An Improved Procedure for the Oxidative Transformation of Hydroanthracenones and Hydronaphthacenones to Hydroxyanthraquinones and Hydroxynaphthacenediones

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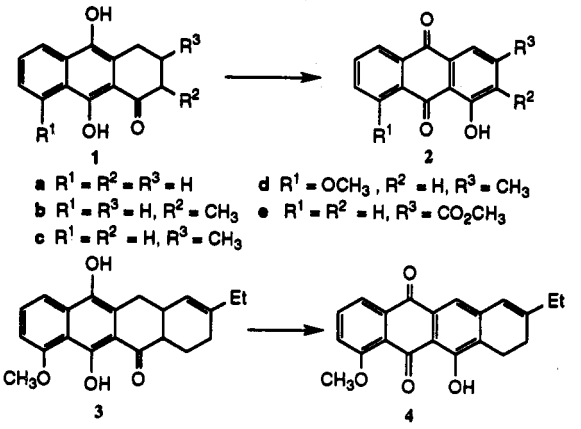
Received April 8, 1993 (Revised Manuscript Received October 25, 1993)

We have previously shown that hydroanthracenones **1a–e**[1] and hydronaphthacenone **3**,[2] prepared through condensation of phenylsulfonyl isobenzofuranones[3] with cyclohexenones and naphthalenones, are useful precursors to hydroxyanthraquinones **2a–e** and the anthracyclinone intermediate **4**. Earlier, we reported that sequential reaction of **1** with NBS in water/acetone followed by treatment with Et_3N furnished **2** in high yield.[1] While this reaction could be accomplished within 1 h, this procedure was incompatible with intermediates containing an olefin or an existing aromatic ring with two or more oxygens. In order to overcome these limitations, a second procedure, involving heating the hydroanthracenone **1** or the hydronaphthacenone **3** in DMF under an oxygen atmosphere, was developed.[2,4] While this latter reaction was normally accomplished in good yield, on occasion we noted the formation of byproducts; moreover, this reaction was slow, usually taking 24 h to go to completion.

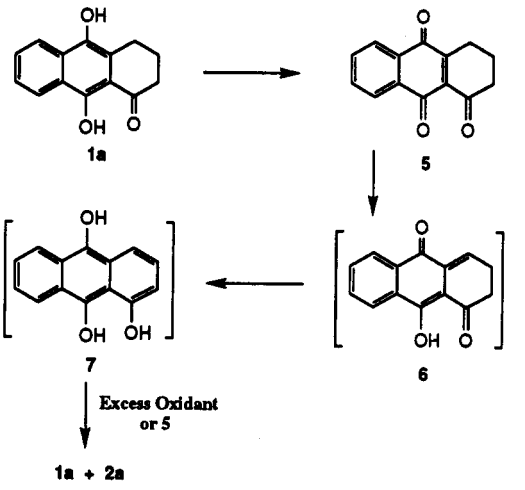
Our hypothesized mechanism for these reactions involved initial oxidation to quinones such as **5** (Scheme 2).[5] Base-catalyzed conversion of **5** to an *ortho*-quinone methide would give **6**, which would then undergo a second base-catalyzed isomerization to the anthracenetriol **7**. Oxidation of **7** by excess oxidant would provide the anthraquinone **2a** or alternatively, the quinone **5** could function as the oxidant furnishing **2a** and the hydroanthracenone **1a**. In the presence of excess oxidizing agent and base, both **1a** and **7** would ultimately be converted to **2a**.

We have now isolated the quinone **5** and demonstrate its intermediacy in the formation of **2a**. Thus, rapid addition of Fetizon's reagent[6] (Ag_2CO_3 on Celite) to a magnetically stirred solution of the hydroanthracenone **1a** followed by filtration of the reaction and evaporation of the solvent gave the unstable quinone **5**. Although **5** could be recrystallized, it could not be chromatographed and on standing, underwent decomposition. Addition of a drop of triethylamine to a solution of **5** furnishes a (ca. 1:1; TLC, NMR) mixture of the anthraquinone **2a** and hydroanthracenone **1a**.

