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PREPARATION OF NATURALLY OCCURRING ANTHRAQUINONES USING THE ARYNE REACTION

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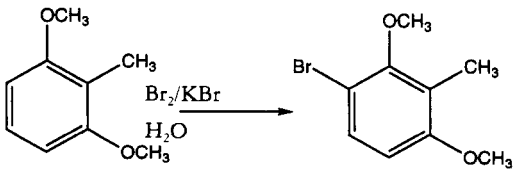
ABSTRACT.—The efficient synthesis of rubiadin 1,3-dimethyl ether [**1**] is described, in which 3,5-dimethoxy-4-methylbenzyne was generated from 3-bromo-2,6-dimethoxy toluene [**5**] with LDA or lithium tetramethylpiperidide in the presence of 3-cyano-1(3H)-isobenzofuranone [**7**] or 1(3H)-isobenzofuranone [**8**]. The subsequent conversion of **1** into the natural products rubiadin 1-methyl ether [**3**], rubiadin [**2**], and damnacathol [**4**] by chemical means is also reported.

We recently reported the synthesis of morindaparvin A and related anthraquinones by the reaction of arynes with 3-lithiated 3-cyanophthalides (1). This methodology was a modification of the arynic reaction with 3-lithiated phthalides developed by Sammes (2), which was utilized by Townsend (3) in the synthesis of averufin and hydroxyversicolorone. We have extended the modified Sammes anthraquinone synthesis and report herein the preparation of the 1,3-dimethyl ether of rubiadin [**1**], and its subsequent conversion by various chemical means to the naturally occurring materials, rubiadin [**2**], rubiadin 1-methyl ether [**3**], and damnacathol [**4**]. Of these naturally occurring materials, **2** and **3** have been isolated from the bark of the tree, *Cassia linariifolia*, and **2**–**4** have been obtained from the bark of a lowland forest shrub, *Coprosma rotundifolia* (4).

Our initial goal was to prepare the key intermediate rubiadin 1,3-dimethyl ether [**1**] by treating 3-bromo-2,6-dimethoxytoluene [**5**] with a phthalide under aryne generating conditions. Prior to this study, only one method, low-temperature bromination using dioxane/dibromide has been reported for the monobromination of resorcinol ethers (5). The other methods available for the preparation of monobrominated resorcinols involved multi-step procedures since the usual bromination procedures yielded a mixture of products (6,7). We found subsequently that the bromo derivative **5** could be prepared more conveniently at room temperrature and in nearly quantitative yield (98%) by treating 2,6-dimethoxytoluene [**6**] with a solution of 1 equivalent of bromine and KBr in H_2O (7) as shown in the equation below.

With adequate quantities of **5** on hand, we next prepared the key intermediate 1,3-dimethyl ether of rubiadin [**1**] by the reaction of **5** with 3-cyano-1(3H)-isobenzofuranone [**7**] and LDA (method A) and with 1(3H)-isobenzofuranone [**8**] and LiTMP (lithium 2,2,6,6-tetramethylpiperidide) (method B). These two methods, shown in Scheme 1, gave **1** in comparable yields (50% and 47%, respectively). The use of LDA in place of LiTMP in the latter reaction, however, afforded **1** in very poor yields (<10%). For multi-gram scale reactions, method A is generally preferred over method B



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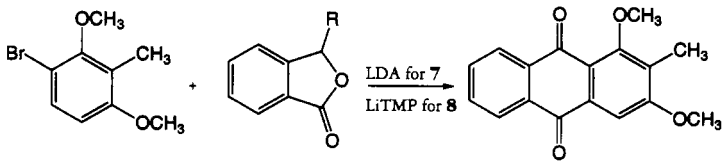


