The Pigments of 'Dragon's Blood' Resin. Part VII.[1] Synthesis of (±)-Draconol, (±)-*O*-Methyldraconol, (±)-*O*-Methylisodraconol, and Derivatives; the Structure of Dracorubin

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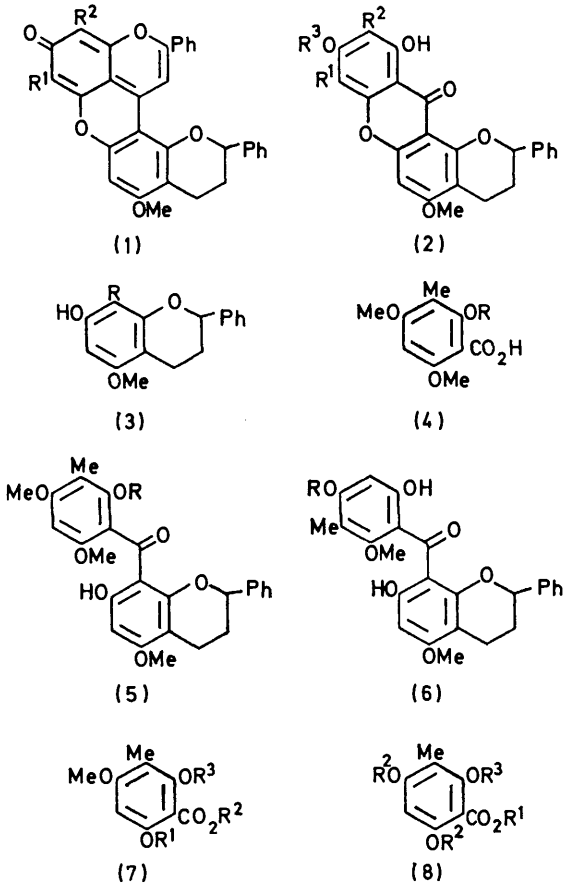
Unequivocal syntheses of (±)-draconol (3,4-dihydro-9,11-dihydroxy-5-methoxy-8-methyl-2-phenyl-2*H*-pyrano-[2,3-*a*]xanthen-12-one), a major degradation product of the pigment dracorubin, and of (±)-*O*-methyldraconol and (±)-*O*-methylisodraconol are described. The structure of dracorubin (3,4-dihydro-5-methoxy-8-methyl-2,12-diphenyl-2*H*-dipyrano[2,3-*a*:2',3',4'-*kl*]xanthen-9-one) is thus uniquely defined. The oxidative coupling of 7-hydroxy-5-methoxyflavan with 7-hydroxy-6 (and 8)-methylflavylium chloride to yield 4-(7-hydroxy-5-methoxyflavan-8-yl)-6(and 8)-methyl-2-phenylbenzopyran-7-one is described.

We have previously defined[2] the structure of the pigment dracorubin as (1; $R^2 = H$, $R^1 = Me$) or (1; $R^2 = Me$, $R^1 = H$), with a preference[2] for the former on biogenetic grounds. It thus follows that draconol, a major degradation product[2] of dracorubin, is represented by (2; $R^2 = R^3 = H$, $R^1 = Me$) or, less likely, by (2; $R^1 = R^3 = H$, $R^2 = Me$). This doubt has now been resolved by the syntheses of (±)-*O*-methyldraconol (2; $R^2 = H$, $R^1 = R^3 = Me$), (±)-*O*-methylisodraconol (2; $R^1 = H$, $R^2 = R^3 = Me$), and (±)-draconol (2; $R^2 = R^3 = H$, $R^1 = Me$).



Condensation of 7-hydroxy-5-methoxyflavan (3; R = H)[2] with 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (4; R = H) in trifluoroacetic anhydride gave the ketone (5; R = H), τ −1·23 (1H, s, OH, exchangeable with D_2O), −0·38 (1H, s, OH, exchangeable), 6·15 (3H, s, OMe), 6·43 (3H, s, OMe), 6·46 (3H, s, OMe), and 7·95 (3H, s, CMe). Cyclisation of this ketone with boiling alcoholic potassium hydroxide[3] gave (±)-*O*-methylisodraconol (2; $R^1 = H$, $R^2 = R^3 = Me$), τ −5·70 (1H, s, OH, exchangeable), 6·12 (6H, s, 2 × OMe), and 7·90 (3H, s, CMe). Condensation of 2-acetoxy-4,6-dimethoxy-3-methylbenzoic acid (4; R = Ac) with 7-hydroxy-5-methoxyflavan (3; R = H) furnished the corresponding acetoxy-ketone (5; R = Ac), which was also cyclised[3] with refluxing alcoholic potassium hydroxide to (±)-*O*-methylisodraconol (2; $R^1 = H$, $R^2 = R^3 = Me$). Attempts to condense 2-acetoxy-4,6-dimethoxy-3-methylbenzoyl chloride with 7-hydroxy-5-methoxyflavan [to yield (5; R = Ac)] gave 8-acetyl-7-hydroxy-5-methoxyflavan (3; R = Ac) as the only isolable product. The orientation of this ketone was confirmed by methylation to give 8-acetyl-5,7-dimethoxyflavan followed by conversion (haloform degradation) into 5,7-dimethoxyflavan-8-carboxylic acid. This observation, together with our syntheses of (±)-draconol and its *O*-methyl ether (see later), the orientations of which are rigorously defined[2] apart from the location of the *C*-methyl residue, confirms that these substitution reactions in 7-hydroxy-5-methoxyflavan proceed at C-8 in accord with general considerations. Attempts to obtain ketones of type (5) by condensation of 5,7-dimethoxyflavan-8-carboxylic acid (or its acid chloride) with derivatives of *C*-methylphloroglucinol were uniformly unsuccessful.

