Synthesis of 6-Bromo- and 6-Chloro-2-acetamidobenzoquinone: A Structure Revision

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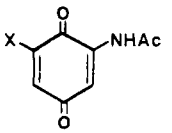
Received March 4, 1983

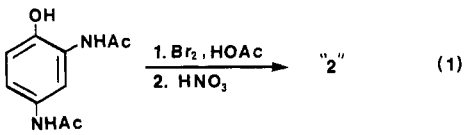
In the course of other studies[1a] we had need of benzoquinone 1. Since preparation of the corresponding bro-



1, X = Cl

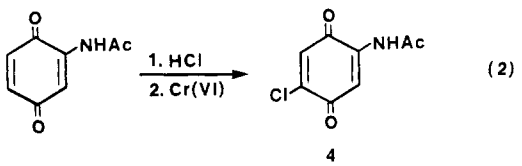
2, X = Br

moquinone 2 by the sequence in eq 1 was claimed by Heller



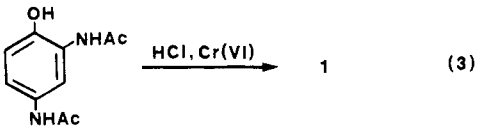
(1)

et al.,[2] it appeared that the minor modification of substituting a chlorination step for the bromination step in eq 1 would provide the desired 1. Indeed this alteration did afford a chloroacetamidobenzoquinone, but subsequent investigations[1b] suggested that its structure was 4 not 1. This tentative assignment gained support when it was found that the chloroacetamidoquinone so prepared from 3 is identical (by direct comparison) with a sample of 4 synthesized according to the procedure of Kehrmann and Bahatrian.[3] Their synthesis[3] (eq 2) is not entirely unam-



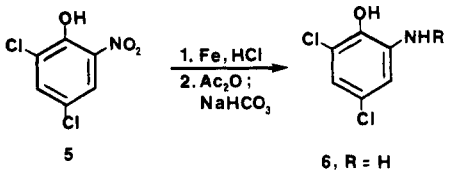
(2)

biguous, however, since the regiochemistry of their product was not rigorously established and, although likely,[4] is not demanded on mechanistic grounds. Furthermore, a subsequent patent claims[5] that a compound exhibiting a melting point identical with that of the Kehrmann–Bahatrian compound and prepared[5] by a seemingly equivalent route (eq 3) possesses structure 1 rather than 4.



(3)

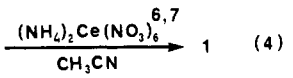
In order to resolve the foregoing ambiguity, we undertook a regiochemically unimpeachable synthesis of 1 which begins from commercially available 5 and gives 1 in 59% overall yield (eq 4).[6,7] The chloroquinone (1) so obtained



5

6, R = H

7, R = Ac

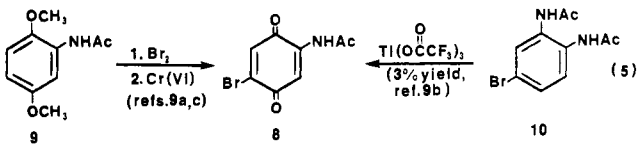


(4)

is different from the chloroquinone (4) generated by the Kehrmann–Bahatrian sequence (eq 2). That 1 and 4 both possess the regiochemistry we have assigned is corroborated by their NMR spectra: no coupling is observed between the two para hydrogens in 4, but the two meta hydrogens in 1 split each other with a coupling constant of 2 Hz.

With authentic samples of 1 and 4 in hand, examination of the apparent incongruity of eq 3 was undertaken. The task was complicated by lack of experimental information in the patent, which merely states "[3] *in Gegenwart von Salzsäure mit Bichromate oder anderen Oxydationsmitteln oxydiert*". After several entirely unsuccessful attempts to effect eq 3 using HCl and $Na_2Cr_2O_7$ in an aqueous medium, we found that conducting the reaction in acetic acid does in fact afford 1 as previously reported, although in ≤15% yield. Use of $(NH_4)_2Ce(NO_3)_6$ in place of $Na_2Cr_2O_7$ raises the yield of 1 to 42%. In both cases we were unable to detect the production of any of 4. That the regiochemical outcome of eq 3 is the complete reverse of that in eq 2 can be accounted for if one postulates that 3 is initially oxidized to a quinone monoimine species. Addition of HCl to the latter should[8] proceed with the regiochemistry reflected in the ultimate product (i.e., 1).