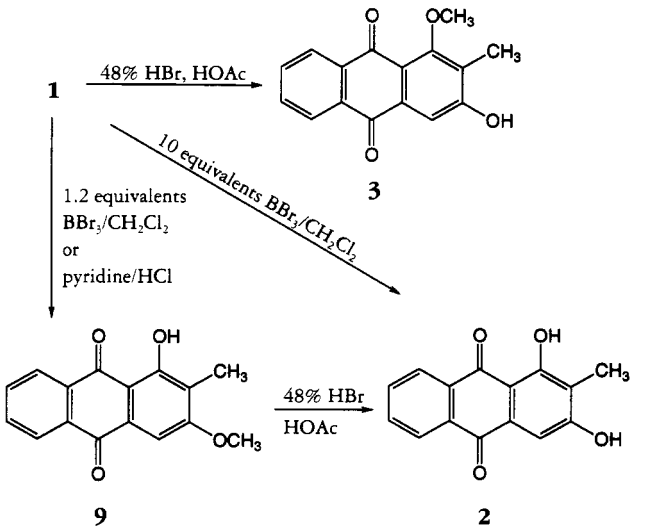
5 **7** R=CN **8** R=H **1**

SCHEME 1

for two major reasons. First, **1** is obtained directly upon proton quench of reaction mixture in the former, whereas the latter requires extended aerial oxidation (>5 h) of initially formed anthrahydroquinones in order to secure **1**. Second, the LDA used in method A is a much less expensive base than lithium 2,2,6,6-piperidide. Method B has some advantage over method A since, of the two phthalides, only isobenzofuranone **8** is commercially available. However, the 3-cyanophthalide [**7**] and its derivatives can be prepared readily by Swenton's method (9).

We next attempted to bidemethylate the 1,3-dimethyl ether **1** directly to rubiadin [**2**] by treating it with 48% hydrobromic acid in HOAc (10). However, as shown in Scheme 2, **1** underwent selective 3-demethylation, yielding the naturally occurring rubiadin 1-methyl ether [**3**] in 72% yield. In contrast, the reaction of **1** with pyridinium hydrochloride (11) or 1.2 equivalents of BBr_3 (12) resulted in selective 1-demethylation affording rubiadin 3-methyl ether [**9**] in 90% and 89% yields, respectively. The 3-methyl ether **9** was then converted to **2** in 93% yield by treatment with 48% HBr in HOAc. We found subsequently that **1** could be bidemethylated to rubiadin [**2**] in 61% yield in the presence of a large excess (10 equivalents) of BBr_3.

We next planned to oxidize the 1,3-dimethyl ether **1** to damnacathal 3-methyl ether using cerium (IV) ammonium nitrate (CAN) in HOAc and H_2O, and then to demethylate selectively the 3-methyl ether to damnacathol [**4**]. However, under these conditions, damnacathol [**4**] was obtained in very poor yield



SCHEME 2. Synthesis of rubiadin 1-methyl ether [**3**] and rubiadin [**2**].

(<10%) along with a complex mixture of other products. This problem was overcome (Scheme 3) by oxidizing **1** with CAN in anhydrous HOAc (13) to the 2-hydroxymethyl derivative **10** in 64% yield, and then selectively 3-demethylating **10** with 48% HBr in HOAc to damnacathol [**4**] in 60% yield.

Subsequent to the CAN oxidation with cerium (IV) ammonium nitrate in HOAc and H_2O, we found that the 2-hydroxymethyl derivative **10** could be prepared in very high overall yield (88%) by treating **1** with NBS (96%), then hydrolyzing the resulting bromomethyl derivative [**11**] (92%).

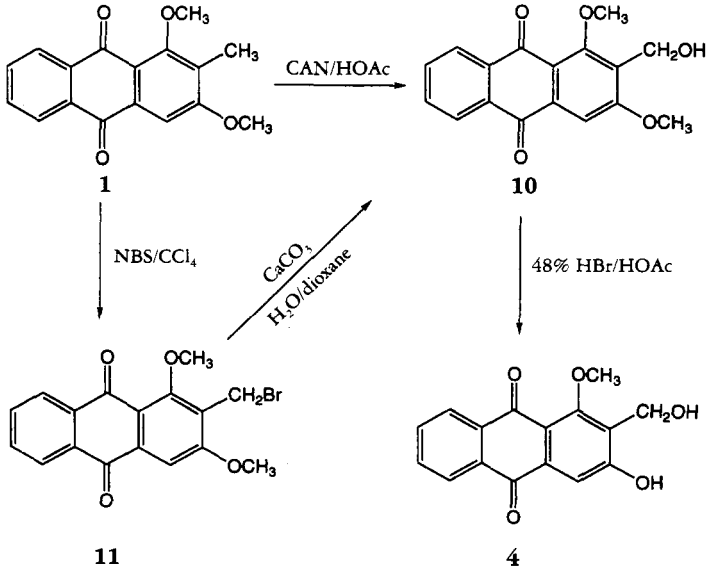
In conclusion, we have developed a convenient arynic method for preparing rubiadin 1,3-dimethyl ether [**1**], and have demonstrated its facile conversion to the natural products, rubiadin [**2**], rubiadin 1-methyl ether [**3**], and damnacathol [**4**].

