10 min. The solution was stirred for an additional 30 min, a solution of **3** (400 mg, 1.5 mmol) in anhydrous ether (50 mL) was added, and the resulting solutiuon was stirred at room temperature for 6 h. The excess hydride was decomposed with water (3 mL) followed by dilute HCl (50 mL), and the product was worked up in the conventional manner and chromatographed on Florisil. Elution with hexane gave 9-vinyl-10-ethylphenanthrene (**18**): 280 mg (79%); colorless oil; NMR (60 MHz, $CDCl_3$) δ 1.40 (t, 3, CH_3), 3.25 (q, 2, CH_2), 5.30–6.00 (m, 2, vinylic), 7.00–7.50 (m, 1, vinylic), 7.60–8.95 (m, 8, aryl).

Reaction of 2 with HI. A solution of **2** (1.2 g, 4.6 mmol) in acetic acid (15 mL) containing HI (57%, 2 mL) was refluxed for 15 min. The dark reaction mixture was poured into a stirred solution of 10% sodium bisulfite (200 mL), and the precipitate was collected by filtration. Chromatography on Florisil and elution with 1:3 benzene–hexane gave **14b**: 2.05 g (92%); mp 183 °C; mass spectrum, *m/e* 482 (P); NMR (60 MHz, $CDCl_3$) δ 6.35 (m, 2, vinyl), 7.40–8.60 (m, 10, aryl and vinyl). The 270-MHz spectrum is better resolved and shows the presence of two isomers in approximately a 1:3 ratio; however, specific assignments of isomer structures could not be made.

Deiodination of 9,10-Bis(β-iodovinyl)phenanthrene. A solution of **14b** (300 mg, 0.6 mmol) in anhydrous THF at −100 °C (acetone, liquid N_2) was treated with a solution (5 mL, 1.4 M in hexane) of *sec*-butyllithium. The resulting solution was stirred at −100 °C for 3 h, and then the reaction was quenched by addition of saturated aqueous solution of ammonium chloride. Conventional workup and chromatography of the product on Florisil gave **14a** (90 mg, 63%) eluted with hexane.

In a similar experiment the reaction mixture was quenched with deuterium oxide to afford **14c** (~85% with 15% of **14a**): NMR (270 MHz, $CDCl_3$) δ 5.60–6.00 (m, 2, β (or α) vinylic), 7.10–7.60 (dd, 1, α-vinylic), 7.70–8.90 (m, 8, aryl).

Hydrogenation of 2. A solution of **2** (600 mg, 2.3 mmol) and 800 mg (6.3 mmol) of quinoline in ethyl acetate (20 mL) containing 100 mg of Pd/C (10%) was stirred under H_2 (15 psi) for 6 h. Filtration to remove the catalyst and removal of the solvent gave 560 mg of **13** identical by NMR with an authentic sample prepared by a reported procedure:[9] NMR (60 MHz, $CDCl_3$) δ 0.7 (t, 6, CH_3), 1.20–1.85 (q, 4, CH_2) 2.90 (br s, 2, OH), 7.10–7.70 (m, 8, aryl).

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Registry No. **1**, 84-11-7; *trans*-**2**, 66415-21-2; *trans*-**3**, 33367-03-2; **4**, 217-59-4; **5**, 17529-30-5; **7**, 18508-00-4; **8**, 6217-22-7; **9**, 2051-10-7; **10**, 215-58-7; **11**, 192-97-2; **12**, 196-78-1; *trans*-**13**, 33367-04-3; **14a**, 77320-67-3; **14b**, 77320-68-4; **14c**, 77320-69-5; *trans*-**15**, 77341-74-3; **16**, 77320-70-8; **17a**, 77320-71-9; **18**, 77320-72-0; 2-methylbenz[*a*]anthro[5,6-*d*][1,3]dioxole, 77320-73-1; *trans*-5,6-dihydroxy-5,6-divinyl-5,6-dihydrobenz[*a*]anthracene, 77320-74-2; *trans*-5,6-dihydroxy-5,6-divinyl-5,6-dihydrochrysene, 77320-75-3; *trans*-4,5-dihydroxy-4,5-divinyl-4,5-dihydropyrene, 77320-76-4; *trans*-5,6-diethynyl-5,6-dihydroxy-5,6-dihydrobenz[*a*]anthracene, 77320-77-5; *trans*-4,5-diethynyl-4,5-dihydroxy-4,5-dihydropyrene, 77320-78-6; *trans*-5,6-diethynyl-5,6-dihydroxy-5,6-dihydrochrysene, 77320-79-7; 5,6-divinylbenz[*a*]anthracene, 77320-80-0; 4,5-divinylpyrene, 77320-81-1.

Amine Addition to Unsymmetrical Benzoquinones

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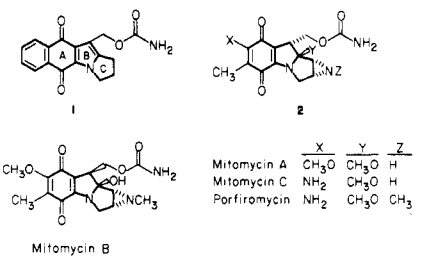
New routes to 2-methoxy-3-methyl-1,4-benzoquinone and 4-methoxy-3-methyl-1,2-benzoquinone have been developed. Both quinones undergo highly regioselective oxidative amination with pyrrolidine and copper acetate, yielding aminoquinones related to the mitomycin antibiotics. The corresponding dibromoquinones have also been prepared and both readily undergo regioselective addition–elimination reactions to give monoamine adducts with the same relative orientation. The regiochemistry has been determined unambiguously by correlation to adducts derived from specificially deuterated quinone intermediates.

Recently the synthesis of the naphthoquinone mitosene analogue **1** was reported[1] as part of a study of synthetic approaches to the mitomycin antibiotics **2** (Chart I). The convergent route developed first joined the A ring (as a quinone) and the C ring (as an amine) and then cyclized to form the B ring. For the purpose of applying this and related methodology to unsymmetrical benzoquinone systems, we have considered the *o*- and *p*-quinones **5**, **8**, **20**, and **25** as potential substrates, bearing substitution patterns which are found in or are convertible to the parent mitomycin system. In this report, we present the syntheses of these substrates and their addition reactions with pyrrolidine as a model amine.

Unlike the naphthoquinone model, the benzenoid system potentially can form isomers, thereby creating a regiochemical problem in the initial amine addition step. We were encouraged, however, to anticipate that this addition might be highly selective by the report that homoproline ethyl ester reacted with quinone **5**, giving addition only at C-5.[2]

Chart I



Quinone **5** has been synthesized many times, invariably in low yield.[2-5] Initial examination of the literature routes suggested that the most facile synthesis would arise from Fremy's salt (potassium nitrosodisulfonate) oxidation of phenol **4**,[3] best obtained by monoether cleavage of **3**.[6]

(1) Falling, S. N.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 1260.

(2) Mandell, L.; Roberts, E. C. *J. Heterocycl. Chem.* **1965**, *2*, 479.
(3) Rashid, A.; Read, G. *J. Chem. Soc. C* **1967**, 1323.
(4) Hanger, W. G.; Howell, W. C.; Johnson, A. W. *J. Chem. Soc.* **1958**, 496.
(5) Parker, K. A.; Sworin, M. *Tetrahedron Lett.* **1978**, 2251.
(6) Giles, R. G. F.; Roos, G. H. P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2057.

