by its characteristic CH resonance at δ 8.04; upon extraction with water, this feature disappeared. The reactions of *N*-methylnitrones in halogenated hydrocarbon solvents produced an insoluble material, soluble in water, which gave a strong $FeCl_3$ test: $^1H$ NMR ($D_2O$, DSS internal standard) δ 8.20 (s), 4.60 (HDO); IR (KBr, $cm^{-1}$) ca. 3500–2700 (br), 1668, 1648, 1385, 1351, 1190. An authentic sample of formohydroxamic acid was prepared by Schroeter's method,[35] mp 72–74 °C (lit.[35] mp 72–74 °C). Its $^1H$ NMR and IR spectra were identical in all respects with those of the reaction product.

**Acknowledgment.** We gratefully acknowledge financial support from Research Corporation and from a National Institutes of Health Biomedical Research Support Grant, administered by San Francisco State University. The Department of Chemistry and Biochemistry at San Francisco State University also acknowledges grants from the National Institutes of Health (RR 02684) and the National Science Foundation (DMB-8516065) for purchase of the QE300 NMR spectrometer.

## Synthesis of Two Useful, Enantiomerically Pure Derivatives of (*S*)-4-Hydroxy-2-cyclohexenone

James E. Audia, Louise Boisvert, Arthur D. Patten, Anabella Villalobos, and Samuel J. Danishefsky*

*Department of Chemistry, Yale University, New Haven, Connecticut 06511*

*Received November 18, 1988*

In connection with several research objectives in our laboratory, we perceived a need for protected versions of the *S* enantiomer of 4-hydroxycyclohexenone (**5**). Since the envisioned compounds were to serve as enantiomerically pure educts in extended journeys, the prospect of resolution was discouraging. Below is described a synthetic route by which substantial quantities of optically pure compounds (see **6** and **7**) can be prepared without recourse to resolution.

The synthesis started with compound **1**, which had been obtained in two easy steps from D(−)-quinic acid by Trost and co-workers.[1] Oxidative cleavage of the vicinal diol ($NaIO_4$) afforded ketone **2**. Elimination of the secondary alcohol via reaction with methanesulfonyl chloride–triethylamine produced enone **3**. Hydrogenation of **3** was carried out with Pearlman's catalyst[2] at 50 psi to give ketone **4** in 75% yield. Fortunately, it was not necessary to obtain **5**[3] in order to reach the goal system **6**. Thus, treatment of **4** with *tert*-butyldimethylsilyl chloride and DBU afforded **6** in 87% yield.

We were unable to devise a corresponding one-step conversion to go from **4** to the *p*-methoxybenzyl protected derivative **7**. To reach that compound it was necessary for us to pass through **5**. This compound was obtained by base (DBU or $K_2CO_3$) induced elimination of **4** in 49% yield. Compound **5** is quite unstable and was transformed to **7** (ca. 60%) through the use of *p*-methoxybenzyltrichloroacetimidate in the presence of boron trifluoride etherate.[4]

Compounds **6** and **7** are particularly versatile because they undergo reaction with a range of nucleophiles. As part of our synthetic route to FK-506,[5] it was found that compound **7** reacts with lithium dimethylcuprate to afford the *trans*-3,4-disubstituted product **8** (R = α-Me; R′ = PMB). By contrast, in connection with our recently completed total synthesis of ML-236A,[6] it was found that Lewis acid ($HgI_2$) induced addition of silylketene acetals to **6** affords cis product **9** (R = β-$CH_2CO_2Et$; R′ = TBS) (Scheme I).

We are currently studying the factors that are responsible for the remarkable preference for cis products in the Lewis acid catalyzed reaction. Other applications of these compounds will be described.

