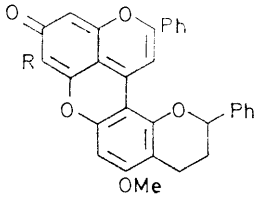
The Pigments of 'Dragon's Blood' Resin. Part VIII.[1] Synthesis of (±)-Dracorubin and of (±)-Nordracorubin

By **Evans O. P. Agbakwuru** and **W. Basil Whalley,*** The School of Pharmacy, The University of London, London WC1N 1AX

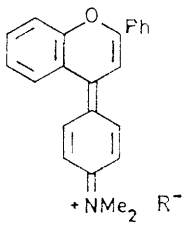
(±)-Dracorubin (3,4-dihydro-5-methoxy-8-methyl-2,12-diphenyl-2*H*-dipyrano[2,3-*a*:2',3',4'-*kl*]xanthen-9-one) has been synthesised. Condensation of 7-benzyloxy-5-methoxy-6-methylflavan-4-ol with 7-hydroxy-5-methoxyflavan gave 7-benzyloxy-4-(7-hydroxy-5-methoxyflavan-8-yl)-5-methoxy-6-methylflavan, which was successively acetylated, debenzylated, and oxidised to 4-(7-acetoxy-5-methoxyflavan-8-yl)-5-methoxy-6-methyl-2-phenyl-1-benzopyran-7-one. Cyclisation of this anhydro-base with sodium methylsulphinylmethanide gave (±)-dracorubin. (±)-Nordracorubin has been synthesised similarly.

OUR synthesis [1] of (±)-draconol and of cognate derivatives defined the structure of dracorubin as (1; R = Me). We now report the total synthesis of (±)-dracorubin, and of (±)-nordracorubin [2] (1; R = H), by a route which simulates the probable biogenetic pathway to these pigments.

It has been shown [1,3-5] that flavylium salts may function as electrophiles: for example with *NN*-dimethylaniline they yield compounds of type (2),[3,4] and with flavans dimeric derivatives [1,5] of type (3). Since it does not appear possible (*cf.* ref. 4) to use flavylium salts with a substituent at C-5 as effective electrophiles, we explored the possibility of using flavan-4-ols, in acidic



(1)



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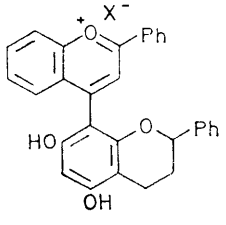

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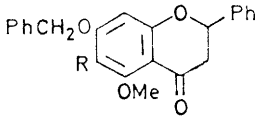
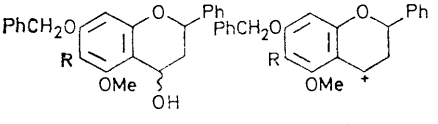


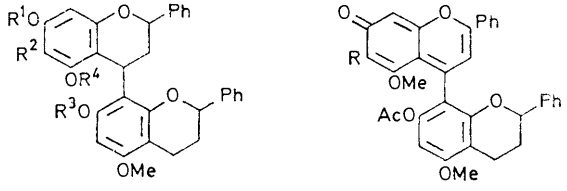
(4)

media, as an alternative source of the requisite carbocation.

Thus (±)-7-benzyloxy-5-methoxy-6-methylflavanone (4; R = Me), prepared by standard procedures, was reduced to the corresponding flavan-4-ol (5; R = Me) with sodium borohydride. When a solution of the



(5) (6) (7)



(8) (9)

carbocation (6; R = Me) obtained by dissolving this flavan-4-ol in acetic acid was added to a solution of 7-hydroxy-5-methoxyflavan (7), in the same solvent, the dimeric flavan (8; R^1 = Bz, R^2 = R^4 = Me, R^3 = H) was rapidly formed. The position of the linkage between the two flavan units follows from general principles and also from the ultimate conversion of (8; R^1 = $PhCH_2$, R^2 = R^4 = Me, R^3 = H) into (±)-dracorubin. The acetate (8; R^1 = $PhCH_2$, R^2 = R^4 = Me, R^3 = Ac) was smoothly debenzylated (catalytically) to yield 4-(7-acetoxy-5-methoxyflavan-8-yl)-7-hydroxy-5-methoxy-6-methylflavan (8; R^1 = H, R^2 = R^4 = Me, R^3 = Ac), which was oxidised by dichlorodicyano-*p*-benzoquinone to the anhydro-base (9; R = Me). Cyclisation of this base, in dimethyl sulphoxide containing sodium hydride,

