Solution Characterization of Carboxybenzoquinone and the Isolation of Derived Quinhydrones

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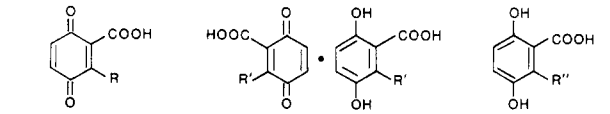
Received June 15, 1984

Surprisingly, in spite of the wide and prolonged interest by a large number of investigators in the chemistry and biology of the benzoquinone moiety,[1,2] the preparation and characterization of carboxybenzoquinone (**1a**) has not been previously reported. Although historically, both the ethyl[3] and methyl ester[3,4] of **1a** and 2-cyano-1,4-benzoquinone[4,5] have been described, successful hydrolyses of these compounds have not been reported (hydrolyses of esters attempted[3]). Fully substituted trimethyl[6] and triphenyl[7] carboxybenzoquinones have been reported; however, the high degree of substitution which is responsible for their stability also limits their utility as intermediates in organic synthesis. Successful synthesis of the corresponding carboxaldehyde[8] has been reported although alternative methods of preparation have failed.[9]

It seemed that the most direct route to the preparation of **1a** would be by oxidation of the hydroquinone, gentisic acid. Electrochemical oxidation of gentisic acid had been previously reported,[10,11] although the oxidized material (**1a**) was not stable under the acidic aqueous conditions utilized. Our initial attempts at direct chemical oxidation of gentisic acid with common chemical oxidants (sodium dichromate; silver oxides; DDQ; $FeCl_3$) led to mostly intractable materials. Our first successful observation (^1H NMR, 250-MHz) of **1a** in solution was accomplished by the oxidation of gentisic acid (8.0 mg, 0.05 mmol) with lead in tetraacetate (LTA; 42 mg, 0.10 mmol) in acetic acid-d_4 (0.6 mL). Complete oxidation of the starting material was observed within 30 min (bright yellow solution); however, decomposition to a complex, dark mixture occurred at slightly longer reaction times. It proved impossible to concentrate this solution or to remove lead salts from such a reaction mixture without decomposition of the desired product.

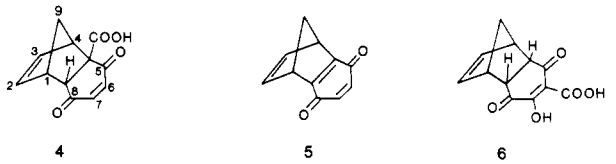
A further survey of chemical oxidants directed toward the use of more easily removable reagents and solvents led to the discovery of ceric(IV) ammonium sulfate (previously employed in the oxidation of polycyclic aromatic hydrocarbons to quinones[12]) as a suitable reagent for this purpose. This oxidant is employed as a practically insoluble reagent in chloroform for "clean" oxidation (approximately 10% conversion within 15 min) of the sparingly soluble gentisic acid. Simple filtration removes both oxidant and any remaining starting material. Attempted isolation of carboxybenzoquinone (**1a**) from this chloroform solution by precipitation with petroleum ether (60–70 °C) or by removal of the solvent in vacuo led to deposition of a dark-brown, crystalline solid which has been characterized as the quinhydrone complex **2a** of gentisic acid and carboxybenzoquinone.



1a, R = H
b, R = NH-C_6H_5-OCH_3
c, R = OH

2a, R' = H
b, R' = OH

3a, R'' = Cl
b, R'' = SEt



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Since **1a** itself could not be isolated in the solid state, a number of reaction products were prepared to define the chemical reactivity of **1a** and aid in the characterization of this novel quinone. For example, reaction of **1a** with gaseous HCl in chloroform provides a mixture of chloro adducts from which the principal product **3a** may be isolated by crystallization. The addition of ethanethiol likewise proceeds in Michael fashion to form **3b** as a white solid isolated in good yield by crystallization. Similar ring-substitution is observed in the nucleophilic addition of *p*-anisidine to a chloroform solution of carboxybenzoquinone (**1a**) to form **1b**. The meta coupling observed in the ^1H NMR spectrum of **1b** suggests that the *o*-quinone imide tautomer is predominant over the para isomer in this oxidized derivative (**1b**).

Further characterization of the reactivity of carboxybenzoquinone (**1a**) in solution was obtained by trapping this reactive quinone as a Diels–Alder adduct (**4**) with freshly prepared cyclopentadiene. Although this adduct (**4**) was not stable for prolonged periods even in neutral methanol (undergoing decarboxylation to the difficulty isolable[13] hydroquinone of **5**), it could be converted by base-catalyzed (Na_2CO_3/MeOH) decarboxylation and subsequent oxidation (MnO_2/Et_2O) to the known bicyclic quinone **5**.[13] Although proton-decoupling experiments allowed assignment of resonances in this adduct (**4**), unambiguous assignment of the exo/endo configuration of the carboxylic acid function was not possible.