### Experimental Section

**3,4-*O*-Isopropylidene-3(*R*),4(*S*),5(*R*)-trihydroxycyclohexanone (2).** Triol **1**[1] (73 g, 0.34 mol) was dissolved in 900 mL of phosphate buffer pH 7, and the solution was cooled to 0 °C. Sodium periodate (94 g, 0.44 mol) was added in portions. After the addition, the ice bath was removed and the mixture was stirred at room temperature for 1 h. The aqueous mixture was then extracted with methylene chloride (8 × 200 mL). The extracts were filtered through a mixture of magnesium sulfate and Celite. The solvent was evaporated to afford 53.6 g (86%) of a white solid. A small amount of the compound was purified by flash chromatography (ethyl acetate–hexanes, 1:1) or recrystallization ($Et_2O$) for characterization: mp ($Et_2O$) 80–81 °C; $^1H$ NMR (250 MHz, $CDCl_3$) δ 4.71 (m, 1 H, 3-H), 4.31 (dt, 1 H, $J$ = 7.1, 2.5 Hz, 4-H), 4.22 (dd, 1 H, $J$ = 6.2, 2.5 Hz, 5-H), 2.82 (dd, 1 H, $J$ = 17.6, 3.6 Hz, 2-H), 2.66 (dm, 2 H, $J$ = ~17.6 Hz, 2,6-H), 2.59 (b s, 1 H, 3-OH), 2.44 (dm, 1 H, $J$ = ~17.9 Hz, 6-H), 1.44 and 1.36 (2 s, 2 × 3 H); IR ($CDCl_3$) 3580, 3420, 2970, 2890, 1710, 1375, 1250, 1205, 1135, 1060, 1050 $cm^{-1}$; EIMS $m/z$ (relative intensity) 186 (1), 171 (100), 129 (61), 111 (55); $[\alpha]_D$ +141.24° (*c* 0.89, $CHCl_3$). Anal. Calcd for $C_9H_{14}O_4$: C, 58.04; H, 7.58. Found: C, 58.20; H, 7.48.

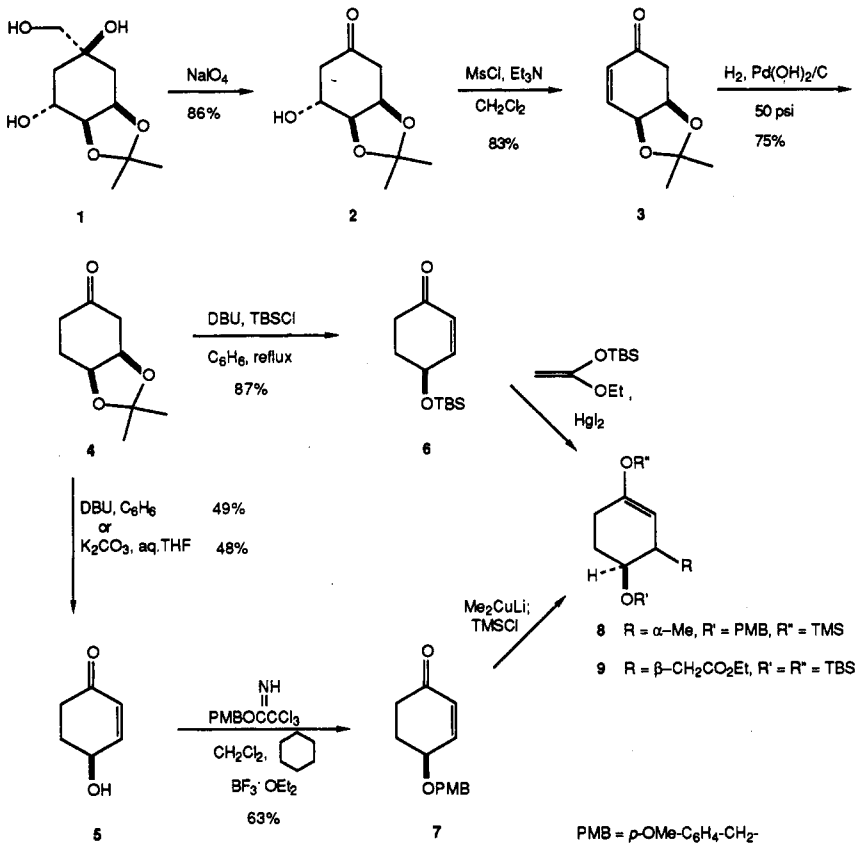
**4,5-*O*-Isopropylidene-4(*S*),5(*R*)-dihydroxy-2-cyclohexen-1-one (3).** To a solution of **2** (53.6 g, 0.30 mol) and triethylamine (125 mL, 0.90 mol) in 900 mL of $CH_2Cl_2$ cooled to 0 °C was added over a period of 40 min a solution of methanesulfonyl chloride (28 mL, 0.36 mol) in 90 mL of $CH_2Cl_2$. The resulting mixture was stirred at room temperature for 2 h after addition was complete. Then, the reaction was washed with water (3 × 200 mL), and the aqueous layers were extracted with ether (2 × 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated. Trituration of the brown oil with ether followed by filtration through a short pad of silica gel (eluted with ether) gave, after solvent removal, desired compound **3** (42 g, 83%). A small amount of **3** was purified by flash chromatography (ethyl acetate–hexanes, 1:3) or Kugelrohr distillation (1 mmHg) for characterization. Distillation gave a white solid: mp 39–40 °C; $^1H$ NMR (250 MHz, $CDCl_3$) δ 6.63 (dd, 1 H, $J$ = 10.4, 2.3 Hz, 3-H), 6.02 (d, 1 H, $J$ = 10.4 Hz, 2-H), 4.69 (m, 2 H, 4,5-H), 2.91 (dd, 1 H, $J$ = 17.6, 2.5 Hz, 6-H), 2.68 (dd, 1 H, $J$ = 17.6, 3.6 Hz, 6-H), 1.38 (s, 3 H), 1.37 (s, 3 H); IR ($CDCl_3$) 2980, 2910, 1680, 1385, 1370, 1255, 1230, 1155, 1140, 1060 $cm^{-1}$; EIMS $m/z$ (relative intensity) 168 (0.5), 153 (100), 111 (84); $[\alpha]_D$ +147.50° (*c* 0.48, $CHCl_3$). Anal. Calcd for $C_9H_{12}O_3$: C, 64.26; H, 7.20. Found: C, 64.31; H, 7.38.