Scheme 1



Scheme 2



We have used this finding to develop a new method for rapid, high-yield oxidation of **1a–e** and **3** to the corresponding quinones. The procedure consists of adding Ag_2CO_3 on Celite to a magnetically stirred solution of either the hydroanthracenones **1a–e** or hydronaphthacenone **3** in CH_2Cl_2, followed by addition of a catalytic amount of Et_3N to effect isomerization of the initially formed quinone intermediate (e.g. **5**). The reaction is stirred for 5 min and then worked up. The procedure is superior to those published previously in that it can be performed in less than 1 h, there are fewer side products, and the reaction is compatible with the presence of an olefin in the starting material. The yields of products **2a–e** and **4** were better than those reported previously.

In summary, this procedure represents an improved and highly efficient method for the oxidative transformation of hydroanthracenones and hydronaphthacenones to their quinone counterparts. Studies are underway to determine if intermediates in the oxidation can be exploited synthetically.

Experimental Section

General Procedure for the Oxidative Transformation of 3,4-Dihydro-9,10-dihydroxy-1(2*H*)-anthracenones (1) and 6,11-Dihydroxy-2-ethyl-7-methoxy-3,4,12,12a-tetrahydronaphthacen-5(4a*H*)-one (3) to 1-Hydroxyanthracene-9,10-diones (2) and 7,8-Dihy-

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(5) Although we were able to isolate an intermediate from the NBS reaction, we were unable to determine its structure due to its rapid disproportionation to the anthraquinone, hydroanthracenone, and other products. On the basis of the observation that **1** and **2** were formed in this reaction, we hypothesized that the quinone was an intermediate. In the DMF/oxygen procedure we were not able to detect an intermediate, but assumed here again that the quinone was an intermediate that disproportionates in the slightly basic medium (DMF).
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0022-3263/94/1959-0258$04.50/0

dro-9-ethyl-4-methoxy-6-hydroxynaphthacene-5,12-dione (4). To a magnetically stirred solution of the hydroanthracenone 1 or hydronaphthacenone 3 (0.41 mmol) in CH_2Cl_2 (10 mL) was added Ag_2CO_3 on Celite (1.74 mmol/g, 1.65 mmol). Triethylamine (1 drop) was added and the mixture was stirred for 5 min. The reaction was filtered and the filtrate was evaporated. Chromatography of the residue on silica (10 g) with CH_2Cl_2 as eluent gave the quinone product.

1-Hydroxyanthracene-9,10-dione (2a): 95% yield; mp 197–198 °C (lit.[7a] mp 194–195 °C); ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 1 H, J = 9.5 Hz), 7.69 (t, 1 H, J = 9.5 Hz), 7.82 (m, 3 H), 8.32 (m, 2 H), 12.62 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 116.1, 119.5, 124.3, 126.9, 127.4, 133.2, 133.4, 133.6, 134.1, 134.6, 136.7, 162.5, 182.3, 188.6; IR (film) 3315 (m), 2936 (w), 1611 (s), 1493 (w), 1444 (m), 1387 (s), 1331 (m).

1-Hydroxy-2-methylanthracene-9,10-dione (2b): 90% yield; mp 180–182 °C (lit.[7b] mp 185–186 °C); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3 H), 7.50 (d, 1 H, J = 7.9 Hz), 7.71 (d, 1 H, J = 7.9 Hz), 7.78 (m, 2 H), 8.27 (m, 2 H), 12.92 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.1, 115.1, 119.2, 126.8, 127.2, 131.2, 133.2, 133.7, 133.9, 134.5, 134.9, 137.2, 161.0, 182.3, 188.9; IR (film) 3382 (w), 2924 (w), 1672 (m), 1637 (m), 1592 (m), 1428 (m), 1358 (m), 1294 (s), 1262 (s).

