SHORT PAPER

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The synthesis of ledgerquinone†

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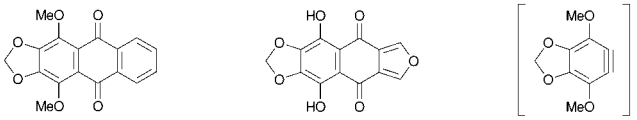
Ledgerquinone (1,4-dimethoxy-2,3-methylenedioxyanthracene-9,10-dione), isolated from the callus tissue of *Cinchona ledgeriana*, has been prepared by intercepting the benzyne, 3,6-dimethoxy-4,5-methylenedioxy-1,2-didehydrobenzene, with the anion of 3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile.

Keyword: ledgerquinone

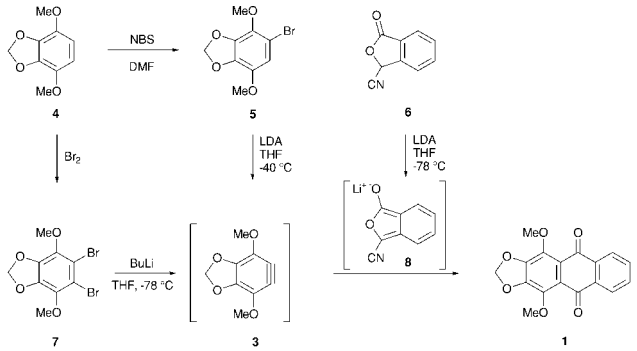
Ledgerquinone (1,4-dimethoxy-2,3-methylenedioxyanthracene-9,10-dione) (**1**) is one of 15 anthraquinones isolated from the callus tissue of *Cinchona ledgeriana*[1] and has also been detected in cell suspension cultures of the same species.[2] Methylenedioxy-substituted quinones are relatively rare within the large family of naturally occurring oxygenated quinones,[3] and we have previously described the synthesis of one such member, ventilone A (**2**),[4] and of related compounds[5,6] using cycloaddition reactions between 3,6-dimethoxy-4,5-methylenedioxy-1,2-didehydrobenzene (**3**) and various dienes. We report here the synthesis of **1** using a stabilised phthalide anion annulation protocol[7] involving the highly substituted benzyne **3**.



1 **2** **3**

The synthesis of **1** was achieved by two routes. In the first, benzyne **3** was generated in the presence of the phthalide anion **8** by treatment of dibromide **7**[5] with butyllithium at –78°C; hydrolytic workup followed by chromatography then gave **1** in 26% yield. A slight improvement in yield (33%) was achieved by forming aryne **3** from monobromide **5** by the action of lithium diisopropylamide (LDA). The requisite bromide **5** was obtained by treating the highly activated arene **4** with N-bromosuccinimide (NBS) in DMF[8] as bromination using one molar equivalent of molecular bromine was found to be difficult to stop at the monosubstitution stage.

The ^{1}H NMR spectrum of synthetic ledgerquinone was identical to that reported for the natural product[1] and other spectroscopic data are given in the experimental section. Although the yields of **1** obtained are only modest, the synthesis is useful because of its simplicity.



4 **5** **6** **7** **3** **8** **1**

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Experimental

Melting points were determined on a Reichert hot stage and are uncorrected. Anhydrous THF was obtained by distillation from K–benzophenone. NMR spectra were recorded on Bruker AM300 and ARX500 instruments and C assignments were made with the aid of DEPT pulse sequences. Mass spectra were recorded using a VG AutoSpec instrument with direct insertion and electron impact ionisation. The elemental analysis was carried out by MHW Laboratories, Phoenix, Arizona.