**3,4-*O*-Isopropylidene-3(*R*),4(*S*)-dihydroxycyclohexanone (4).** Cyclohexenone **3** (41 g, 0.24 mol) was hydrogenated in several portions using a Parr shaker (50 psi). The compound (~8 g) was dissolved in 100 mL of EtOAc, and 300 mg of the Pearlman's catalyst was added. The reaction was complete after 24 h. The mixture was filtered through Celite, washed with EtOAc (200 mL), and concentrated. The combined crude was distilled under vacuum (85 °C, 1.5 mmHg) to give 31.1 g (75%) of desired compound **4** as a clear oil: $^1H$ NMR (250 MHz, $CDCl_3$) δ 4.65 (m, 1 H, 3-H), 4.54 (dt, 1 H, $J$ = 7.5, 2.7 Hz, 4-H), 2.66 (dd, 1 H, $J$ = 16.9, 2.7 Hz, 2-H), 2.50 (dd, 1 H, $J$ = 18.5, 4.9 Hz, 6-H), 2.43 (dd, 1 H, $J$ = 16.9, 3.7 Hz, 2-H), 2.23 (dt, 1 H, $J$ = 18.5, 3.2 Hz, 6-H), 2.08 (dm, $J$ = 14.8 Hz, 5-H), 1.86 (~tdd, $J$ = 14.8, 4.3, 3.2 Hz, 5-H), 1.42 (s, 3 H), 1.34 (s, 3 H); IR ($CHCl_3$) 3020, 2930, 1720,

(1) Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332.
(2) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.
(3) The preparation of this compound on much larger scales than that reported in the Experimental Section leads, on occasion, to 1,4-cyclohexanedione.
(4) Clizbe, L. A.; Overman, L. E. *Org. Synth.* **1978**, *58*, 4.
(5) Jones, A. B.; Yamaguchi, M.; Patten, A.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17.
(6) Danishefsky, S. J.; Simoneau, B. *Pure Appl. Chem.* **1988**, *60*, 1555.

0022-3263/89/1954-3738$01.50/0 © 1989 American Chemical Society

**Scheme I**




1385, 1260, 1160, 1090, 1030 cm$^{-1}$; EIMS $m/z$ (relative intensity) 170 (0.5), 155 (65), 113 (100); $[\alpha]_D$ +154.38° ($c$ 0.78, $CHCl_3$); HRMS calcd for $C_9H_{14}O_3$ 170.0943, found 170.0938.