(±)-*O*-Methyldraconol (2; $R^2 = H$, $R^1 = R^3 = Me$) was similarly synthesised. Condensation of 7-hydroxy-5-methoxyflavan (3; R = H) with 6-hydroxy-2,4-dimethoxy-3-methylbenzoic acid gave the ketone (6; R = Me), τ −1·17 (1H, s, OH, exchangeable), −0·2 (1H, s, OH, exchangeable), 6·13 (3H, s, OMe), 6·31 (3H,

[1] Part VI, N. B. Dean and W. B. Whalley, *J. Chem. Soc.*, 1954, 4638.

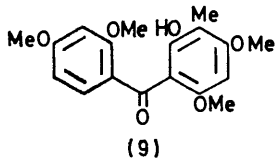
[2] A. Robertson, W. B. Whalley, and J. Yates, *J. Chem. Soc.*, 1950, 3117.

[3] D. H. R. Barton and A. I. Scott, *J. Chem. Soc.*, 1958, 1767.

s, OMe), 6·69 (3H, s, OMe), and 8·32 (3H, s, CMe). This ketone was cyclised with base to (±)-*O*-methyldraconol (2; $R^2 = H$, $R^1 = R^3 = Me$), identical in i.r., u.v., n.m.r., and mass spectra with (−)-*O*-methyldraconol, and different in these characteristics from (±)-*O*-methylisodraconol (2; $R^1 = H$, $R^2 = R^3 = Me$). These conclusions were further substantiated by a comparison of (−)-di-*O*-methyldraconol, (±)-di-*O*-methyldraconol, and (±)-di-*O*-methylisodraconol. The n.m.r. spectrum of (±)-*O*-methyldraconol [and that of (−)-*O*-methyldraconol] exhibited signals at τ −3·71 (1H, s, OH, exchangeable), 6·10 (3H, s, OMe), 6·12 (3H, s, OMe), and 7·80 (3H, s, CMe). The 6-hydroxy-2,4-dimethoxy-3-methylbenzoic acid (7; $R^1 = R^2 = H$, $R^3 = Me$) required for this synthesis was prepared as follows. Methyl 2,6-dihydroxy-4-methoxy-3-methylbenzoate (7; $R^1 = R^3 = H$, $R^2 = Me$) was monobenzylated to yield the 6-benzyloxy-derivative (7; $R^3 = H$, $R^2 = Me$, $R^1 = PhCH_2$) which was *O*-methylated at position 2. Catalytic debenzylation then gave the 6-hydroxy-2,4-dimethoxy-compound (7; $R^1 = H$, $R^2 = R^3 = Me$) the orientation of which and hence of its precursors follows from general principles and also from its non-identity with an authentic specimen of the isomeric methyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoate and from its conversion on complete methylation into methyl 2,4,6-trimethoxy-3-methylbenzoate. Alkaline hydrolysis gave the acid (7; $R^1 = R^2 = H$, $R^3 = Me$).

With the certainty that (−)-draconol was represented by (2; $R^2 = R^3 = H$, $R^1 = Me$) we proceeded to the synthesis of (±)-draconol. Condensation of 7-hydroxy-5-methoxyflavan (3; R = H) with 4,6-dihydroxy-2-methoxy-3-methylbenzoic acid in the presence of trifluoroacetic anhydride gave the ketone (6; R = H), τ 6·12 (3H, s, OMe), 6·67 (3H, s, OMe), and 8·34 (3H, s, CMe). Base-catalysed cyclisation of this ketone gave (±)-draconol, having i.r., u.v., n.m.r., and mass spectral characteristics identical with those of (−)-draconol and converted successively by methylation into (±)-*O*-methyl- and (±)-di-*O*-methyl-draconol. The 4,6-dihydroxy-2-methoxy-3-methylbenzoic acid required for this synthesis was prepared from methyl 2,4,6-trihydroxy-3-methylbenzoate (8; $R^2 = R^3 = H$, $R^1 = Me$) by 4,6-di-*O*-benzylation, 2-*O*-methylation, hydrolysis, and catalytic debenzylation of the resulting acid (8; $R^1 = H$, $R^3 = Me$, $R^2 = PhCH_2$). The orientation of the product (8; $R^1 = R^2 = H$, $R^3 = Me$) follows from general considerations and from the non-identity of the methoxy-ester (8; $R^1 = R^3 = Me$, $R^2 = H$) with the isomeric methyl 2,6-dihydroxy-4-methoxy-3-methylbenzoate (7; $R^1 = R^3 = H$, $R^2 = Me$) and methyl 2,4-dihydroxy-6-methoxy-3-methylbenzoate, and its conversion on complete methylation into 2,4,6-trimethoxy-3-methylbenzoate (8; $R^1 = R^2 = R^3 = Me$).