If the gentisic acid oxidation (ceric(IV) ammonium sulfate/$CHCl_3$) is allowed to proceed for a longer time (45–60 min), or if CCl_4 is used as a solvent, carboxybenzoquinone (**1a**) is converted to the yellow, hydroxylated quinone **1c**. This compound (**1c**) may be isolated as bright yellow crystals by solvent evaporation; however, upon standing in solution, or even in the solid state, this hydroxylated quinone is gradually (within hours) transformed into a deep-blue solid, which has been characterized as the quinhydrone **2b** by spectral and elemental analyses. This conversion is facilitated by dissolution of **1c** in polar solvents (e.g., acetone, methanol), which are likely to contain water. Compound **1c** may be stored at 0 °C protected by a dry, inert atmosphere. Confirmation of the structure of the hydroxylated carboxybenzoquinone **1c** was obtained

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by Diels–Alder reaction with cyclopentadiene leading to formation of adduct **6**.

Experimental Section

General Procedures. Melting points were determined with an Electrothermal Engineering apparatus and are uncorrected. ^1H nuclear magnetic resonance spectra were determined at 90 MHz on a JEOL FX-90Q spectrometer and at higher resolution, as indicated, on either a Bruker WM-250 (Department of Biochemistry) or a Nicolet 300-MHz (Department of Chemistry) spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 281 spectrometer and ultraviolet analyses were performed on a Beckman DU-8 spectrophotometer. Satisfactory elemental analyses for all new compounds except **1a** were determined by M-H-W Laboratories, Phoenix, AZ. Mass spectra were obtained on an Associated Industries MS-30 spectrometer.

Oxidation of Gentisic Acid. A chloroform solution of carboxybenzoquinone (**1a**) was prepared by the addition of 5.0 g (32 mmol) of 2,5-dihydroxybenzoic acid (gentisic acid; Aldrich Chemical Co.) to a rapidly stirred suspension of 20.5 g (30 mmol) of ceric(IV) ammonium sulfate (G. Frederick Smith Co., Columbus, OH) in 275 mL of $CHCl_3$. Approximately 10% conversion of gentisic acid to **1a** occurred during a 15-min reaction period; prolonged reaction times led to formation of the hydroxylated products **1c** and **2b** (as described below). Subsequent filtration removes both oxidant and remaining starting material. The following spectroscopic data has been obtained for compound **1a** in solution: ^1H NMR (300 MHz; $CDCl_3/Me_4Si$ reference): δ 6.98 (2 H, d, J = 1.21 Hz) and 7.68 (1 H, dd, largest J = 1.21 Hz) (Decoupling either of these two signals collapses the other to a singlet. Resolution of these signals is enhanced in the ^1H NMR spectrum of quinhydrone **2a**, although these signals are shifted); IR ($CHCl_3$; cm^{-1}) 3075, 1695, 1630, 1580; UV (AcOH; λ_{max} nm) 338 (ϵ 2400) and 255 (ϵ 6900) (This ultraviolet spectrum was obtained by oxidation of gentisic acid with 1 equiv of lead tetraacetate in acetic acid.); mass spectrum, m/e (relative intensity) 152 $M^{+\cdot}$ (base), 136 (33), 124 (34).

The quinhydrone **2a** of carboxybenzoquinone was best prepared by precipitation from the filtered chloroform solution (as described above) by the addition of two volumes of petroleum ether (60–70 °C). The resulting precipitate after drying was analytically pure and revealed the following physical and spectral characteristics: mp 168–169 °C; ^1H NMR (300 MHz; acetone-d_6/Me_4Si) δ 7.33 (d, J_{AX} = 3.1 Hz, 1 H), 7.16 (m, 1 H), 7.07 (dd, J_{AB} = 8.9 Hz, J_{AX} = 3.1 Hz, 1 H), 6.95 (m, 2 H), 6.82 (dd, J_{AB} = 8.9 Hz); IR (Nujol, cm^{-1}) 3260, 3080, 1725, 1665, 1630, 1580; mass spectrum; m/e (relative intensity) 154 $M^{\cdot+}_{red}$ (33), 152 $M^{\cdot+}_{ox}$ (32), 136 (100), 108 (97), 82 (52); UV (ether; λ_{max} nm) 331 (ϵ 6663) and 220 (ϵ 21 165).