**4(*S*)-(*tert*-Butyldimethylsiloxy)-2-cyclohexen-1-one (6).** To a solution of 4 (10 g, 60 mmol) in 500 mL of benzene was added *tert*-butyldimethylsilyl chloride (9.7 g, 64 mmol) and DBU (10 mL, 67 mmol). The mixture was stirred at room temperature for 10 min and heated to reflux for 5$^1/_2$ h. More DBU (2.6 mL, 17 mmol) was added after 3 h. The reaction mixture was cooled to room temperature and diluted with ether. The organic layer was washed with water (1 × 200 mL), 0.1 N aqueous hydrochloric acid (2 × 200 mL), saturated aqueous sodium bicarbonate (1 × 200 mL), and brine (1 × 200 mL). The solution was dried over magnesium sulfate, and the solvent was removed in vacuo. The residue was placed on a 7 cm i.d. flash silica gel column (20 cm of silica gel) and eluted with ethyl acetate–hexanes (1:20) to give, after solvent removal, 11.5 g (87%) of the desired compound as a clear oil. A small amount was purified further by Kugelrhor distillation (1 mmHg): $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 6.83 (ddd, 1 H, $J$ = 10.2, 2.4, 1.7 Hz, 3-H), 5.92 (ddd, 1 H, $J$ = 10.2, 2.0, 1.0 Hz, 2-H), 4.53 (dddd, 1 H, $J$ = 9.1, 4.7, 2.4, 2.0 Hz, 4-H), 2.58 (dtd, 1 H, $J$ = 16.7, 4.7, 1.0 Hz, 6-H), 2.35 (ddd, 1 H, $J$ = 16.7, 12.7, 4.7 Hz, 6-H), 2.21 (dqd, 1 H, $J$ = 12.7, 4.7, 1.7 Hz, 5-H), 2.00 (tdd, 1 H, $J$ = 12.7, 9.1, 4.7 Hz, 5-H), 0.92 (s, 9 H), 0.13 and 0.12 (2 s, 2 × 3 H); IR ($CHCl_3$) 3000, 2940, 2920, 2840, 1675, 1375, 1250, 1100 cm$^{-1}$; EIMS $m/z$ (relative intensity) 226 (0.1), 169 (100), 151 (26); $[\alpha]_D$ −115.94° ($c$ 1.06, $CHCl_3$). Anal. Calcd for $C_{12}H_{22}O_2Si$: C, 63.67; H, 9.79. Found: C, 63.50; H, 9.55.

**4(*S*)-Hydroxy-2-cyclohexen-1-one (5). Method A.** A 4 M aqueous solution of potassium carbonate (1.35 mL, 5.41 mmol) was added to a solution of 4 (923 mg, 5.41 mmol) in 11 mL of tetrahydrofuran at room temperature. The heterogeneous mixture was stirred for 4 days, diluted with ether (50 mL), and dried over magnesium sulfate. Concentration under reduced pressure gave a brown oil, which was purified by flash chromatography ($SiO_2$), with ethyl acetate–hexanes, 60:40, as eluant, to afford 293 mg (48%) of the desired compound as an oil.

**Method B.** To acetonide 4 (120 mg, 0.71 mmol) in 7 mL of benzene was added DBU (116 mL, 0.78 mmol) at room temperature. The reaction was complete after 48 h. The mixture was then filtered through a short column ($SiO_2$), eluting with ethyl acetate–hexanes, 2:1, and concentrated. The crude was purified further by chromatography (ethyl acetate–hexanes, 2:1) to afford 39 mg (49%) of the title compound 5: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 6.94 (ddd, 1 H, $J$ = 10.2, 3.3, 1.7 Hz, 3-H), 5.97 (ddd, 1 H, $J$ = 10.2, 1.9, 1.0 Hz, 2-H), 4.54–4.63 (m, 1 H, 4-H), 2.59 (dtd, 1 H, $J$ = 17.2, ~4.9, 1.0 Hz, 6-H), 2.29–2.45 (m, 2 H, 5,6-H), 2.00 (tdd, 1 H, $J$ = 12.7, 9.3, ~4.9 Hz, 5-H), 1.80 (s, 1 H, 4-OH); IR ($CDCl_3$) 3580, 3420 (br), 2940, 2920, 2860, 1680, 1375, 1245, 1200, 1060 cm$^{-1}$; EIMS $m/z$ (relative intensity) 112 (17), 95 (1), 84 (100); $[\alpha]_D$ −110° ($c$ 0.92, $CHCl_3$); HRMS calcd for $C_6H_8O_2$ 112.0524, found 112.0531.

