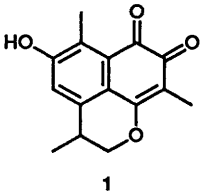
Synthesis of Azanzone A, a New Naturally Occurring *o*-Naphthoquinone

Roy M. Letcher* and Man-Ching Wong
Chemistry Department, University of Hong Kong, Bonham Road, Hong Kong

The synthesis is reported of 7-hydroxy-5-isopropyl-3,8-dimethylnaphthalene-1,2-dione **2** which was found to be identical with the natural product azanzone A, thus confirming the structure of the latter. The synthesis was achieved using the Stobbe condensation to obtain the butanedioic acid mono-ester **8** which readily cyclised to give the naphthoate **9**. Reduction of the ester to a methyl group, followed by Fremy's salt oxidation and *O*-demethylation with boron tribromide completed the synthesis.

From the heartwood of *Azanza garckeana* we have isolated[1] four well-known *o*-naphthoquinones (*viz.* mansonones E, F, G and H), as well as azanzones A and B. The structure of azanzone B has been established[2] as **1** from an X-ray crystallographic structure determination; from spectroscopic and biosynthetic considerations azanzone A was considered to have structure **2**,[1]



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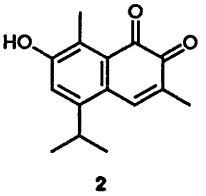

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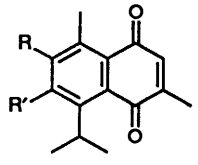
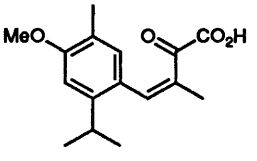


3 R = H, R′ = OH
4 R = OH, R′ = H



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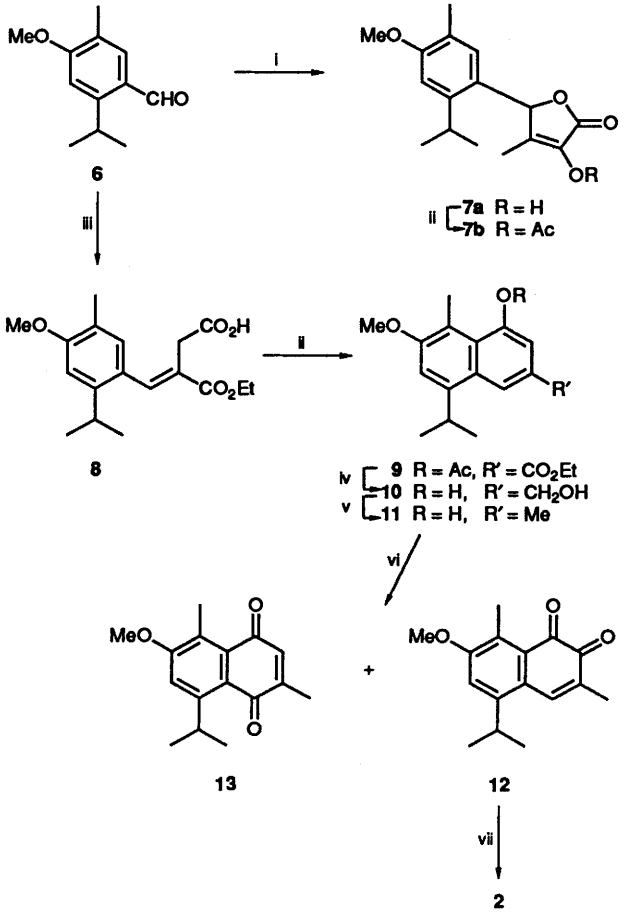
with the evidence for the naphthalene-1,2-dione moiety being based on weak mass spectral signals. No rigorous structure elucidation of azanzone A has been carried out and other structures such as those arising from a non-cadinane type of sesquiterpene biosynthesis, or even those with a naphthalene-1,4-dione structure (*e.g.* **3** or **4**) cannot be entirely excluded. In an endeavour to confirm, or otherwise, the proposed structure for azanzone A, the naphthalene-1,2-dione **2** was synthesised.

