Synthesis of Nephroarctin and Phenarctin

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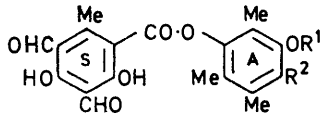
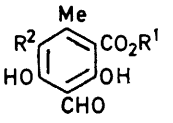
The synthesis of the lichen depsides nephroarctin (3-methoxy-2,5,6-trimethylphenyl 3,5-diformyl-2,4-dihydroxy-6-methylbenzoate) (1) and phenarctin (3-hydroxy-4-methoxycarbonyl-2,5,6-trimethylphenyl 3,5-diformyl-2,4-dihydroxy-6-methylbenzoate) (2) is described.

THE lichen *Nephroma arcticum* (L) Torss. produces the depsides nephroarctin (1) [1,2] and phenarctin (2) [2] which are highly unusual because of their large number of C_1 substituents. Phenarctin is the only known fully substituted depside.

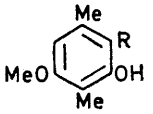
For the synthesis of these metabolites the acid (6) was required as the S-component. Methyl haematommate (3) on basic hydrolysis undergoes decarboxylation.[3] We have found that treatment of the ester (3) with boron tribromide [4] smoothly gives haematommic acid (4). Gattermann formylation of methyl haematommate (3) gave the dialdehyde (5) which on treatment with boron tribromide gave the acid (6).



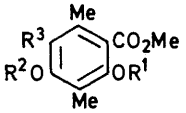
(1) R^1 = Me, R^2 = H
(2) R^1 = H, R^2 = CO_2Me



(3) R^1 = Me, R^2 = H
(4) R^1 = R^2 = H
(5) R^1 = Me, R^2 = CHO
(6) R^1 = H, R^2 = CHO



(7) R = CHO
(8) R = Me



(9) R^1 = R^2 = Me, R^3 = H
(10) R^1 = H, R^2 = Me, R^3 = CHO
(11) R^1 = H, R^2 = R^3 = Me
(12) R^1 = R^2 = H, R^3 = CHO
(13) R^1 = R^2 = H, R^3 = Me

The A-component (8) of nephroarctin (1) was readily available by catalytic reduction of rhizinonaldehyde (7). Formylation of methyl *o*-methylrhizinonate by the Gattermann method gave an aldehyde assigned structure (10) since the reduction product (11) still exhibited a signal for an intramolecularly hydrogen-bonded hydroxy-proton in its n.m.r. spectrum. Demethylation of the aldehyde (10) with boron trichloride furnished the phenol (12) which on reduction gave the A-component (13) required for phenarctin.

Condensation of the phenols (8) and (13) separately with the acid (6) in the presence of trifluoroacetic anhydride [5] gave nephroarctin (1) and phenarctin (2), both of which were identical with authentic samples.

EXPERIMENTAL

General directions have been given before.[6]

3-Formyl-2,4-dihydroxy-6-methylbenzoic Acid (Haematommic Acid) (4) (with P. VOGEL).—Methyl haematommate (3) [3] (500 mg) and boron tribromide (5.0 g) in dry dichloromethane (20 ml) were stirred at −78 °C for 1.5 h and then at room temperature for 12 h. Work-up in the usual way gave the acid (4) (450 mg, 97%), which formed small needles (from ethyl acetate), m.p. 172—173° (lit.,[7] 173°), identical with an authentic sample.