[1] Part VII, A. A. Olaniyi, J. W. Powell, and W. B. Whalley, *J.C.S. Perkin I*, 1973, 179.
[2] G. Cardillo, L. Merlini, G. Nasini, and P. Salvadori, *J. Chem. Soc.* (*C*), 1971, 3967.
[3] R. Wizinger and H. Luthiger, *Helv. Chim. Acta*, 1953, **36**, 526.
[4] M. Blackburn, G. B. Sankey, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1957, 1573.
[5] L. Jurd, *Tetrahedron*, 1967, **23**, 1057.

gave (±)-dracorubin, identical in i.r., u.v., n.m.r., and mass spectra and R_F values with (−)-dracorubin. (±)-Dracorubin exhibited the same characteristic crystalline form as (−)-dracorubin. This cyclisation is clearly mechanistically similar to the analogous base-catalysed cyclisation of 2-hydroxy-2′-methoxybenzophenones to xanthones.[1,6]

In preliminary, model experiments we synthesised (±)-nordracorubin [2] (1; R = H) by a similar method. Thus the acid-catalysed condensation of the carbocation (6; R = H), derived from 7-benzyloxy-5-methoxyflavan-4-ol (5; R = H), with 7-hydroxy-5-methoxyflavan (7) furnished the dimeric flavan (8; R^1 = $PhCH_2$, R^2 = R^3 = H, R^4 = Me), which was converted by way of (8; R^1 = $PhCH_2$, R^2 = H, R^3 = Ac, R^4 = Me), (8; R^1 = R^2 = H, R^3 = Ac, R^4 = Me), and (9; R = H), into (±)-nordracorubin (1; R = H), identical in i.r., u.v., and mass spectra and R_F values with (−)-nordracorubin, and having the same crystalline form.

In agreement with the behaviour of the natural material, (±)-dracorubin and (±)-nordracorubin tenaciously retained varying amounts of solvent of crystallisation and did not afford consistent, satisfactory elemental analyses.

An examination of our (−)-dracorubin by t.l.c.[2] revealed small quantities of nordracorubin (*cf.* ref. 2).

During preliminary experiments designed to close the epoxy-bridge between C-5 and C-7′ in biflavans of type (8) we prepared 7-benzyloxy-4-(7-hydroxy-5-methoxyflavan-8-yl)-5-tosyloxyflavan (8; R^1 = CH_2Ph, R^2 = R^3 = H, R^4 = Ts) by condensation of 7-benzyloxy-5-tosyloxyflavan-4-ol with 7-hydroxy-5-methoxyflavan. However, neither this biflavan nor 7-benzyloxy-5-methoxy-4-(7-tosyloxy-5-methoxyflavan-8-yl)flavan (8; R^1 = CH_2Ph, R^2 = H, R^3 = Ts, R^4 = Me) could be cyclised under a variety of conditions.

EXPERIMENTAL

7-Benzyloxy-5-methoxy-6-methylflavan-4-ol.—Aqueous potassium hydroxide (60%; 20 ml) was added (under nitrogen) to a suspension of 4-benzyloxy-2-hydroxy-6-methoxy-5-methylacetophenone (1 g) in methanol (16 ml) containing benzaldehyde (0.53 ml); 24 h later this viscous mixture was diluted with water (50 ml) and the solution acidified (pH 5) with 2N-hydrochloric acid. After 12 h, at 0 °C, the precipitate was collected and purified from methanol to yield *4-benzyloxy-2-hydroxy-6-methoxy-5-methylphenyl styryl ketone* (0.9 g) in orange prisms, m.p. 84° (Found: C, 77.2; H, 6.3. $C_{24}H_{22}O_4$ requires C, 77.0; H, 6.0%). A solution of potassium hydroxide (60%; 20 ml) was added rapidly to a suspension of the ketone (1 g) in methanol (16 ml); after 18 h, at 20 °C, the red mixture was diluted with water and the product collected. Purification from methanol gave *7-benzyloxy-5-methoxy-6-methylflavanone* (0.94 g) in needles, m.p. 140° (Found: C, 76.8; H, 5.9%; M^+, 374. $C_{24}H_{22}O_4$ requires C, 77.0; H, 6.0%; *M*, 374), τ 2.60 (10 H, s, aromatic), 3.63 (1 H, s, aromatic), 4.6 (1 H, dd, benzylic CH, J_{AX} + J_{BX} = 16 Hz), 4.95 (2 H, s, benzylic CH_2), 6.18 (3 H, s, OMe), 7.08 (2 H, m, $CO{\cdot}CH_2$), and 7.88 (3 H, s, ArMe).