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All air-sensitive preparations were done under an atmosphere of dry O_2-free N_2 contained in a balloon possessing a needle protruding through a rubber septum attached to one of the reaction flask necks. All reagents were obtained from Aldrich and were distilled or recrystallized prior to use. The glassware was heated at 125° in an oven overnight prior to use. Mps were taken on an electrochemical apparatus and are reported uncorrected. Ir spectra were determined on a Ft-ir spectrometer and the ^{1}H- and ^{13}C-nmr spectra were recorded on a 200 MHz spectrometer; chemical shifts are related to TMS as internal standard. E. Merck Si gel 9385 (230–240 mesh) was used for flash cc. Elemental analyses were carried out by Analytical Services, Southern Methodist University.

SYNTHESIS OF 3-BROMO-2,6-DIMETHOXYTOLUENE [**5**].—To a solution containing KBr (8 g, 67 mmol), Br_2 (3.52 g, 22 mmol), and distilled H_2O (80 ml), 2-methylresorcinol (**6**, 0.304 g, 20 mmol) was added in one portion and at room temperature. After stirring 1 h, the solution was extracted with EtOAc (3×150 ml). The combined extracts were then dried over anhydrous Na_2SO_4, and concentrated to yield an oil, which was distilled to give **5** (0.453 g, 98%), bp 94–96°/0.3 Torr [lit. (8) 92–94°/2.5 Torr]; ^{1}H nmr ($CDCl_3$) δ 2.17 (3H, s), 3.79 (3H, s), 3.80 (3H, s), 6.51 (1H, d, J=8.85 Hz), 7.31 (1H, d, J=8.85 Hz).

SYNTHESIS OF RUBIADIN 1,3-DIMETHYL ETHER [**1**].—*Method A.*—Reaction of 3-cyano-1(3H)-isobenzofuranone [**7**] with 3-bromo-2,6-dimethoxytoluene [**5**] and LDA. In a flame-dried flask flushed with N_2, LDA (75 mmol) was prepared by adding *n*-BuLi (30 ml, 2.5 M in hexanes, 75 mmol) to a solution of diisopropylamine (10 ml, 75 mmol) in THF (100 ml) at −70°. After stirring for 10 min, 3-cyano-1(3H)-isobenzofuranone (**7**, 4 g, 25 mmol) in THF (50 ml) was added dropwise over 20 min and the stirring was continued for 20 min at −70°. The solution



SCHEME 3. Synthesis of damnacathol [**4**].

was then allowed to warm to −40° at which point 3-bromo-2,6-dimethoxytoluene (**5**, 7.0 g, 30 mmol) in THF (50 ml) was added dropwise while the temperature remained at −40°. The resulting solution was then allowed to warm to room temperature, when it was stirred overnight. The mixture was then quenched with saturated NH_4Cl, the THF evaporated under reduced pressure, and the remaining residue was extracted with CH_2Cl_2 (4×100 ml). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated (rotary evaporator) to provide the crude anthraquinone [**1**], which was purified by flash cc using a mixture of hexane-EtOAc (3:1) as the eluent to give rubiadin 1,3-dimethyl ether (**1**, 3.58 g, 50%) as yellow needle crystals, mp 158–159°; ir (KBr) ν max 3019, 1670, 1578, 1223, 1209, 787, 766 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.27 (3H, s), 3.91 (3H, s) 4.03 (3H, s), 7.63 (1H, s), 7.75 (2H, m), 8.25 (2H, m); ^{13}C nmr ($CDCl_3$) δ 9.13, 56.13, 61.13, 104.58, 119.87, 126.44, 127.08, 128.70, 132.50, 132.93, 134.08, 124.38, 134.85, 160.20, 162.64, 181.33, 183.13; *anal.*, calcd for $C_{17}H_{14}O_4$ C, 72.33; H, 5.00; found C, 72.30; H, 5.04.

Method B.—Reaction of 1(3H)-isobenzofuranone [**8**] and 3-bromo-2,6-dimethoxytoluene [**5**] and lithium 2,2,6,6-tetramethylpiperidide. 2,2,6,6-Piperidine (2.7 ml, 2.26 g, 16 mmol) in 10 ml THF was treated at −60° (CH_2Cl_2/dry ice) with *n*-butyllithium (6.72 ml of 2.5 M solution in hexanes, 16.8 mmol) and the resulting solution was stirred for 10 min. Then 1(3H)-isobenzofuranone (**8**, 700 mg, 5.2 mmol) in THF (50 ml) was added to that solution and stirred at −60° for 20 min. The orange solution was then warmed to −40° and a solution of 3-bromo-2,6-dimethoxytoluene (**5**, 1.16 g, 5.0 mmol) in THF (30 ml) was added. After being stirred to 15 min, the mixture was allowed to warm gradually to room temperature during which time the solution became dark reddish-purple. The mixture was stirred for 1 h at room temperature then opened to air and stirred for 5 h, then worked up in a similar fashion to that described in method A above to yield **1** (609 mg, 47%).

