872. *Flavan Derivatives. Part VI.*[1] *The Absolute Configurations of Some Flavan-3,4-diol Leucoanthocyanidins: (−)-Melacacidin, (−)-Teracacidin, and (+)-Mollisacacidin.*

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The absolute configuration of (−)-melacacidin has been established as 2R,3R,4R by conversion of its tetramethyl ether into (−)-7,8,3′,4′-tetramethoxy-2,3-*cis*-flavan-3-ol, an analogue of (−)-epicatechin tetramethyl ether; (−)-teracacidin is assigned the 2R,3R,4R-configuration by analogy with (−)-melacacidin. The 2R,3S-configuration of (+)-mollisacacidin has been confirmed by conversion of its trimethyl ether into (−)-7,3′,4′-trimethoxy-2,3-*trans*-flavan-3-ol, an analogue of (+)-catechin tetramethyl ether.

MELACACIDIN TETRAMETHYL ETHER (I) is known to be a *cis-cis*-compound,[2, 3] and hydrogenolysis of the 4-hydroxyl group over a palladium catalyst gave (−)-7,8,3′,4′-tetramethoxy-2,3-*cis*-flavan-3-ol (II), as already briefly reported.[4] The expected 2,3-*cis*-configuration in the product (II) was confirmed by the ready formation of the flaven (III)

¹ Part V, *J.*, 1962, 3858.
² King and Clark-Lewis, *J.*, 1955, 3384.
³ Clark-Lewis and Mortimer, *J.*, 1960, 4106.
⁴ Clark-Lewis and Katekar, *Proc. Chem. Soc.*, 1960, 345.

by *trans*-elimination of the elements of toluene-*p*-sulphonic acid from the 3-toluene-*p*-sulphonate. The new (−)-flavan-3-ol is thus a *cis*-compound, like epicatechin, and its lævorotation shows that it is an analogue of (−)-epicatechin tetramethyl ether (IV) rather than the enantiomorph. This is supported by the greater lævorotation of the acetate and lower lævorotation of the toluene-*p*-sulphonate when compared with the parent (−)-7,8,3′,4′-tetramethoxy-2,3-*cis*-flavan-3-ol (II), as in the case of the corresponding derivatives of (−)-epicatechin tetramethyl ether (IV). The latter is known to have the 2*R*,3*R*-configuration [5] and it follows that the new flavan-3-ol has the same configuration (II).
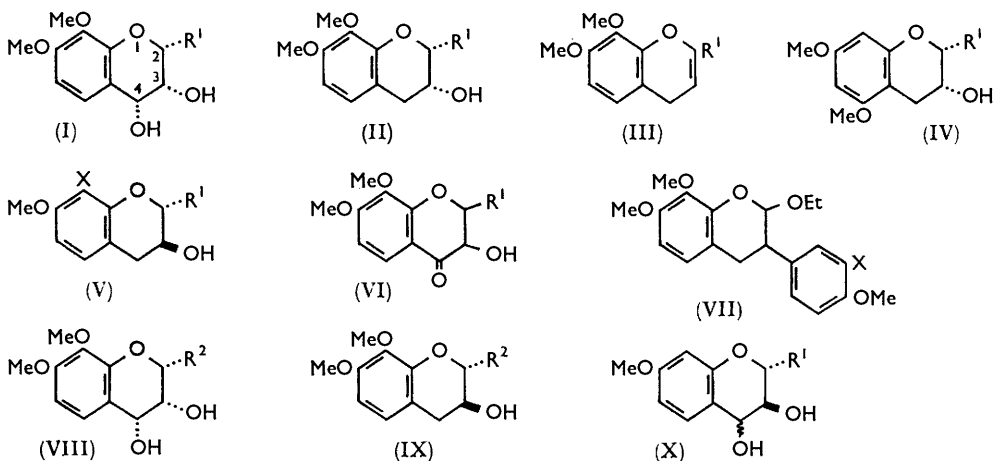
[R¹ = 3,4-Dimethoxyphenyl;   R² = *p*-Methoxyphenyl]