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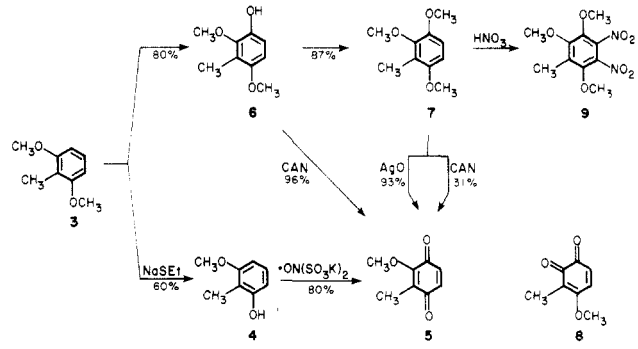
Scheme I. Various Routes to 2-Methoxy-3-methyl-1,4-benzoquinone (5)



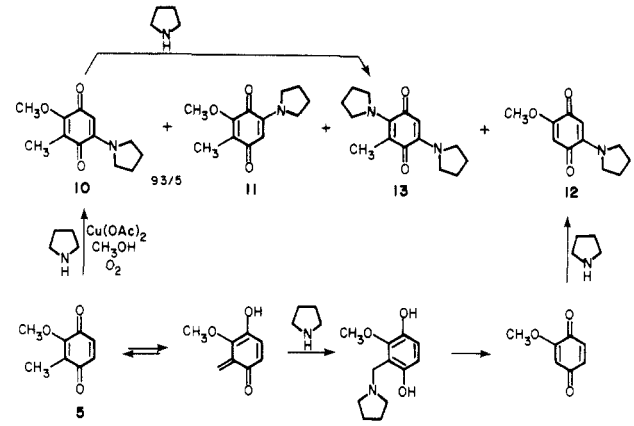
Although a 99% yield is claimed for this cleavage, in our hands treatment of **3** with freshly generated sodium ethylmercaptide in dry dimethylformamide under a variety of conditions gave only moderate yields (~60%) of **4**. Small-scale oxidations with Fremy's salt afforded quinone **5** in greater than 80% yield. Unfortunately, this method requires extremely large volumes of solvent (500 mL/g of **5**) and involves tedious extractions. Furthermore, the synthesis and manipulation of Fremy's salt on a large scale have led to explosive decompositions.

For these reasons we abandoned this process and sought an alternative synthesis amenable to large-scale preparations from readily available starting materials. The method examined was the oxidative demethylation of hydroquinone monomethyl ether **6**.[7] Although one might obtain both *p*-quinone **5** and its ortho isomer **8** by oxidation of **6**, and indeed with argentic oxide (AgO)[8] or nitric acid[9] complex mixtures resulted, ceric ammonium nitrate (CAN)[10] provided a high yield of only the para isomer. Phenol **6** was conveniently prepared from **3** by formylation followed by peracid rearrangement and hydrolysis.[11]

To see if methylation of phenol **6** might change the course of oxidation and provide a sample of the isomeric orthoquinone **8**, a substrate also of potential use in mitomycin synthesis, we prepared methyl ether **7**. Treatment of **7** with CAN in the usual manner gave good mass recovery but of a mixture of several compounds. Since quinone **5** is known to be stable under these conditions, it appears that this reagent gives predominately **8** which rapidly reacts further in the aqueous medium. Concentrated nitric acid gave the corresponding dinitro arene **9** while argentic oxide provided only **5** in excellent yield. These reactions are summarized in Scheme I.

The reaction of quinone **5** with pyrrolidine as the model amine was explored next. A slight excess of pyrrolidine with **5** under oxidative amination conditions gave a major and a minor amine adduct in high yield and in a ratio of 93/5. Structural analysis using the methods discussed below showed that the major isomer was pyrrolidinoquinone **10** and resulted from amine addition at C-5. Addition at C-6 to form the minor adduct **11** is no doubt suppressed in part due to the deactivating vinylogous ester resonance contribution. In larger scale experiments, chromatography led to the isolation of a trace side product,

Scheme II. Oxidative Amination of 2-Methoxy-3-methyl-1,4-benzoquinone (5) with Pyrrolidine



demethylated aminoquinone **12** (<1%). Similarities with **10** in the infrared spectrum allowed the regiochemical assignment shown.

Loss of a methyl group from a quinone during amine addition has been observed previously and is known to proceed via a retro-Mannich reaction.[1,12] When too large an excess of pyrrolidine is used (~115 mol %), the diamine adduct **13** appears as another trace contaminant (<1%). That the structure is as shown was proved by independent synthesis from **10**. Reaction in the absence of the copper salt changes the relative amounts of **10**, **11**, and **13** to 6/3/1, thereby suggesting a key role of copper in selectivity enhancement. These amine additions are summarized in Scheme II.

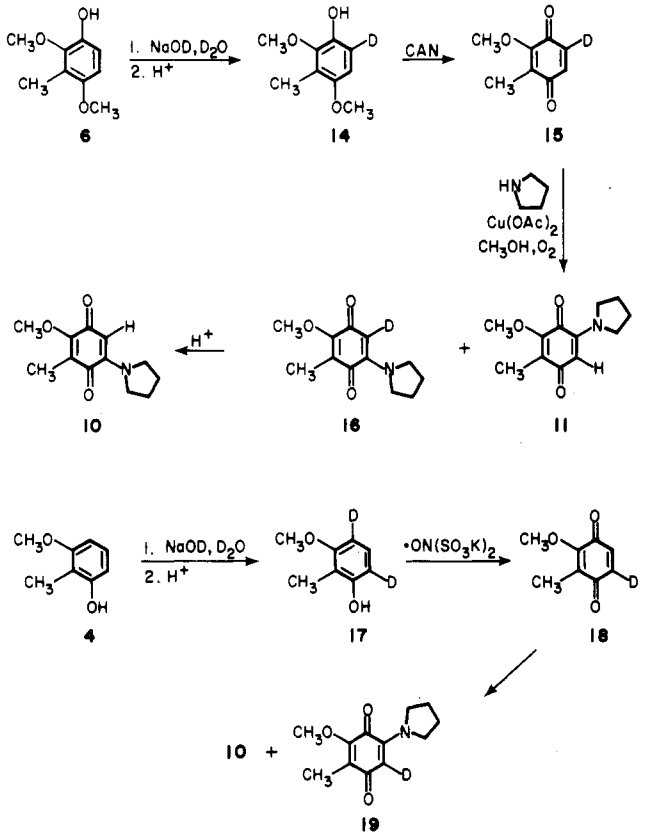
In the past, drastic degradative methods have been used to determine the regioisomer of aminoquinone formation. Thus the adduct has been hydrolyzed in hot sulfuric acid to give the corresponding hydroxyquinone,[2,13] and identification has been by melting point. Yields for these degradations are not reported, and the melting points for the isomeric hydroxyquinones are both broad and similar. We have developed a more straightforward method, by the utilization of deuterium labels, which is applicable to other quinone adducts as well.