PREPARATION OF RUBIADIN 1-METHYL ETHER [**3**].—Rubiadin 1,3-dimethyl ether (**5**, 70 mg, 0.25 mmol) was dissolved in a solution containing HOAc (4.4 ml) and 48% HBr (0.56 ml, 5 mmol), and the resulting solution was heated under reflux for 48 h. After cooling to room temperature, the mixture was diluted with H_2O (15 ml) and extracted with CH_2Cl_2 (3×25 ml). The combined CH_2Cl_2 extracts were dried (Na_2SO_4), concentrated (rotary evaporator), and the remaining material was purified by flash cc using a 1:1 mixture of EtOAc and hexane as the eluent to yield 48 mg (72%) rubiadin 1-methyl ether [**3**] as a yellow solid, mp 283–285° (Me_2CO/hexane) [lit. (4) 282–284° (dioxane)]; ir (KBr) ν max 3386, 1664, 1618, 1577, 1337, 1324, 1308, 1275 cm^{-1}; ^1H nmr (Me_2CO-d_6) δ 2.14 (3H, s), 4.04 (3H, s), 7.31 (1H, s), 7.87 (2H, m), 8.23 (2H, m).

PREPARATION OF RUBIADIN 3-METHYL ETHER [**9**].—*Method A.*—Rubiadin 1,3-dimethyl ether (**1**, 70 mg, 0.25 mmol) was heated with pyridine hydrochloride (2.5 g, 22 mmol) at 180–190° (oil bath temperature) for 8 h. The mixture was cooled to room temperature and treated with H_2O (30 ml) to yield a yellow needle precipitate. The crystals were collected, washed with H_2O, and air-dried to afford rubiadin 3-methyl ether (**9**, 60 mg, 90%).

Method B.—Into a solution of the 1,3-dimethyl ether **1** (85 mg, 0.3 mmol) in anhydrous CH_2Cl_2 (5 ml), BBr_3 (0.35 ml, 1 M in CH_2Cl_2) was added dropwise at −78° under N_2. The *i*-PrOH/dry ice bath was removed, and after the mixture was stirred for 24 h at room temperature, H_2O was added and the resulting mixture extracted with CH_2Cl_2 (3×25 ml). The combined CH_2Cl_2 extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The remaining material was treated in similar fashion to that described in method A above to yield rubiadin 3-methyl ether (**9**, 72 mg, 89%) as yellow needles, mp 189–190° (CH_2Cl_2/Et_2O); ir (KBr) ν max 3362, 2945, 1673, 1581, 1317, 1283, 1226, 1133, 1004, 716 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.15 (3H, s), 3.99 (3H, s), 7.33 (1H, s), 7.75 (2H, m), 8.23 (2H, m); ^{13}C nmr ($CDCl_3$) δ 8.16, 56.09, 102.28, 110.78, 120.55, 126.65, 127.08, 132.16, 133.31, 133.40, 133.91 (2C), 161.95, 163.45, 182.31, 187.00; *anal.*, calcd for $C_{16}H_{12}O_4$ C, 71.64; H, 4.51; found : C, 71.81; H, 4.57.

PREPARATION OF RUBIADIN [**2**].—*Method A.*—Rubiadin 3-methyl ether (**9**, 68 mg, 0.25 mmol) was heated under reflux with AcOH (4.4 ml) and 48% HBr (0.56 ml, 5 mmol) for 24 h. After cooling to room temperature, H_2O (20 ml) was added to the mixture to yield a yellow solid which was collected by filtration and air-dried to give 31 mg of rubiadin [**2**]. The filtrate was extracted with EtOAc and worked up as described in the preparation of **3** to give another 18 mg of **2**. Combination of the two solid portions gave a total of 53 mg (93%) of **2**, mp 301–302° (AcOH/H_2O) [lit. (4) 301° (AcOH or $CHCl_3$)]; recrystallization of **2** from Me_2CO/hexane gave mp 305–307°; ir (KBr) ν max 3396, 1662, 1624, 1590, 1337, 1310, 1122 cm^{-1}; ^1H nmr (Me_2CO-d_6) δ 2.16 (3H, s), 7.35 (1H, s), 7.92 (2H, m), 8.26 (2H, m).