Our initial attempt to form the methyl ether of compound **2** *via* the ring closure of the hypothetical keto acid **5**, proved to be unsuccessful as the condensation reaction between the aldehyde **6**[3] (obtained by methylation of the Gattermann product of carvacrol) and 2-oxobutyric acid did not give the keto acid **5** but gave the furanone **7a** which could not be induced to yield a naphthalene-1,2-dione; treatment with acetic anhydride–sodium acetate merely gave the acetate **7b**.

An alternative approach (see Scheme 1) using the Stobbe condensation between the aldehyde **6** and diethyl succinate, was more successful as it gave the dicarboxylic acid monoester **8** and not the lactone; this route however requires extra steps in order to convert the ester into a methyl group and for the oxidation. Cyclisation of the mono-ester **8** was readily achieved and gave the naphthoate **9** which was satisfactorily reduced in two steps (lithium aluminium hydride followed by hydrogenation of the benzyl alcohol **10**) to give the naphthol **11**. On oxidation with Fremy's salt,[4] compound **11** gave the naphthalene-1,2-dione **12** as the major product; a minor product was the naphthalene-



Scheme 1 *Reagents:* i, $EtCOCO_2H$–KOH; ii, Ac_2O/NaOAc; iii, $(CH_2CO_2Et)_2$–NaOEt; iv, $LiAlH_4$; v, Pd–C, H_2; vi, $(KSO_3)_2NO$; vii, BBr_3

1,4-dione **13**. Having both naphthalenedione isomers made it possible to distinguish between the two structures using UV[5] and ^1H NMR data; since the chemical shift of the C-4 quinonoid proton of the naphthalene-1,2-dione is known[6] to be at low field, and from the fact that the quinonoid proton in the major product resonates at δ 7.59 and that of the minor isomer at δ 6.65, it was concluded that the former is the naphthalene-1,2-dione **12**. The presence of the 1,2-dione moiety was further confirmed by the fact that the major isomer formed a quinoxaline derivative with *o*-phenylenediamine. Attempts to demethylate the methoxy dione **12** caused extensive decomposition when attempted with sodium cyanide[7] or trimethylsilyl iodide,[8] but with boron tribromide[9] the demethylated product **2** was isolated albeit in only 10% yield; the product was found to be

identical [^{1}H NMR (270 MHz), IR, UV, TLC, m.p.] with a sample of azanzone A.[1] Consequently structure **2** for azanzone A is confirmed.

Experimental

General Experimental Details.—^{1}H and ^{13}C NMR spectra were determined at 89.56 and 22.50 MHz respectively on a JEOL FX90Q Fourier Transform spectrometer for $CDCl_3$ solutions with tetramethylsilane as internal standard, unless otherwise stated; ^{1}H and ^{13}C NMR spectra measured at 270.05 and 67.94 MHz respectively were recorded on a JEOL GSX270 spectrometer; *J*-values are given in Hz and ^{13}C spectral editing was performed using the DEPT pulse sequence technique. IR spectra were determined as Nujol mulls unless otherwise stated. Mass spectra were recorded on an Hitachi RMS-4 spectrometer; the accurate mass determination was measured on a VG MM 70-70 mass spectrometer. UV spectra were recorded in 95% ethanol. Thin layer chromatography (TLC) was on glass plates coated (1 mm) with Merck GF_{254} silica gel.

