All structural determinations and refinement calculations were carried out with the SHELXTL package on the Nicolet R3m/E crystallographic system.[13] On the basis of four molecules of $C_{15}H_{18}O_5$ in a unit cell with a volume of 1337.08 Å^3, the calculated density was 1.337 g/cm^3. The experimental density measurement was 1.393 g/cm^3. The final difference map revealed no abnormal features.

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Registry No. 1, 24959-84-0; 2, 29431-84-3.

Supplementary Material Available: Figure 1 showing the packing diagram of the unit cell of canin and Tables I–V listing bond distances and bond angles for canin and chrysartemin B, final atomic parameters, and final anisotropic thermal parameters (8 pages). Ordering information is given on any currrent masthead page.

(13) Programs used for data reduction, Fourier syntheses, direct method structure solution, least-squares refinement, error analysis, least-squares planes calculation, and calculation of hydrogen positions are those described in: Sheldreck, G. M., Ed. "Nicolet SHELXTL Structure Determination Manual"; Nicolet XRD Corp: Cupertino, CA, 1980.

Synthesis of Acamelin

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Australian blackwood (*Acacia melanoxylon* R. Brown) is one of the commercial timbers exhibiting a potential for human health injury.[1] Cases of contact dermatitis and bronchial asthma have been reported since 1925 among workers exposed to wood dust and shavings.[2] Hausen and his co-workers have demonstrated a sensitizing capacity of crude extracts of the heartwood. At least two quinone constituents having contact allergenic activity were isolated and identified by X-ray crystallographic analysis as 2,6-dimethoxy-1,4-benzoquinone (1)[3] and 2-methyl-6-methoxy-4,7-benzofurandione (2).[4] For the latter, which exhibited the stronger and longer lasting skin response in sensitized guinea pigs, the name acamelin was proposed. We report here a synthesis of this product, which had been obtained only in minute amounts from the natural source.

Inspection of the oxygen substitution pattern of acamelin indicated that the benzofuranoid skeleton might be readily constructed from phloroglucinol or phloroglucinol dimethyl ether by attachment of an appropriate three-carbon chain. To this end, phloroglucinol (3) was acylated with 2-chloropropionitrile under Houben–Hoesch conditions[5,6] to yield, after cyclization with potassium acetate solution, the dihydroxydihydrobenzofuranone 5 (Scheme I). This was readily converted to the dimethyl ether 6 by treatment with dimethyl sulfate in dimethoxyethane. Alternatively, the dimethyl ether 6 could be isolated directly as one of two major products obtained by the same acylation–cyclization sequence on 3,5-dimethoxyphenol (4).

Selective partial demethylation of 6 was achieved in excellent yield to give the monomethyl ether 7 by the action of aluminium chloride in dichloromethane at room temperature. At reflux temperature, further demethylation to the dihydroxydihydrobenzofuranone 5 occurred. The conversion of 7 to the desired intermediate benzofuran 8 by the action of lithium aluminium hydride was examined.[7] When the reduction was carried out in the usual way by heating the reactants under reflux in diethyl ether or tetrahydrofuran solution, there was obtained a mixture of the benzofuran 8 and dihydrobenzofuran 9, with the latter predominating. This difficulty was overcome, however, and the benzofuran 8 was cleanly obtained by conducting the reduction in tetrahydrofuran at room temperature.

Conventional oxidation of this phenolic benzofuran with Fremy's salt yielded in bright orange-red crystalline form 6-methoxy-2-methyl-4,7-benzofurandione (2), i.e., the structure attributed to acamelin, with spectroscopic data (^{1}H NMR, UV, IR) fully concordant with expectations for that structure. Since paucity of the natural specimen prevented direct comparison, identification was sought by determination of the unit cell dimensions of the synthetic specimen, measured by least-squares analysis of 15 X-ray reflections by using Mo Kα X-rays on a Nicolet diffractometer. They are in complete agreement with those reported for the crystal of the natural specimen.[8]

The second product obtained from phloroglucinol dimethyl ether (4) by the action of 2-chloropropionitrile followed by potassium acetate gave empirical analytical data corresponding to $C_{11}H_{13}O_4Cl$ and a ^{1}H NMR spectrum consistent with the structure of α-chloroethyl 4-hydroxy-2,6-dimethoxyphenyl ketone (10). Cleavage of one methyl ether function was effected by aluminium chloride treatment to give the dihydroxymethoxyphenyl ketone 11, which by potassium acetate cyclization yielded a product differing from but isomeric with the dihydrobenzofuranone 7. This product can accordingly be formulated as 6-hydroxy-4-methoxy-2-methyl-2,3-dihydrobenzofuran-3-one (12). It yielded, as expected, the same dimethyl ether (6) from which 7 had been obtained.