(−)-Melacacidin tetramethyl ether is therefore (2*R*,3*R*,4*R*)-7,8,3′,4′-tetramethoxy-flavan-3,4-diol (I), and (−)-melacacidin itself has the 2*R*,3*R*,4*R*-configuration (configurations are specified in the *R* and *S* notation described by Cahn, Ingold, and Prelog [6]). The 2*R*,3*R*-configurations of melacacidin and its tetramethyl ether (I) follow directly from the 2*R*,3*R*-configuration of the derived flavan-3-ol (II) and the 3*R*,4*R*-configuration from the *cis*-glycol formulation, which was inferred originally from the ready formation of an isopropylidene derivative from the tetramethyl ether.[2,3] The *cis*-*cis*-configuration of melacacidin tetramethyl ether is confirmed by the spin-spin coupling constants (J) for the 2-, 3-, and 4-protons derived from nuclear magnetic resonance measurements.[7] Values [8] for melacacidin tetramethyl ether ($J_{2,3} = ca.$ 1; $J_{3,4} = 4·0$ c./sec.) and its diacetate ($J_{2,3} = 1$; $J_{3,4} = 4·1$ c./sec.) are consistent with the 2(*ax*)H : 3(*eq*)H : 4(*ax*)H-conformation of the *cis*-*cis*-configuration.[7]

The absolute configurations of (−)-melacacidin and its tetramethyl ether (I) rest on that of (−)-7,8,3′,4′-tetramethoxyflavan-3-ol (II), and to provide unequivocal proof that the latter compound is a 2,3-*cis*-flavan-3-ol we prepared (±)-7,8,3′,4′-tetramethoxy-2,3-*cis*-flavan-3-ol (racemate of II) and the (±)-*trans*-isomer (racemate of V; X = OMe). The authentic *cis*-racemate, prepared by hydrogenolysis of synthetic 7,8,3′,4′-tetramethoxy-2,3-*cis*-flavan-3,4-*cis*-diol [(±)-melacacidin tetramethyl ether [2]], gave an infrared absorption spectrum (in chloroform) indistinguishable from that of the lævorotatory enantiomer (II). Its 3-toluene-*p*-sulphonate was smoothly converted into the flaven (III) identical with that

[5] Freudenberg, *Sci. Proc. Roy. Dublin Soc.*, 1956, **27**, 153; Birch, Clark-Lewis, and Robertson, *J.*, 1957, 3586; Hardegger, Gempeler, and Züst, *Helv. Chim. Acta*, 1957, **40**, 1819; Züst, Lohse, and Hardegger, *Helv. Chim. Acta*, 1960, **43**, 1274.

[6] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.

[7] Clark-Lewis and Jackman, *Proc. Chem. Soc.*, 1961, 165.

[8] Jackman and Clark-Lewis, unpublished results.

formed, as already mentioned, from the (—)-3-toluene-*p*-sulphonate in a reaction with hydrazine which is diagnostic for the 2,3-*cis*-configuration. The authentic *trans*-racemate (V; X = OMe) was prepared in two stages from (±)-7,8,3′,4′-tetramethoxy-2,3-*trans*-flavanonol (VI): reduction with sodium borohydride, or catalytically over Adams catalyst in ethanol, gave the intermediate 2,3-*trans*-3,4-*cis*-diol,[9a] which was hydrogenolysed over a palladium catalyst to (±)-7,8,3′,4′-tetramethoxy-2,3-*trans*-flavan-3-ol (racemate of V; X = OMe). The infrared absorption of the *trans*-flavanol differed considerably from that of the *cis*-isomer, as is the case with the catechin–epicatechin derivatives, and the configuration of the product was confirmed by the 1,2-rearrangement which is diagnostic for the 2,3-*trans*-configuration in flavan-3-ols: the racemic tetramethyl ether (racemate of V; X = OMe) was treated with phosphorus pentachloride in benzene, and the intermediate 2-chloroisoflavan was converted by boiling ethanol into 2-ethoxy-7,8,3′,4′-tetramethoxy-isoflavan (VII; X = OMe). The geometrical configurations of the (—)-*cis*-flavan-3-ol (II) and its racemate, and of the (±)-*trans*-flavan-3-ol (racemate of V; X = OMe) are thus firmly established. They are, moreover, supported by nuclear magnetic resonance measurements (*cis*-isomer, $J_{2,3}$ = *ca.* 1; *trans*-isomer, $J_{2,3}$ = 7·9 c./sec.).[8]