3-*Hydroxy*-5-(2′-*isopropyl*-4′-*methoxy*-5′-*methylphenyl*)-4-*methylfuran*-2(5H)-*one* **7a**.—Potassium hydroxide (3.5 g) dissolved in absolute ethanol (30 cm^3) was slowly added to an ice-cooled mixture of 2-oxobutyric acid (0.76 g) and 2-isopropyl-4-methoxy-5-methylbenzaldehyde **6**[3] (1.3 g). After being shaken for 5 h, the mixture was acidified with dilute hydrochloric acid and then extracted with ether. The ether extracts were shaken with saturated aqueous sodium hydrogen carbonate solution which was then acidified with hydrochloric acid and extracted with ether. The dried ether extracts were evaporated to yield the *title compound* **7a** (0.85 g, 45%) as colourless prisms, m.p. 145–146 °C (ether–light petroleum) (Found: C, 69.2; H, 7.3%; M$^+$, 276. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.3%; *M*, 276.336); ν_{max}/cm^{-1} 3335, 1734 and 1704; δ_H 1.30 (6 H, d, *J* 6.8, gem-Me_2), 1.81 (3 H, d, *J* 1.1, 4-Me), 2.13 (3 H, s, 5′-Me), 3.32 (1 H, septet, *J* 6.8, isopropyl-CH), 3.85 (3 H, s, OMe), 6.06 (1 H, br s, 5-H), 6.72 (1 H, s, ArH) and 6.77 (1 H, s, ArH); δ_C 10.1 (4-CH_3), 15.7 (5′-CH_3), 24.2 (gem-Me_2), 28.8 (isopropyl-*C*H), 55.3 (OCH_3), 79.2 (C-5), 107.1, 128.9 (both aryl CH), 122.1, 125.0, 131.3, 138.1, 147.5, 158.8 (all quaternary sp^2 C) and 170.9 (C=O).

3-*Acetoxy*-5-(2′-*isopropyl*-4′-*methoxy*-5′-*methylphenyl*)-4-*methylfuran*-2(5H)-*one* **7b**.—The above hydroxy compound (0.15 g), acetic anhydride (1.0 cm^3) and fused sodium acetate (0.1 g) were heated under reflux for 2 h, before water (50 cm^3) was added. The resultant product was filtered and recrystallised from ether–light petroleum to give the *title compound* **7b** (0.11 g, 61%), m.p. 132–133 °C (Found: C, 67.95; H, 6.85%; M$^+$, 318. $C_{18}H_{22}O_5$ requires C, 67.9; H, 6.95%; *M*, 318.374); ν_{max}/cm^{-1} 1776, 1753 and 1694; δ_H(270 MHz) 1.30 (3 H, d, *J* 6.8, gem-Me), 1.31 (3 H, d, *J* 6.8, gem-Me), 1.81 (3 H, d, *J* 1.0, 4-Me), 2.14 (3 H, s, 5′-Me), 2.35 (3 H, s, OAc), 3.30 (1 H, septet, *J* 6.8, isopropyl-CH), 3.85 (3 H, s, OMe), 6.14 (1 H, br s, 5-H), 6.78 (1 H, s, ArH) and 6.81 (1 H, s, ArH); δ_C(67.94 MHz) 11.3 (4-CH_3), 15.8 (5′-CH_3), 20.3 (CO*C*H$_3$), 24.2 (gem-Me_2), 28.9 (isopropyl-*C*H), 55.3 (OCH_3), 78.7 (C-5), 107.0, 129.1 (both aryl CH), 121.3, 125.2, 134.9, 147.4, 149.4, 158.9 (all quaternary sp^2 C), 167.3 and 167.4 (both C=O).

1-*Ethyl* 4-*Hydrogen* 2-[(2′-*Isopropyl*-4′-*methoxy*-5′-*methylphenyl*)*methylene*]*butanedioate* **8**.—A mixture of the freshly distilled benzaldehyde **6** (8.46 g) and diethyl succinate (11.5 g) was slowly added under nitrogen to a well stirred solution of sodium (2.03 g) dissolved in absolute ethanol (250 cm^3) and the mixture heated under reflux overnight. The solution was evaporated to half its volume, acidified with dilute hydrochloric acid and then extracted with ethyl acetate, which in turn was extracted with saturated aqueous sodium hydrogen carbonate. The aqueous solution was acidified with hydrochloric acid and extracted with ethyl acetate which was dried and evaporated to give the *title compound* **8** (14.0 g, 95%) m.p. 100–101 °C (ethyl acetate–light petroleum) (Found: C, 67.8; H, 7.5%; M$^+$, 320. $C_{18}H_{24}O_5$ requires C, 67.5; H, 7.55%; *M*, 320.390); ν_{max}/cm^{-1} 3200–2500, 1698 and 1635; δ_H 1.20 (6 H, d, *J* 6.8, gem-Me_2), 1.34 (3 H, t, *J* 7.0, CH_2CH_3), 2.17 (3 H, s, ArMe), 3.04 (1 H, septet, *J* 6.8, isopropyl-CH), 3.44 (2 H, br s, 3-H_2), 3.86 (3 H, s, OMe), 4.30 (2 H, q, *J* 7.0, CH_2CH_3), 6.76 (1 H, s, ArH), 6.94 (1 H, s, ArH), and 8.03 (1 H, s, olefinic H); δ_C 14.2 (CH_2CH_3), 15.7 (5′-CH_3), 23.5 (gem-Me_2), 30.5 (isopropyl-*C*H), 33.6 (C-3), 55.3 (OCH_3), 61.2 (CH_2CH_3), 107.0, 130.9, 142.2 (all sp^2 CH), 124.1, 124.8, 125.5, 146.8, 158.6 (all quaternary sp^2 C), 156.4 and 167.6 (both C=O).