Experimental Section

Melting points were determined with a Gallenkamp or Fisher-Johns apparatus. NMR spectra were obtained with a Varian EM-390 spectrometer with Me_4Si as an internal standard. Infrared spectra were recorded with a Perkin-Elmer 683 spectrophotometer and ultraviolet spectra with a Perkin-Elmer 323 spectrophotometer.

4,6-Dihydroxy-2-methyl-2,3-dihydrobenzofuran-3-one (5). Dry hydrogen chloride gas was passed through a stirred mixture of phloroglucinol (4.58 g), anhydrous zinc chloride (9 g), and 2-chloropropionitrile (2.24 g) in diethyl ether (200 mL) for 3 h at room temperature, with continued stirring overnight. The resultant red lower layer was separated from the upper ether (yellow) layer and added carefully to water (100 mL) at ice-bath temperature. After it had dissolved, the solution was heated under reflux for 1.5 h, cooled, and extracted with ethyl acetate (3 × 100 mL). The extract was washed with saturated brine, and the solvent removed under reduced pressure to yield a yellow solid residue (8 g) to which was added a solution of potassium acetate

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(8) We express our gratitude to Ms. Cynthia Korhonen and Professor T. N. Margulis (University of Massachusetts, Boston) for this dimension determination.

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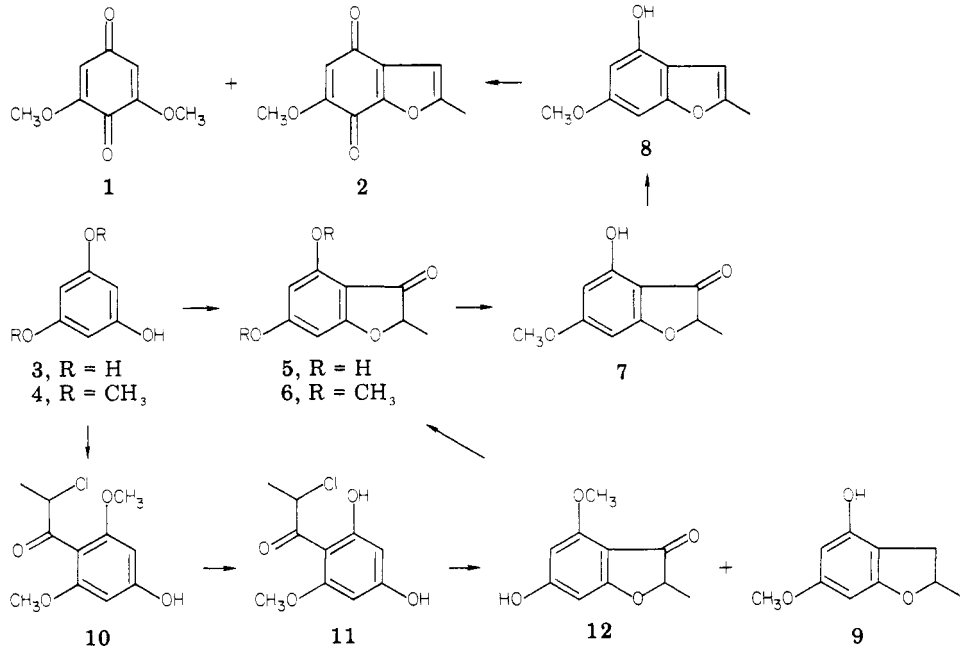
Scheme I



(12 g) in water (60 mL). The mixture was then heated under reflux for 5 h, allowed to stand overnight at room temperature, and extracted with ether (4 × 100 mL). Evaporation of the washed and dried extract gave an orange solid (3.35 g) from which unchanged phloroglucinol was removed by washing with ether. The residual product (0.73 g, 16% yield) was recrystallized from water to give the dihydrobenzofuranone **5** as rosettes: mp 220–224 °C; ^{1}H NMR ($(CD_3)_2CO$) δ 1.39 (d, J = 7 Hz, CH_3), 4.60 (q, J = 7 Hz, OCHMe), 5.11 (br s, OH), 5.93 (d, J = 2 Hz, Ar H), 5.98 (d, J = 2 Hz, Ar H). The analytical sample was prepared by sublimation (138 °C, 0.5 mmHg). Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.61; H, 4.69.