(—)-Teracacidin[9b] is regarded as a *cis*-*cis*-compound, and molecular rotation values of its derivatives compared with those of (—)-melacacidin show that these flavandiols are configurationally analogous, so that (—)-teracacidin may be designated (2R,3R,4R)-7,8,4′-trihydroxyflavan-3,4-diol. Intended confirmation of the stereochemistry of teracacidin trimethyl ether (VIII) through hydrogenolysis to the corresponding *cis*-flavan-3-ol was prevented by formation of phenolic products in the hydrogenation of (—)-teracacidin trimethyl ether (VIII) and of its synthetic racemate, and no crystalline *cis*-flavanol was obtained. Crystalline (±)-7,8,4′-trimethoxy-2,3-*trans*-flavan-3-ol (racemate of IX) was isolated without difficulty after hydrogenation of the corresponding synthetic 2,3-*trans*-compound [(±)-7,8,4′-trimethoxy-2,3-*trans*-3,4-*cis*-diol[9b]].

(—)-7,3′,4′-Trihydroxyflavan-3,4-diol [(—)-leucofisetinidin] is known to have the 2S,3R-configuration as hydrogenolysis gives (+)-fisetinidol, an analogue of 2S,3R-(—)-catechin.[10] (+)-Mollisacacidin[11] is the enantiomorph of the (—)-leucofisetinidin from quebracho wood, and its 2R,3S-configuration has now been confirmed by hydrogenolysis of (+)-mollisacacidin trimethyl ether (X) to (—)-fisetinidol trimethyl ether (V; X = H) over palladous chloride. The physical constants of the (—)-fisetinidol trimethyl ether obtained in this way agree with those reported for the enantiomorph[10] and are close to the values recorded recently for the trimethyl ether prepared from natural (—)-fisetinidol isolated from *Acacia mollissima* heartwood.[12] Weinges[10] used molecular-rotation differences in a series of derivatives of catechin and (+)-fisetinidol to show that the latter is an analogue of (—)-catechin. (—)-Fisetinidol trimethyl ether (V; X = H), obtained by hydrogenolysis of (+)-mollisacacidin trimethyl ether, is an analogue of (+)-catechin tetramethyl ether, and this was proved by effecting the molecular rearrangement already discussed in the case of (±)-7,8,3′,4′-tetramethoxy-2,3-*trans*-flavan-3-ol (racemate of V; X = OMe): (—)-fisetinidol trimethyl ether (V; X = H), $[\alpha]_D$ —28° (in $C_2H_2Cl_4$), was converted with phosphorus pentachloride into the 2-chloroisoflavan and thence into (+)-2-ethoxy-7,3′,4′-trimethoxyisoflavan (VII; X = H), $[\alpha]_D$ +102° (in $CHCl_3$). Occurrence of the rearrangement proves the 2,3-*trans*-configuration of (—)-fisetinidol trimethyl ether, and the high dextrorotation of the isoflavan produced shows that the flavanol belongs to the (+)-catechin series, for (+)-catechin tetramethyl ether, $[\alpha]_D$ —13° (in $C_2H_2Cl_4$), gives (+)-2-ethoxy-5,7,3′,4′-tetramethoxyisoflavan with $[\alpha]_D$ +119° (in $C_2H_2Cl_4$) when submitted to the rearrangement.[13] The 2R,3S-configurations for (—)-fisetinidol

[9] (*a*) Joshi and Kulkarni, *Chem. and Ind.*, 1954, 1456; *J. Sci. Ind. Res. India*, 1957, **16**, *B*, 307; (*b*) Clark-Lewis, Katekar, and Mortimer, *J.*, 1961, 499.
[10] Weinges, *Annalen*, 1958, **615**, 203.
[11] Clark-Lewis and Roux, *J.*, 1959, 1402.
[12] Roux and Paulus, *Biochem. J.*, 1961, **78**, 120.
[13] Clark-Lewis and Korytnyk, *J.*, 1958, 2367.