A solution of this flavanone (0.5 g) in ethanol (100 ml) was maintained at 30 °C while sodium borohydride (0.25 g) was added in portions during 5 min. After 1.5 h, an excess of acetic acid was added and the clear solution was evaporated *in vacuo*. Extraction of the residue with peroxide-free ether gave *7-benzyloxy-5-methoxy-6-methylflavan-4-ol* (0.46 g), in needles, m.p. 94° (from peroxide-free ether) (Found: C, 76.6; H, 6.5%; M^+, 376. $C_{24}H_{24}O_4$ requires C, 76.6; H, 6.4%; *M*, 376).

(±)-Dracorubin.— 7-Benzyloxy-5-methoxy-6-methylflavan-4-ol (0.2 g) and 7-hydroxy-5-methoxyflavan (0.14 g) were dissolved in acetic acid (50 ml). The solution was maintained at 50 °C while water (850 ml) (preheated to 50 °C) was added during 1—2 min. The resultant suspension was stirred for 10 min. After 15 h at 20 °C sodium chloride (7 g) was added to coagulate the micro-crystalline suspension, which resisted recrystallisation, but was chromatographically pure. *7-Benzyloxy-4-(7-hydroxy-5-methoxyflavan-8-yl)-5-methoxy-6-methylflavan* (0.34 g) had m.p. 115—125° (decomp.) (Found: C, 77.2; H, 6.3%; M^+, 614. $C_{40}H_{38}O_6$,0.5H_2O requires C, 77.0; H, 6.3%. $C_{40}H_{38}O_6$ requires *M*, 614), $\nu_{max.}$ (CCl_4) 3 460 cm^{-1} (OH); $\lambda_{max.}$ 210 (log ε 4.91), 235sh (4.31), and 280 nm (3.66), τ 2.63 (15 H, s, aromatic), 3.60 (1 H, s, aromatic), 4.0 (1 H, s, aromatic), 4.54 (1 H, s, OH, exchanged with D_2O), 4.96 (5 H, m, benzylic CH_2 and three CH), 6.20—6.52 (6 H, m, 2 OMe), and 7.3—8.4 (9 H, m, 3 CH_2 and ArMe).

Acetylation (pyridine–acetic anhydride) gave (quantitatively) *4-(7-acetoxy-5-methoxyflavan-8-yl)-7-benzyloxy-5-methoxy-6-methylflavan* in micro-needles, m.p. 75—78° (from ethanol) (Found: C, 76.8; H, 6.3%; M^+, 656. $C_{42}H_{40}O_7$ requires C, 76.8; H, 6.1%; *M*, 656).

Hydrogenolysis of this acetate (0.9 g) dissolved in acetic acid (45 ml) containing 1 drop of hydrochloric acid (10N) and palladium–charcoal (0.45 g, 20%) occurred rapidly to yield *4-(7-acetoxy-5-methoxyflavan-8-yl)-7-hydroxy-5-methoxy-6-methylflavan* in micro-prisms (0.7 g), m.p. 120° (decomp.) (Found: C, 74.1; H, 6.2%; M^+, 566. $C_{35}H_{34}O_7$ requires C, 74.2; H, 6.1%; *M*, 566).

A solution of this phenol (0.2 g) in benzene (80 ml) containing 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (0.16 g) was refluxed for 1 h. The cooled solution was separated from deposited solid and diluted with benzene (100 ml). After washing with 1% sodium hydroxide solution, followed by water, solvent was removed to yield *4-(7-acetoxy-5-methoxyflavan-8-yl)-5-methoxy-6-methyl-2-phenyl-1-benzopyran-7-one* (15 mg) in bright red needles, m.p. 210° (decomp.) [from acetone–water (1 : 1)] (Found: C, 72.7; H, 5.5%; M^+, 562. $C_{35}H_{30}O_7$,H_2O requires C, 72.4; H, 5.6%. $C_{35}H_{30}O_7$ requires *M*, 562), $\nu_{max.}$ 1 755 (OAc) and 1 644 cm^{-1} (C:O); $\lambda_{max.}$ 277 (log ε), 286 (4.34), 316 (3.95), 330 (3.95), 385 (4.04), and 490 nm (4.16); τ 2.25 (2 H, m, aromatic), 2.53 (3 H, m, aromatic), 2.83 (5 H, s, aromatic), 3.2 (1 H, d, *J* 10 Hz, C-3 olefinic), 3.53 (1 H, s, aromatic), 3.65 (1 H, s, aromatic), 5.0 (1 H, m, benzylic CH), 6.12 (3 H, s, OMe), 7.73 (3 H, s, OMe), 7.1 (2 H, m, CH_2), and 7.9 (8 H, m, ArMe, OAc, and CH_2).