Methyl 3,5-Diformyl-2,4-dihydroxy-6-methylbenzoate (5).—Aluminium chloride (5.1 g) in dry ether (25 ml) was added at 0 °C to a stirred mixture of methyl haematommate (3) (4.0 g) and zinc cyanide (15.1 g) in dry ether (160 ml). The mixture was saturated at 0 °C with hydrogen chloride and then set aside for 24 h. The ethereal layer was decanted and the residual oil was heated on a steam-bath for 20 min with water (120 ml). The oil remaining after removal of the ether was treated similarly and the combined products in ethyl acetate were washed with brine and dried. The crude product was chromatographed over silica gel (3.5 × 45 cm) with 0—25% ethyl acetate–light petroleum as eluant. Early fractions gave the starting material (670 mg), which was followed by the product (5) (3.20 g, 71%). A sample formed needles (from methanol), m.p. 155.5—157° (lit.,[8] 156—157°) (Found: C, 55.3; H, 4.4%; M^+, 238. Calc. for $C_{11}H_{10}O_6$: C, 55.45; H, 4.25%; *M*, 238), τ (60 MHz; CCl_4) −3.74 and −3.13 (each 1 H, s, OH), −0.33 and −0.17 (each 1 H, s, CHO), 6.06 (3 H, s, OMe), and 7.42 (3 H, s, Me).

3,5-Diformyl-2,4-dihydroxy-6-methylbenzoic Acid (6).—The ester (5) (2.4 g) and boron tribromide (34 g) in 1,2-dichloroethane (175 ml) were stirred and heated under reflux for 3 h, and then stirred at room temperature for 12 h. Work-up in the usual way gave the *acid* (6) (2.2 g, 96%). A sample crystallised from ethyl acetate–light petroleum (charcoal) as prisms, m.p. 183—185° (Found: C, 53.4; H, 3,85%; M^+, 224. $C_{10}H_8O_6$ requires C, 53.6; H, 3.6%; *M*, 224), τ [90 MHz; $(CD_3)_2CO$] −0.30 and −0.28 (each 1 H, s, CHO) and 7.31 (3 H, s, Me).

3-Methoxy-2,5,6-trimethylphenol (8).—Rhizinonaldehyde (7) [9] (3.03 g) and 10% palladised charcoal (600 mg) in ethyl acetate (50 ml) were stirred in hydrogen until uptake ceased. Work-up in the usual way gave the product (8) (2.79 g, 99%). A sample formed prisms (from light petroleum), m.p. 70—71° (lit.,[8] 70—71°) (Found: C, 72.1;

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[4] *Cf.* P. S. Manchand, *Chem. Comm.*, 1971, 667.
[5] J. A. Elix, *Austral. J. Chem.*, 1974, **27**, 1767 and references therein.
[6] P. Djura, M. V. Sargent, and P. Vogel, *J.C.S. Perkin I*, 1976, 147.
[7] Y. Asahina and M. Hiraiwa, *Ber.*, 1939, **72**, 1402.
[8] T. Bruun, *Acta Chem. Scand.*, 1971, **25**, 2837.
[9] T. M. Cresp, J. A. Elix, S. Kurokawa, and M. V. Sargent, *Austral. J. Chem.*, 1972, **25**, 2167.

H, 8.35%; M^+, 166. Calc. for $C_{10}H_{14}O_2$: C, 72.25; H, 8.5%; M, 166), τ (60 MHz; CCl_4) 3.84 (1 H, s, ArH), 5.38 (1 H, s, OH), 6.27 (3 H, s, OMe), 7.80 (3 H, s, Me), and 7.98 (6 H, s, 2 × Me).

Formylation of Methyl O-Methylrhizinonate (9).—Aluminium chloride (12.4 g) in dry ether (80 ml) was added to a stirred mixture of the substrate (9)[9] (10.2 g) in dry ether (200 ml) at 0 °C. The mixture was saturated with hydrogen chloride and set aside for 36 h. Work-up as before gave a crude product which was again subjected to the same conditions. Hydrolysis of the oily layer gave a crude product which was chromatographed over silica gel (3 × 4.5 cm) with 0—2.5% ethyl acetate–light petroleum as eluant. Early fractions afforded methyl rhizinonate (1.1 g) as plates (from methanol), m.p. 98—100° (lit.,[9] 101—102.5°). Later fractions gave *methyl 5-formyl-2-hydroxy-4-methoxy-3,6-dimethylbenzoate* (10) (800 mg), which formed needles (from light petroleum), m.p. 117—118° (Found: C, 60.3; H, 5.95%; M^+, 238. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%; M, 238), τ (60 MHz; CCl_4) −1.73 (1 H, s, OH), −0.33 (1 H, s, CHO), 6.03 and 6.20 (each 3 H, s, OMe), and 7.37 and 7.88 (each 3 H, s, Me). A sample on hydrogenation as before gave *methyl 2-hydroxy-4-methoxy-3,5,6-trimethylbenzoate* (11) as an oil (Found: M^+, 224.1035. $^{12}C_{12}{}^{1}H_{16}{}^{16}O_4$ requires M, 224.1049), τ (CCl_4) −1.00 (1 H, s, OH), 6.08 and 6.37 (each 3 H, s, OMe), 7.63 (3 H, s, Me), and 7.90 (6 H, s, 2 × Me).

