Unambiguous synthesis and spectral characterization of 1,8-dihydroxy-4-methylanthraquinone

Anlai Wang, Cheng-Han Wu, and Ed Biehl*

Department of Chemistry, Southern Methodist University, Dallas, TX 75275, USA
E-mail: ebiehl@mail.smu.edu

Abstract
1,8-Dihydroxy-4-methylanthraquinone was recently isolated as a red liquid from cyanobacterium. We have confirmed that assignment by synthesizing unambiguously the titled compound in a two-step process. This synthetic methodology consisted of treating 4-methoxy-3-cyanophthalide with 2-bromo-4-methylanisole under aryne-forming conditions then demethylating the1,8-dimethoxy-4-methylanthra-quinone so formed.

Keywords: Cyanobacterium, 1,8-dihydroxy-4-methylanthraquinone, aryne, 4-methoxy-3-cyanophthalide

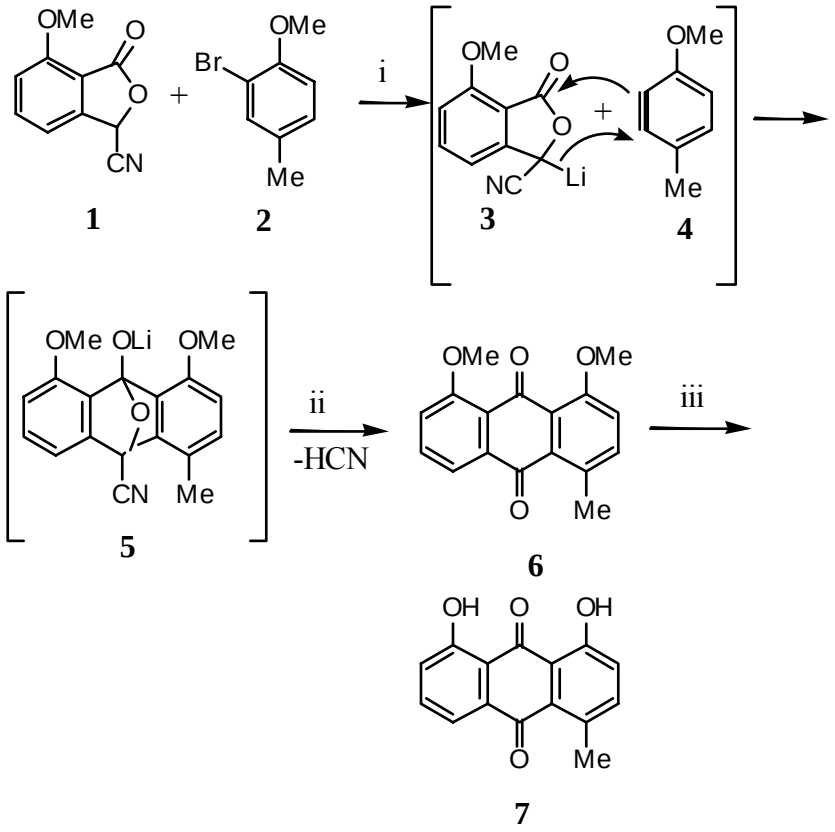
Introduction

Recently several new antibacterial metabolites were isolated from cyanobacterium *Nostoc commune*.[1] Among these metabolites was suggested to be 1,8-dimethoxy-4-methylanthraquinone (**7**), which presumably was the first anthraquinone to be isolated from a cyanobacterium. The structure of **7** was proposed on the basis of spectral analysis.

Results and Discussion

The finding that **7** existed as a red oil intrigued us. This is somewhat unusual since simple substituted anthraquinones are solid substances. We thus decided to confirm further the structure and physical form of **7** by preparing it unambiguously by a two-step reaction outlined in Scheme 1.

The first step involves an aryne reaction in which 7-methoxy-3-cyanophthalide (**1**)[2] and 2-bromo-4-methylanisole (**2**) are converted to 3-lithio-3-cyanophthalide (**3**) and 3-methoxy-6-methylbenzyne (**4**), respectively. Intermediate **3** then adds regioselectively to the 1-position of aryne **3** to get adduct **5**. Regioselective additions to 3-methoxyarynes



(i) LDA, -78 ^{0}C ⟶ rt; (ii) HCl/HOH; (iii) BBr_3 -78 ^{o}C ⟶ 20 ^{0}C.

