone and the αβ-unsaturated carbonyl systems in the isocoumarin (VI) has occurred; there are well-established examples of both processes.[5,6]

[1] Chan, Forsyth, and Hassall, *Chem. and Ind.*, 1957, 264.
[2] Chan, Forsyth, and Hassall, *J.*, 1958, 3174.
[3] Robinson and Robinson, *J.*, 1935, 744.
[4] Algar and Flynn, *Proc. Roy. Irish Acad.*, 1934, *B*, **42**, 1.
[5] Hochstein and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3484.
[6] Siegel and Coburn, *J. Amer. Chem. Soc.*, 1951, **73**, 5494.

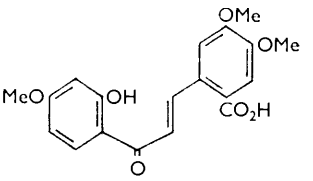
One notable difference in the properties of tri-*O*-methylpeltogynol and of the synthetic isomer deserves comment. The synthetic product, unlike the isomer derived from natural sources, is not oxidised by manganese dioxide to the corresponding 4-keto-derivative (VII). We attribute this difference to steric hindrance. Studies on the absolute configuration of peltogynol [7] have shown that the 4-hydroxyl-group in the isomer obtained from natural sources is relatively unhindered, but consideration of molecular models



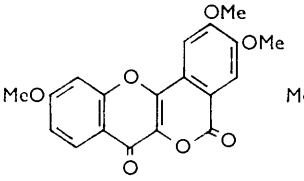
(I) R = H. (II) R = Me.



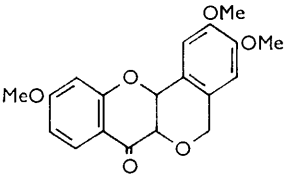
(III) R = H. (IV) R = Me.



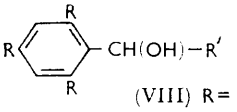
(V)



(VI)



(VII)



(VIII) R = H, R′ = CPh_3
(IX) R = OMe, R′ = Me
(X) R = H, R′ = Me

makes it clear that in some stereoisomers it is subject to very significant steric hindrances. We have established that the action of manganese dioxide on activated carbinols may be determined by steric hindrance. 1,2,2,2-Tetraphenylethanol (VIII) and 1-(2,4,6-trimethoxyphenyl)methanol (IX) were not oxidised by active manganese dioxide that, under similar conditions, converted tri-*O*-methylpeltogynol and 1-phenylethanol (X) into the corresponding ketones, in high yields.

The synthetic isomer (II) was converted into the corresponding anthocyanidin chloride by the action of hydrochloric acid in the presence of oxygen. The crystalline product was identical with tri-*O*-methylpeltogynidin chloride (IV) prepared in a similar manner from tri-*O*-methylpeltogynol.

Experimental

M. p.s were determined on a Kofler hot-stage apparatus. Ultraviolet absorption spectra were determined for ethanol solutions with a Unicam S.P. 500 and an Optica C.F. 4 spectrophotometer. Infrared spectra were measured with an Infracord 137 spectrometer for potassium bromide discs. Alumina for chromatography was Spence's type H, washed with ethyl acetate and activated at 110° for 48 hr.

Tri-O-methylpeltogynidin Chloride (IV).—Tri-*O*-methylpeltogynol (507 mg.), ethanol (5 ml.), and 2N-hydrochloric acid (50 ml.) were heated under reflux in a stream of oxygen for 3 hr. The mixture was cooled and filtered to remove starting material (281 mg.). The filtrate, when kept for one day, deposited clusters of dark purple needles of *tri-O-methylpeltogynidin chloride* (57 mg.), m. p. (with decomp.) 177—183° (Found: C, 57·0; H, 5·5; Cl, 8·2. $C_{19}H_{17}ClO_5,2H_2O$ requires C, 57·5; H, 5·3; Cl, 8·9%), $\lambda_{max.}$ 530 mμ (log ε 4·40).

2′Hydroxy-4,4′,5-trimethoxychalcone-2-carboxylic Acid (V) (with W. R. Chan).—Peonol (18·6 g.),[8] *m*-opianic acid (23·4 g.),[9] and 60% aqueous potassium hydroxide (45 ml.) were heated with methanol (45 ml.) for 2 hr. at 60—70°, then set aside for 2 days. The solid product was dissolved in water (100 ml.); acidification with 5N-hydrochloric acid gave a yellow solid which was removed and recystallised from chloroform–ethanol to give the *compound* (V) (27·5 g.),

[7] Hassall and Weatherston, unpublished work.
[8] Adams, *J. Amer. Chem. Soc.*, 1919, **13**, 260.
[9] Brown and Newbold, *J.*, 1952, 4397.

yellow needles, m. p. 227—228° (Found: C, 63·5; H, 5·0; O, 31·4. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·1; O, 31·3%), $\lambda_{max.}$ 260, 370 mμ (log ε 4·21, 4·44).