The inadequacy (vide supra) of eq 1 as a precedent for the synthesis of 1 caused us to view the structure assigned by Heller et al.[2] to the product of eq 1 as suspect, especially since the melting point they report for that material (183 °C) is very similar to the melting points (180, 186, and 190–192 °C) reported[9] for its regioisomer 8, a compound whose structure seems secure in view of the methods of its synthesis (eq 5). Accordingly, the work of Heller et



(5)

9 8 10

al.[2] (eq 1) was repeated. The bromoquinone thereby obtained (and which exhibited the melting point reported[2]

(1) (a) Kelly, T. R.; Behforouz, M.; Echavarren, A.; Vaya, J. *Tetrahedron Lett.* **1983**, *24*, 2331. (b) Compare footnote 11 therein.

(2) Heller, G.; Dietrich, W.; Hemmer, T.; Kätzel, H.; Rottsahl, E.; Zambalos, P. G. *J. Prakt. Chem.* **1931**, *129*, 211.

(3) Kehrmann, F.; Bahatrian, G. *Ber.* **1898**, *31*, 2399.

(4) Houk, K. N.; Tegmo-Larrson, I. M.; Rozeboom, M. D. *J. Org. Chem.* **1981**, *46*, 2338.

(5) Farbwerke Höchst a. M. German Patent 292176; *Chem. Zentralbl.* **1916**, 117a.

(6) The use of $(NH_4)_2Ce(SO_4)_3$ for the oxidation of halophenols to quinones has been reported:[7] Gopinathan, M. B.; Bhatt, M. V. *Indian J. Chem., Sect. B* **1981**, *20B*, 71. We thank a referee for bringing this paper to our attention.

(7) For a leading reference to the use of $(NH_4)_2Ce(NO_3)_6$ for other purposes see: Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627.

(8) Grünanger, P. In "Methoden der Organischen Chemie (Houben-Weyl)", 4th ed.; Müller, E., Bayer, O., Eds.; Georg Thieme Verlag: Stuttgart, 1979; Vol. 7/3b (Gründmann, C., Ed.), p 332.

(9) (a) J. R. Geigy, A. G. French Patent 1345524; *Chem. Abstr.* **1964**, *60*, 11952c. (b) Lau, K. S. Y.; Basiulis, D. I. *Tetrahedron Lett.* **1981**, *22*, 1175. (c) J. R. Geigy, A. G. French Patent 1384270; *Chem. Abstr.* **1965**, *63*, 6936*b*.

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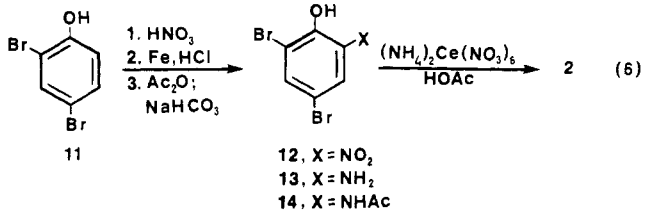
by Heller et al.) proved to be identical with independently prepared[9a] 8 by direct comparison (e.g., mixture melting point[10]). Thus the structure of the product of eq 1 was erroneously assigned by Heller et al.:[2] it is 8 not 2.

It remained only to devise a synthesis of 2 to knot the final loose end. This was readily achieved by oxidizing 14 to 2 (68%) with ceric ammonium nitrate.[6,7] The known 14 was prepared in 72% overall yield from 11 by using a modification of previously reported procedures.[11a] As expected, the bromoquinone (2) so obtained (eq 6) is



different from 8 and gives an NMR spectrum very similar to that of the chloro analogue 1.

In summary, the product from eq 1 is established as 8 and not 2 as claimed by Heller et al.[2] The first synthesis of 6-bromo-2-acetamidobenzoquinone (2) and practical routes to its chloro analogue (1) are described.