In the course of exploratory experiments designed to define the conditions for the cyclisation of ketones of type (5) to xanthones of type (2) we synthesised 6-hydroxy-2,2′,4,4′-tetramethoxy-5-methylbenzophenone (9), which was converted with base into 2,4,7-trimethoxy-1-methylxanthone (10).



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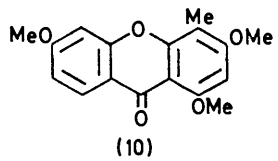

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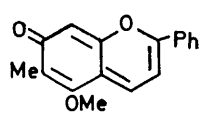

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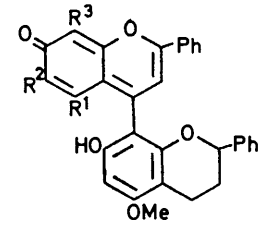

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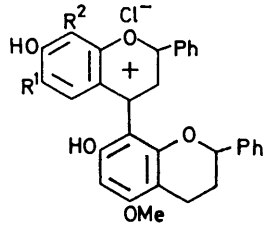

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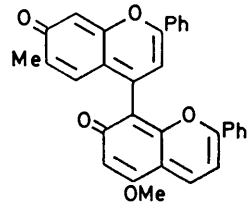

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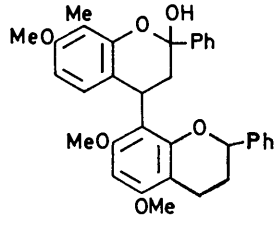

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With the structure of draconol defined it follows that dracorubin is represented by (1; $R^2 = H$, $R^1 = Me$) as previously [2] adumbrated. This structure is in keeping with the co-occurrence of dracorubin and dracorhodin (11) and the biogenetic possibility that dracorubin arises from the oxidative coupling of two units of general type (11) followed by cyclisation. Since it does not appear possible (*cf.* ref. 4) to couple oxidatively, at C-4, flavylium salts having a substituent at C-5, we explored the feasibility of synthesising a dimeric intermediate of type (12), following the method of Jurd.[5]

Oxidative coupling of 7-hydroxy-5-methoxyflavan and 7-hydroxy-6-methylflavylium chloride (which was initially explored by using 3,5-dimethoxyphenol and 3,5-dimethoxy-4-methylphenol as phenolic components) occurred readily at room temperature in aqueous acetic acid to yield the salt (13; $R^2 = H$, $R^1 = Me$). However, attempts to convert the corresponding

[4] M. Blackburn, G. B. Sankey, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1957, 1573.
[5] L. Jurd, *Tetrahedron*, 1967, **23**, 1057.

anhydro-base (12; $R^1 = R^3 = H$, $R^2 = Me$) into (±)-dracorubin under a variety of oxidative (and other) conditions were unsuccessful, but by using activated manganese dioxide a small yield of the corresponding bis-anhydro-base (14) was obtained. 7-Hydroxy-5-methoxyflavan (3; R = H) was converted similarly into the corresponding anhydro-base, which was characterised as a perchlorate.

Similarly, oxidative coupling of 7-hydroxy-5-methoxyflavan with 7-hydroxy-8-methylflavylium chloride proceeded smoothly to yield the dimeric salt (13; $R^1 = H$, $R^2 = Me$). The corresponding anhydro-base (12; $R^1 = R^2 = H$, $R^3 = Me$) could not be converted into a draucorubin-type system. Methylation of the anhydro-base (12; $R^1 = R^2 = H$, $R^3 = Me$) proceeded only slowly to yield the fully methylated pyranol (15), τ ($CF_3 \cdot CO_2D$) 5·80 (3H, s, OMe), 5·85 (3H, s, OMe), 5·88 (3H, s, OMe), and 7·35 (3H, s, CMe).

EXPERIMENTAL

Unless otherwise stated n.m.r. spectra were determined for solutions in deuteriochloroform with a Perkin-Elmer R12A spectrometer. We thank the S.R.C. for provision of the MS 902 mass spectrometer.

(±)-O-*Methylisodraconol*.—(*a*) Prepared from the methyl ester by alkaline hydrolysis, *2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid* separated from benzene in prisms, m.p. 183—184° (Found: C, 56·8; H, 5·8. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%). Formed by the pyridine–acetic anhydride method, *2-acetoxy-4,6-dimethoxy-3-methylbenzoic acid* separated from benzene in needles, m.p. 107° (Found: C, 56·8; H, 5·7. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·6%).

A solution of 2-acetoxy-4,6-dimethoxy-3-methylbenzoyl chloride [prepared from the acid (1·8 g) and oxalyl chloride (1·4 ml) in benzene (15 ml)] in nitrobenzene (5 ml) was added to 7-hydroxy-5-methoxyflavan (1·7 g) dissolved in nitrobenzene (5 ml) containing aluminium chloride (1·2 g) at 0°. After 48 h at room temperature the product was isolated with methylene chloride and purified to yield 8-acetyl-7-hydroxy-5-methoxyflavan (0·25 g) in yellow prisms, m.p. 149—150° (from methanol), identical with an authentic specimen [6] (Found: C, 72·7; H, 6·1%; M^+, 298. Calc. for $C_{18}H_{18}O_4$: C, 72·5; H, 6·1%; *M*, 298).

Methylation of this flavan (0·2 g) with acetone–potassium carbonate–methyl iodide gave 8-acetyl-5,7-dimethoxyflavan (150 mg) in prisms, m.p. 221° (from methanol) (Found: C, 72·9; H, 6·6%; M^+, 312. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·5%; *M*, 312).