trimethyl ether (V; X = H) and (+)-mollisacacidin trimethyl ether (X) are therefore well established. On the assumption that mollisacacidin (leucofisetinidin) is a *cis*-glycol [11] the complete configuration may be specified as 2*R*,3*S*,4*S*, although formulation of the leucofisetinidins as *cis*-glycols rests on their easy conversion into cyclic derivatives and some flavan-3,4-*trans*-diols are now known to yield cyclic derivatives also.[14, 15] Flavan-3,4-*cis*- and -*trans*-diol carbonates have been obtained,[14, 15] and it has been shown that several flavan-3,4-*trans*-diols give the isopropylidene derivatives of the corresponding flavan-3,4-*cis*-diol, usually in low yield.[15] Final solution of the 3,4-configuration of mollisacacidin therefore awaits the results of nuclear magnetic resonance measurements.* The racemic 7,8,4′-trimethoxy- and 7,8,3′,4′-tetramethoxy-flavan-3,4-diols already mentioned are obtained from the corresponding 2,3-*trans*-dihydroflavonols by methods which are known in other cases [15] to lead to 2,3-*trans*-flavan-3,4-*trans*-diols. These two diols are described above as 2,3-*trans*-3,4-*cis*-compounds to conform with previous descriptions,[9] which may, however, shortly need revision to 2,3-*trans*-flavan-3,4-*trans*-diols.*

<div align="center">EXPERIMENTAL</div>

(±)-7,8,3′,4′-*Tetramethoxy*-2,3-cis-*flavan*-3,4-cis-*diol* (*Racemate of* I).—This was prepared by hydrogenation of 7,8,3′,4′-tetramethoxyflavonol [2] (3 g.) and purified by chromatography on alumina (100 g.) deactivated with water (10 g.). The diol (1·6 g.), m. p. 136° (lit.,[2] m. p. 135—136°), was eluted with benzene–ether (1 : 1); it gave the isopropylidene derivative, m. p. 163°, and the carbonate, m. p. 205° (decomp.) (lit.,[2] 163° and 204—205°). The diacetate crystallised from ethanol in needles, m. p. 176° alone and when mixed with a sample m. p. 176°, which had changed from m. p. 157—158° during storage.[2]

(±)-7,8,3′,4′-*Tetramethoxy*-2,3-cis-*flavan*-3-ol (*Racemate of* II).—(±)-Melacacidin tetramethyl ether (0·2 g.) in methanol (10 c.c.) was hydrogenated for 12 hr. at 50°/66 atm. over palladous chloride (0·02 g.). The filtrate from the catalyst was diluted with water before extraction with chloroform, and evaporation of the extract left an oil which was chromatographed on alumina (10 g.) deactivated with water (1 g.). The column was developed with benzene (50 c.c.) and with benzene–ether (1 : 1; 20 c.c.) before this eluent (30 c.c.) removed (±)-7,8,3′,4′-*tetramethoxy*-2,3-cis-*flavan*-3-ol (0·05 g., 26%) which crystallised from methanol in prisms, m. p. 118—119° (Found: C, 65·9; H, 6·5. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%). Further elution with benzene–ether (1 : 1; 30 c.c.) containing ethanol (1%) removed the diol (0·06 g.). (±)-3-*Acetoxy*-7,8,3′,4′-*tetramethoxy*-2,3-cis-*flavan* crystallised from ethanol in prisms, m. p. 135°, raised to m. p. 137° by two recrystallisations (Found: C, 65·0; H, 6·3. $C_{21}H_{24}O_7$ requires C, 64·9; H, 6·2%). The 3-*toluene*-p-*sulphonate*, prepared by heating the flavan-3-ol (0·5 g.) with toluene-*p*-sulphonyl chloride (0·4 g.) in pyridine (1 c.c.) at 100° for 40 min. and then diluting the mixture with ethanol, crystallised from ethanol in prisms (0·35 g., 48%), m. p. 183° (decomp.), which became orange on exposure to air and light (Found: C, 62·3; H, 5·7. $C_{26}H_{28}O_8S$ requires C, 62·4; H, 5·6%).