**4(*S*)-[(4-Methoxybenzyl)oxy]-2-cyclohexen-1-one (7).** A solution of *p*-methoxybenzyl alcohol (5.2 g, 37.6 mmol) in 35 mL of ether was added to a suspension of 60% sodium hydride (0.15 g, 3.8 mmol) in 40 mL of ether at room temperature. The resulting mixture was stirred at room temperature for 30 min and cooled to 0 °C. Trichloroacetonitrile (3.8 mL, 37.6 mmol) was added, and the reaction mixture was allowed to warm slowly to room temperature during 4 h. The solution was concentrated to an orange syrup, which was dissolved in petroleum ether (50 mL) containing methanol (0.16 mL, 4.0 mmol). This suspension was filtered through Celite, and the filtrate was concentrated to a yellow syrup. The crude imidate was dissolved in cyclohexane (60 mL), and a solution of 5 (2.82 g, 25.1 mmol) in 30 mL of methylene chloride was added. The resulting solution was cooled to 0 °C and treated with boron trifluoride etherate (25 $\mu$L). The reaction mixture was warmed to room temperature and stirred for 12 h, slowly developing a white precipitate. The solution was filtered through Celite, and the solids were washed with 1:2 methylene chloride–cyclohexane (2 × 25 mL). The filtrate was washed with saturated aqueous sodium bicarbonate (50 mL), dried over magnesium sulfate, and concentrated. The crude was purified by flash chromatography ($SiO_2$), with ethyl acetate–hexanes, 20:80, as eluant, to give 3.80 g (63%) of a nearly colorless oil: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 7.26–7.30 (m, 2 H), 6.97 (ddd, 1 H, $J$ = 10.2, 2.2, 1.5 Hz), 6.87–6.93 (m, 2 H), 5.98 (ddd, 1 H, $J$ = 10.2, 1.8, 0.7 Hz), 4.58 (AB quartet, 2 H, $\Delta\nu$ = 10.9 Hz, $J$ = 11.3 Hz), 4.20–4.29 (m, 1 H), 3.81 (s, 3 H), 2.60 (ddd, 1 H, $J$ = 15.7, 4.0, 3.7 Hz), 2.26–2.40 (m, 2 H), 1.94–2.14 (m, 1 H); IR ($CHCl_3$) 3005, 1680, 1615, 1515, 1305, 1255, 1180, 1085, 1040 cm$^{-1}$; EIMS $m/z$ (relative

intensity) 232 (20), 201 (1), 136 (20), 121 (100); $[\alpha]_D$ -89.2° (c 1.01, $CHCl_3$). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.35; H, 6.97.

**Acknowledgment.** This research was supported by PHS Grant AI 16943, PHS Postdoctoral Fellowships to J.E.A. (Grant 1 F32 11104-01) and A.V. (Grant GM 11747), and an American Cancer Society Fellowship (Grant PF 2764) to A.D.P. are gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

## Electrochemical Reduction of Nitroaromatics to Anilines in Basic Media: Effects of Positional Isomerism and Cathode Composition

K. J. Stutts,* C. L. Scortichini, and C. M. Repucci

*Central Research, The Dow Chemical Company, Midland, Michigan 48674*

*Received December 30, 1988*

### Introduction

This laboratory has previously reported a high yield synthesis of 3-amino-4-hydroxybenzoic acid via electrochemical reduction of the corresponding nitroaromatic in basic medium at a copper cathode.[1] The scope of reaction in basic medium, the effects of cathode material, and several electrochemical parameters have been investigated and a mechanistic hypothesis is proposed.

The electrochemical reduction of nitroaromatics with the goal of obtaining the aniline has classically been performed in acidic media. Basic conditions are sometimes desirable for solubility or because of process considerations. Synthetic endeavors in basic media have generally failed because of coupling reactions that form azoxy and other dimeric products. Reduction typically proceeds through nitroso and hydroxylamino intermediates to yield azoxy-, azo-, and hydrazobenzenes via coupling reactions and subsequent reductions.[2] Hydrazo benzenes cannot be reduced to the corresponding anilines in base under typical electrolytic conditions.

Many literature accounts indicate that azoxybenzene is obtained by electrolytic reduction of unsubstituted nitrobenzene in basic media at copper and most other cathode materials. The one exception recently reported by Belot et al.[3] is the conversion of nitrobenzene to aniline at a specially activated alloy ("Devarda copper"; 50% Cu, 45% Al, 5% Zn) at low current density (8 mA/cm$^2$) in 0.3 M KOH/MeOH (1.5% $H_2O$).

There are a few examples of the electrolytic reduction of substituted nitroaromatics to the corresponding anilines in basic media. Brown and Warner[4,5] and others[6,7] have shown that the conversion of *o*-nitrophenol to *o*-aminophenol proceeds smoothly in base. A series of cathode materials was investigated with the conclusion that copper is a suitable cathode for this chemistry only at low current density (20 mA/cm$^2$) while lead and zinc are the cathodes of choice at higher current densities. They also indicate the catalytic effect of Pb and Zn for reduction of nitrophenol as evidenced by the spongy surface of the electrode formed by redeposition of dissolved metal formed during the reduction.