The hydroxylated quinone **1c** was prepared most readily by oxidation of gentisic acid (0.8 g, 5 mmol) with an excess of ceric(IV) ammonium sulfate (6.3 g, 10 mmol) in CCl_4 (60 mL). Rapid stirring of this mixture for 45 min followed by filtration and evaporation of the solvent led to the isolation of **1c** as a crystalline, yellow solid (13% yield). Compound **1c** does not melt (sealed capillary) but darkens at 81 °C and is converted upon further heating to compound **2b** which does not melt up to 355 °C. The following analytical data have been obtained for the hydroxylated quinone **1c**: ^1H NMR ($CDCl_3/Me_4Si$) δ 7.91 (q, J_{AB} = 10.8 Hz); IR (Nujol; cm^{-1}) 3070, 1713, 1697, 1630, 1578; UV (EtOH; λ_{max} nm) 417 (ϵ 1662), 255 (ϵ 14 790), and 207 (ϵ 13 206); mass spectrum, m/e (relative intensity) 168 (M^+, 26), 136 (69), 108 (49), 82 (base).

The quinhydrone **2b** was prepared by allowing the clear yellow filtered CCl_4 solution of **1c** (described above) to stand at room temperature for 48 h. During this time period the deep blue **2b** was deposited as a solid while the yellow color of the solution gradually faded. Solid **2b** was removed by filtration and dried in vacuo. Compound **2b** was observed to not melt up to 355 °C, which is the highest temperature obtainable with our melting point apparatus. Other analytical data for **2b** were obtained as follows: ^1H NMR (Me_2SO-d_6/Me_4Si) δ 6.76 (s, 1 H), 6.56 (s, 1 H), 6.37 (s, 1 H), and 5.95 (s, 1 H); IR (KBr, cm^{-1}) 3395, 1672, 1625, 1608; UV (EtOH; λ_{max} nm) br 559 (ϵ 1750), 324 (ϵ 9260), and 221 (ϵ 21 651). Anal. ($C_{14}H_{10}O_{10}\cdot H_2O$) C, H.

Addition of HCl to 1a To Form 3a. A clear, filtered chloroform solution of **1a** (400 mL) prepared by the oxidation of 4.60 g (30 mmol) of gentisic acid with 37.9 g (60 mmol) of ceric(IV) ammonium sulfate was treated with HCl gas which was bubbled slowly beneath the liquid surface with stirring at room temperature for a period of 50 min. The flask was then thoroughly flushed with nitrogen, sealed, and refrigerated overnight. The resulting crude grayish solid was then filtered off, dried under vacuum, and recrystallized from EtOAc by the addition of benzene to provide 160 mg of the chloro adduct **3a** as an off-white solid (30% yield): mp 205–207 °C (sublimes); ^1H NMR (acetone-d_6/Me_4Si) δ 7.40 (bs, 3 H), 7.55 (d, J = 9.7 Hz, 1 H), 6.81 (d, J = 9.7 Hz, 1 H); IR (KBr, cm^{-1}) 3430, 3080, 1927, 1657, 1650, 1643, 1608; mass spectrum, m/e (relative intensity) 188 M^+ (27), 190 M^{+2} (9), 172 (35), 170 (base), 144 (17), 142 (38).

Addition of EtSH to 1a To Form 3b. To a clear, filtered chloroform solution (75 mL) of **1a** prepared by the oxidation of 1.54 g (10 mmol) of gentisic acid with 12.6 g (20 mmol) of ceric(IV) ammonium sulfate protected by a nitrogen atmosphere was added all at once 0.8 mL (0.7 g, 11 mmol) of ethanethiol (Aldrich). The immediate dark brown color which formed was observed to fade over time. After stirring this mixture for 14 h, a small amount of gentisic acid (27 mg, formed by thiol-catalyzed quinone reduction) was removed by filtration. The volume of the chloroform filtrate was reduced by one-half and a small amount of petroleum ether (60–70 °C) was added to induce crystallization of the desired product **3b**. Upon refrigeration two crops of crystals were recovered (117 mg, 73% yield), combined, and recrystallized from $CHCl_3$/hexane to provide pure **3b** as a white crystalline solid: mp 115–118 °C; ^1H NMR (acetone-d_6/Me_4Si) δ 9.60 (bs, 1 H), 7.80 (bs, 2 H), 7.03 (d, J = 10.1 Hz, 1 H), 6.95 (d, J = 10.1 Hz, 1 H), 2.89 (q, 2 H), 1.18 (t, 3 H); IR (KBr, cm^{-1}) 3300, 3060, 2960, 2920, 1665, 1655, 1592; mass spectrum, m/e (relative intensity) 214 M^+ (32), 196 (base), 167 (69). Concentration of the mother liquor enabled isolation of a small amount of the ethyl thio ester of **3b** (mp 125–127 °C; characterized by ^1H NMR and MS).