(−)-7,8,3′,4′-*Tetramethoxy*-2,3-cis-*flavan*-3-ol (II).—(*a*) (−)-Melacacidin tetramethyl ether [3] (0·2 g.), m. p. 146°, $[\alpha]_D^{17}$ −84° (in EtOH), was hydrogenated in methanol (10 c.c.) for 12 hr. at 50°/66 atm. over palladous chloride (0·02 g.). The filtrate from the catalyst was diluted with water, and extraction of the solution with chloroform gave an oil which was chromatographed on alumina (10 g.) deactivated with water (1 g.). The column was developed with benzene (40 c.c.) and then with benzene–ether (1 : 1; 50 c.c.) which removed the flavan-3-ol as an oil (0·04 g., 21%); further elution with benzene–ether mixture (1 : 1; 25 c.c.) containing ethanol (1%) gave recovered diol (0·05 g.). Crystallisation of the oily flavanol from aqueous methanol gave (−)-7,8,3′,4′-*tetramethoxy*-2,3-cis-*flavan*-3-ol *dihydrate* in prisms, m. p. 88—89°, $[\alpha]_D^{18}$ −101° (1·5% in ethanol) (Found: C, 59·5; H, 6·8. $C_{19}H_{22}O_6,2H_2O$ requires C, 59·7; H, 6·9%). The anhydrous flavanol did not crystallise. (−)-3-*Acetoxy*-7,8,3′,4′-*tetramethoxy*-2,3-cis-*flavan*, prepared by acetylation with acetic anhydride–pyridine at room temperature for 24 hr., crystallised from ethanol in needles, m. p. 111—112° raised by two recrystallisations

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* *Note added in the proof.* Nuclear magnetic resonance on the diacetates indicates *trans–trans* stereochemistry. Mollisacacidin therefore has the 2*R*,3*S*,4*R*-configuration.

[14] Corey, Philbin, and Wheeler, *Tetrahedron Letters*, 1961, No. 13, 429.
[15] Bokadia, Brown, Kolker, Love, Newbould, Somerfield, and Wood, *J.,* 1961, 4663.

to 112—113°, $[\alpha]_D^{15 \cdot 5}$ —111° (0·95% in $CHCl_3$) (Found: C, 64·9; H, 6·2%). The infrared absorption spectra of the ($\pm$)- and the (—)-acetate in chloroform were identical. The (—)-3-*toluene*-p-*sulphonate* (48%) was prepared as described above for the racemate and crystallised from ethanol in needles, m. p. 167° (decomp.), $[\alpha]_D^{15 \cdot 5}$ —39° (1·6% in $CHCl_3$) (Found: C, 62·8; H, 5·8%). The m. p. was not depressed on admixture with the racemate.

(*b*) Crude melacacidin [3] (0·5 g.) in methanol was hydrogenated for 12 hr. at 30°/70 atm. over palladous chloride (0·05 g.). The filtrate from the catalyst was evaporated under reduced pressure and the residue (0·5 g.) was treated with dimethyl sulphate (1·0 g.) and potassium carbonate (3·8 g.) in acetone (20 c.c.) for 10 hr. The filtrate was mixed with aqueous ammonia (*d* 0·88; 0·5 c.c.) before evaporation under reduced pressure; the residue was dissolved in benzene–ether and washed with aqueous sodium hydroxide before being chromatographed on alumina (20 g.) deactivated with water (2 g.) as described under (*a*); this gave a dark brown oil (0·17 g.), the flavan-3-ol (0·05 g., 9%), m. p. 88—89°, and (—)-melacacidin tetramethyl ether (0·1 g.), m. p. 142°.

7,8,3′,4′-*Tetramethoxyflav-2-en* (III).—(*a*) The (—)-7,8,3′,4′-tetramethoxy-2,3-*cis*-flavan-3-ol toluene-*p*-sulphonate (0·35 g.) was heated with anhydrous hydrazine (10 c.c.) in a sealed tube at 132° (chlorobenzene vapour) for 40 min. and next day the crystalline flaven (0·1 g., 47%) was collected on a sintered-glass filter; 7,8,3′,4′-*tetramethoxyflav-2-en* crystallised from ethanol in prisms, m. p. 104—105° (decomp.) unchanged by recrystallisation (Found: C, 69·5; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%), $\lambda_{max.}$ (in 95% EtOH) 210 (ϵ 42,000), 248 (ϵ 17,200), and 275 mμ (ϵ 10,000), $\lambda_{min.}$ 240 (ϵ 16,700) and 270 mμ (ϵ 9800).

(*b*) The flav-2-en was similarly obtained in prisms, m. p. 104—105° alone and when mixed with that described under (*a*), from the ($\pm$)-toluene-*p*-sulphonate.