First studied was the amine addition to deuterioquinone **15**, easily synthesized by monodeuterating phenol **6** and then oxidizing deuteriophenol **14** with CAN. Addition of pyrrolidine to quinone **15** again gave a mixture of two amine adducts (95/5), the major one of which was seen to retain 95% ^2H by NMR; therefore, structure **16** can be unambiguously assigned to this product, and the minor isomer is **11**. Curiously, quinone **16** readily exchanged its label in the presence of traces of acid (wet ether/silica or acetonitrile/0.01 M HCl, 1:3). Exchange could be minimized (to 5–6%) in the isolation by adding triethylamine (4% by volume) to the eluent during chromatography. Thus, the appearance of a characteristic ring proton (generally found between 5.0 and 5.3 ppm) in the NMR spectrum of the crude mixture provides evidence for the presence of a regioisomer.

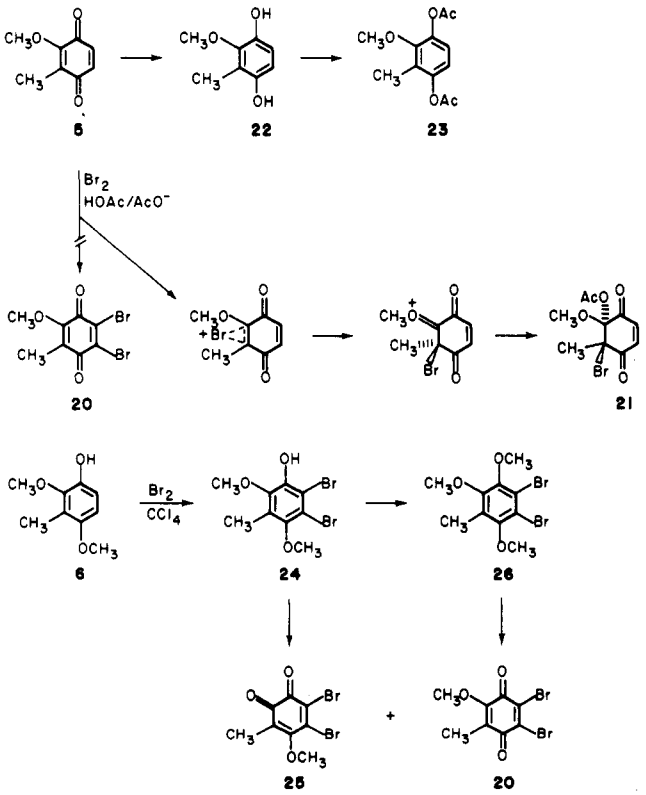
As complementary evidence, the pyrrolidine addition was also performed on deuterioquinone **18**, easily synthesized by dideuteration of phenol **4** followed by Fremy's salt oxidation. Examination of the amine addition reaction revealed retention of deuterium in the minor isomer **19**,

(7) For a similar example of oxidative demethylation of a hydroquinone monomethyl ether see: Hannan, R. L.; Barber, R. B.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2153.
(8) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227; **1974**, *96*, 8046.
(9) Musgrave, O. C. *Chem. Rev.* **1969**, *69*, 499.
(10) Peyton, J.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627.
(11) Godfrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353.
(12) (a) Cameron, D. W.; Scott, P. M.; Todd, A. *J. Chem. Soc.* **1964**, 42. (b) Cameron, D. W.; Scott, P. M. *Ibid.* **1964**, 5569. (c) Cameron, D. W.; Giles, R. G. F.; Titman, R. B. *J. Chem. Soc. C* **1969**, 1245.
(13) Shaikh, Y. A. *J. Heterocycl. Chem.* **1977**, *14*, 925.

Scheme III. Assignment of Regioisomers by Amine Addition to Deuterioquinones



Scheme IV. Routes to *o*- and *p*-Dibromoquinones



thus unequivocally establishing the mode of addition. These structural assignments based on addition to the deuterated quinones are shown in Scheme III.

Next we turned our attention to amine additions to the corresponding dibromoquinones (Scheme IV). As there is little information on the dibromination of 2,3-disubstituted quinones, the procedure for dibromination of naphthoquinone[14] was tried. However, after treatment of **5** with bromine in acetic acid no dibromoquinone **20** could be isolated. Instead, a mixture of two other compounds was formed. The major component was isolated in 66% yield and was shown to be bromoacetate **21** (or an isomer of **21**). The other compound was unstable and was not further characterized.

Table I. Oxidative Demethylation of 24 to Dibromo-*p*-quinone 20 and *o*-Quinone 25

oxidizing agent	reaction medium	time, min	% yield[a] 20	25
CAN	CH_3CN/H_2O (1:1)	60	26	19
		20	28	46
		5	26	52
AgO	dioxane/6 M HNO_3	20	5	87
HNO_3	16 M HNO_3	15	47	0
HNO_3	6 M HNO_3	15	29	0
HNO_3	6 M HNO_3	60	33	0
HNO_3	CH_2Cl_2, half-satd with HNO_3	10	0	89

[a] Ratios determined by ^1H NMR and HPLC (±2%).

Dibromination of the diacetate **23**, prepared by acetylation of hydroquinone **22**, was tried next; however, treatment with bromine in carbon tetrachloride gave a sluggish reaction and many products.

The successful substrate was phenol **6**. When **6** was treated with excess bromine in carbon tetrachloride, a rapid reaction took place, leading to crystalline dibromophenol **24** in excellent yield. Oxidative demethylation of **24** could conceivably provide both *p*-quinone **20** and *o*-quinone **25**, each of which is of potential use. In practice both quinones were formed, and the yields and the ortho/para ratios varied, depending on the reagent used, as shown in Table I.

When dibromoquinone **24** was treated with CAN for 1 h, a mixture of isomeric quinones was isolated in only modest yield. The yield of this mixture could be improved by shortening the reaction time since prolonged exposure to the reaction medium led to consumption of dibromo-*o*-quinone **25**. Argentic oxide displayed a greater preference for the ortho isomer, and aqueous nitric acid, though providing only **20** on isolation, probably also forms **25** which is known to be unstable to these reaction conditions.

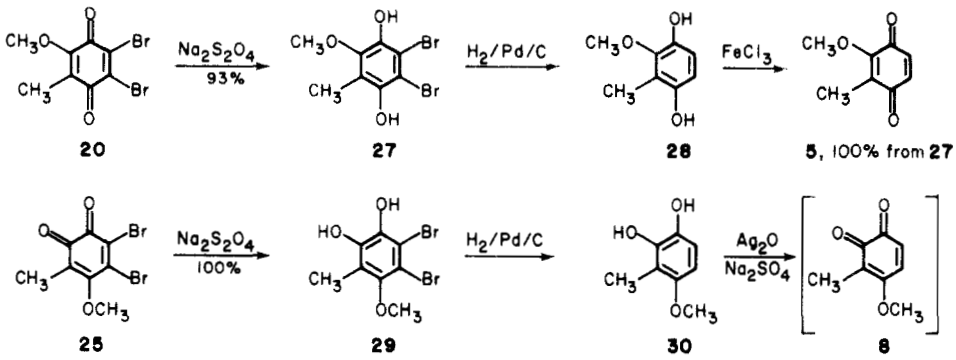
To see what effect methylation of the phenol would have on the direction of the subsequent oxidation, we prepared dibromo methyl ether **26** and treated it with CAN in the usual manner. Only **20** and substantial amounts of starting material (48% **26**, 32% **20**) could be isolated. Additional side products were formed with extended reaction times and incremental addition of more CAN. Similar behavior was observed upon treatment with argentic oxide. As before, reaction with concentrated nitric acid gave **20** as the sole isolated product (40%).