6,7,7′-*Trimethoxychromono*(3′,2′,4)*isocoumarin* (VI).—The preceding chalcone (23·4 g.) in methanol (702 ml.) was treated with 15% sodium hydroxide solution (140 ml.) and hydrogen peroxide (100-vol.; 70·2 ml.) at 0° for 16 hr. The pale yellow precipitate which was formed when the reaction mixture was acidified with 3N-hydrochloric acid recrystallised from chloroform–ethanol as colourless plates of *compound* (VI) (11·2 g.), m. p. 323—325° (Found: C, 64·4; H, 4·1. $C_{19}H_{14}O_7$ requires C, 64·4; H, 4·0%), $\lambda_{max.}$ 266, 324, 342, 358 mμ (log ε 4·44, 4·32, 4·42, 4·42), $\nu_{max.}$ 1740 cm.$^{-1}$ (lactone).

Reduction of 6,7,7′-*Trimethoxychromono*(3′,2′:3,4)*isocoumarin with Lithium Aluminium Hydride.*—6,7,7′-Trimethoxychromono(3′,2′:3,4)isocoumarin (9 g.) and lithium aluminium hydride (8·44 g.) were stirred in dry tetrahydrofuran (750 ml.) for 67 hr. On removal of the solvent under reduced pressure, water was added to the residue with cooling. Acidification with N-sulphuric acid caused the formation of a grey colloidal precipitate. This was extracted with chloroform (3 × 500 ml.); removal of the solvent from the dried extract gave a brown gum (7·0 g.). Purification on an alumina column with benzene and chloroform as solvents yielded colourless needles (2·35 g.) m. p. 201—202°, and a brown gum (4·65 g.) which gave a positive anthocyanidin test with hot concentrated hydrochloric acid. The crystalline *product* [Found: C, 65·9; H, 5·7. $C_{16}H_{11}O_3(OMe)_3$ requires C, 66·3; H, 5·9%], $\lambda_{max.}$ 280 and 286 mμ (log ε 3·86 and 3·86), $\nu_{max.}$ 3400 cm.$^{-1}$ (OH), gave a positive anthocyanidin test and a blue-violet colour with the Fearon–Mitchell reagent [10] but a negative ferric chloride test. The n.m.r. spectra of authentic tri-*O*-methylpeltogynol and the reduction product of the isocoumarin (VI) were measured in deuteriochloroform on a Perkin-Elmer 40 Mc./sec. spectrometer. The signals in the regions τ (p.p.m.) 2·4—3·5 (aromatic H) and 6·05—6·2 (OMe) were similar and gave the same integrals. Differences between the spectra are attributed to differences in stereochemistry.

Synthetic tri-O-methylpeltogynidin chloride (IV).—The product from the preceding experiment (540 mg.) was heated with ethanol (5 ml.) and 2N-hydrochloric acid (50 ml.) under reflux in a stream of oxygen for 3 hr. On cooling for 24 hr. a microcrystalline precipitate separated. Recrystallisation from methanol-2N-hydrochloric acid (1 : 1) gave dark purple needles (97 mg.), m. p. (with decomp.) 180—185°, m. p. after admixture with authentic tri-*O*-methylpeltogynidin chloride, 183—187° (Found: C, 56·9; H, 5·2; Cl, 8·7. Calc. for $C_{19}H_{17}ClO_5,2H_2O$: C, 57·5; H, 5·3; Cl, 8·9%), $\lambda_{max.}$ 528 mμ (log ε 4·39). The infrared and ultraviolet spectra of the synthetic and authentic tri-*O*-methylpeltogynidin chlorides were identical. Paper chromatography with butanol–acetic acid–water (4 : 1 : 5) and butan-1-ol–2N-hydrochloric acid with Whatman's No. 1 paper gave R_F 0·8 and 0·2, respectively, for both the synthetic and the authentic material.

Manganese Dioxide Oxidations.—(*a*) Active manganese dioxide [11] (2 g.) and 1-phenylethanol (500 mg.) in 99 : 1 chloroform–ethanol (50 ml.) were stirred vigorously at room temperature for 24 hr. The residue obtained by filtration and removal of solvent was an oil which gave an excellent yield (1·01 g.) of acetophenone 2,4-dinitrophenylhydrazone, m. p. 248—250°.

(*b*) 1,2,2,2-Tetraphenyl- [12] (VIII) and 1-(2,4,6-trimethoxyphenyl)-methanol [13] (IX) gave rise to quantitative yields of unchanged material when treated with manganese dioxide as in (*a*).

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[10] Fearon and Mitchell, *Analyst,* 1932, **57**, 372.
[11] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1104.
[12] Levy and Lagrave, *Bull. Soc. chim. France,* 1928, **1928**, **43**, 437.
[13] Kenyon and Mason, *J.*, 1952, 4964.