Experimental Section

NMR spectra were recorded on a Hitachi Perkin-Elmer Model R-24 or a Varian FT-80A instrument; chemical shifts are reported in parts per million downfield from internal Me_4Si. IR spectra were recorded on a Perkin-Elmer Model 599B spectrometer. EM silica gel 60 F_{254} plates (0.2 mm) were used for analytical TLC, and preparative separations were performed by using flash column chromatography on silica gel 60 (particle size 0.040–0.063 mm, EM reagents). Melting points (Pyrex capillary) are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc.

Preparation of 2-Acetamido-5-chloro-1,4-benzoquinone (4) from 2,4-Diacetamidophenol (3). A solution of 13.35 g (0.1 mol) of *N*-chlorosuccinimide in 80 mL of DMF was added dropwise over 5 min at room temperature to a stirred solution of 20.8 g (0.1 mol) of 3[3] in 80 mL of DMF. The reaction mixture was stirred for 90 min, added with stirring to 600 mL of an ice/water mixture, stirred for 1 h, filtered, and dried, giving 5-chloro-2,4-diacetamidophenol: 18 g (75%); mp 234 °C; ^1H NMR (Me_2SO-d_6) 9.2 (s, 2 H), 7.84 (s, 1 H), 6.85 (s, 1 H), 2.04 (s, 3 H), 1.95 (s, 3 H).

Jones reagent (5 mL) was added dropwise at room temperature to a stirred slurry of 2 g (8.3 mmol) of 5-chloro-2,4-diacetamidophenol in 125 mL of acetone, and the mixture was stirred for 30 min. Water (50 mL) was added, and the mixture was then extracted with four 50-mL portions of ether. The ether extracts were washed with water and brine, dried (Na_2SO_4), and evaporated to give 1.0 g (62%) of the yellow 4, mp 174–176 °C (lit.[3] mp 174–175 °C). Recrystallization from benzene gave material melting at 179–180 °C: ^1H NMR ($CDCl_3$/Me_2SO-d_6) 9.35 (br s, 1 H), 7.67 (s, 1 H), 6.98 (s, 1 H), 2.25 (s, 3 H). The 4 obtained by this route is identical (by direct comparison) with material prepared by the procedure of Kehrmann and Bahatrian[3] (eq 2); the present route to 4 is more efficient.

2-Amino-4,6-dichlorophenol (6). 2,4-Dichloro-6-nitrophenol (5) (10.0 g, 48 mmol) was dissolved in 200 mL of 1:1 80% aqueous EtOH/HOAc, and 20 g or iron powder (100 mesh) was added portionwise (exothermic reaction) with vigorous stirring. After ca. 15 min, 0.2 mL of 12 M HCl was added and the mixture heated at 100–105 °C for 2–3 h with mechanical stirring. The suspension was decanted to remove the excess iron, poured into 500 mL of H_2O, and extracted with ethyl acetate (3 × 250 mL). The organic extract was washed with water and the ethyl acetate evaporated. The residue (which contained some water) was triturated with ca. 10 mL of water and filtered to give 7.9 g (92%) of aniline 6, which was ordinarily used without further purification. Recrystallization from water (twice) gave material melting at 92–93 °C (lit.[12] mp 95–96 °C).

2-Acetamido-4,6-dichlorophenol (7). Aminophenol 6 (4.0 g, 22.5 mmol) and acetic anhydride (10 mL, 106 mmol) were stirred at room temperature for 15 min. The mixture was poured into 200 mL of water. The precipitate was filtered, washed with H_2O, and stirred with a mixture of 200 mL of 5:1 MeOH/H_2O and 100 mL of saturated aqueous $NaHCO_3$ for 20 min at 20 °C. Acidification with 2.5 M HCl gave a precipitate that was filtered and washed with water to give 4.55 g (92%) of 7, which was used directly in the next step. Recrystallization from aqueous ethanol gave analytically pure 7: mp 134–135 °C; ^1H NMR (Me_2SO-d_6) 9.64 (1 H, br s), 7.69 (1 H, d, J = 2.5 Hz), 7.29 (1 H, d, J = 2.5 Hz), 2.15 (3 H, s); IR (Nujol) 3325, 1653, 1595, 1577, 1531 cm^{-1}. Anal. Calcd for $C_8H_7Cl_2NO_2$: C, 43.66; H, 3.21. Found: C, 43.39; H, 3.21.

