A Simple Synthesis of the Natural Benzofuranoquinone, Acamelin

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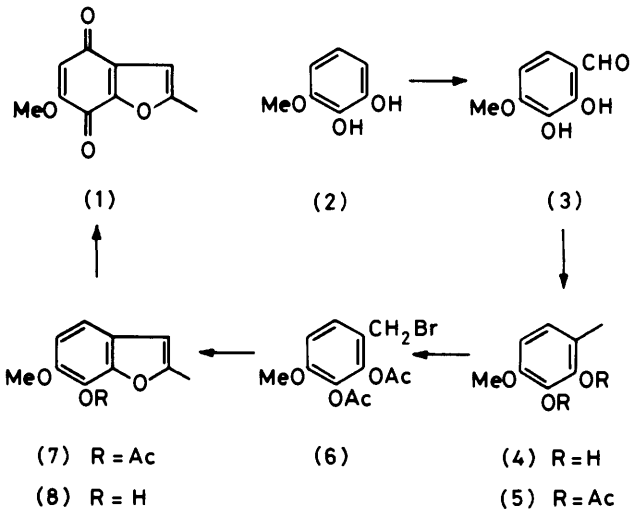
Acamelin, an allergy-inducing benzofuranoquinone extractive of Australian blackwood has been synthesized from 3-methoxypyrocatechol in six steps. The key step involved formation of a 2-methylbenzofuran by the intramolecular Wittig reaction of an *ortho*-acetoxybenzyl bromide.

Australian blackwood (*Acacia melanoxylon* R. Br.) is a commercial timber which may present health hazards to workers exposed to sawdust and shavings.[1] In addition to toxic effects, there have been reports of allergic contact dermatitis and bronchial asthma.[2] Although the causative reagent for the asthmatic condition has not been identified, two quinonoid constitutents found in the heartwood are known to be responsible for the allergy-inducing properties.[2,3] The more potent sensitizer, isolated in minute quantity and named acamelin, was shown by *X*-ray crystal structure analysis to have the structure, 6-methoxy-2-methylbenzofuran-4,7-dione (1)[3] and a synthesis of this product has recently been described.[4]

In the interests of providing larger quantities of acamelin for more extensive biological testing, we have examined an alternative synthesis pathway. This involves as the key step an intramolecular Wittig reaction of an ester of an *o*-hydroxybenzyl bromide to yield a benzofuran suitably functionalized for ready conversion into the benzofuranoquinone system. This method of benzofuran formation has also been utilized for the synthesis of eupomatenoids[5] and a *Sophora tomentosa* extractive.[6]



3-Methoxypyrocatechol (2), which is commercially available or readily obtained by the Dakin reaction on *o*-vanillin,[7] was formylated by triethyl orthoformate and aluminium chloride to provide 2,3-dihydroxy-4-methoxybenzaldehyde (3). This method proved more convenient than the Gattermann procedure previously described for the preparation of this compound.[8] The aldehyde (3) underwent smooth hydrogenolysis with palladium–carbon at atmospheric pressure to give the dihydroxytoluene (4) which was then converted into the diacetoxy derivative (5). By the action of *N*-bromosuccinimide on (5), the benzylic bromide (6) was obtained, treatment of which with triphenylphosphine in acetonitrile to form the phosphonium salt, followed by heating with triethylamine in toluene, afforded in 50—60% yield the desired benzofuran (7).

Conversion of (7) into the benzofuranoquinone (1) was readily accomplished. Reductive hydrolysis of the acetate (7) with lithium aluminium hydride yielded in *ca.* 90% yield the phenol (8) which on oxidation with Fremy's salt produced in 73% yield acamelin (1) with properties identical with those reported from the earlier synthesis.[4]

Experimental

M.p.s. were determined with a Gallenkamp apparatus and are uncorrected. Varian EM-390 and Bruker FT/90 MHz spectrometers were employed for the determination of ^{1}H n.m.r. spectra, with tetramethylsilane (TMS) as internal reference and deuteriochloroform as solvent (unless otherwise stated). The silica gel used for chromatography was J. T. Baker (40—140 mesh) and light petroleum refers to the fraction boiling in the range 54—105 °C.

2,3-*Dihydroxy*-4-*methoxybenzaldehyde* (3).—To a mixture of 3-methoxypyrocatechol (2) (6.0 g) and triethyl orthoformate (43 ml) in ether (300 ml) under nitrogen at 5 °C was added aluminium chloride (9.06 g) portionwise with stirring during 30 min with maintenance of temperature below 15 °C. The mixture was then stirred at this temperature for an additional 90 min after which it was cooled (ice-bath) and the reaction quenched by addition of cold hydrochloric acid (10%; 90 ml) and water. The layers were separated, and the aqueous phase further extracted with ether. The combined ether extracts were evaporated and the residual dark oil distilled (130 °C at 0.15 mmHg) as an orange semi-solid which was recrystallized from water to give the aldehyde (3) as straw coloured needles (1.63 g), m.p. 115—116 °C (lit.,[8] 117—118 °C); δ 3.98 (3 H, s, OMe), 5.53br (1 H, s, OH), 6.62 (1 H, d, *J* 8.5 Hz, 5-H), 7.15 (1 H, d, *J* 8.5 Hz, 6-H), 9.76 (1 H, s, CHO), and 11.10 (1 H, s, OH).