In addition to spectral differentiation of the isomeric quinones,[15] a chemical proof was undertaken. The plan was to reduce separately both quinones to their hydroquinones, to debrominate hydrogenolytically, and to reoxidize **28** to **5** and **30** to **8** (Scheme V). The latter conversion might also provide a convenient preparative route to the previously unknown *o*-quinone **8**. In practice, both

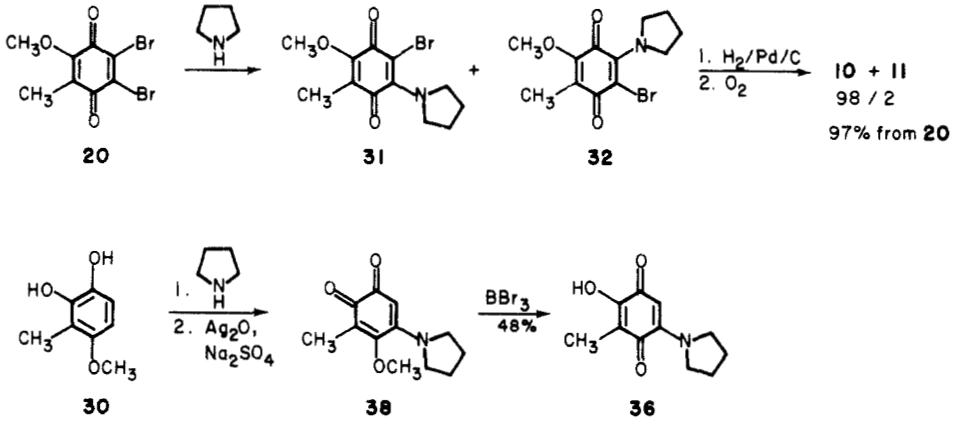
(14) McElvain, S. M.; Engelhardt, E. L. *J. Am. Chem. Soc.* **1944**, *66*, 1077.

(15) For a discussion of the chemistry and spectral properties of quinones see: Patai, S., Ed. "The Chemistry of the Quinoid Compounds"; Wiley: New York, 1974; Part 1.

Scheme V



Scheme VI

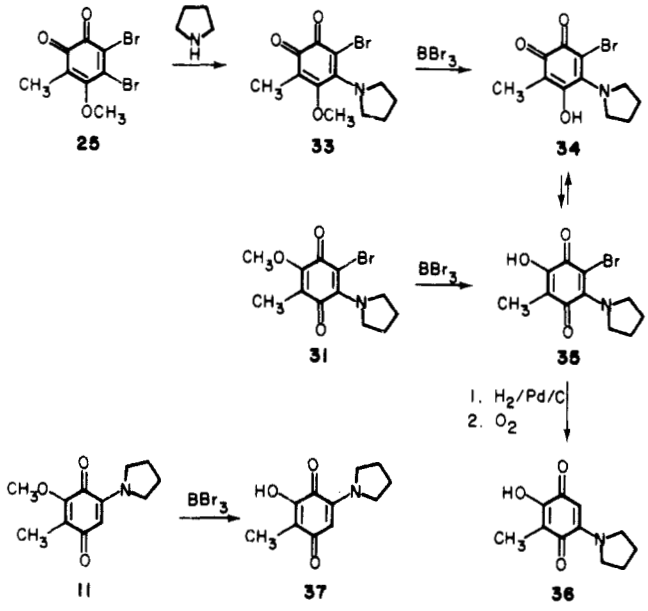


quinones were reduced readily with dithionite to provide crystalline hydroquinones **27** and **29**. Catalytic hydrogenolysis of **27** provided debromohydroquinone **28** which was cleanly oxidized to quinone **5** in quantitative yield. The hydrogenolysis of **29** proceeded quite sluggishly; consequently, **25** was reduced and hydrogenolyzed in one pot. Working quantities of the very unstable debromohydroquinone **30** were obtainable in high yield by this method.

The oxidation of **30** to the corresponding quinone was less successful. Though several attempts were made by using reagents of various oxidation strengths, only intractable black mixtures could be isolated. Finally, however, conditions were found under which **8** could be observed on TLC, but not isolated. That **8** was indeed formed by argentous oxide oxidation[16] was confirmed by trapping via amine addition as described below. Although these experiments did not provide a preparative method for obtaining **8**, they did confirm the structural assignment of **20** and **25**.

p-Dibromoquinone **20** undergoes an addition/elimination reaction with pyrrolidine to give a mixture of amine adducts **31** and **32** (Scheme VI). The reaction was best done at room temperature with only a slight excess of pyrrolidine and in the dark since solutions of these aminobromoquinones, like those reported previously,[1] lost bromine in light to give the corresponding debromoaminoquinones. Controlled conversion to the debrominated quinones followed by LC analysis provided a good method for determining the regiochemical preference of addition. Thus, analysis of the crude product mixture from **20** derived from amine addition, catalytic hydrogenolysis, and reoxidation showed that amine addition proceeded with slightly higher selectivity than was the case for the debromoquinone **5**.

Scheme VII. Regioisomer Assignment of Amine-Dibromo-*o*-quinone Adduct 33



Treatment of *o*-quinone **25** with pyrrolidine under similar conditions gave a single isomeric bromoaminoquinone **33** (Scheme VII) which is unstable, partially decomposing during removal of solvent under high vacuum and rapidly losing bromine in a solution exposed to light. Unlike quinones **31** and **32**, orthoquinone **33** cannot be related easily to another quinone of known regiochemistry, and so an alternate regiochemical probe was devised. Successful preparation of the hydroquinone dimethyl ether of **33** and comparison of it with those of **31** and **32** would reveal the mode of pyrrolidine addition to quinone **25**. However, these derivatizations were complicated by partial hydrogenolysis during the reduction step and by partial

(16) Cason, J. *Org. React.* **1948**, *4*, 305.

decomposition of the various bromo- and debromohydroquinones during the very sluggish and incomplete methylation step. The methylation of the debromo-*o*-hydroquinone also was unsuccessful.

Since the conversion of bromoamino-*o*-quinone **33** to a dimethyl ether derivative of known regiochemistry failed, another structure proof was formulated via the conversion of **33** to a *p*-quinone derivative which in turn can be related to amino-*p*-quinones of known regiochemistry. To this end, an ether cleavage was performed on **33** to give hydroxy-*o*-quinone **34**. Since hydroxyquinones of this sort prefer to exist as the para isomer,[17] compound **34** rapidly tautomerizes to hydroxy-*p*-quinone **35** which is capable of hydrogen bonding. Similar treatment of **31** gave a hydroxyquinone which was identical with **35**. As both ether cleavage reactions were accompanied by partial debromination, the products of both reactions were converted to a single product **36**. For the assignment of regiochemistry by this method to be valid, however, the cleavage product derived from **11** must be distinguishable from those obtained by the other cleavages. Treatment of **11** with boron tribromide gave the isomeric quinone **37** which indeed was spectroscopically and chromatographically differentiated from **36**. This proof of the mode of addition of pyrrolidine to dibromo-*o*-quinone **25** is illustrated in Scheme V.