Addition of *p*-Anisidine to 1a To Form 1b. To a clear, filtered chloroform solution of **1a** (500 mL) prepared by the oxidation of 8.0 g (52 mmol) of gentisic acid with 33.0 g (52 mmol) of ceric(IV) ammonium sulfate was added 150 mg (1.2 mmol) of *p*-anisidine (Aldrich) dropwise as a solution in chloroform (2.0 mL) to form a deep purple mixture. This mixture was stirred at room temperature for 10 min and then filtered to remove the insoluble gentisic acid which forms as a byproduct in this reaction. The deep purple filtrate was then passed rapidly through a short column of silica gel to remove minor impurities (**1b**, R_f 0.8 silica gel/$CHCl_3$). This purple eluent was then taken to dryness by rotary evaporation to provide 300 mg (90% yield based on *p*-anisidine) of **1b** as dark brown crystals: sharp mp 187 °C; ^1H NMR ($CDCl_3/Me_4Si$) δ 14.06 (s, 1 H), 12.88 (s, 1 H), 7.05 (dd, J = 8.7 Hz, J = 1.8 Hz, 2 H), 6.90 (dd, J = 8.7 Hz, J = 1.8 Hz, 2 H), 6.86 (d, J = 10.2 Hz, 1 H), 6.60 (d, J = 10.2 Hz, 1 H), 3.84 (s, 3 H); IR (KBr, cm^{-1}) 3420 (br), 3050, 3000, 2960, 2930, 2815, 1690, 1670, 1620, 1605; mass spectrum, m/e (relative intensity) 273 M^+ (28), 255 (base), 227 (87), 213 (49); UV (EtOH, λ_{max} nm) 522 (ϵ 2145), 439 (ϵ 2242), 264 (ϵ 9841), 231 (ϵ 14 295). Anal. ($C_{14}H_{11}NO_5\cdot H_2O$) C, H, N.

Diels–Alder Addition of Cyclopentadiene to 1a To Form Adduct 4. To a clear, filtered chloroform solution (500 mL) of **1a** formed by the oxidation of gentisic acid (4.0 g, 26 mmol) with ceric(IV) ammonium sulfate (16.6 g, 26 mmol) at −78 °C (dry ice/acetone) was added dropwise 80 mg (1.2 mmol) of freshly distilled cyclopentadiene. This mixture was stirred for 30 min and then allowed to warm at room temperature. Evaporation of the solvent provided the unstable Diels–Alder adduct **4** as a brownish solid residue. This adduct (**4**) has been characterized by ^1H NMR (300 MH; $CDCl_3/Me_4Si$) with decoupling experiments to allow assignment of resonances: δ 9-CH_2- 1.62 (dt, J = 9.0 Hz, J = 1.5 Hz) and 1.72 (dt, J = 9.0 Hz, J = 1.1 Hz); 1-CH 3.55 (m) and 4-CH 3.77 (m); 8a-CH- 3.64 (d, J = 4.0 Hz); 2,3-CH- 6.11 (dd, J = 6.0 Hz, J = 2.9 Hz) and 6.18 (J = 6.0 Hz, J = 2.8 Hz); 6 and 7-CH- 6.65 (s, 2 H).

Decarboxylation of 4 and Oxidation Leading to Bicyclic Quinone 5. Decarboxylation of Diels–Alder adduct **4** which was observed to occur upon standing was promoted by base treatment. The intiial chloroform solution (500 mL) as described above was diluted with methanol (150 mL), and 2.0 g of anhydrous sodium carbonate was added. This mixture was then heated to 50 °C

for 60 min to promote decarboxylation. However, since the bicyclic hydroquinone derivative produced by decarboxylation is not easily purified (ref 13), this gummy residue (260 mg after filtration and solvent removal) was dissolved in ether (50 mL; filtered to clarify) and oxidized with activated MnO_2 (400 mg, 4.6 mmol) by stirring at room temperature for 90 min. The ethereal oxidation mixture was then filtered through a Celite bed and dried over anhydrous sodium sulfate, and the solvent was removed by rotary evaporation to provide crude quinone **5**, which was purified by sublimation (50 °C at 0.05 mmHg). The purified yellow quinone **5** showed mp 65–67 °C (lit.[13] mp 66–67 °C).