Ethyl 4-*Acetoxy*-8-*isopropyl*-6-*methoxy*-5-*methyl*-2-*naphthoate* **9**.—The ester **8** (14.20 g), sodium acetate (3.64 g) and acetic anhydride (50 cm^3) were heated under reflux for 3 h, after which water (200 cm^3) was added, and the solution extracted with ethyl acetate. The ethyl acetate extracts were washed with aqueous sodium hydrogen carbonate followed by saturated brine, dried, and evaporated. The residue was chromatographed on silica (light petroleum–ether, 6:4) and yielded the *title compound* **9** (7.9 g, 52%), m.p. 100–100.5 °C (light petroleum) (Found: C, 69.65; H, 6.8%; M$^+$, 344. $C_{20}H_{24}O_5$ requires C, 69.75; H, 7.0%; *M*, 344.412); ν_{max}/cm^{-1} 1757 and 1700; δ_H 1.40 (6 H, s, *J* 6.9, gem-Me_2), 1.42 (3 H, t, *J* 7.1, CH_2CH_3), 2.39 (3 H, s, ArMe), 2.60 (3 H, s, OAc), 3.84 (1 H, septet, *J* 6.9, isopropyl-CH), 3.93 (3 H, s, OMe), 4.42 (2 H, q, *J* 7.1, CH_2), 7.25 (1 H, s, 7-H), 7.64 (1 H, d, *J* 1.6, 3-H) and 8.78 (1 H, d, *J* 1.6, 1-H); δ_C 12.7 (CH_3), 14.4 (CH_3), 21.5 (CO*C*H$_3$), 23.8 (gem-Me_2), 29.2 (isopropyl-*C*H), 56.6 (OCH_3), 61.1 (CH_2), 111.2, 119.6, 125.1 (all aryl CH), 116.1, 124.5, 128.5, 130.8, 146.5, 147.6, 157.3 (all quaternary aryl C), 166.2 and 169.8 (both C=O).

3-*Hydroxymethyl*-5-*isopropyl*-7-*methoxy*-8-*methyl*-1-*naphthol* **10**.—To a suspension of lithium aluminium hydride (1.65 g) in dry tetrahydrofuran (THF) (110 cm^3) under dry nitrogen, a solution of the naphthoate **9** (5.0 g) in dry THF (40 cm^3) was slowly added, and the mixture heated under reflux for 3 h. After being cooled to 0 °C, ethyl acetate (50 cm^3) was added and the mixture poured into cold dilute sulfuric acid and extracted with ethyl acetate. The extracts were dried and after evaporation yielded the *title compound* **10** (3.43 g, 91%), m.p. 156–157 °C (ethyl acetate–light petroleum) (Found: C, 73.8; H, 7.75%; M$^+$, 260. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.75%; *M*, 260.336); ν_{max}/cm^{-1} 3485 and 3260; δ_H([$^2H_6$]acetone) 1.35 (6 H, d, *J* 6.8, gem-Me_2), 2.79 (3 H, s, 8-Me), 3.12* (1 H, s, OH), 3.70 (1 H, septet, *J* 6.8, isopropyl-CH), 3.89 (3 H, s, OMe), 4.65 (2 H, s, CH_2), 6.89 (1 H, d, *J* 1.5, 2-H), 7.24 (1 H, s, 6-H), 7.57 (1 H, br s, 4-H) and 8.68* (1 H, s, OH) with * signals disappearing on D_2O exchange; δ_C([$^2H_6$]acetone) 14.5 (8-CH_3), 23.8 (gem-Me_2), 29.6 (isopropyl-*C*H), 57.5 (OCH_3), 65.1 (CH_2), 109.8, 112.2, 113.1 (all aryl CH), 119.7, 126.1, 130.7, 138.4, 143.9, 155.1 and 156.6 (all quaternary aryl C).