A solution of potassium iodide (3 g) in water (50 ml) was added to a warm solution of 8-acetyl-5,7-dimethoxyflavan (150 mg) in water (10 ml) and dioxan (10 ml); 5% sodium hypochlorite solution (150 ml) was then added, followed by 2N-potassium hydroxide in alcohol (20 ml), and the mixture was heated at the b.p. for 10 min. The precipitate of iodoform was collected and the clear mixture was acidified to yield 5,7-dimethoxyflavan-8-carboxylic acid (50 mg) in prisms, m.p. 186—187° (from benzene), identical with an authentic specimen prepared as follows. Methylation of 7-hydroxy-5-methoxyflavan-8-carbaldehyde [2] (1 g) with methyl iodide–potassium carbonate–acetone gave (quantitatively) *5,7-dimethoxyflavan-8-carbaldehyde* in prisms, m.p. 132° (from benzene–light petroleum) (Found: C, 72·3; H, 6·0. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·1%). Oxidation of this aldehyde (1 g) in acetone (40 ml) with potassium permanganate (2 g) in water (40 ml) during 1 h at 40° gave *5,7-dimethoxyflavan-8-carboxylic acid* (0·4 g) in prisms, m.p. 188° (from benzene) (Found: C, 68·4; H, 5·6. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%). Methylation with diazomethane gave methyl 5,7-dimethoxyflavan-8-carboxylate identical with a specimen prepared by an alternative method.[2]

7-Hydroxy-5-methoxyflavan (0·75 g) was added to a stirred solution of 2-acetoxy-4,6-dimethoxy-3-methylbenzoic acid (0·8 g) in trifluoroacetic anhydride (10 ml) at 0°. The flavan dissolved during 1 h to furnish a deep red solution. The mixture was stirred for a further 23 h at 25°; the neutral product was then isolated and purified from methanol to yield *2-acetoxy-4,6-dimethoxy-3-methylphenyl 7-hydroxy-5-methoxyflavan-8-yl ketone* (0·2 g) in bright yellow needles, m.p. 170°, giving an intense red-brown colour with Fe^{III} in alcohol (Found: C, 68·3; H, 5·8%; M^+, 492. $C_{28}H_{28}O_8$ requires C, 68·3; H, 5·7%; *M*, 492).

A solution of this ketone (150 mg) in alcoholic 10% potassium hydroxide (20 ml) was refluxed during 5 h; the cooled solution was then acidified and extracted with ethyl acetate, to yield (±)-O-*methylisodraconol* (*3,4-dihydro-11-hydroxy-5,9-dimethoxy-10-methyl-2-phenyl-2H-pyrano*[2,3-a]*xanthen-12-one*) (42 mg) in pale yellow prisms, m.p. 252—254° (from ethyl acetate) (Found: C, 71·8; H, 5·5%; M^+, 418. $C_{25}H_{22}O_6$ requires C, 71·8; H, 5·3%; *M*, 418) [mixed m.p. with (±)-*O*-methyldraconol *ca.* 237°]. The product gave an intense green-brown colour with Fe^{III} in alcohol.

(*b*) A solution of 7-hydroxy-5-methoxyflavan (0·5 g) and 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (0·46 g) in trifluoroacetic anhydride (5 ml) was kept for 1 h at 10° then for 23 h at 25°. The product was isolated to give *2-hydroxy-4,6-dimethoxy-3-methyl 7-hydroxy-5-methoxyflavan-8-yl ketone* (0·35 g) bright yellow prisms, m.p. 174° (from methanol) (Found: C, 69·3; H, 5·7%; M^+, 450. $C_{26}H_{26}O_7$ requires C, 69·3; H, 5·8%; *M*, 450), giving an intense red-brown colour with Fe^{III} in alcohol. Cyclisation of this ketone (0·2 g) in boiling alcoholic 10% potassium hydroxide (20 ml) during 5 h gave (±)-*O*-methylisodraconol (50 mg), identical (m.p., mixed m.p., i.r., u.v., n.m.r., and mass spectra, and R_F) with the product from route (*a*).

Prepared quantitatively from (±)-*O*-methylisodraconol with methyl iodide–acetone–potassium carbonate, (±)-*di-O-methylisodraconol* formed prisms, m.p. 198° (from acetone) (Found: C, 72·1; H, 5·9%; M^+, 432. $C_{26}H_{24}O_6$ requires C, 72·2; H, 5·6%; *M*, 432).

(±)-O-*Methyldraconol*.—A solution of methyl 2,6-dihydroxy-4-methoxy-3-methylbenzoate (2 g) in acetone (50 ml) containing benzyl bromide (1·6 g) and potassium carbonate (3 g) was refluxed for 1·5 h. Isolated in the normal manner, *methyl 6-benzyloxy-2-hydroxy-4-methoxy-3-methylbenzoate* formed needles (0·9 g), m.p. 98° (from methanol) (Found: C, 67·3; H, 5·9. $C_{17}H_{18}O_5$ requires C, 67·5; H, 6·0%), giving an intense red-brown colour with Fe^{III} in alcohol.

Methylation of this ester (3 g) with excess of methyl iodide in boiling acetone (100 ml) containing potassium carbonate (4·5 g) during 12 h gave *methyl 6-benzyloxy-2,4-dimethoxy-3-methylbenzoate* (2·7 g) in prisms, m.p. 89° (from methanol), giving no colour with Fe^{III} (Found: C, 68·4; H, 6·2. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%).