As mentioned above, *o*-quinone **8** could not be isolated due to its instability. The potential for **8** as a useful synthetic intermediate lies in the possibility that it might be generated in situ and trapped as its amine adduct. Toward this end, hydroquinone **30** was placed in the presence of a slight excess of amine. Then ferric chloride in ether was added with the intention that oxidation of **30** in the presence of pyrrolidine would lead to amine addition faster than decomposition. Even under these conditions no definitive products could be isolated. Finally, the unstable amine adduct **38** was isolated when the oxidation was carried out with argentous oxide in the presence of sodium sulfate. The regiochemistry of addition was determined by the ether cleavage technique via **36** and was as shown in **38**.

In summary, these amine addition reactions with quinones **5**, **8**, **20**, and **25** proceed regioselectively and in high yield. They establish a clear precedent for further additions to these quinones with a variety of amines and amino acids.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Reagents and solvents were distilled as follows: dichloromethane from phosphorus pentoxide, *N*,*N*-dimethylformamide from calcium hydride, methyl iodide from itself, and pyrrolidine from barium oxide.

Melting points (Pyrex capillary) are uncorrected. IR spectra were determined with Perkin-Elmer Model 137 and 337 grating spectrophotometers with polystyrene film for calibration (1601.4-cm^{-1} absorption). UV spectra were determined in methanol with a Cary Model 219 spectrophotometer. ^1H NMR spectra were determined on a Varian EM-390 (90 MHz) spectrometer. For complex multiplets (m) the chemical shift given is the center of the multiplet. ^{13}C NMR spectra were measured at 25 MHz (25.14 MHz) with a Nicolet TT-23 spectrometer. NMR spectra were taken in $CDCl_3$ and chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were obtained with Atlas MS-12 and Consolidated 12-110B mass spectrometers. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley. High-pressure liquid chromatography (HPLC) was done on an Altex analytical system consisting of two Model 110A pumps, a Model 115-10 UV–vis detector, and a Model 420 microprocessor controller/programmer. The following stainless-steel Altex columns were used: (A) Lichrosorb Si60 normal-phase silica gel, 5 μm, 3.2 × 250 mm; (B) Lichrosorb C_{18}, reverse-phase silica gel, 10 μm, 3.2 × 250 mm. Unless otherwise noted, a flow rate of 2.0 mL/min was used, with monitoring at 280 nm and with the solvent mixture described (isochratic). Preparative medium-pressure liquid chromatography (MPLC) was done by using an Altex Model 110A pump equipped with a preparative liquid head and an Altex Model 151 UV detector, with monitoring at 280 nm. An Altex stainless-steel column packed with Spherisorb ODS reverse-phase silica gel (10 × 250 mm, 10 μm) was used. Column chromatography was performed with silica gel 60 (EM reagents, 63–200 μm). Analytical TLC was done with aluminum-backed silica plates (E. Merck). Preparative TLC (PTLC) was carried out on Analtech silica gel GF, 1000 or 2000 glass-backed plates. Unless otherwise noted, all reactions were conducted under a nitrogen atmosphere with magnetic stirring at room temperature, and final product solutions were dried over $MgSO_4$, filtered, and evaporated on a Berkeley rotary evaporator. Bulb to bulb distillations were carried out on a Kugelrohr-type apparatus.

2-Methoxy-3-methyl-1,4-benzoquinone (5). To 2,4-dimethoxy-3-methylphenol (**6**;[11] 21.9 g, 0.130 mol) in acetonitrile (250 mL) was added with rapid stirring ceric ammonium nitrate (178 g, 0.326 mol) in water (250 mL) over the course of 10 min. Stirring was continued for 45 min at which time water (900 mL) was added, and the mixture was extracted with dichloromethane (3 × 250 mL). The combined organic extract was washed with water (250 mL), 10% $NaHCO_3$ (2 × 250 mL), water (250 mL), and brine (200 mL). Drying and evaporation gave quinone **5** as a yellow oil which solidified on cooling: 19.0 g (96%); mp 29–30 °C (lit. mp 18–30 °C,[2] 19–30 °C[4]); NMR δ 2.01 (s, 3 H, CH_3), 4.11 (s, 3 H, OCH_3), 6.67 (d, 1 H, C-6 H, J_{AB} = 9 Hz), 6.87 (d, 1 H, C-5 H); IR (neat) 3058, 1675, 1653, 1600, 1439, 1368, 1295, 1200, 1149, 1073, 1008, 968, 827, 783, 736 cm^{-1}; mass spectrum, *m/e* (relative intensity) 154 (M + 2, 3.2), 153 (M + 1, 3.7), 152 (M^+, 38.8), 122 (18.7), 109 (6.3), 94 (2.9), 82 (10.9). Anal. Calcd for $C_8H_8O_3$: C, 63.1; H, 5.3. Found: C, 63.0; H, 5.4.

2,3,6-Trimethoxytoluene (7). To phenol **6** (2.00 g, 11.9 mmol) in dimethylformamide (12 mL) was added barium hydroxide (2.04 g, 11.9 mmol) and methyl iodide (5.11 g, 36.0 mmol). The mixture was stirred for 9 h and then partitioned between water (40 mL) and chloroform (20 mL). The aqueous layer was extracted with chloroform (2 × 20 mL), and the combined organic phase was washed with saturated sodium carbonate (20 mL) and brine (20 mL). Drying, evaporation, and bulb to bulb distillation gave **7** as white crystals: 1.89 g (87%); R_f (chloroform) 0.33; mp 35–36 °C; NMR δ 2.14 (s, 3 H, CH_3), 3.74, 3.77, 3.80 (3 s, OCH_3), 6.52, 6.69 (2 d, 1 H each, Ar H, J_{AB} = 9 Hz); IR (neat, thin film) 2915, 2817, 1727, 1597, 1477, 1451, 1431, 1410, 1248, 1221, 1160, 1110, 1082, 1046, 1027, 1003, 950, 859, 792, 758, 718, 684 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7. Found: C, 65.6; H, 7.7.

Oxidative Demethylation of 7. (A) With CAN. To **7** (67.7 mg, 0.372 mmol) in acetonitrile (0.95 mL) was added in one portion ceric ammonium nitrate (0.511 g, 0.930 mmol) in water (0.95 mL) with stirring. After 5 min water (4 mL) and dichloromethane (4 mL) were added, and the layers were separated. The aqueous phase was extracted with dichloromethane, and the combined organic solution was washed with water (2 × 3 mL), dried (Na_2SO_4), and evaporated to an oil (56.0 mg). The oil was chromatographed on 1 g of silica (chloroform) to give 17.5 mg (31%) of **5** identical with material prepared from **6**.