($\pm$)-7,8,3′,4′-*Tetramethoxy-2,3-trans-flavanonol* (VI).—This was prepared as described by Joshi and Kulkarni; [9a] when the chalcone dibromide (from 0·6 g. of 2′-acetoxy-3′,4′,3,4-tetramethoxychalcone) was boiled with 1 : 4 aqueous acetone (10 c.c.) for 13—15 min. and then extracted with ether, an intermediate bromo-compound (2-acetoxy-3,4-dimethoxyphenyl α-bromo-β-hydroxy-β-3,4-dimethoxyphenethyl ketone ?) crystallised from the dried ($MgSO_4$) ethereal solution in prisms (0·32 g., 42%), m. p. 152—153° (Found: C, 53·4; H, 5·0; Br, 15·9. $C_{21}H_{23}BrO_8$ requires C, 52·2; H, 4·8; Br, 16·5%). Alteration of the period of heating (13—15 min.) or the scale of reaction reduced the yield of the bromo-compound. The bromo-compound (0·32 g.) was converted by boiling it for 3 min. with 10% aqueous sodium carbonate into ($\pm$)-7,8,3′,4′-tetramethoxy-2,3-*trans*-flavanonol (0·2 g., 84%), needles, m. p. 166° (from ethanol).

($\pm$)-7,8,3′,4′-*Tetramethoxy-2,3-trans-flavan-3,4-cis-diol*.—(*a*) 7,8,3′,4′-Tetramethoxyflavanonol (2 g.) in methanol (150 c.c.) was reduced with sodium borohydride (0·6 g.) as described for the 5,7,3′,4′-tetramethoxy-isomer.[16] The *trans-cis*-flavandiol crystallised from methanol in needles (1·2 g., 60%), m. p. 131—132° (lit.,[9a] m. p. 131—132°). The diacetate crystallised from ethanol in prisms, m. p. 123° (lit.,[9a] m. p. 120°). It failed to give an isopropylidene derivative under the conditions used for ($\pm$)-melacacidin tetramethyl ether.[2]

(*b*) The *trans-cis*-diol (1·2 g., 60%) was also obtained by hydrogenation of the flavanonol (2 g.) in ethanol (50 c.c.) at 50°/66 atm. over Adams catalyst for 12 hr. The diol was also prepared by reducing the flavanonol with lithium aluminium hydride in tetrahydrofuran.

($\pm$)-7,8,3′,4′-*Tetramethoxy-2,3-trans-flavan-3-ol* (V; X = OMe).—The *trans-trans*-diol (2·0 g.) in ethanol (50 c.c.) was hydrogenated at 100°/100 atm. over palladium black for 15 hr. The filtrate from the catalyst was evaporated. The residual solid consisted of ($\pm$)-7,8,3′,4′-*tetramethoxy-2,3-trans-flavan-3-ol* (1·4 g., 73%), m. p. 138—139° raised to m. p. 139·5—140° by two recrystallisations from methanol (Found: C, 66·0; H, 6·5. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%). The flavan-3-ol did not depress the m. p. of the 3,4-diol. Attempts to repeat the hydrogenation with other (more active) samples of palladium black were unsuccessful, but hydrogenation of the diol (0·2 g.) in methanol over palladous chloride at 50°/70 atm. for 12 hr. gave the flavan-3-ol (0·13 g., 68%), isolated after chromatography on alumina. ($\pm$)-3-*Acetoxy*-7,8,3′,4′-*tetramethoxy-2,3-trans-flavan* crystallised from ethanol in prisms, m. p. 112—113° (Found: C, 64·3; H, 6·3. $C_{21}H_{24}O_7$ requires C, 64·9; H, 6·2%).

($\pm$)-2-*Ethoxy-7,8,3′,4′-tetramethoxyisoflavan* (VII; X = OMe).—Phosphorus pentachloride (0·14 g.) was added to a solution of the foregoing *trans*-flavan-3-ol (0·2 g.) in sodium-dried benzene

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[16] Ganguly and Seshadri, *Tetrahedron*, 1959, **6**, 21.

(4 c.c.), and the flask was immediately closed with a calcium chloride guard-tube and shaken. After 5 min. the reddish-brown solution was stirred with 10% aqueous sodium carbonate (5 c.c.), and the organic layer was separated and washed with aqueous sodium carbonate and then with water. The benzene solution was evaporated and the residue was boiled with ethanol (10 c.c.) for 30 min.; crystallisation gave ($\pm$)-2-*ethoxy*-7,8,3',4'-*tetramethoxyisoflavan* (0·1 g., 46%), in prisms, m. p. 96—97° (Found: C, 67·3; H, 7·0; OMe, 39·9. $C_{21}H_{26}O_6$ requires C, 67·4; H, 7·0; Alkoxyl calc. as OMe, 41·4%).