[6] A. Robertson, V. Venkateswarlu, and W. B. Whalley, *J. Chem. Soc.*, 1954, 3137.

Debenzylation of this ester (1 g) in acetic acid (40 ml) containing 10% palladium–charcoal (0·5 g) in an atmosphere of hydrogen, was complete in 10 min to yield *methyl 6-hydroxy-2,4-dimethoxy-3-methylbenzoate* (0·6 g) in flat prisms, m.p. 104° (from methanol) (Found: C, 58·5; H, 6·4. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). Hydrolysis of the product (1 g) in boiling aqueous 10% potassium hydroxide (20 ml) during 1·5 h gave *6-hydroxy-2,4-dimethoxy-3-methylbenzoic acid* (0·7 g) in needles (from benzene) (Found: C, 56·7; H, 5·8. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%).

Methylation of this acid with dimethyl sulphate–acetone–potassium carbonate gave (quantitatively) methyl 2,4,6-trimethoxy-3-methylbenzoate [7] in prisms, m.p. 78° (from methanol) (Found: C, 59·9; H, 6·7. Calc. for $C_{12}H_{16}O_5$: C, 60·0; H, 6·7%). The same product was obtained from methylation of 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid.

7-Hydroxy-5-methoxyflavan (0·5 g) was added to a stirred solution of 6-hydroxy-2,4-dimethoxy-3-methylbenzoic acid (0·46 g) in trifluoroacetic anhydride (5 ml) at 10°, during 1 h. After 23 h at 25° the product was isolated to yield *2-hydroxy-4,6-dimethoxy-5-methylphenyl 7-hydroxy-5-methoxyflavan-8-yl ketone* (0·4 g) in pale yellow prisms, m.p. 148° (from methanol), giving an intense red-brown colour with Fe^{III} in alcohol (Found: C, 69·2; H, 5·9%; M^+, 450. $C_{26}H_{26}O_7$ requires C, 69·3; H, 5·8%; *M*, 450) (mixed m.p. with 2-hydroxy-4,6-dimethoxy-3-methylphenyl 7-hydroxy-5-methoxyflavan-8-yl ketone *ca.* 133°).

Cyclisation of the ketone (200 mg) in refluxing alcoholic 10% potassium hydroxide (20 ml) during 5 h gave (±)-*O-methyldraconol* (*3,4-dihydro-11-hydroxy-5,9-dimethoxy-8-methyl-2-phenyl-2H-pyrano*[2,3-a]*xanthen-12-one*) (35 mg) in pale yellow needles, m.p. 247—248° (from ethyl acetate) (Found: C, 71·6; H, 5·5%; M^+, 418. $C_{25}H_{22}O_6$ requires C, 71·8; H, 5·3%; *M*, 418) [mixed m.p. with (−)-*O*-methyldraconol 245—246°; with (±)-*O*-methylisodraconol 237°]. Methylation of (±)-*O*-methyldraconol with methyl iodide–acetone–potassium carbonate gave (quantitatively) (±)-*di-O-methyldraconol* in prisms, m.p. 282—283° (from acetone) (Found: C, 71·8; H, 5·9%; M^+, 432. $C_{26}H_{24}O_6$ requires C, 72·2; H, 5·6%; *M*, 432) [mixed m.p. with (±)-di-*O*-methylisodraconol 195—197°].

Acetylation of 6-hydroxy-2,4-dimethoxy-3-methylbenzoic acid (1 g) with acetic anhydride (5 ml) and sodium acetate (1 g) during 6 h at 100° gave *6-acetoxy-2,4-dimethoxy-3-methylbenzoic acid* (0·8 g) in needles, m.p. 90° (from light petroleum) (Found: C, 57·0; H, 5·7. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·6%). This acetate (0·8 g), dissolved in trifluoroacetic anhydride (10 ml) containing 7-hydroxy-5-methoxyflavan (0·75 g) at 25° during 24 h, furnished 8-acetyl-7-hydroxy-5-methoxyflavan (0·2 g) as the only recognised product.

(±)-*Draconol*.—Benzyl bromide (2·8 ml) in acetone (15 ml) was added during 3 h to a boiling solution of methyl 2,4,6-trihydroxy-3-methylbenzoate (2 g) in acetone (30 ml) containing potassium carbonate (2 g). After one further hour the product was isolated to yield *methyl 2,4-dibenzyloxy-6-hydroxy-5-methylbenzoate* (0·8 g) in needles, m.p. 118° (from methanol) (Found: C, 72·9; H, 6·0. $C_{23}H_{23}O_5$ requires C, 73·0; H, 5·9%), giving an olive green colour with Fe^{III} in alcohol.