(B) With Argentic Oxide. To dimethyl ether **7** (51.5 mg, 0.283 mmol) and argentic oxide (142 mg, 1.13 mmol) was added dioxane (2.8 mL) with rapid stirring followed by nitric acid (0.28 mL, 6 M solution) in one portion. After 15 min, water/chloroform (3 mL/10 mL) was added, and the layers were separated. The aqueous phase was extracted with chloroform (2 × 2 mL), and the combined organic solution was washed with water (2 mL), dried (Na_2SO_4), and evaporated to pure crystalline **5** (40.0 mg, 93%)

(17) (a) Remers, W. A.; James, P. N.; Weiss, M. J. *J. Org. Chem.* **1963**, *28*, 1169. (b) Allen, G. R., Jr.; Poletto, J. F.; Weiss, M. J. *Ibid.* **1965**, *30*, 2897.

4,5-Dinitro-2,3,6-trimethoxytoluene (9). To dimethyl ether **7** (53.0 mg, 0.291 mol) was added concentrated nitric acid (2 mL) with stirring. After 5 min, water (4 mL) and dichloromethane (4 mL) were added with stirring, and the layers were separated. The aqueous phase was extracted with dichloromethane (4 × 3 mL), and the combined organic phase was washed with water (2 × 3 mL), dried, and evaporated to give **9**: 46.5 mg (59%); mp 77–79 °C (sublimed); NMR δ 2.21 (s, 3 H, CH_3), 3.84, 3.88, 3.90 (3 s, 3 H each, OCH_3); IR (Nujol) 1534, 1353, 1264, 1205, 1124, 1075, 1020, 1011, 976, 957, 948, 905, 887, 796, 775, 758, 724 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_2O_7$: C, 44.1; H, 4.4; N, 10.3. Found: C, 44.4; H, 4.5; N, 10.1.

Pyrrolidine Addition to Quinone 5. Isolation of 2-Methoxy-3-methyl-5-(1-pyrrolidinyl)-1,4-benzoquinone (10), 2-Methoxy-3-methyl-6-(1-pyrrolidinyl)-1,4-benzoquinone (11), 2-Methoxy-5-(1-pyrrolidinyl)-1,4-benzoquinone (12), and 2-(1-Pyrrolidinyl)-3-methyl-5-(1-pyrrolidinyl)-1,4-benzoquinone (13). Copper acetate monohydrate (6.47 g, 32.4 mmol) was partially dissolved in methanol (100 mL) with pyrrolidine (1.07 g, 15.1 mmol) while being stirred under oxygen. Then quinone **5** (2.19 g, 14.4 mmol) dissolved in methanol (25 mL) was added dropwise over the course of 15 min. After 5 h, evaporation gave a residue which was suspended in chloroform (25 mL) and filtered. The solids were washed with chloroform, and the combined organic phase was washed with water (50 mL). The aqueous phase was back-extracted with chloroform (25 mL), and the wash and back-extraction were repeated. The combined organic solution was washed with brine, dried, filtered, and evaporated to a purple crystalline mass (3.05 g, 96%). The extractive isolation can be replaced with a filtration through a short column of silica with ether. Quinones **12** and **13** were isolated from the mixture by simple column chromatography (90% ether, 10% hexane, silica) of a portion of the crude material in yields corresponding to about 1% each. Separation of **10** and **11** required preparative reverse-phase MPLC (25% CH_3CN) or column chromatography (silica/sample, 250:1 w/w; 70% ether, 30% hexane). Analytical reverse-phase HPLC separation of the crude product mixture (25% CH_3CN, 280 nm, corrected) shows 93% **10**, 5% **11**, 1% **12**, and 1% **13**.

10: red crystals; mp 72–73 °C; R_f (SiO_2, ether) 0.48; NMR δ 1.86 (s, 3 H, CH_3), 1.94 (m, 4 H, $NCH_2CH_2CH_2$), 3.52 (m, 4 H, CH_2NCH_2), 4.08 (s, 3 H, OCH_3), 5.27 (s, 1 H, quinone H); IR (Nujol) 2933, 1667, 1623, 1580, 1427, 1335, 1294, 1230, 1172, 1138, 1083, 1017, 987, 877, 862, 812, 776, 745 cm^{-1}; UV λ_{max} 225 nm (ϵ 22 200), 317 (10 300), 512 (2980); mass spectrum, *m/e* (relative intensity) 224 (M + 3, 2.6), 223 (M + 2, 9.2), 222 (M + 1, 35.7), 221 (M^+, 100), 206 (26.5), 2.03 (8.9), 192 (22.8), 178 (81.4). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3. Found: C, 65.1; H, 6.8; N, 6.3.

11: red crystals; mp 70–72 °C; R_f (SiO_2/ether) 0.48; NMR δ 1.97 (s, 3 H, CH_3; m, 4 H, $NCH_2CH_2CH_2$), 3.49 (m, 4 H, CH_2NCH_2), 3.80 (s, 3 H, OCH_3), 5.37 (s, 1 H, quinone H); IR (Nujol) 2899, 1672, 1658, 1613, 1575, 1330, 1295, 1247, 1198, 1145, 1120, 1098, 1019, 978, 788 cm^{-1}; UV λ_{max} 229 nm (ϵ 22 900), 312 (7820), 523 (2940); mass spectrum, *m/e* (relative intensity) 224 (M + 3, 5.7), 223 (M + 2, 20.2), 222 (M + 1, 22.7), 221 (M^+, 81.8), 206 (57.8), 193 (18.3), 190 (25.6), 178 (45.8); found *m/e* 221.1050 (M^+), $C_{12}H_{15}NO_3$ requires *m/e* 221.1052.

12: R_f (SiO_2/ether) 0.11; NMR δ 1.94 (m, 4 H, $NCH_2CH_2CH_2$), 3.6 (m, 4 H, CH_2NCH_2), 3.77 (s, 3 H, OCH_3), 5.42 (s, 1 H, NC=CH), 5.63 (s, 1 H, HC=$COCH_3$); IR (Nujol) 1661, 1605, 1567, 1239, 1211, 1004, 881, 732 cm^{-1}; mass spectrum, found *m/e* 207.0893 (M^+), $C_{11}H_{13}NO_3$ requires *m/e* 207.0895.

13: red-brown crystals; mp 140–142 °C; R_f (SiO_2, ether) 0.42; NMR δ 1.86 (m, 8 H, 2 $NCH_2CH_2CH_2$), 1.97 (s, 3 H, CH_3), 3.6 (m, 8 H, CH_2NCH_2), 5.14 (s, 1 H, quinone H); IR (Nujol) 2999, 1613, 1590, 1527, 1323, 1245, 1067, 1010, 820, 782, 742, 725 cm^{-1}. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.2; H, 7.7; N, 10.8. Found: C, 69.1; H, 7.9; N, 10.6.

Conversion of 10 to 13. To aminoquinone **10** (0.0208 g, 0.0940 mmol) in methanol (1.0 mL) was added pyrrolidine (6.8 g, 0.096 mmol) with rapid stirring. After 7 h the reaction mixture was evaporated to a red-brown solid (23.2 mg, 100%) identical with **13** reported above.