Scheme 1. Synthesis of 1,8-dimethoxy-4-methylanthraquinone.

by nucleophiles in general[2] and specifically by 3-cyano-3-lithiophthalides[3] are well documented. During the acidic aqueous workup, adduct **5** is converted to 1,8-dimethoxy-4-methylanthraquinone **6**. Treatment of **6**, which was obtained as a yellow solid, with BBr_3 affords title compound **7**.

The ^{1}H NMR, ^{13}C NMR, IR, and UV spectra of **6** were consistent with proposed structure. For example, the ^{1}H NMR spectrum of **6** exhibited five resonances characteristic of 5-aromatic hydrogen atoms and three resonances corresponding to the two methoxy and methyl groups, In addition, the ^{13}C NMR of **6** contained 14 signals for the aromatic carbons and two carbonyl carbon resonances at 183.9 and 186.4 ppm. Additionally, its IR spectrum exhibited a carbonyl stretching frequency of 1671 cm^{-1} and its UV spectrum showed a λ_{max} at 389 nm as well as 271 and 259 nm. Final structural proof of **6** was obtained by single crystal X-ray diffraction. See ORTEP of compound **6** below

Purification of **7** was accomplished by column chromatography and was found to be a bright orange solid (UV [$CHCl_3$], λ_{max} 442, 285 and 253 nm), rather than a red oil as previously reported. The IR spectrum of **7** showed two separated carbonyl absorption bands at 1626 cm^{-1}

belonging to the chelated carbonyl group at C-9 and at 1729 cm^{-1} belonging to the free carbonyl group at C-10. Interestingly, the IR of **6**, in which chelation with neither carbonyl is possible, reveals only one absorption band at 1671 cm^{-1}. This value is consistent with aromatic carbonyl groups.

The ^1H NMR spectrum of **7**, which was obtained in $CDCl_3$ revealed all characteristic signals of all hydrogen atoms including the 1-OH (δ 12.05) and 8-OH (δ 12.58). The relatively high chemical shifts of the OH hydrogens are indicative of H-bonding between the nearby OH and C=O groups.[4] Other support for such intramolecular hydrogen bonding was the observation that **7** dissolved readily in the non-polar solvent $CDCl_3$. Comparison of the ^{1}HNMR of the synthesized **7** with that reported for the red liquid (which was obtained in MeOH-d_4) could not be accomplished due to the insolubility of the former in MeOH-d_4 In any case, our data confirms clearly the structure of **7** to be 1,8-dihydroxy-4-methylanthraquinone.

Experimental Section

General Procedures. Melting points were taken on a Mel-Temp II capillary apparatus, and are uncorrected with respect to stem correction. IR spectra were

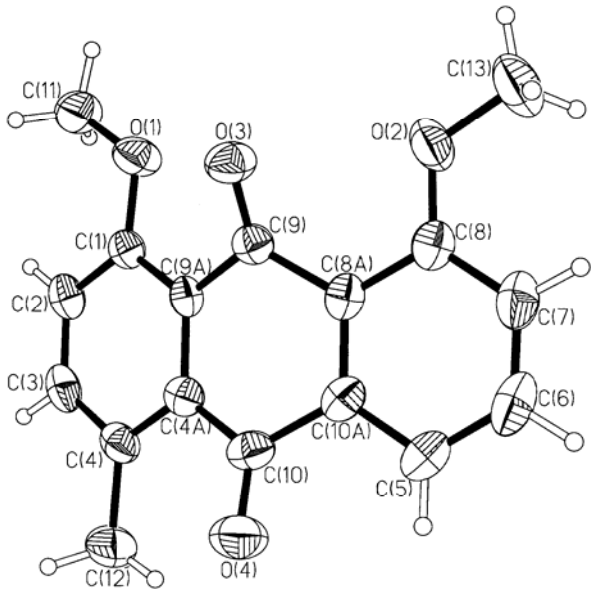


Figure 1. ORTEP of Compound **7**.

recorded on a Nicolet Magna-IR™ 550 FTIR spectrometer and the ^1H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker AVANCE DRX-400 Multi-nuclear NMR spectrometer; chemical shifts were referenced to TMS as internal standard. The UV/VIS spectra were recorded on a Beckman DU 660 Spectrometer. Elemental analyses were obtained from SMU Analytical Services Laboratories. 3-Cyano-7-methoxyphthalide and 2-bromo-4-methylanisole were available from previous studies. LDA, BBr_3, and THF were purchased from Aldrich Chemical Company. THF was distilled from Na/benzophenone immediately prior to use. The glassware was heated at 125 ^oC in an oven overnight prior to use. All reactions were done under an atmosphere of dry O_2-free N_2 *via* balloon.