2-Acetamido-6-chloro-1,4-benzoquinone (1). Phenol 7 (3.5 g, 15.9 mmol) was dissolved in 22 mL of acetonitrile. A solution of 26.3 g (48.0 mmol) of ceric ammonium nitrate in 44 mL of water was added portionwise over 5 min. After being stirred at 20 °C for 15 min, the mixture was cooled to 0 °C and the precipitate collected to give 2.30 g of pure quinone. The filtrate was extracted with $CHCl_3$ (2 × 20 mL), the organic extract was washed with water (2 × 10 mL), dried (Na_2SO_4), and evaporated, and the residue was column chromatographed (silica gel, 1:2 AcOEt/petroleum ether) to afford an additional 0.25 g of 1 for a total yield of 80%. Recrystallization from ethanol gave analytically pure material as small yellow crystals: mp 168–169 °C; ^1H NMR (1:1 $CDCl_3$/Me_2SO-d_6) 9.46 (1 H, br s), 7.52 (1 H, d, J = 2 Hz), 6.90 (1 H, d, J = 2 Hz), 2.23 (3 H, s); IR (Nujol) 3275, 1714, 1684, 1628, 1595, 1522 cm^{-1}. Anal. Calcd for $C_8H_6ClNO_3$: C, 48.16; H, 3.03. Found: C, 48.35; H, 2.97.

Conversion of 3 to 1. (A) Using Sodium Dichromate. 2,4-Diacetamidophenol[3] (3; 100 mg, 0.48 mmol) was suspended in 5 mL acetic acid containing 1 drop of 12 M HCl. Solid $Na_2Cr_2O_7 \cdot 2H_2O$ (200 mg, 0.67 mmol) was added portionwise over ca. 5 min, and the mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into 50 mL of H_2O and extracted with benzene (3 × 50 mL). The organic extract was washed with H_2O (25 mL) and brine and dried (Na_2SO_4). Evaporation of the solvent gave 16 mg of benzoquinone 1 (crude yield 15%), identical with authentic 1.

(B) Using Ceric Ammonium Nitrate. 2,4-Diacetamidophenol[3] (3; 500 mg, 2.60 mmol) was suspended in 20 mL of acetic acid containing 0.3 mL of 12 M HCl. A solution of $(NH_4)_2Ce(NO_3)_6$ (8.70 g, 15.87 mmol) in 20 mL of H_2O was added, and the mixture was stirred for 30 min at 20 °C. The reaction mixture was poured into 200 mL of H_2O and extracted with benzene (3 × 100 mL). The organic extract was washed with H_2O (3 × 100 mL) and brine and dried (Na_2SO_4). Evaporation of the solvent gave 340 mg of benzoquinone 1 (crude yield 65%). Recrystallization from 80% EtOH gave 220 mg of pure quinone (42%), identical with an authentic sample.

2-Amino-4,6-dibromophenol (13). 2,4-Dibromo-6-nitrophenol (12;[13] 10.0 g, 33.7 mmol) was dissolved in 200 mL of 1:1 80% aqueous EtOH/HOAc, and 14.2 g of iron powder (100 mesh) was added portionwise with vigorous stirring. After ca. 15 min, 0.3 mL of 12 M HCl was added and the mixture heated at 100–105 °C for 3 h. The hot mixture was filtered, diluted with 500 mL of H_2O, and extracted with ethyl acetate (3 × 250 mL). The organic extracts were washed with water (3 × 250 mL), and the ethyl acetate was evaporated. The wet residue was triturated with ca. 10 mL of H_2O and filtered to give 8.2 g of 13 (91%) which was ordinarily used without further purification. Recrystallization from aqueous MeOH gave material melting at 97–98 °C (lit.[14] mp 99 °C).

2-Acetamido-4,6-dibromophenol (14). Aminophenol 13 (8.2 g, 30.7 mmol) and acetic anhydride (15 mL) were stirred at 20

(10) Samples of 8 prepared by the methods of ref 2 and 9a,c both give ^1H NMR spectra identical with those reported by Lau and Basiulis[9b] for 8.