Methyl 2,4-Dihydroxy-3,5,6-trimethylbenzoate (13).—The ester (10) (600 mg) in dry dichloromethane (20 ml) was added at −10 °C to a stirred solution of boron trichloride (1.5 g) in dry dichloromethane (40 ml). After 0.75 h at −10 °C and 2 h at room temperature the mixture was worked up in the usual way and the crude product filtered through a column of silica gel (1.5 × 2.8 cm) with 2.5—5% ethyl acetate–light petroleum as eluant. This afforded methyl 5-formyl-2,4-dihydroxy-3,6-dimethylbenzoate (12)[8] (263 mg), which was hydrogenated as before. The product (13) (227 mg, 42% overall) formed fine needles (from light petroleum), m.p. 96—97° (lit.,[8] 97—98°) (Found: C, 62.7; H, 6.7%; M^+, 210. Calc. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.7%; M, 210), τ (60 MHz; CCl_4) −1.38 and 4.84 (each 1 H, s, OH), 6.13 (3 H, s, OMe), 7.67 (3 H, s, Me), and 7.95 (6 H, s, 2 × Me).

3-Methoxy-2,5,6-trimethylphenyl 3,5-Diformyl-2,4-dihydroxy-6-methylbenzoate (*Nephroarctin*) (1).—The acid (6) (200 mg) and the phenol (8) (150 mg) were stirred for 3 h at room temperature with trifluoroacetic anhydride (3 ml) and dry toluene (8 ml). The solvents were removed and the residue was chromatographed over silica gel (1.5 × 25 cm) with 0—5% ethyl acetate–light petroleum as eluant. This gave *nephroarctin* (1) (75 mg, 23%), which formed prisms (from acetone), m.p. and mixed m.p. 199—200° (lit.,[1] 192—193°; lit.,[2] 200—201°) (Found: C, 64.3; H, 5.6%; M^+, 372. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%; M, 372), τ (90 MHz; $CDCl_3$) −3.85 and −3.47 (each 1 H, s, OH), −0.35 and −0.20 (each 1 H, s, CHO), 3.36 (1 H, s, ArH), 6.18 (3 H, s, OMe), 7.25 and 7.70 (each 3 H, s, Me), and 7.86 (6 H, s, 2 × Me), identical (mass and n.m.r. spectra, R_F values in three solvent systems) with an authentic sample.

3-Hydroxy-4-methoxycarbonyl-2,5,6-trimethylphenyl 3,5-Diformyl-2,4-dihydroxy-6-methylbenzoate (*Phenarctin*) (2).—Condensation of the acid (6) (228 mg) and the phenol (13) (214 mg) followed by chromatography as before gave *phenarctin* (2) (146 mg, 35%) as prisms (from acetone), m.p. and mixed m.p. 173—174° (lit.,[2] 167—168°) (Found: C, 60.5; H, 4.8%; M^+, 416. $C_{21}H_{20}O_9$ requires C, 60.6; H, 4.85%; M, 416), τ (90 MHz; $CDCl_3$) −3.86, −3.52, and −1.06 (each 1 H, s, OH), −0.36 and −0.21 (each 1 H, s, CHO), 6.03 (3 H, s, OMe), 7.26 and 7.54 (each 3 H, s, Me), and 7.82 (6 H, s, 2 × Me), identical (mass and n.m.r. spectra, R_F values in three solvent systems) with an authentic sample.

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