A solution of sodium methylsulphinylmethanide (0.5 ml, 2 mol equiv.) [prepared from sodium hydride (0.43 g) and dimethyl sulphoxide (50 ml)] was added to the finely powdered anhydro-base (50 mg) under nitrogen. After 40 min at 60—65° (with slow stirring) the cooled mixture was diluted with water (8 ml) and the red, semi-crystalline solid

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

was collected. Purification by t.l.c. on alumina in chloroform–methanol (98 : 2), followed by elution with chloroform, gave (±)-dracorubin (10 mg) in dark red plates with a green reflex, m.p. 320° (decomp.) [from benzene–methanol (3 : 1)] (Found: M^+, 488. $C_{32}H_{24}O_5$ requires M, 488), $\nu_{max.}$ 1 660 cm^{-1} (C:O), τ 1.88 (1 H, s, ArH), 2.37 (5 H, s, ArH), 2.66 (5 H, m, ArH), 3.34 (1 H, s, ArH), 3.63 (1 H, s, ArH), 5.0 (1 H, m, ArCH·O), 6.26 (3 H, s, OMe), 7.45 (2 H, m, CH_2), 8.10 (2 H, m, CH_2), and 8.18 (3 H, s, ArMe).

(±)-*Nordracorubin*.—Reduction of 7-benzyloxy-5-methoxyflavanone (0.5 g) in ethanol (100 ml) at 30 °C with sodium borohydride during 1 h gave *7-benzyloxy-5-methoxyflavan-4-ol* in small needles, m.p. 109° (0.5 g) (from peroxide-free ether) (Found: C, 76.1; H, 6.1. $C_{23}H_{22}O_4$ requires C, 76.2; H, 6.1%). 7-Benzyloxy-5-methoxyflavan-4-ol (1 g) and 7-hydroxy-5-methoxyflavan (0.7 g) were dissolved in acetic acid (50 ml) at 50 °C, and water (850 ml) at 50 °C was added. After 15 h at 20 °C, *7-benzyloxy-4-(7-hydroxy-5-methoxyflavan-8-yl)-5-methoxyflavan* (1.7 g) was obtained as an amorphous solid, m.p. 100—110° (decomp.), which was chromatographically homogeneous but could not be induced to crystallise (Found: C, 76.9; H, 6.2%; M^+, 600. $C_{39}H_{36}O_6$,0.5H_2O requires C, 76.8; H, 6.1%. $C_{39}H_{36}O_6$ requires M, 600).

Acetylation of this dimer (pyridine–acetic anhydride) gave (quantitatively) *4-(7-acetoxy-5-methoxyflavan-8-yl)-7-benzyloxy-5-methoxyflavan* in needles, m.p. 118° (from ethanol) (Found: C, 76.5; H, 6.1%; M^+, 642. $C_{41}H_{38}O_7$ requires C, 76.6; H, 6.0%; M, 642).

Debenzylation of this acetate (1 g) in acetic acid (50 ml) containing 10N-hydrochloric acid (1 drop) and palladium–charcoal (20%; 0.5 g), in hydrogen occurred during 1 h, to yield (quantitatively) *4-(7-acetoxy-5-methoxyflavan-8-yl)-7-hydroxy-5-methoxyflavan*, in micro-needles, m.p. 135° (from aqueous acetic acid) (Found: C, 73.6; H, 6.0%; M^+, 552. $C_{34}H_{32}O_7$ requires C, 73.9; H, 5.8%; M, 552).