4,6-Dimethoxy-2-methyl-2,3-dihydrobenzofuran-3-one (6). (a) Dimethyl sulfate (1.13 g) was added dropwise over 5 min to a stirred refluxing mixture of the resorcinol (**5**, 0.72 g) and potassium carbonate (1.30 g) in 1,2-dimethoxyethane (30 mL) under nitrogen, and refluxing was continued for 2.5 h. After most of the solvent was removed by sweeping with nitrogen at room temperature, water (50 mL) was added and the mixture extracted with ether. The extract was washed successively with water (3 × 50 mL), aqueous sodium hydroxide solution (1 N, 2 × 50 mL), saturated brine (3 × 50 mL), water and dried (Na_2SO_4). Removal of solvent under reduced pressure gave a residual amber oil (355 mg) which was dissolved in chloroform (200 mL) and filtered through alumina (50 g) to yield the dimethyl ether **6** as a solid: 286 mg (34% yield); mp 69–75 °C [raised to 76.5–78 °C on recrystallization from petroleum ether (bp 30–57 °C)]; IR ($CHCl_3$) 1697 (CO), 1623, 1598, 1162, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.49 (d, J = 7 Hz, CH_3), 3.85 (s, OMe), 3.90 (s, OMe), 4.58 (q, J = 7 Hz, OCHMe), 5.98 (d, J = 2 Hz, Ar H), 6.10 (d, J = 2 Hz, Ar H). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.76; H, 5.91.

(b) Dry hydrogen chloride was passed for 3 h through a stirred mixture of 3,5-dimethoxyphenol (3.10 g), zinc chloride (4 g), and 2-chloropropionitrile (1.79 g) at room temperature with continued stirring overnight. A pink solid precipitate was collected by decantation of the solvent, heated under reflux in water (100 mL) for 1 h, and allowed to stand overnight at room temperature, during which a viscous solid separated. The reaction mixture was extracted with ether, washed and dried in the usual way, and evaporated to yield a red viscous oil (3.55 g) which was taken up in a solution of potassium acetate (5.1 g) in water (125 mL) and ethanol (25 mL) and heated under reflux for 3.5 h. A workup in the usual way via ether and sodium hydroxide washing gave the dimethyl ether **6** as a tan solid (1.02 g, 25% yield) which was purified by recrystallization as in part a.

Acidification of the sodium hydroxide washings with 15% aqueous sulfuric acid precipitated a red oil which solidified on standing. The mixture was extracted with ether, washed and dried in the usual way, and evaporated under reduced pressure to give **α-chloroethyl 4-hydroxy-2,6-dimethoxyphenyl ketone (10)** as an orange solid (1.56 g, 32% yield) which crystallized from benzene as colorless needles: mp 137.5–138 °C; IR ($CHCl_3$) 3586 (OH), 3296 (OH), 1701 (CO), 1615, 1599, 1138 cm^{-1}; ^{1}H NMR ($(CD_3)_2CO$) δ 1.55 (d, J = 7 Hz, CH_3), 3.76 (s, C-2 and C-6 OMe), 4.98 (q, J = 7 Hz, CHClMe), 6.17 (s, H-3 and H-5), 8.74 (br s, OH). Anal. Calcd for $C_{11}H_{13}O_4Cl$: C, 54.00; H, 5.36. Found: C, 54.21; H, 5.37.

4-Hydroxy-6-methoxy-2-methyl-2,3-dihydrobenzofuran-3-one (7). A solution of the dimethyl ether **6** (600 mg) in dichloromethane (25 mL) was added to a suspension of aluminium chloride (1.2 g) in the same solvent (25 mL) under nitrogen. More solvent (25 mL) was added, and the mixture was stirred at room temperature for 18 h. Water (100 mL) was then added, and the layers were separated. The aqueous layer was extracted with ether, and the combined dichloromethane–ether extract was washed and dried. Removal of solvents under reduced pressure gave a residual solid (504 mg, 90% yield) which on recrystallization from hexane gave the monomethyl ether **7** as prisms: mp 103–104 °C; IR ($CHCl_3$) 3450 (OH), 1680 (CO), 1644, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50 (d, J = 7 Hz, CH_3), 3.82 (s, OMe), 4.64 (q, J = 7 Hz, CHMe), 5.97 (d, J = 2 Hz, H-7), 6.03 (d, J = 2 Hz, H-5), 7.80 (br s, OH); ^{1}H NMR ($(CD_3)_2CO$) δ 1.41 (d, J = 7 Hz, CH_3), 3.85 (s, OMe), 4.63 (q, J = 7 Hz, CHMe), 5.99 (d, J = 2 Hz, H-7), 6.11 (d, J = 2 Hz, H-5). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.95; H, 5.32.