1-Hydroxy-3-methylanthracene-9,10-dione (2c): 80% yield; mp 176–177 °C (lit.[8] mp 176–177 °C); ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3 H), 7.09 (s, 1 H), 7.63 (s, 1 H), 7.79 (m, 2 H), 8.27 (m, 2 H), 12.56 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.2, 114.1, 120.8, 124.1, 126.8, 127.3, 133.1, 133.3, 133.6, 134.1, 134.4, 148.6, 162.7, 182.6, 188.0; IR (film) 3388 (m), 2924 (w), 1672 (m), 1637 (s), 1590 (s), 1368 (s), 1278 (s).

1-Hydroxy-8-methoxy-3-methylanthracene-9,10-dione (2d): 81% yield; mp 196–197 °C (lit.[9] mp 198 °C); ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3 H), 4.06 (s, 3 H), 7.06 (s, 1 H), 7.33 (d, 1 H, J = 7.8 Hz), 7.55 (s, 1 H), 7.71 (t, 1 H, J = 7.8 Hz), 7.92 (d, 1 H, J = 7.8 Hz), 12.90 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.0, 56.6, 114.9, 118.0, 119.9, 120.0, 120.7, 124.5, 132.3, 135.5, 135.7, 147.5, 160.7, 162.6, 182.8, 188.4; IR (film) 3406 (w), 2924 (w), 1676 (w), 1636 (s), 1583 (m), 1274 (s), 1244 (s), 783 (m), 750 (m).

4-Hydroxy-5-methoxy-9,10-dioxo-2-anthracenecarboxylic acid, methyl ester (2e): 100% yield; mp 222–224 °C (lit.[2] mp 224–225 °C); ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3 H), 4.08 (s, 3 H), 7.38 (d, 1 H, J = 7.8 Hz), 7.76 (t, 1 H, J = 7.8 Hz), 7.90 (d, 1 H, J = 1.8 Hz), 7.96 (d, 1 H, J = 7.8 Hz), 8.34 (d, 1 H, J = 1.8 Hz), 12.86 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.8, 56.7, 118.3, 119.2, 120.3, 120.5, 125.3, 132.9, 135.5, 136.2, 136.5, 161.0, 162.3, 165.1, 181.9, 188.4; IR (film) 3380 (w), 2924 (w), 1719 (m), 1664 (w), 1637 (m), 1583 (m), 1292 (s), 1271 (m), 1224 (s).

9-Ethyl-7,8-dihydro-4-methoxy-6-hydroxynaphthacene-5,12-dione (4): 98% yield; mp 172–173 °C (lit.[2] mp 168–171 °C); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3 H, J = 7.6 Hz), 2.28 (q, 2 H, J = 7.6 Hz), 2.34 (t, 2 H, J = 8.8 Hz), 2.90 (t, 2 H, J = 8.8 Hz), 4.03 (s, 3 H), 6.22 (s, 1 H), 7.28 (d, 1 H, J = 8.0 Hz), 7.34 (s, 1 H), 7.64 (t, 1 H, J = 8.0 Hz), 7.86 (d, 1 H, J = 8.0 Hz), 13.21 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.6, 19.9, 26.5, 30.3, 56.5, 114.9, 116.4, 117.8, 119.8, 120.2, 120.8, 128.6, 130.6, 135.1, 135.7, 142.0, 149.6, 159.3, 160.5, 182.5, 188.1; IR (film) 3435 (w), 2960 (w), 1665 (w), 1626 (m), 1584 (m), 1260 (s).

3,4-Dihydroanthracene-1(2*H*),9,10-trione (5). The reaction was run as described above, but Et_3N was not added. Recrystallization of the initial product from EtOAc afforded pure 5 (95% yield) with mp 180 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.19 (m, 2 H), 2.66 (t, 2 H, J = 7.0 Hz), 2.89 (t, 2 H, J = 7.0 Hz), 7.75 (m, 2 H), 8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.0, 23.4, 39.3, 120.0, 125.9, 126.6, 131.3, 132.0, 133.5, 134.7, 154.5, 181.9, 186.1, 196.9; IR (film) 2954 (w), 1708 (s), 1668 (m), 1589 (m), 1284 (s), 1116 (m). Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.32; H, 4.46. Found: C, 74.25; H, 4.29.

Acknowledgment. This work was generously supported by the National Institutes of Health (GM/CA 18141).

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