Hydrogenation of (−)- *and* ($\pm$)-*Teracacidin Trimethyl Ether* (VIII). (−)-7,8,4'-Trimethoxy-flavan-3,4-diol [(−)-teracacidin trimethyl ether [1]] (0·2 g.) was hydrogenated at 50°/70 atm. over palladous chloride (0·01 g.) and chromatographed on alumina as described for the (−)-mela-cacidin analogue. This yielded an oil which failed to crystallise after repeated chromatography and did not yield a crystalline derivative on acetylation or toluene-*p*-sulphonylation. Oily products were also obtained after similar hydrogenations of ($\pm$)-teracacidin trimethyl ether.[9b]

($\pm$)-7,8,4'-*Trimethoxy*-2,3-trans-*flavan*-3-*ol* (Racemate of V; X = H).—($\pm$)-7,8,4'-Tri-methoxy-2,3-*trans*-flavan-3,4-*cis*-diol [9b] (0·2 g.) in methanol (10 c.c.) was hydrogenated at 50°/70 atm. over palladous chloride (0·01 g.) for 12 hr. The filtrate from the catalyst was diluted with water before being extracted with chloroform, and evaporation of the extract left an oil containing ($\pm$)-7,8,4'-*trimethoxy*-2,3-trans-*flavan*-3-*ol*, which crystallised from benzene–hexane in prisms (0·076 g., 40%), m. p. 115—116° raised to m. p. 118—119° by two further crystallisations from benzene–hexane (Found: C, 68·3; H, 6·3. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%). The 3-*toluene*-p-*sulphonate* crystallised from ethanol in needles, m. p. 141—142° (Found: C, 63·6; H, 5·6; S, 6·8. $C_{25}H_{26}O_7S$ requires C, 63·8; H, 5·6; S, 6·8%).

(−)-7,3',4'-*Trimethoxy*-2,3-trans-*flavan*-3-*ol* (IX).—Mollisacacidin trimethyl ether (0·2 g.), m. p. 130°, $[\alpha]_D^{17\cdot5}$ −10·3° (2% in $C_2H_2Cl_4$) {lit.,[11] m. p. 130°, $[\alpha]_D^{16}$ −9·5 (0·5% in $C_2H_2Cl_4$)} in methanol (10 c.c.) was hydrogenated for 12 hr. at 50°/70 atm. over palladous chloride (0·01 g.). The filtrate from the catalyst was diluted with water before being extracted with chloroform, and evaporation of the extract left an oil which was chromatographed on alumina (10 g.) de-activated with water (1 g.). Development with benzene (40 c.c.) and then with benzene–ether (1 : 1; 50 c.c.) removed (−)-7,3',4'-trimethoxy-2,3-*trans*-flavan-3-ol [(−)-fisetinidol trimethyl ether] (0·094 g., 50%), which crystallised from methanol in needles, m. p. 119—120°, $[\alpha]_D^{15\cdot5}$ −26° (2% in EtOH), $[\alpha]_D^{15\cdot5}$ −28° (1·7% in $C_2H_2Cl_4$) (Found: C, 68·4; H, 6·5. Calc. for $C_{18}H_{20}O_5$: C, 68·3; H, 6·4%) (Roux and Paulus [12] record m. p. 121—123° and $[\alpha]_D^{23}$ −32·1° ± 0·7° (in $C_2H_2Cl_4$); Weinges [10] records m. p. 119—120°, $[\alpha]_D$ +30·5° (in $C_2H_2Cl_4$), for the enantiomorph). The acetate crystallised from ethanol in needles, m. p. 91—92° (lit.,[12] m. p. 95—97°, and for the enantiomorph [10] 90—91°), $[\alpha]_D^{15\cdot5}$ −19° (2% in $CHCl_3$) (lit.,[12] −19° in $C_2H_2Cl_4$) (Found: C, 66·9; H, 6·2. Calc. for $C_{20}H_{22}O_6$: C, 67·0; H, 6·2%). The *toluene*-p-*sulphonate* crystallised from ethanol in plates, m. p. 130°, $[\alpha]_D^{17\cdot5}$ +67° (2% in $CHCl_3$) (lit.,[10] for the enantiomorph m. p. 129—130° and $[\alpha]_D$ −69° in $C_2H_2Cl_4$) (Found: C, 64·5; H, 6·0; S, 6·8. $C_{25}H_{26}O_7S$ requires C, 63·9; H, 6·6; S, 6·8%).