When this reaction was performed at reflux temperature for 3.5 h there was obtained in approximately equal amounts a mixture of the monomethyl ether **7** and the resorcinol **5**.

4-Hydroxy-6-methoxy-2-methylbenzofuran (8). (a) A solution of the dihydrobenzofuranone **7** (197 mg) in tetrahydrofuran (30 mL) was added dropwise over 20 min to a suspension of lithium aluminium hydride (120 mg) in the same solvent under nitrogen. The mixture was stirred at room temperature for 1.25 h, followed by addition of ethyl acetate and dilute hydrochloric acid (1 N, 15 mL). Separation of the layers and a workup in the usual way via ether gave an oil (190 mg) which was dissolved in chloroform and chromatographed on silica gel (20 g, Baker, 40–140 mesh). Elution with chloroform (250 mL) yielded the benzofuran **8** as an oil which crystallized from hexane as slender needles: 92 mg (52% yield); mp 100–101 °C; ^{1}H NMR ($CDCl_3$) δ 2.39 (d, J = 1 Hz, Me), 3.79 (s, OMe), 5.12 (br s, OH), 6.24 (d, J = 2 Hz, H-5), 6.27 (m, H-3), 6.58 (dd, J = 1, 2 Hz, H-7). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.42; H, 5.83.

(b) A solution of **7** (70 mg) in tetrahydrofuran (10 mL) was added to lithium aluminium hydride (44 mg) in the same solvent

(10 mL) and the mixture heated under reflux (nitrogen atmosphere) overnight. A workup in the usual way gave 4-hydroxy-6-methoxy-2-methyl-2,3-dihydrobenzofuran (**9**): 92% yield; as oil; ^{1}H NMR ($CDCl_3$) δ 1.43 (d, J = 6 Hz, CH_3), 2.63 (dd, J = 7, 14 Hz, H-3β), 3.18 (dd, J = 9, 14 Hz, H-3α), 3.70 (s, OMe), 4.94 (m, H-2α), 5.38 (br s, OH), 5.87 (d, J = 2 Hz, ArH), 5.98 (d, J = 2 Hz, H-5); exact mass m/e 180.0786 (calcd for $C_{10}H_{12}O_3$ m/e 180.0786).

A mixture of **8** and **9** was obtained with shorter reaction times in ether and tetrahydrofuran.

6-Methoxy-2-methyl-4,7-benzofurandione (Acamelin, 2). A solution of potassium nitrosodisulfonate (Fremy's salt, 705 mg) in water (60 mL) containing sodium acetate (280 mg) was added to a solution of the benzofuran **8** (200 mg) in methanol (6 mL) and the mixture stirred at room temperature for 30 min. The orange precipitate (150 mg, 70% yield) which formed was collected, washed with water, and recrystallized from chloroform–acetone (1:2) to give acamelin as bright orange-red needles: mp 253–255 °C;[9] IR (KBr) 1686, 1679, 1656, 1646, 1601, 1571, 1525 cm^{-1}; UV (EtOH) λ 219 nm (ϵ 21 000), 263 (9400), 307 (10 600), 417 (820); ^{1}H NMR ($CDCl_3$) δ 2.45 (d, J = 0.8 Hz, Me), 3.83 (s, OMe), 5.74 (s, H-5), 6.41 (d, J = 0.8 Hz, H-3). Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.25; H, 4.35.

α-Chloroethyl 2,4-Dihydroxy-6-methoxyphenyl Ketone (11). A solution of the 4-hydroxy-2,6-dimethoxyphenyl ketone **10** (2.6 g) in dichloromethane (125 mL) was added to aluminium chloride (5.31 g) in the same solvent (125 mL) and the mixture stirred under nitrogen at room temperature for 3 days. Ice–water (100 mL) was then added, the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated to yield a solid (2.4 g) which was recrystallized from carbon tetrachloride to give the dihydroxymethoxyphenyl ketone as small yellow needles: 89% yield; mp 134–135.5 °C; an analytical specimen was obtained by sublimation: mp 137–139 °C; ^{1}H NMR ($(CD_3)_2CO$) δ 1.62 (d, J = 7 Hz, Me), 3.93 (s, OMe), 5.68 (q, J = 7 Hz, CHCl), 5.98 (d, J = 2 Hz, H-3), 6.04 (d, J = 2 Hz, H-5). Anal. Calcd for $C_{10}H_{11}O_4Cl$: C, 52.07; H, 4.81. Found: C, 52.11; H, 4.85.