2,3-*Dihydroxy*-4-*methoxytoluene* (4).—A solution of the aldehyde (3) (590 mg) in ethyl acetate (125 ml) was stirred overnight with 5% palladium–charcoal (260 mg) under hydrogen at atmospheric pressure. Removal of catalyst and solvent gave a solid residue, which crystallized from water as flakes (490 mg), m.p. 91.5—92.5 °C which sublimed (60 °C at 0.10 mmHg) to give (4) as needles, m.p. 92.5—93.5 °C (Found: C, 62.3; H, 6.6. $C_8H_{10}O_3$ requires C, 62.3; H, 6.5%), δ 2.20 (3 H, s, ArMe), 3.85 (3 H, s, OMe), 5.43br (2 H, s, two OH), 6.35 (1 H, d, *J* 9 Hz, 5-H), and 6.62 (1 H, d, *J* 9 Hz, 6-H).

2,3-*Diacetoxy*-4-*methoxytoluene* (5).—Acetic anhydride (30 ml) was added to a solution of the dihydric phenol (4) (7.1 g) in pyridine (40 ml) and the mixture heated under nitrogen for 3.25 h at 80—90 °C. Concentration to low bulk under reduced pressure and addition of water (75 ml) precipitated a solid

(10.6 g), which was collected and recrystallized from aqueous ethanol, to yield the *diacetate* (5) as prisms, m.p. 98—100 °C (Found: C, 60.1; H, 5.9. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%), δ 2.13 (3 H, s, ArMe), 2.33 (6 H, s, two OAc), 3.82 (3 H, s, OMe), 6.77 (1 H, d, *J* 9 Hz, 5-H), and 7.03 (1 H, d, *J* 9 Hz, 6-H).

7-Acetoxy-6-methoxy-2-methylbenzofuran (7).—*N*-Bromosuccinimide (6.93 g) was added to a solution of the diacetate (5) (9.0 g) in tetrachloromethane (360 ml) and the mixture heated under reflux for 35 min; it was then cooled (ice-bath) and filtered. Evaporation of the solvent gave the benzylic bromide (6) as a cream-coloured solid (12.52 g), δ (CCl_4) 2.23 (3 H, s, OAc), 2.30 (3 H, s, OAc), 3.77 (3 H, s, ArOMe), 4.30 (2 H, s, CH_2Br), 6.75 (1 H, d, *J* 8.5 Hz, 5-H), and 7.17 (1 H, d, *J* 8.5 Hz, 6-H). Since this intermediate immediately darkened on attempted recrystallization, it was used without further purification.

Triphenylphosphine (10.9 g) was added to a solution of (6) (12.5 g) in acetonitrile (75 ml) and the mixture was heated under reflux under N_2 for 2 h, and then evaporated to give the phosphonium bromide as a frothy solid [δ(CD_3CN) 5.17 (2 H, d, *J* 14 Hz, $ArCH_2PPh_3Br$)] which was suspended in toluene (300 ml) and heated under reflux with triethylamine (15.8 ml) under N_2 for 4 h. The mixture was stored at room temperature for a further 12 h, and then filtered and evaporated. A solution of the residual oil in light petroleum–dichloromethane (1 : 1) was filtered through silica gel (210 g) and eluted with the same solvent (*ca.* 1 l) to give the *benzofuran* (7) as a solid (4.7 g) which crystallized from light petroleum as needles, m.p. 67.5—69 °C (Found: C, 65.1; H, 5.45. $C_{12}H_{12}O_4$ requires C, 65.4; H, 5.5%), δ 2.39 (3 H, d, *J* 1 Hz, ArMe), 2.40 (3 H, s, OAc), 3.83 (3 H, s, ArOMe), 6.25 (1 H, q, *J* 1 Hz, 3-H), 6.83 (1 H, d, *J* 8.5 Hz, 5-H), and 7.20 (1 H, d, *J* 8.5 Hz, 4-H).

7-Hydroxy-6-methoxy-2-methylbenzofuran (8).—A solution of the acetoxybenzofuran (7) (3.39 g) in ether (100 ml) was added slowly to a suspension of lithium aluminium hydride (430 mg) in ether (50 ml). The mixture was stirred at room temperature for 45 min, then ethyl acetate, water, and dilute acetic acid were sequentially added. The layers were separated, and the aqueous phase re-extracted with ether after further acidification with dilute hydrochloric acid. Evaporation of the washed and dried combined ether extracts gave the *hydroxybenzofuran* (8) as a colourless oil (Found: C, 67.2; H, 5.7. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%), δ 2.42 (3 H, d, *J* 1 Hz, ArMe), 3.90 (3 H, s, ArOMe), 6.22 (1 H, q, *J* 1 Hz, 3-H), 6.76 (1 H, d, *J* 8.5 Hz, 5- or 4-H), and 6.88 (1 H, d, *J* 8.5 Hz, 4- or 5-H).

6-Methoxy-2-methylbenzofuran-4,7-dione (*Acamelin*) (1).—A solution of potassium nitrosodisulphonate (Fremy's salt; 8.7 g) in water (190 ml) containing sodium acetate (3.28 g) was added to a stirred solution of the phenol (8) (2.40 g) in methanol (30 ml) with external ice-bath cooling. After 30 min, the resultant orange precipitate (4.01 g, m.p. 240—275 °C after vacuum drying) was collected. It was dissolved in chloroform (400 ml) and washed successively with 0.5M-sodium hydroxide solution, water and brine. Evaporation of the solvent gave an orange powder (2.27 g) [m.p. 250—253 °C (sealed tube)] which was recrystallized from chloroform–acetone (1 : 2) to yield acamelin (1) as small bright orange needles (1.88 g), m.p. and mixed m.p. 250—252 °C (lit.,[4] m.p. 253—255 °C) with a ^1H n.m.r. spectrum identical with that previously reported.[4]

The colourless hydroxybenzofuran (8) turned orange with time. It could be purified by silica-gel chromatography which separated (8) from the orange product shown to be acamelin (1).

Acknowledgements

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