(+)-2-*Ethoxy*-7,3',4'-*trimethoxyisoflavan* (VII; X = H).—Phosphorus pentachloride (0·12 g.) was added to the foregoing (−)-*trans*-flavan-3-ol (0·12 g.) in dry (Na) benzene (2 c.c.), and the flask was closed with a calcium chloride guard-tube and shaken. After 5 min. the reddish solution was stirred with 10% aqueous sodium carbonate (3 c.c.), and the organic layer was separated and washed with further aqueous sodium carbonate and with water. The solution was evaporated under reduced pressure and the residue was boiled with ethanol (5 c.c.) for 30 min. Crystallisation from ethanol gave the (+)-2-*ethoxyisoflavan* in prisms (0·06 g., 46%) m. p. 89—90° raised to m. p. 90° by recrystallisation, $[\alpha]_D^{19}$ +102° (2% in $CHCl_3$) (Found: C, 69·3; H, 7·0; OMe, 34·2. $C_{20}H_{24}O_5$ requires C, 69·8; H, 7·0; Alkoxyl calc. as OMe, 36·0%).

($\pm$)-7,3',4'-*Trimethoxy*-2,3-cis-*flavan*-3,4-cis-*diol*.—7,3',4'-Trimethoxyflavonol (2 g.) in ethanol (100 c.c.) was hydrogenated at 100°/100 atm. over Raney nickel (W7, aged 6 months under ethanol at 0°) (*ca.* 4·0 g.) for 2 hr. and the catalyst was removed by filtration through kieselguhr. The filtrate was evaporated under reduced pressure and the residue, in benzene, was chromatographed on alumina (100 g.) deactivated with water (10 g.) and developed with benzene (150 c.c.) and then with benzene–ether (1 : 1; 200 c.c.); further development with benzene–ether (1 : 1; 100 c.c.) containing ethanol (1%) removed the 3,4-diol (1·03 g.), m. p. 145—146°, and elution with ethanol gave further diol (0·3 g., total 1·33 g., 66%). ($\pm$)-7,3',4'-*Trimethoxy*-2,3-cis-*flavan*-3,4-cis-*diol* crystallised from ethanol in needles, m. p. 148—149°

(Found: C, 64·7; H, 6·3. $C_{18}H_{20}O_6$ requires C, 65·0; H, 6·1%). The *diacetate* crystallised from ethanol in needles, m. p. 128—129° (Found: C, 63·5; H, 5·9. $C_{22}H_{24}O_8$ requires C, 63·5; H, 5·8%). The *isopropylidene derivative* crystallised from methanol in needles, m. p. 108—109° (Found: C, 67·8; H, 6·4. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%). The *carbonate* crystallised from ethanol in plates, m. p. 209° (Found: C, 63·2; H, 5·1. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·1%).

(±)-7,3′,4′-*Trimethoxy*-2,3-cis-*flavan*-3-*ol*.—The foregoing *cis-cis*-diol (0·1 g.) in methanol (10 c.c.) was hydrogenated for 15 hr. at 50°/70 atm. over palladous chloride (0·01 g.). The filtrate from the catalyst was diluted with water before being extracted with chloroform, and the oily residue from evaporation of the extract was chromatographed on alumina (10 g.) deactivated with water (1 g.). The column was developed with benzene (50 c.c.) and then benzene–ether (1 : 1; 50 c.c.), which removed the flavanol (0·033 g., 35%), m. p. 153°; two recrystallisations from methanol gave (±)-7,3′,4′-*trimethoxy*-2,3-cis-*flavan*-3-*ol* in prisms, m. p. 155—156° (Found: C, 68·4; H, 6·4. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%). Recovered *cis-cis*-diol (0·05 g.) was obtained by eluting the column with benzene–ether (1 : 1) containing 1% ethanol. Acetylation of the flavan-3-ol gave (±)-3-*acetoxy*-7,3′,4′-*trimethoxy*-2,3-cis-*flavan* which crystallised from ethanol in plates, m. p. 171° (Found: C, 67·1; H, 6·4. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%).

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[17] Clark-Lewis and Mitsuno, *J.*, 1958, 1724.