General procedure for the preparation of 6

To a flame-dried flask was added 20 mL of LDA (2.0 M, 40 mmol) at -70 ^oC. After stirring for 10 min, 7-methoxy-3-cyanophthalide (0.95 g, 5 mmol) was added, and the stirring continued for 20 min to ensure complete anion formation. 2-Bromo-4-methylanisole (1.2g, 6 mmol) was added, the resulting solution was allowed to warm to room temperature, where it was stirred for 6 h. The reaction was then quenched with saturated NH_4Cl solution (30 mL) and extracted with methylene chloride. The combined extracts were washed with dilute HCl then dried (Na_2SO_4) and concentrated (rotary evaporator) to give a crude material. Chromatography of this material on silica gel (hexane/ethyl acetate, 4:1) gave the pure product **6** (180 mg, 15%). The physical and spectral properties for **6** are shown below.

General procedure for the preparation of 7

To a solution of **6** (28 mg, 0.1 mmol) in dry CH_2Cl_2 (1 mL) was added at –78 ^0C a soln of BBr_3 (1 mL of 1 in 1 M BBr_3 in CH_2Cl_2). After 1 h, the mixture was warmed to rt. then quenched with saturated $NaHCO_3$. The usual work up gave **7** (13 mg, 49%).

Physical and Spectroscopic Data.

Compound 6. yellow solid (needles), mp 178-180 ^oC (recrystallized from EtOAc/HOH). ; IR (KBr disk) ν_{max} 1671 cm^{-1} ; UV (MeOH) ν_{max} 259, 271, 389 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.94 (s, 3 H), 3.97 (s, 3 H), 7.42 (d, *J* = 8.24 Hz, 1 H), 7.45 (d,*J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 8.8 Hz, 1 H), 7.67 (dd, *J* = 8.8, 7.6 Hz, 1 H), 7.72 (d, *J* = 7.6 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.5 (q), 56.5 (q), 56.7 (q), 117.0 (s), 117.8 (d), 118.7 (d), 124.0 (d), 125.7 (s), 132.3 (s), 132.5 (d), 133.8 (s), 136.4 (d), 137.6 (s), 157.6 (s), 158.6 (s), 183.9 (s), 186.4 (s). *anal*:. Calcd for $C_{17}H_{14}O_4$, C, 72.33; H, 5.00 Found: C, 72.50; H, 5.03.

Compound 7. bright orange solid (needles), mp 189-191 ^0C (recrystallized from EtOAc/HOH). IR (KBr disk) ν_{max}3459, 1729, and 1626 cm^{-1} ; UV (MeOH) ν_{max} 253, 285, 442 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 2.74 (s, 3 H), 7.21 (d, *J* = 8.8 Hz, 1 H), 7.27 (d, *J* = 8.8.Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 1 H), 7.67.(dd, *J* = 8.4, 7.6 Hz, 1 H), 7.78 (d, *J* = 7.6 Hz, 1 H), 12.05 (s), 12.58 (s). (Reported[1] ^1H NMR in CD_3OD for **7**: δ 2.60 (s, 3 H), 6.70 (dd, *J* = 2.7, 8.0 Hz, 1 H), 6.74 (br d, *J* = 8.0 Hz, 1 H), 7.21 [d, *J* = 8.7 Hz, 1 H], 6.76 [dd, *J* = 2.7, 8.0 Hz, 1 H), 7.21 [d, *J* = 8.7 Hz, 1 H], 7.49 [d, *J* = 8.7 Hz, 1 H]). ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.3 (q), 115.6 (s), 116.3, (d)

118.2 (d), 119.8 (d), 123.6 (s), 124.4 (d), 125.0 (s), 134.8 (s), 137.2 (d), 142.2 (s) 142.3 (s), 162.0 (s), 183.7 (s), 193.3 (s). *Anal* Calcd for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96, C, 70.90; H, 4.01.

Acknowledgements

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