Method B.—Rubiadin 1,3-dimethyl ether (**1**, 60 mg, 0.2 mmol) was dissolved in anhydrous CH_2Cl_2 (5 ml) and cooled to −78° under N_2, then BBr_3 (2 ml, 1 M in CH_2Cl_2, 2 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 24 h, then worked up as described in method A for the preparation of

compound **7** to give 31 mg (61%) of **2**, mp 305–307° after recrystallization from Me_2CO/hexane. The spectral properties of **2** were identical to those reported in method A above.

PREPARATION OF LUCIDIN 1,3-DIMETHYL ETHER [**10**].—*Method A.*—A solution of rubiadin 1,3-dimethyl ether (**5**, 282 mg, 1 mmol), *N*-bromosuccinimide (1.95 mg, 1.1 mmol), and benzoyl peroxide (5 mg) in CCl_4 (12 ml) was refluxed under irradiation with a sun lamp for 3 h. After cooling to room temperature, the succinimide was filtered off, and the solvent evaporated *in vacuo*. The residue was purified by flash cc using EtOAc-hexane (1:3) as eluent to furnish the monobromide **11** (347 mg, 96%), mp 172–173.5° (CH_2Cl_2/hexane); ir (KBr) ν max 3462, 3029, 2254, 1672, 1579, 1237, 911, 732, 651 cm^{-1}; ^1H nmr ($CDCl_3$) δ 4.10 (3H, s), 4.12 (3H, s), 4.71 (2H, s), 7.68 (1H, s), 7.78 (2H, m), 8.27 (2H, m); ^{13}C nmr δ ($CDCl_3$) 30.91, 56.65, 62.58, 105.35, 119.83, 126.70, 127.25, 127.72, 132.38, 133.27, 134.42, 134.72, 136.77, 160.98, 162.21, 180.87, 182.83 ppm; *anal.*, calcd for $C_{17}H_{13}O_4Br$ C, 56.53; H, 3.63; found C, 56.31; H, 3.66.

H_2O (3 ml) and $CaCO_3$ (250 mg, 2.5 mmol) were added to a solution of compound **11** (180 mg, 0.5 mmol) in 3 ml of dioxane, and the mixture was refluxed for 24 h. The solution was cooled to room temperature and CH_2Cl_2 (20 ml) was added followed by the addition of dilute HCl until all solids had dissolved. The organic phase was separated, and the H_2O phase was extracted with CH_2Cl_2 (2×25 ml). The combined organic phases were washed with saturated $NaHCO_3$, dried (Na_2SO_4), and filtered. Removal of the solvent left a yellow solid which was purified by flash cc (EtOAc/hexane) to afford lucidin 1,3-dimethyl ether (**10**, 138 mg, 92%), mp 182–184° (AcOH/hexane).

Method B.—A solution of ceric ammonium acetate (2.2 g, 4 mmol) in HOAc (10 ml) was added dropwise to a stirred, warm (85°) solution of rubiadin 1,3-dimethyl ether (**1**, 282 mg, 1 mmol) in HOAc (5 ml). The mixture was stirred for 2 h at 85°, then cooled to room temperature. H_2O (15 ml) was added and the resulting mixture extracted with CH_2Cl_2 (2×25 ml). The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated (rotary evaporator) to yield a solid which was recrystallized from HOAc/hexane to yield 188 mg (64%) of lucidin 1,3-dimethyl ether [**10**] with the same mp as that reported in method A above. Ir ν max (KBr) 2254, 1673, 1653, 1582, 1326, 1287, 1272, 907, 725 cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.98 (3H, s), 4.05 (3H, s), 5.67 (2H, s), 7.67 (1H, s), 7.7 (2H, m), 8.24 (2H, m).

PREPARATION OF DAMNACATHOL [**4**].—Lucidin 1,3-dimethyl ether (**10**, 60 mg, 0.2 mmol) was heated with HOAc (3.5 ml) and 48% HBr (0.45 ml, 4 mmol) and refluxed for 24 h. The mixture then was worked up in similar manner as that described above for **3** to give 34 mg (60%) of damnacathol [**4**], mp 286–288° [lit. (4) 288°]; ir (KBr) ν max 3422, 1664, 1627, 1614, 1588, 1572, 1331, 1298, 1172 cm^{-1}; ^1H nmr (Me_2CO-d_6) δ 4.16 (3H, s), 4.67 (2H, s), 7.41 (1H, s), 7.95 (2H, m), 8.26 (2H, m).

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