Methylation of this ester (2 g) with methyl iodide–potassium carbonate–acetone during 12 h gave (quantitatively) *methyl 2,4-dibenzyloxy-6-methoxy-5-methylbenzoate*, in needles, m.p. 68° (from methanol) (Found: C, 73·4; H, 6·1. $C_{24}H_{24}O_5$ requires C, 73·5; H, 6·2%). Debenzylation of this ester (1 g) in acetic acid (20 ml) containing 10% palladium–charcoal (1 g) with hydrogen was complete in 10 min at normal pressure, to give *methyl 2,4-dihydroxy-6-methoxy-5-methylbenzoate* (0·4 g) in needles, m.p. 138° (from benzene or aqueous methanol) (Found: C, 56·3; H, 5·6. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%). A solution of methyl 2,4-dibenzyl-6-methoxy-5-methylbenzoate (1 g) in methanol (20 ml) containing aqueous 25% sodium hydroxide (20 ml) was refluxed for 4 h. The resultant *2,4-dibenzyloxy-6-methoxy-5-methylbenzoic acid* (0·75 g) formed needles, m.p. 148—149° (from benzene–light petroleum) (Found: C, 73·0; H, 6·2. $C_{23}H_{22}O_5$ requires C, 73·0; H, 5·9%). Debenzylation of this acid (1 g) in acetic acid (30 ml) containing 20% palladium–charcoal (0·5 g) occurred during 10 min to form *4,6-dihydroxy-2-methoxy-3-methylbenzoic acid* (0·4 g) in needles, as a hydrate, m.p. 161—162° (from dilute acetic acid) (Found: C, 49·6; H, 5·4. $C_9H_{10}O_5,H_2O$ requires C, 50·0; H, 5·6%).

7-Hydroxy-5-methoxyflavan (0·35 g) was added to a stirred solution of 4,6-dihydroxy-2-methoxy-3-methylbenzoic acid (0·3 g) in trifluoroacetic anhydride at 10°. After 24 h at 25° the product was isolated and purified by t.l.c. on silica from ethyl acetate–benzene (1 : 4) to yield *2,4-dihydroxy-6-methoxy-5-methylphenyl 7-hydroxy-5-methoxyflavan-8-yl ketone* in yellow prisms, m.p. 199—200° (from methanol) (Found: C, 69·9; H, 5·6%; M^+, 436. $C_{25}H_{24}O_7$ requires C, 68·8; H, 5·5%; *M*, 436), giving an intense red-brown colour with Fe^{III} in alcohol.

A solution of this ketone (35 mg) in alcoholic 10% potassium hydroxide (10 ml) was refluxed for 5 h, to yield (±)-*draconol* (*3,4-dihydro-9,11-dihydroxy-5-methoxy-8-methyl-2-phenyl-2H-pyrano*[2,3-a]*xanthen-12-one*), which formed pale yellow prisms, m.p. 265—268° (from methanol) (Found: C, 71·2; H, 5·1%; M^+, 404. $C_{24}H_{20}O_6$ requires C, 71·3; H, 5·0%; *M*, 404), showing an intense green-brown colour with Fe^{III} in alcohol.

(−)-*Di-O-Methyldraconol*.—Prepared (quantitatively) from (−)-draconol (0·1 g) with methyl iodide–potassium carbonate in boiling acetone during 24 h, (−)-*di-O-methyldraconol* formed prisms, m.p. 282° (from acetone), $[\alpha]_D^{23}$ −200° (*c* 1·0 in $CHCl_3$) (Found: C, 71·9; H, 5·7%; M^+, 432. $C_{26}H_{24}O_6$ requires C, 72·2; H, 5·6%; *M*, 432).

2,4,7-Trimethoxy-1-methylxanthone.—A solution of 2,4-dimethoxybenzoyl chloride (1·5 g) in nitrobenzene (5 ml) was added at 0° to a solution of 2-hydroxy-4,6-dimethoxytoluene (1·2 g) in nitrobenzene (2·5 ml). The mixture was kept at 0° for 1 h, and at room temperature for 72 h; ice (100 g) and concentrated hydrochloric acid (10 ml) were then added. The product was extracted with methylene chloride and the neutral fraction purified from methanol to yield *6-hydroxy-5-methyl-2,2′,4,4′-tetramethoxybenzophenone* (0·2 g) in prisms, m.p. 150—151°, giving an intense red-brown colour with Fe^{III} in alcohol (Found: C, 64·8; H, 5·9%; M^+, 332. $C_{18}H_{20}O_6$ requires C, 65·1; H, 6·1%; *M*, 332).

A solution of this benzophenone (0·14 g) in alcoholic 2N-potassium hydroxide (30 ml) was refluxed for 4 h. Purification of the product from methanol gave *2,4,7-trimethoxy-1-methylxanthone* (40 mg) in pale yellow needles, m.p. 214—215°, giving no colour with Fe^{III} in alcohol (Found: C, 68·1; H, 5·6%; M^+, 300. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%; *M*, 300).

Oxidative Condensations of 7-Hydroxy-6-methylflavylium Chloride.—(*a*) Prepared by the condensation of the 2,4-

[7] F. H. Curd and A. Robertson, *J. Chem. Soc.*, 1933, 437.

dihydroxy-5-methylbenzaldehyde (5 g) and acetophenone (6 ml) in ethyl acetate at 0° with hydrogen chloride 7-*hydroxy*-6-*methylflavylium chloride* (5·5 g) formed brownish-yellow needles, m.p. 161—162° (decomp.) (from 10% hydrochloric acid) (Found: C, 70·7; H, 4·8; Cl, 12·6. $C_{16}H_{13}ClO_2$ requires C, 70·5; H, 4·8; Cl, 12·9%). Addition of aqueous sodium acetate to a solution of this salt in methanol afforded 6-*methyl*-2-*phenylbenzopyran*-7-*one*, which separated from aqueous methanol in bright red needles, m.p. 168° (decomp.) (Found: C, 81·3; H, 5·1. $C_{16}H_{12}O_2$ requires C, 81·3; H, 5·1%). Prepared from this product in acetic acid containing perchloric acid, 7-*hydroxy*-6-*methylflavylium perchlorate* separated from acetic acid in orange needles, m.p. 244—246° (decomp.) (Found: C, 57·1; H, 4·1; Cl, 10·4. $C_{16}H_{13}ClO_6$ requires C, 57·1; H, 3·9; Cl, 10·6%).