(11) (a) Hölz, O. *J. Prakt. Chem.* **1885**, *32* (2), 65. (b) Lindemann, H.; Schultheis, W. *Justus Liebigs Ann. Chem.* **1926**, *451*, 241.

(12) Meyer, J. *Helv. Chim. Acta* **1958**, *41*, 1890.

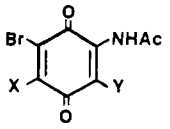
(13) Kohn, M.; Krasso, O. *J. Org. Chem.* **1946**, *11*, 641.

(14) Thiele, J.; Eichwede, H. *Justus Liebigs Ann. Chem.* **1900**, *311*, 363.

°C for 15 min; the mixture was poured into 150 mL of H_2O and filtered to give a crude product which was a mixture of N-acylated and O,N-diacylated **13**. This mixture was stirred with 300 mL of 5:1 MeOH/H_2O, and 100 mL of saturated aqueous $NaHCO_3$ was added. After being stirred at 20 °C for 15 min, the mixture was acidified with 2.5 M HCl, and the precipitate was filtered and washed with water to give 7.88 g (83%) of **14** which was used directly. A sample recrystallized from aqueous MeOH melted at 179 °C (lit.[11b] mp 178 °C).

2-Acetamido-6-bromobenzoquinone (2). Phenol **14** (692 mg, 2.24 mmol) was dissolved in 23 mL of acetic acid. A solution of 3.70 g (6.75 mmol) of ceric ammonium nitrate in 23 mL of H_2O was added portionwise over 2 min, and the solution was stirred at 20 °C for 10 min. The mixture was poured into 200 mL of H_2O and extracted with AcOEt (2 × 200 mL); the organic extracts were washed with water (3 × 100 mL), dried (Na_2SO_4), and evaporated to give 366 mg of pure quinone (67%). Recrystallization from benzene gave analytically pure material as yellow-orange crystals: mp 159–160 °C; ^1H NMR ($CDCl_3$/Me_2SO-d_6) 9.10 (1 H, br s), 7.55 (1 H, d, J = 2.3 Hz), 7.17 (1 H, d, J = 2.3 Hz), 2.23 (3 H, s); IR (Nujol) 3280, 1716, 1684, 1639, 1625–1600, 1525–1500 cm^{-1}. Anal. Calcd for $C_8H_6BrNO_3$: C, 39.37; H, 2.48. Found: C, 39.58; H, 2.48.

Longer reaction times in HOAc or the use of CH_3CN as a solvent gave a dibromoquinone assigned[15] structure **15**: yellow



15, X = Br, Y = H
16, X = H, Y = Br

crystals; mp 198–200 °C (from benzene); ^1H NMR ($CDCl_3$) 7.43 (s, 1 H), 7.4 (br s, 1 H), 2.24 (s, 3 H); IR (Nujol) 3305, 1698, 1680, 1660, 1655, 1627, 1594 cm^{-1}. Anal. Calcd for $C_8H_5Br_2NO_3$: C, 29.75; H, 1.56. Found: C, 29.75; H. 1.51.

Acknowledgment. We thank the National Institutes of Health for support of this project (Grant CA 17631).

Registry No. 1, 87013-11-4; 2, 87013-12-5; 3, 38847-62-0; 4, 2072-09-5; 5, 609-89-2; 6, 527-62-8; 7, 55202-45-4; 8, 2072-30-2; 12, 15969-09-2; 13, 10539-14-7; 14, 55202-09-0.

(15) Structure **15** is preferred over **16** on the basis of mechanistic considerations; it is also in accord with the chemical shift observed for the nuclear proton.

The Two Hydrogen–Oxygen Bond-Dissociation Energies of Hydroquinone

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Received March 28, 1983

There are few experimental determinations of the first bond-dissociation energy (BDE) of hydroquinone. The most recent determination was by Mahoney,[1] who concluded that the first BDE for this most important hydrogen-transfer agent is 85 kcal/mol. There are no literature reports for the second BDE of hydroquinone.