Preparation of Diels–Alder Adduct 6. To 72 mg (0.4 mmol) of yellow quinone **1c** in 15 mL of benzene at room temperature was added with stirring 0.07 mL (0.85 mmol) of freshly distilled cyclopentadiene. The initial deep yellow color of the solution faded within 1 min to pale yellow. After stirring for 10 min, the solvent volume was reduced to 1.0 mL by rotary evaporation. In a short time the product (**6**) crystallized as pale-yellow plates (80 mg, 80% yield): mp 121–123 °C, ^1H NMR ($CDCl_3/Me_4Si$) δ OH 7.26 (s, 2 H); olefinic-CH 6.17 (dd, J = 5.9 Hz, J = 3.1 Hz) and 6.12 (dd, J = 5.9 Hz, J = 2.8 Hz); bridgeheads 1- and 4-CH 3.68 (m, 2 H); 4a- and 8a-CH 3.55 (dd, J = 8.0 Hz, J = 4.0 Hz); 9-CH_2 1.67 (dt, J_d = 9.0 Hz, J_t = 1.8 Hz) and 1.55 (dt, J_d = 9.0 Hz, J_t = 1.2 Hz); IR (KBr, cm^{-1}) 3400, 3070, 3020, 2995, 2978, 2951, 1708, 1692, 1593; mass spectrum m/e 234 (M^+, 2), 216 (7), 66 (base).

Acknowledgment. We acknowledge the generous financial support of the National Institutes of Health through New Investigator Research Award (T.J.H., Jr.) No. R23-29844. We appreciate the assistance of Mr. Steve Philson, Department of Chemistry, and Mr. Gerald Bratt, Department of Biochemistry, University of Minnesota, in obtaining high-resolution NMR spectra and performing extensive decoupling experiments.

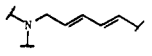
Registry No. **1a**, 5794-62-7; **1b**, 92544-18-8; **1c**, 92544-13-3; **2a**, 92544-15-5; **2b**, 92544-14-4; **3a**, 92544-16-6; **3b**, 92544-17-7; **4**, 92544-19-9; **5**, 6829-72-7; **6**, 92544-20-2; HCl, 7647-01-0; EtSH, 75-08-1; *p*-anisidine, 104-94-9; cyclopentadiene, 542-92-7; gentisic acid, 490-79-9; ceric ammonium sulfate, 7637-03-8.

Communications

Direct Preparation of 5-Amino-1,3-pentadienes through Use of Palladium-Promoted Reactions[1a]

Summary: 5-Amino-1,3-pentadienes are available by condensation of aldehydes and ketones with 1-phosphono-4-(dialkylamino)-2-butenes which in turn are prepared by palladium-catalyzed difunctionalization of 1,3-butadiene.

Sir: The 5-amino-1,3-pentadiene moiety **1** and the corresponding amide system are structural features of several naturally occurring compounds. Some representative



1

examples are the kirromycin (mocimycin) antibiotics,[2] the streptogramin antibiotics,[3] the *Asiasarum* and *Fagara amides*,[4] and the macbecin antitumor antibiotics.[5] Various synthetic efforts have been directed toward these diene derivatives previously,[6,7] and herein we report our own

Scheme I

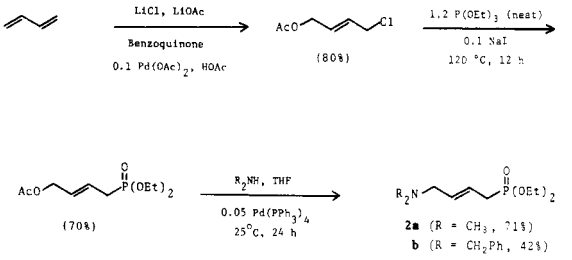
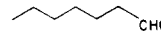
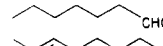
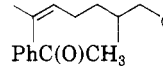


Table I. Condensations of Potassium Derivative of 2

entry	substrate	yield,[a] %	isomer ratio[b]
1	PhCHO	84	2.5:1
2		72	2.5:1
3		79[c]	2.5:1
4		74	2.5:1
5	$PhC(O)CH_3$	66	2.1:1.2:1:1[d]
6		82	3:1
7		42	*e*

[a] Yield of chromatographically purified product obtained using **2a**. [b] Ratio of 2*E*,4*E*:2*E*,4*Z* unless otherwise noted. [c] Obtained using **2b**. [d] 2.1:1.2 2*E*,4*E*:2*E*,4*Z* plus two additional components which appear to be 2*Z* isomers but which were not fully characterized. [e] See ref 16.

(1) (a) This work was presented in part at the 186th National Meeting of the American Chemical Society, Washington, D.C., Aug 1983; Abstract No. ORGN 120. (b) Current address of this author: Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556.

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