7-Hydroxy-6-methylflavylium chloride (1·1 g) and 7-hydroxy-5-methoxyflavan (0·52 g) were dissolved in acetic acid (10 ml) and water (10 ml), by warming to 60°; after 48 h at room temperature the orange-red precipitate was collected; the filtrate was acidified with 6N-hydrochloric acid (20 ml) and the precipitate collected. The combined precipitates were dissolved in acetic acid (8 ml) and water (12 ml) by warming: the solution was acidified with 6N-hydrochloric acid until turbid. The solid which separated was dissolved in hot methanol containing 10N-hydrochloric acid (0·5 ml) and the resultant solution diluted with ethyl acetate and concentrated until orange-brown crystals commenced to separate from the hot solution. These crystals were collected and dissolved in 1% hydrochloric acid (25 ml) and acetic acid (25 ml). Addition of 6N-hydrochloric acid (20 ml) to the warm solution furnished 7-*hydroxy*-4-(7-*hydroxy*-5-*methoxyflavan*-8-*yl*)-6-*methylflavylium chloride* (0·3 g) in orange-brown needles, m.p. 256—258° (decomp.) (Found: C, 72·5; H, 5·3; Cl, 6·6. $C_{32}H_{27}ClO_5$ requires C, 72·8; H, 5·2; Cl, 6·7%).

The corresponding *anhydro-base* separated from benzene in deep red prisms, m.p. 305—307° (decomp.) or from aqueous methanol in dark red needles, m.p. 305—307° (decomp.) (Found: C, 78·2; H, 5·5%; M^+, 490. $C_{32}H_{26}O_5$ requires C, 78·4; H, 5·3%; *M*, 490). The *perchlorate* separated from acetic acid containing 1% perchloric acid in orange-red needles, m.p. 269—271° (decomp.) (Found: C, 64·7; H, 4·6; Cl, 5·9. $C_{32}H_{27}ClO_9$ requires C, 65·0; H, 4·6; Cl, 6·0%).

A solution of anhydro 6-methyl-4-(7-hydroxy-5-methoxyflavan-8-yl)-6-methyl-2-phenylbenzopyran-7-one (100 mg) in warm chloroform (100 ml) containing active manganese dioxide (1 g) was heated under reflux for 4 h in nitrogen. The crude product was isolated and separated by t.l.c. on silica [methanol–ethyl acetate (1 : 9)] to give (i) unchanged starting material (20 mg) and (ii) the *bis-anhydro-base* (14) (3 mg) as intensely red micro-needles, m.p. 340° [from benzene–methanol (9 : 1)] (Found: C, 78·6; H, 4·8%; M^+, 486. $C_{32}H_{22}O_5$ requires C, 79·0; H, 4·6%; *M*, 486).

(*b*) 7-Hydroxy-6-methylflavylium chloride (1·2 g) and 3,5-dimethoxyphenol (0·3 g) were dissolved in a warm mixture of acetic acid (4 ml) and water (16 ml). Precipitation of a brown flavylium salt commenced after 15 min and was complete after 24 h. Isolation of the product as in (*a*) gave 7-*hydroxy*-4-(6-*hydroxy*-2,4-*dimethoxyphenyl*)-6-*methylflavylium chloride* or the isomeric 7-*hydroxy*-4-(4-*hydroxy*-2,6-*dimethoxyphenyl*)-6-*methylflavylium chloride* in orange-red needles, m.p. 225—227° (decomp.) (Found: C, 67·7; H, 5·2; Cl, 8·1. $C_{24}H_{21}ClO_5$ requires C, 68·0; H, 5·0; Cl, 8·3%).

The corresponding *anhydro-base* separated from benzene in red needles, m.p. 202—204° (decomp.) (Found: C, 74·4; H, 5·1%; M^+, 388. $C_{24}H_{20}O_5$ requires C, 74·2; H, 5·2%; *M*, 388). The *perchlorate* separated from acetic acid containing 1% perchloric acid in orange-red needles, m.p. 244—245° (decomp.) (Found: C, 58·8; H, 4·4; Cl, 7·1. $C_{24}H_{21}ClO_9$ requires C, 59·0; H, 4·3; Cl, 7·3%).

(*c*) Condensation of 7-hydroxy-6-methylflavylium chloride (1·1 g) with 3,5-dimethoxy-4-methylphenol (0·35 g) in acetic acid (8 ml) and water (8 ml) during 24 h, as in (*a*), furnished 7-*hydroxy*-4-(6-*hydroxy*-2,4-*dimethoxy*-3-*methylphenyl*)-6-*flavylium chloride*, which formed deep brown needles, m.p. 234—236° (decomp.) (from aqueous acetic–hydrochloric acid) (Found: C, 68·7; H, 5·4; Cl, 7·8. $C_{25}H_{23}ClO_5$ requires C, 68·4; H, 5·3; Cl, 8·1%).