A variety of methods exist to determine hydrogen bond-dissociation energies (BDEs). These methods have been reviewed periodically[2] and include equilibrium methods, kinetic methods, electron-impact studies, spectroscopic determinations, chemical activation, and theoretical calculations. The uncertainty in BDEs is ±2–5 kcal/mol.

For those weak acids whose pK_as can be determined and whose conjugate bases can be reversibly oxidized to their neutral radicals, a simple thermodynamic cycle can be constructed that leads to the free energy of bond dissociation (eq 1–4). The sum of the reactions is given by eq

$$RH \rightleftarrows R^- + H^+ \qquad \Delta F_0 = -RT \ln 10^{-pK_a} \tag{1}$$

$$R^- \rightleftarrows R\cdot + e^- \qquad \Delta F_0 = F\mathcal{E}_0 \tag{2}$$

$$H^+ + e^- \rightleftarrows {}^1/_2H_2 \qquad \Delta F_0 = 0 \tag{3}$$

$${}^1/_2H_2 \rightleftarrows H\cdot \qquad \Delta F_0 = 48.6 \text{ kcal/mol} \tag{4}$$

5. For some purposes, the free energy of bond dissociation

$$RH \rightleftarrows R\cdot + H\cdot \tag{5}$$

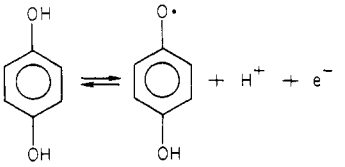
$$\Delta F_0 = 2.303RT(pK_a) + F\mathcal{E}_0 + 48.6 \text{ kcal/mol}$$

is the desired quantity, but formally, the BDE is an enthalpic quantity. For medium to large molecules, the entropies of RH and R· are approximately equal at 25 °C. The major $T\Delta S_0$ correction is due to H·, which at 25 °C is 8.2 kcal/mol.[3] Therefore

$$\text{BDE}(25\ ^\circ\text{C}) \approx 1.36pK_a + 23.1\mathcal{E}_0 + 56.8 \text{ kcal/mol} \tag{6}$$

This electrochemical–acidity method is not new. Breslow[4] has used electrochemistry extensively and has determined the relative carbon–oxygen BDEs of several alcohols. Most important, Brauman has applied the method in the gas phase to determine the bond-dissociation energy of several species.[5] But this method has not been used with readily available solution-phase pK_a and electrochemical data.

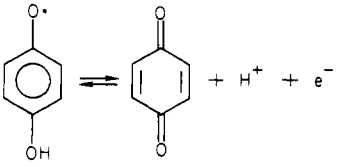
As applied to hydroquinone, the published half-cell reactions in water are[6] as shown in eq 7 and 8. The pK_as



(7)

1 **2**

$\Delta F_0 = 23.1 \times 1.084$ kcal/mol



(8)

2 **3**

$\Delta F_0 = 23.1 \times 0.326$ kcal/mol

are included in the published $\mathcal{E}_0$s so that only the free energy and entropy of formation for H· need to be added to obtain the BDEs.[7] The first and second BDEs for **1**

(1) Mahoney, L. R.; DaRouge, M. A. *J. Am. Chem. Soc.* **1975**, *97*, 4722.

(2) (a) Cottrell, T. L. "The Strengths of Chemical Bonds"; Academic Press: New York, 1954. (b) Szwarc, M. *Chem. Rev.* **1950**, *47*, 75. (c) Benson, S. W. *J. Chem. Educ.* **1965**, *42*, 502. (d) Kochi, J. K., Ed. "Free Radicals"; Wiley: New York, 1973; Vol. I, II.

(3) Benson, S. W. "Thermochemical Kinetics"; Wiley: New York, 1968.

(4) Wasielewski, M. R.; Breslow, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 4222.

(5) Janousek, B. K.; Reed, K. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 3125 and references cited therein.

(6) Lee, W. E.; Brown, E. R. In "The Theory of the Photographic Process", 4th ed.; James, T. H., Ed.; Macmillan: New York, 1977; p 308.

(7) Insignificant entropy corrections (R ln 2) are also required to correct for the twofold symmetry of **1** and **3**.

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