5-*Isopropyl*-7-*methoxy*-3,8-*dimethyl*-1-*naphthol* **11**.—A suspension of 10% palladium on carbon (70 mg) in a solution of the naphthol **10** (0.91 g) dissolved in ethanol (30 cm^3), was shaken in a Parr hydrogenator (with hydrogen at 30 psi)* at room temperature for 3 days. After being filtered the solution was evaporated and the residue chromatographed on silica (light petroleum–ether, 8:2) to give the *title compound* **11** (0.44 g, 51%)

* 1 psi = 6.895 × 10^3 Pa.

as an air-sensitive gum (Found: M^+, 244.1485. $C_{16}H_{20}O_2$ requires M, 244.1458); ν_{max}(neat)/cm^{-1} 3530–3375 and 2965; δ_H 1.34 (6 H, d, J 6.8, gem-Me_2), 2.30 (3 H, s, 3-Me), 2.84 (3 H, s, 8-Me), 3.62 (1 H, septet, J 6.8, isopropyl-CH), 3.86 (3 H, s, OMe), 5.80 (1 H, s, OH), 6.32 (1 H, d, J 1.3, 2-H), 7.17 (1 H, s, 6-H) and 7.37 (1 H, br s, 4-H); δ_C 14.1 (8-CH_3), 21.5 (3-CH_3), 23.5 (gem-Me_2), 28.9 (isopropyl-*C*H), 57.9 (OCH_3), 112.4, 112.6, 115.5 (all aryl CH), 119.2, 123.8, 130.3, 133.1, 142.9, 154.0 and 154.2 (all quaternary aryl C); m/z 244 (M^+, 100%) and 229 (54). The sample was pure according to ^{1}H NMR and TLC analysis.

Oxidation of the Naphthol **11**.—A solution of the naphthol **11** (0.44 g) dissolved in methanol (40 cm^3) was added to a solution of potassium nitrosodisulfonate (1.45 g) dissolved in water (100 cm^3) and 0.17 mol dm^{-3} potassium dihydrogen phosphate (29 cm^3), and the mixture stirred overnight at room temperature. The resultant solution was extracted with ether, which on being evaporated gave a residue from which two products were obtained. (i) Recrystallisation of the residue from benzene–hexane gave *5-isopropyl-7-methoxy-3,8-dimethylnaphthalene-1,2-dione* **12** as red needles (0.41 g, 88%), m.p. 201–202 °C (Found: C, 74.1; H, 6.95. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%); ν_{max}/cm^{-1} 1682, 1660, 1650 and 1622; λ_{max}/nm (log ε) 214 (4.33), 275 (4.44), 364 (2.97) and 486 (3.48); δ_H 1.30 (6 H, d, J 6.8, gem-Me_2), 2.03 (3 H, d, J 1.3, 3-Me), 2.49 (3 H, s, 8-Me), 3.40 (1 H, septet, J 6.8, isopropyl-CH), 3.89 (3 H, s, OMe), 6.93 (1 H, s, 6-H) and 7.59 (1 H, br s, 4-H); δ_C 12.9 (8-CH_3), 15.7 (3-CH_3), 23.8 (gem-Me_2), 28.6 (isopropyl-*CH*), 55.9 (OCH_3), 112.2 (C-6), 138.7 (C-4), 124.8, 131.1, 132.1, 133.4, 146.6, 159.7 (all quaternary sp^2 C), 182.7, and 183.7 (both C=O); m/z 258 (M^+, 26%), 230 (100), 215 (62) and 187 (10).