Bradt and Hart[8] have shown that 3-nitro-4-hydroxytoluene can be converted to the aniline in sodium carbonate at a tin cathode in high yield. In contrast, Honda et al.[9] state that 2-hydroxy-4-nitrobenzoic acid cannot be converted into the aniline under basic conditions.

We report here that certain classes of ortho/para-substituted nitroaromatics give good yields of the corresponding anilines in base, *especially* when reduced at copper. High current densities (≫20 mA/cm$^2$) can be utilized to make this a practical synthetic procedure for consideration as more than a laboratory curiosity. Increased solubility, preclusion of Gatterman rearrangement chemistry, and ease of workup are advantages to electrochemical reduction in base for some of these compounds. A mechanistic explanation of the ortho/para effect is given and the electrocatalytic effect of copper is investigated.

### Results

**Cyclic Voltammetry.** Voltammetry of the three isomers of nitrophenol at a glassy carbon electrode in 1 N NaOH is quite scan rate dependent. In strong base, a reversible wave at 100 mV/s is indicative of a relatively stable (on the voltammetric time scale) radical anion for the meta isomer whereas no reversibility is noted up to 1 V/s for the ortho and para isomers. Secondary reduction waves are observed for all isomers although that for the ortho isomer converges with the primary wave at low scan rates. Normal inert-electrode electron transfer is postulated at carbon.

Electrocatalytic reduction of nitrophenols at a copper electrode in the same solvent is illustrated in Figure 1. The upper portion of the figure shows a cyclic voltammetric scan at copper in 1 N NaOH with no organic substrate added which exhibits several surface waves which have been the subject of extensive investigations.[10-13] A voltammetric scan in the positive direction from a potential of -1.2 V exhibits an oxidation wave at -0.43 V that corresponds to formation of a film of $Cu_2O$ that has barrier properties which limit its thickness. Continuing the scan to more positive potentials causes oxidation of this film and hence removal of the barrier allowing oxidation of the underlying copper surface to a much thicker film of $Cu(OH)_2$ and/or CuO (wave at -0.15 V). On the negative scan, the wave at -0.63 V corresponds to a partial reduction of the copper(II) surface species to a duplex oxide consisting of $Cu_2O$ together with the remaining CuO. Finally, the wave at -0.99 V corresponds to reduction of the $Cu_2O$ and CuO to copper metal.

Upon addition of 0.2 M nitrophenol to the electrolyte, the reductive surface wave at -0.95 V increases. (The voltammetry at glassy carbon indicates that reduction to the amine requires potentials 350-600 mV more negative than at copper for the para and meta isomers, which is

(1) Submitted to *J. Appl. Electrochem.*
(2) Baizer, M. M.; Lund, H. *Organic Electrochemistry*, 2nd Ed.; 1983, 285ff and 508ff.
(3) Belot, G.; Desjardins, S.; Lessard, J. *Tetrahedron Lett.* **1984**, *25*, 5347.
(4) Brown, O. W.; Warner, J. C. *Trans. Electrochem. Soc.* **1922**, *41*, 255.
(5) Brown, O. W.; Warner, J. C. *J. Phys. Chem.* **1923**, *27*, 455.
(6) Weber, J. E.; Meister, A. E. *J. Chem. Educ.* **1950**, *27*, 571.
(7) McKee, R. H.; Gerapostolou, B. G. *Trans. Electrochem. Soc.* **1935**, *68*, 329.
(8) Bradt, W. E.; Hart, E. J. *Trans. Electrochem. Soc.* **1931**, *60*, 205.
(9) Honda, K.; Yokouchi, R.; Kikuchi, S. *J. Electrochem. Soc. Jpn.* **1952**, *20*, 15; *Chem. Abstr.* **1952**, *46* 4930e.
(10) Hampson, N. A.; Lee, J. B.; Macdonald, K. I. *J. Electroanal. Chem.* **1971**, *32*, 165.
(11) Abd El Haleem, S. M.; Ateya, B. G. *J. Electroanal. Chem.* **1981**, *117*, 309.
(12) Abrantes, L. M.; Castillo, L. M.; Norman, C.; Peter, L. M. *J. Electroanal. Chem.* **1984**, *163*, 209.
(13) Deutscher, R. L.; Woods, R. *J. Appl. Electrochem.* **1986**, *16*, 413.

0022-3263/89/1954-3740$01.50/0 © 1989 American Chemical Society