2,4-Dimethoxy-3-methylphenol-*6*-*d* (14). To phenol **6** (2.50 g, 14.9 mmol) was added 40 mL of NaOD (prepared by adding 1.85 g of sodium to 40 mL of D_2O). The reaction mixture was then brought to reflux where it was maintained for 179 h at which time the NMR showed 98% deuterium incorporation. The reaction mixture was cooled, made slightly acidic with concentrated HCl, diluted with water (100 mL), and extracted with chloroform (4 × 10 mL). The combined organic solution was washed with brine, dried, and evaporated to an oil: 2.30 g (92%); NMR δ 2.15 (s, 3 H, $ArCH_3$), 3.74 (s, 6 H, $ArOCH_3$), 5.27 (s, 1 H, quinone H), 6.54 (s, 1 H, ArH); IR (neat) 3448, 2976, 2857, 1736, 1715, 1613, 1475, 1412, 1346, 1236, 1190, 1114, 1086, 1079, 983, 926, 865, 833, 765, 725, 699 cm^{-1}.

2-Methoxy-3-methyl-1,4-benzoquinone-*6*-*d* (15). Quinone **15** was prepared from phenol **14** by the procedure used to make quinone **5**: NMR δ 1.95 (s, 3 H, CH_3), 3.99 (s, 3 H, OCH_3), 6.66 (t, 1 H, quinone H, J_{AB} = 1 Hz); IR (neat) 2985, 2907, 1667, 1600, 1456, 1379, 1342, 1325, 1285, 1193, 1143, 1035, 987, 983, 919, 818, 755 cm^{-1}.

Pyrrolidine Addition to Quinone 15: Synthesis of 2-Methoxy-3-methyl-5-(1-pyrrolidinyl)-1,4-benzoquinone-*6*-*d* (16) and Aminoquinone 11. Copper acetate monohydrate (0.377 g, 1.88 mmol) was partially dissolved in methanol (6.25 mL) with pyrrolidine (68 mg 0.96 mmol) while stirring under oxygen. Then quinone **15** (129 mg, 0.84 mmol) dissolved in methanol (1.50 mL) was added in one portion with rapid stirring. After 2.5 h, evaporation gave a residue which was suspended in ether/triethylamine (98/2) and filtered through a short column of silica (250 mg) equilibrated with that solvent. Evaporation gave red crystals (181 mg, 97%). NMR analysis showed 5–6% loss of ^2H. Analytical HPLC (25% CH_3CN) showed 4% **11** and 96% **16**. Quinone **16** could be separated from **11** without further loss of ^2H eluting 20 mg of the mixture on a 1000-μm preparative TLC plate (SiO_2, 76% ether/4% triethylamine/20% hexane).

2-Methyl-3-methoxyphenol-*4*,*6*-d_2 (17). To D_2O (40 mL) was added sodium (1.80 g, 78.3 mmol), phenol **4** (0.90 g, 6.5 mmol) was then added, and the mixture was heated to reflux. After 70 h the solution was made slightly acidic with 10% HCl, water (30 mL) was added, and the mixture was extracted with ether (4 × 20 mL). The combined organic extract was washed with water (20 mL), dried, evaporated, and bulb to bulb distilled to give **17** (0.83 g, 91%) as an oily solid. NMR comparison with **4** shows that dideuteration has taken place to the extent of 99%: NMR δ 2.16 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 7.13 (s, 1 H, Ar H).

2-Methoxy-3-methyl-1,4-benzoquinone-*5*-*d* (18). Quinone **18** was prepared from phenol **17** in 80% yield by treatment with Fremy's salt according to a literature procedure:[3] NMR δ 2.01 (s, 3 H, CH_3), 4.10 (s, 3 H, OCH_3), 6.70 (s, 1 H, quinone H); IR (neat) 3077, 1667, 1595, 1447, 1370, 1340, 1309, 1266, 1199, 1149, 1085, 1026, 978, 914, 890, 783, 768, 728 cm^{-1}.

5-Bromo-5-methyl-6-methoxy-6-acetoxycyclohex-2-ene-1,4-dione (21). To quinone **5** (1.00 g, 6.57 mmol) in glacial acetic acid (21 mL) was added fused sodium acetate (4.15 g, 50.7 mmol). The mixture was stirred until homogeneous, and bromine (2.6 g, 16.2 mmol) was added in one portion. Stirring was continued for 9.5 h at which time the reaction mixture was poured into water (85 mL). Bromoacetate **21** was then filtered off and dried under reduced pressure: 1.27 g (66%); mp 122–124 °C (sublimed); NMR δ 1.97, 2.07 (2 s, 6 H, CH_3, $COCH_3$), 3.70 (s, 3 H, OCH_3), 6.55, 6.87 (2 d, 1 H each, C=CH, J_{AB} = 10.5 Hz); IR (Nujol) 1739, 1715, 1684, 1605, 1458, 1368, 1267, 1209, 1142, 1119, 1085, 1029, 997, 949, 915, 850, 770, 751, 697 cm^{-1}; mass spectrum, *m/e* (relative intensity) 231, 233 (M^+ – OAc, 8.5, 8.5), 169 (100), 152 (69.3), 137 (56.0), 122 (37.9), 109 (22.0). Anal. Calcd for $C_{10}H_{11}O_5Br$: C, 41.3; H, 3.8. Found: C, 41.0; H, 3.8.

2-Methoxy-3,6-diacetoxytoluene (23). To quinone **5** (0.20 g, 1.3 mmol) in ether (10 mL) was added an aqueous solution of sodium dithionite (0.87 g, 5.00 mmol, in 5 mL of H_2O) in one portion with rapid stirring. After 20 min more dithionite solution (5 mL) was added. Fifteen minutes later the layers were separated, and the organic solution was dried (Na_2SO_4 containing $Na_2S_2O_4$). Rapid filtration and evaporation gave hydroquinone **22** as a white powder (0.12 g, 60%) to which acetic anhydride (2.14 g, 21 mmol) and pyridine (0.5 mL) were added with stirring. After 12 h the reaction mixture was poured into water (30 mL) and extracted with chloroform (3 × 12 mL). The combined organic extract was dried and evaporated to give **23** as an oil (0.15 g, 83%) which crystallized upon standing: mp 65–66 °C (sublimed); NMR δ 2.21

(s, 3 H, CH_3), 2.31 (s, 6 H, 2 $COCH_3$), 3.82 (s, 3 H, OCH_3), 6.83, 7.03 (2 d, 1 H each, Ar H, J_{AB} = 9 Hz); IR (neat) 2933, 1754, 1613, 1587, 1473, 1451, 1412, 1362, 1269, 1190, 1078, 1029, 989, 922, 895, 870, 821 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.5; H, 5.9. Found: C, 60.5; H, 6.0.

2,3-Dibromo-4,6-dimethoxy-5-methylphenol (24). To phenol **6** (5.47 g, 32.5 mmol) in carbon tetrachloride (60 mL) at 0 °C was added bromine (10.9 g, 68.2 mmol) in carbon tetrachloride (50 mL) over the course of 35 min with stirring. The cold bath was removed, and the solution was evaporated to leave **24** as a white solid: 10.25 g (97%); mp 100–101 °C; NMR δ 2.27 (s, 3 H, CH_3), 3.80, 3.87 (2 s, 3 H each, $Ar(OCH_3)_2$), 5.6 (br s, 1 H, OH); IR (Nujol) 3413, 1582, 1449, 1406, 1330, 1267, 1233, 1195, 1109, 997, 912, 816, 771 cm^{-1}. Anal. Calcd for $C_9H_{10}Br_2O_3$: C, 33.2; H, 3.1. Found: C, 33.3; H, 3.1.