(ii) The mother liquor was further concentrated and chromatographed on TLC (benzene) and from the yellow band, *8-isopropyl-6-methoxy-2,5-dimethylnaphthalene-1,4-dione* **13** was obtained as yellow needles (32 mg, 7%), m.p. 128–129 °C (95% ethanol) (Found: M^+, 258.1211. $C_{16}H_{18}O_3$ requires M, 258.1251); ν_{max}/cm^{-1} 1646; λ_{max}/nm (log ε) 215 (4.72), 264 (4.68) and 385 (3.95); δ_H 1.29 (6 H, d, J 6.8, gem-Me_2), 2.11 (3 H, d, J 1.3, 2-Me), 2.54 (3 H, s, 5-Me), 3.94 (3 H, s, OMe), 4.24 (1 H, septet, J 6.8, isopropyl-CH), 6.65 (1 H, q, J 1.3, 3-H) and 7.10 (1 H, s, 7-H); δ_C 13.0 (5-CH_3), 16.2 (2-CH_3), 23.8 (gem-Me_2), 29.4 (isopropyl-*C*H), 55.8 (OCH_3), 111.6 (C-7), 135.4 (C-3), 124.0, 128.4, 133.2, 148.3, 152.6, 161.6 (all quaternary sp^2 C), 187.5 and 188.2 (both C=O); m/z 258 (M^+, 100%), 243 (48), 241 (65) and 215 (12).

4-Isopropyl-2-methoxy-1,6-dimethylbenzo[a]*phenazine*.—A mixture of the naphthalene-1,2-dione **12** (40 mg), absolute ethanol (6 cm^3), and *o*-phenylenediamine (50 mg) were heated under reflux for 4 h, before the solvent was evaporated under reduced pressure. The residue was chromatographed on silica (ether–light petroleum, 1:20) and gave yellow needles (44 mg, 85%) of the *title compound*, m.p. 125–126 °C (from 95% ethanol) (Found: C, 79.95; H, 6.75; N, 8.25%; M^+, 330. $C_{22}H_{22}N_2O$ requires C, 79.95; H, 6.7; N, 8.45%; M, 330.434); ν_{max}/cm^{-1} 1582; δ_H 1.45 (6 H, d, J 6.8, gem-Me_2), 2.84 (3 H, d, J 1.1, 6-Me), 3.26 (3 H, s, 1-Me), 3.83 (1 H, septet, J 6.8, isopropyl-CH), 4.01 (3 H, s, OMe), 7.34 (1 H, s, 3-H), 7.69–7.89 (2 H, m, ArH), 8.11 (1 H, br s, 5-H) and 8.18–8.37 (2 H, m, ArH).

7-Hydroxy-5-isopropyl-3,8-dimethylnaphthalene-1,2-dione **2**.—Using a microsyringe, boron tribromide (0.11 cm^3) was added to a stirred solution of the methoxynaphthalenedione **12** (92 mg) in dichloromethane (5 cm^3) at −80 °C under nitrogen. After 4 h the mixture was poured into water and extracted with ether. The ether extracts were dried and purified by TLC (methanol–chloroform, 1:20) to give the *title compound* **2** (8.2 mg, 10%) as violet needles (chloroform), m.p. 198–200 °C (decomp.) (lit.,[1] m.p. 200–201 °C) (Found: M^+, 244.1122. $C_{15}H_{16}O_3$ requires M, 244.1099); ν_{max}/cm^{-1} 3415, 1677, 1645 and 1616; λ_{max}/nm (log ε) 216 (4.44), 276 (4.58), 369 (3.34), 500 (3.61) and 546 (3.58); δ_H(270 MHz; $CDCl_3$–CD_3OD), 1.28 (6 H, d, J 6.8, gem-Me_2), 2.01 (3 H, d, J 1.5, 3-Me), 2.49 (3 H, s, 8-Me), 3.35 (1 H, septet, J 6.8, isopropyl-CH), 6.99 (1 H, s, 6-H) and 7.65 (1 H, br s, 3-H); δ_C(67.94 Hz; $CDCl_3$–CD_3OD), 13.34 (8-CH_3), 15.60 (3-CH_3), 23.81 (gem-Me_2), 28.53 (isopropyl-*C*H), 117.70 (C-6), 140.77 (C-4), 124.70, 131.24, 131.30, 132.22, 147.65, 158.76 (all quaternary sp^2 C), 183.08 and 183.97 (both C=O); identical (TLC, IR, UV and ^{1}H NMR) with a sample of azanzone A.[1]

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