Oxidation of this phenol (0.2 g) with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (0.17 g) in boiling benzene (80 ml) during 2 h gave *4-(7-acetoxy-5-methoxyflavan-8-yl)-5-methoxy-2-phenyl-1-benzopyran-7-one* (0.06 g) in red prisms, m.p. 197° (decomp.) (from aqueous acetone) (Found: C, 73.4; H, 5.4%; M^+, 548. $C_{34}H_{28}O_7$,0.5H_2O requires C, 73.3; H, 5.2%. $C_{34}H_{28}O_7$ requires M, 548), $\nu_{max.}$ (KBr) 1 760 (OAc) and 1 640 cm^{-1} (C:O) $\lambda_{max.}$ 279 (log ε 4.29), 288 (4.29), 313 (3.99), 328sh (3.93), 390 (4.04), and 480 nm (4.08), τ 2.28 (2 H, m, ArH), 2.55 (3 H, m, ArH), 2.82 (5 H, s, ArH), 3.3 (1 H, s, ArH), 3.72 (2 H, m, ArH), 3.97 (1 H, s, ArH), 4.98 (1 H, m, ArCH·O), 6.15 (3 H, s, OMe), 6.48 (3 H, s, OAc), 7.2 (2 H, m, CH_2), 7.85 (2 H, m, CH_2), and 7.97 (3 H, s, ArMe).

Cyclisation of this anhydro-base (0.1 g) with sodium methylsulphinylmethanide, as for the dracorubin analogue, gave (±)-nordracorubin (20 mg) in red plates, m.p. 285° (decomp.) (Found: M^+, 474. $C_{31}H_{22}O_5$ requires M, 474).

5-Acetoxy-4-(7-acetoxy-5-methoxyflavan-8-yl)-7-benzyloxyflavan.—Reduction of 7-benzyloxy-5-hydroxyflavanone (0.5 g) in ethanol (50 ml) during 1 h, gave after isolation with peroxide-free ether, *7-benzyloxy-5-hydroxyflavan-4-ol* (0.5 g) in pale yellow prisms, m.p. 204° (decomp.) (from peroxide-free ether) (Found: C, 75.9; H, 5.8. $C_{22}H_{20}O_4$ requires C, 75.8; H, 5.8%).

7-Benzyloxy-5-hydroxyflavan-4-ol (0.2 g) and 7-hydroxy-5-methoxyflavan (0.15 g) were dissolved in acetic acid (50 ml) at 50 °C. Water (800 ml; at 50 °C) was added during several min: 24 h later the precipitate was collected and purified from aqueous acetic acid to yield *7-benzyloxy-5-hydroxy-4-(7-hydroxy-5-methoxyflavan-8-yl)flavan* (0.35 g) in micro-prisms, m.p. 90° (Found: C, 76.6; H, 5.7. $C_{38}H_{34}O_6$,-0.5H_2O requires C, 76.6; H, 5.9%). The *diacetate* formed prisms, m.p. 118° [from methanol–ether (20 : 1)] (Found: C, 75.4; H, 5.8. $C_{42}H_{38}O_8$ requires C, 75.2; H, 5.7%).

7-Benzyloxy-4-(7-hydroxy-5-methoxyflavan-8-yl)-5-tosyloxyflavan.—Prepared quantitatively from 7-benzyloxy-5-hydroxyflavanone, *7-benzyloxy-5-tosyloxyflavanone* separated from methanol in stout yellow needles, m.p. 126° (Found: C, 69.5; H, 4.7; S, 6.4. $C_{29}H_{24}O_6S$ requires C, 69.6; H, 4.8; S, 6.4%).

Reduction of this flavanone with sodium borohydride furnished the corresponding flavan-4-ol (0.2 g), which was too unstable to be purified, and was condensed immediately with 7-hydroxy-5-methoxyflavan (0.1 g) in acetic acid (50 ml) and water (680 ml) to yield 7-benzyloxy-4-(7-hydroxy-5-methoxyflavan-8-yl)-5-tosyloxyflavan (0.3 g) as an unstable solid, m.p. 214° (decomp.).

7-Benzyloxy-5-methoxy-4-(7-tosyloxy-5′-methoxyflavan-8-yl)-flavan.—Prepared from a solution of 7-benzyloxy-4-(7-hydroxy-5-methoxyflavan-8-yl)-5-methoxyflavan (0.5 g) in sodium hydroxide solution (10%; 4 ml) by addition of toluene-*p*-sulphonyl chloride (1.1 g) in acetone (5 ml), the *tosylate* formed needles (0.4 g), m.p. 125° (from acetone) (Found: C, 73.5; H, 5.4; S, 4.2%; M^+, 754. $C_{46}H_{42}O_9S$ requires C, 73.2; H, 5.6; S, 4.3%; M, 754).

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