The corresponding *anhydro-base* formed deep purple prisms, m.p. 340° [from methanol–benzene (1 : 9)] (Found: C, 74·4; H, 5·8%; M^+, 402. $C_{25}H_{22}O_5$ requires C, 74·6; H, 5·5%; *M*, 402). The *perchlorate* separated from methanol–1% perchloric acid in purple prisms, m.p. 239—241° (decomp.) (Found: C, 59·5; H, 4·8; Cl, 6·8. $C_{25}H_{23}ClO_9$ requires C, 59·7; H, 4·6; Cl, 7·1%).

Oxidation of 7-*Hydroxy*-5-*methoxyflavan*.—A solution of 7-hydroxy-5-methoxyflavan (100 mg) in warm chloroform (20 ml) containing activated manganese dioxide was refluxed for 4 h in nitrogen. Purification of the alkali-insoluble portion of the product from methanol gave 5-methoxy-2-phenylbenzopyran-7-one base which was difficult to crystallise and was characterised as the *perchlorate*. This separated from acetic acid–1% perchloric acid in red-brown needles, m.p. 264—265° (decomp.) (Found: C, 54·3; H, 3·9; Cl, 9·8. $C_{16}H_{13}ClO_7$ requires C, 54·5; H, 3·7; Cl, 10·1%).

7-*Hydroxy*-5-*methoxyflavylium Chloride*.—This was prepared from acetophenone and 2,4-dihydroxy-6-methoxybenzaldehyde, in the usual manner, and formed orange-red needles, m.p. 235—236° (decomp.) (from 2N-hydrochloric acid) (Found: C, 66·4; H, 4·6; Cl, 11·9. $C_{16}H_{13}ClO_3$ requires C, 66·6; H, 4·5; Cl, 12·3%). The perchlorate was identical with that obtained by oxidation of 7-hydroxy-5-methoxyflavan.

Oxidative Condensations of 7-*Hydroxy*-8-*methylflavylium Chloride*.—(*a*) Condensation of acetophenone (6 g) with 2,4-dihydroxy-3-methylbenzaldehyde (5 g) in ethyl acetate (150 ml) at 0° with hydrogen chloride furnished 7-*hydroxy*-8-*methylflavylium chloride* (4·5 g), which separated from 10% hydrochloric acid in red needles, m.p. 245—247° (decomp.) (Found: C, 70·7; H, 4·9; Cl, 12·7. $C_{16}H_{13}ClO_2$ requires C, 70·5; H, 4·8; Cl, 12·9%). 8-*Methyl*-2-*phenylbenzopyran*-7-*one* crystallised from benzene in brownish-red needles, m.p. 148—149° (decomp.) (Found: C, 81·3; H, 5·2. $C_{16}H_{12}O_2$ requires C, 81·3; H, 5·1%). 7-*Hydroxy*-8-*methylflavylium perchlorate* formed orange-brown needles, m.p. 250—252° (decomp.) (from acetic acid–1% perchloric acid) (Found: C, 56·8; H, 3·8; Cl, 10·5. $C_{16}H_{13}ClO_6$ requires C, 57·1; H, 3·9; Cl, 10·6%).

A solution of 7-hydroxy-8-methylflavylium chloride (0·55 g) and 7-hydroxy-5-methoxyflavan (0·26 g) in a mixture of acetic acid (7·5 ml) and water (7·5 ml) was kept at 60° for 15 min followed by 28 h at room temperature. Isolation of the product in the normal manner gave 7-*hydroxy*-4-(7-*hydroxy*-5-*methoxyflavan*-8-*yl*)-8-*methylflavylium chloride* (0·25 g) in orange-red needles, m.p. 248—250° (decomp.) (from 10% hydrochloric acid) (Found: C, 72·6; H, 5·1; Cl, 6·5. $C_{32}H_{27}ClO_5$ requires C, 72·8; H, 5·2; Cl,

6·7%). Prepared from this hydrochloride in the usual manner 4-(*7-hydroxy-5-methoxyflavan-8-yl*)-8-*methyl*-2-*phenylbenzopyran-7-one* formed scarlet needles, m.p. 330—332° (decomp.) (from benzene) (Found: C, 78·3; H, 5·2%; M^+, 490. $C_{32}H_{26}O_5$ requires C, 78·4; H, 5·3%; *M*, 490). The *perchlorate* crystallised from acetic acid–1% perchloric acid in orange-brown needles, m.p. 304—305° (decomp.) (Found: C, 64·9; H, 4·7; Cl, 6·1. $C_{32}H_{27}ClO_9$ requires C, 65·0; H, 4·6; Cl, 6·0%).

Methylation of 4-(7-hydroxy-5-methoxyflavan-8-yl)-8-methyl-2-phenylbenzopyran-7-one with methyl iodide–acetone–potassium carbonate gave 4-(5,7-dimethoxyflavan-8-yl)-7-methoxy-8-methyl-2-phenylbenzopyran which was characterised as the *perchlorate*. This salt formed deep crimson needles, m.p. 300—302° (violent decomp.) (from methanol–1% perchloric acid (Found: C, 65·9; H, 5·1; Cl, 5·7. $C_{34}H_{31}ClO_9$ requires C, 66·0; H, 5·1; Cl, 5·7%).

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