6-Hydroxy-4-methoxy-2-methyl-2,3-dihydrobenzofuran-3-one (12). A solution of the α-chloroethyl phenyl ketone **11** (126 mg) and potassium acetate (720 mg) in water (30 mL) was heated under reflux for 3.5 h. After being stored overnight at room temperature, it was acidified (1 N hydrochloric acid) and worked up in the usual way via ether. Removal of solvent gave a solid (75 mg, 70% yield) which on recrystallization from benzene yielded the **dihydrobenzofuranone 12** as prisms: mp 194–196 °C; ^{1}H NMR ($(CD_3)_2CO$) δ 1.36 (d, J = 7 Hz, Me), 2.90 (br s, OH), 3.83 (s, OMe), 4.50 (q, J = 7 Hz, CHMe), 6.06 (s, H-5 and H-7). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.76; H, 5.32.

Methylation of **12** with dimethyl sulfate and potassium carbonate in 1,2-dimethoxyethane yielded the 4,6-dimethoxydihydrobenzofuranone **6** in 44% yield, identical with that prepared from **5**.

Acknowledgment. We are grateful to the National Institutes of Health (General Medical Sciences) for a research grant.

Registry No. **2**, 74161-27-6; **3**, 108-73-6; **4**, 500-99-2; **5**, 83949-03-5; **6**, 83949-04-6; **7**, 83949-05-7; **8**, 83949-06-8; **9**, 83949-07-9; **10**, 83949-08-0; **11**, 83949-09-1; **12**, 83949-10-4; 2-chloropropionitrile, 1617-17-0.

(9) This melting point, determined on a Fisher-Johns apparatus or in a sealed tube capillary differs from that reported (mp 175–176 °C) for the natural product. In correspondence with Dr. Hausen, he has expressed reservations regarding the correctness of his melting point determination. We have also observed sublimation of the compound at lower temperatures than the melting point.

Convenient Monoketalization of 1,4-Cyclohexanedione. Synthesis of New Quinone Methides

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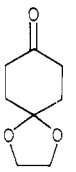
Considerable utility in the synthesis of natural products[1a-e] and of theoretically interesting molecules[1f] has been demonstrated for the ethylene monoketal (**1**) of 1,4-cyclohexanedione. Access to this extremely useful starting



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material has not, in general, been easy. Routes employing partial reaction of 1,4-cyclohexanedione with ethylene glycol gave low (to 30%) yields of **1** after a difficult (extraction/derivatization or chromatographic) workup,[2,3] a route based on cyclohexanone ring formation gave a low yield,[4] and a process involving partial oxidation of 1,4-cyclohexanediol followed by ketalization and further oxidation also gave about 30% overall yield.[5] Marshall and Flynn[6] have recently described a high-yielding (88%) preparation of **1** from hydroquinone monomethyl ether. Although efficient and suitable for mole-scale operation, this route was quite time consuming[7] and involved some potential hazards.[8] The purpose of this paper is to suggest the use of a more accessible compound, 7,12-dioxaspiro-[5.6]dodecan-3-one (**2**), which is functionally equivalent to **1**. The use of **2** in synthesizing some new quinone methides is reported.

Reaction of 1,4-cyclohexanedione (**3**) with ethylene glycol, propylene glycol, neopentyl glycol, or 1,3-propanediol gave the expected, hard-to-separate mixtures of residual **3**, monoketal, and bisketal in proportions close to 1:2:1.[9] It was surprising to observe that **3**, upon reaction with 1 equiv of 1,4-butanediol under normal ketalization conditions, gave a product mixture comprising (as shown by VPC analysis) 6% **3**, 80% monoketal **2**, and 14% bisketal **4** (Scheme I). Most of the undesired crystalline bisketal **4** was removed by filtration, and vacuum fractional distillation of the filtrate gave pure **2** in 40–60% yield.[10]

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(7) The three-step sequence[6] involves a dissolving-metal reduction followed by a 2-day period of NH_3 evaporation before the workup.

(8) The authors[6] point out that a potential for uncontrolled reaction exists in the Birch reduction; large quantities of toxic chromium(VI) are used in the final step.

(9) Reactions were carried out with 0.1 mol each of **3** and diol, 0.2 g of *p*-toluenesulfonic acid, toluene solvent, and Dean–Stark water removal; washed and neutralized reaction mixtures were analyzed by VPC.

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