1-Bromo-2,5-dimethoxy-3,4-methylenedioxybenzene (**7**): – A solution of NBS (411 mg, 2.31 mmol) in DMF (15 ml) was added dropwise under argon to a stirred solution of 1,4-dimethoxy-2,3-methylenedioxybenzene (**4**)[5,9] (500 mg, 2.75 mmol) in DMF (15 ml) and stirring was continued overnight. The solution was diluted with water and extracted thoroughly with CH_2Cl_2. The extract was washed with water, brine and dried and evaporated. The residue was filtered through a plug of silica and eluted with light petroleum to afford 1-bromo-2,5-dimethoxy-3,4-methylenedioxybenzene (**7**) as colourless needles (579 mg, 81%), m.p. 55–57°C (Found: C, 41.68; H, 3.60; Br 30.39. $C_9H_9BrO_4$ requires C, 41.41; H, 3.47; Br, 30.61%). Mass spectrum *m/z* 262 (M+2, 100%), 260 (M, 97%), 247 (61), 245 (64), 189 (17), 138 (26). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 5.99 (s, 2 H, OCH_2O), 6.68 (s, 1 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 56.9 (OCH_3), 60.4 (OCH_3), 102.1 (OCH_2O), 106.9 (C), 111.2 (CH), 135.8 (C) 136.4 (C), 139.4 (C), 139.7, (C).

1,4-Dimethoxy-2,3-methylenedioxyanthracene-9,10-dione (ledgerquinone) (**1**): (a) BuLi in hexane (0.80 ml of 1.60M, 1.28 mmol) was added to a stirred solution of diisopropylamine (115 mg, 1.14 mmol) in THF (3 ml) at –78°C under an argon atmosphere. After 5 min a solution of 3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (**6**)[10] (159 mg, 1.00 mmol) in THF (2 ml) was added dropwise over 3 min and stirring was continued for 15 min. A solution of 1,2-dibromo-3,6-dimethoxy-4,5-methylenedioxybenzene (**7**)[5] in THF (3 ml) was added, and then BuLi in hexane (0.80 ml of 1.60M, 1.28 mmol) was added dropwise over 5 min. The cooling bath was removed and the dark solution was stirred at room temperature for 1 h after which it was diluted with water and extracted thoroughly with ether. The extract was washed with water, dried and evaporated and the residue subjected to rapid silica-filtration. Elution with EtOAc–light petroleum 1:5 gave ledgerquinone (**1**) as a bright yellow solid (82 mg, 26%) which crystallised from CH_2Cl_2–light petroleum as yellow needles, m.p. 196–198°C (lit.[1] no m.p. given). (Found: M^+. 312.0634. $C_{17}H_{12}O_6$ requires M^+. 312.0634). Mass spectrum *m/z* 313 (M+1, 49%), 312 (100%) and numerous fragment peaks of intensity range 10 – 24%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (s, 6 H, OCH_3), 6.19 (s, 2 H, OCH_2O), 7.68–7.72 (XX' part of AA'XX', 2 H, H 6 and H 7), 8.12–8.16 (AA' part of AA'XX', 2 H, H 5 and H 8) in agreement with the reported spectrum.[1] ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 61.2 (OCH_3), 103.1 (OCH_2O), 126.4 (CH), 133.3 (CH), 134.0 (C), 140.9 (C), 145.0, (C), 182.5 (CO). Electronic spectrum (MeOH) λ_{max} (log ε)/nm 207 (4.45), 242 (4.25), 280 (4.55), 379 (3.71). IR spectrum (KBr) υ_{max}/cm^{-1} 2941 w, 1666 s, 1581 m, 1466 m, 1457 m, 1333 s, 1311 s, 1256 m, 1069 s, 1036 m, 983 m, 734 m.

(b) BuLi in hexane (4.86 ml of 1.18M, 5.73 mmol) was added to a stirred solution of diisopropylamine (784 mg, 7.66 mmol) in THF (5 ml) at –78°C under an argon atmosphere. After 45 min a solution of 3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (**6**) (305 mg, 1.92 mmol) in THF (5 ml) was added dropwise over 10 min and stirring was continued for 10 min after which the red-orange solution was allowed to warm to –40°C. A solution of 1-bromo-2,5-dimethoxy-3,4-methylenedioxybenzene (**7**) (500 mg, 1.92 mmol) in THF (5 ml) was then added dropwise over 10 min and the mixture was then

allowed to warm to room temperature. After 2 h the mixture was diluted with aqueous NH_4Cl solution and after workup by extraction with CH_2Cl_2 and chromatography as before afforded ledgerquinone (199 mg, 33%) identical with the material obtained in (a).

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