Oxidation of 24 to 2,3-Dibromo-5-methoxy-6-methyl-1,4-benzoquinone (20) and 3,4-Dibromo-5-methoxy-6-methyl-1,2-benzoquinone (25). (A) With CAN. The following procedure is representative. To phenol **24** (102 mg, 0.31 mmol) in acetonitrile (0.8 mL) was added with rapid stirring ceric ammonium nitrate (428 mg, 0.78 mmol) in water (0.8 mL). After 5 min, water (2.5 mL) was added, and the mixture was extracted with dichloromethane (4 × 1 mL). The combined extract was washed with water (1 mL), 10% $NaHCO_3$ (2 × 1 mL), water (1 mL), brine (1 mL), dried, and evaporated to give **20** and **25** as a red crystalline mass (75 mg, 78%). NMR integration values were compared with those of a sample of known composition and showed the mixture to be composed of 34% **20** and 66% **25**. Alternately, the ratio could be determined by HPLC (30% $CHCl_3$/70% C_6H_{14}). Preparative separation was achieved by column chromatography (SiO_2/sample, 50/1 w/w) with dichloromethane, giving >90% mass recovery.

20: yellow-orange crystals; R_f (SiO_2, dichloromethane) 0.61; mp 88–89 °C (sublimed); ^1H NMR δ 2.02 (s, 3 H, CH_3), 4.04 (s, 3 H, OCH_3); IR (Nujol) 1678, 1658, 1637, 1462, 1376, 1318, 1300, 1208, 1157, 1131, 1047, 1000, 895, 836, 794, 776, 726 cm^{-1}. ^{13}C NMR δ 10.2, 61.2, 129.2, 136.6, 139.8, 155.6, 173.8, 178.4; UV λ_{max} 294 nm (ϵ 12 310), 395 (300). Anal. Calcd for $C_8H_6Br_2O_3$: C, 31.0; H, 2.0. Found: C, 31.3; H, 2.1.

25: red crystals; R_f (SiO_2, dichloromethane) 0.43; mp 126–128 °C (sublimed); ^1H NMR δ 2.01 (s, 3 H, CH_3), 3.92 (s, 3 H, OCH_3); IR (Nujol) 1689, 1603, 1522, 1464, 1376, 1319, 1236, 1212, 978, 915, 825, 781, 724 cm^{-1}; ^{13}C NMR δ 9.8, 62.0, 124.3, 127.0, 143.0, 161.0, 170.6, 178.4; UV λ_{max} 206 nm (15 100) 255 (5120), 293 (3420), 437 (1250). Anal. Calcd for $C_8H_6Br_2O_3$: C, 31.0; H, 2.0. Found: C, 31.2; H, 2.0.

(B) With AgO. Phenol **24** (65.2 mg, 0.200 mmol), silver(II) oxide (100 mg, 0.800 mmol), and dioxane (2 mL) were stirred as 6 M HNO_3 (0.20 mL) was added in one portion. After 20 min the reaction mixture was added to chloroform/water (8 mL/2 mL). The organic layer was washed with water, dried, and evaporated to give **20** and **25** as a red solid (57.0 mg, 92%). HPLC showed the mixture to be composed of 5% **20** and 95% **25**.

(C) With HNO_3. A 15-min reaction time with 16 M HNO_3 was used. To phenol **24** (32.0 mg, 0.098 mol) was added concentrated HNO_3 (2 mL) with stirring. After 15 min the acid solution was extracted with dichloromethane (3 × 1.5 mL). The combined extract was washed with 10% $NaHCO_3$ (2 × 1.5 mL) and brine (1.5 mL), dried, and evaporated to give pure **20** as a yellow-orange solid (14.0 mg, 47%).

(D) With HNO_3 in Dichloromethane. Dichloromethane (4 mL) and concentrated HNO_3 (1 mL) were mixed rapidly for 1 h. The layers were separated, and 1.0 mL of the organic phase was added to phenol **24** (31 mg, 0.094 mmol) with stirring in dichloromethane (1.0 mL). After 10 min, water (1.0 mL) was added followed by enough 10% $NaHCO_3$ to make the aqueous layer pH 7–8. The layers were separated, and the organic phase was washed with water (1 mL). Drying and evaporating gave pure red **25** (26.0 mg, 89%).

3,4-Dibromo-2,5,6-trimethoxytoluene (26). To phenol **24** (1.00 g, 3.07 mmol) in dimethylformamide (3 mL) were added barium hydroxide (526 mg, 3.07 mmol) and methyl iodide (1.31 g, 9.21 mmol) with rapid stirring. After 10 h the reaction mixture was partitioned between water (5 mL) and chloroform (10 mL). The aqueous phase was then extracted with chloroform (2 × 4 mL), and the combined organic solution was washed with saturated Na_2CO_3 (1 × 5 mL) and brine (1 × 5 mL), dried, and evaporated to give **26**: 0.88 g (85%); R_f (SiO_2/chloroform) 0.46; mp 35–36 °C (sublimed); NMR δ 2.24 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 3.90 (s, 6 H, 2 OCH_3); IR (neat) 2924, 2849, 1555, 1449, 1387, 1374, 1305, 1233, 1196, 1110, 1059, 1013, 1008, 962, 914, 805, 784, 754 cm^{-1}; mass spectrum, m/e (relative intensity) 342, 340, 338 (M^+ for dibromo; 49.2, 100, 51.0), 325 (54.5), 297 (23.2), 282 (15.6). Anal. Calcd for $C_{10}H_{12}Br_2O_3$: C, 35.3; H, 3.6. Found: C, 35.5; H, 3.6.

Conversion of 20 to 5. To quinone **20** (750 mg, 2.42 mmol) in ether (20 mL) was added an aqueous solution of sodium dithionite (2.95 g, 16.9 mmol in 10 mL water) in one portion with rapid stirring. After 10 min the layers were separated, and solid sodium dithionite (50 mg) was added to the organic phase. The aqueous phase was extracted with ether, and the combined organic solution was dried under nitrogen. Evaporation gave **27** as an air-sensitive solid (0.703 g, 93%) which was used without further purification: R_f (SiO_2, dichloromethane) 0.48; NMR δ 2.22 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3); IR (Nujol) 3413, 2899, 2849, 1449, 1406, 1374, 1342, 1297, 1225, 1217, 1182, 1091, 1042, 1000, 834, 771 cm^{-1}. To hydroquinone **27** (200 mg, 0.641 mmol) in methanol (10 mL) was added 10% Pd/C (0.050 g). Hydrogenation (50 psi of H_2, Parr shaker) was performed for 57 h at which time the catalyst was removed by filtration. Evaporation gave crystalline **28** which was dissolved in 12.5 mL of ferric chloride/HCl solution (0.5 M $FeCl_3$ in aqueous 0.1 M HCl) and 12.5 mL of methanol. Water (50 mL) was added after 15 min, and the solution was extracted with dichloromethane (4 × 10 mL). The combined organic extract was washed with brine (10 mL), dried, and evaporated to give pure crystalline **5** (97 mg, 100%).

Addition of Pyrrolidine to Quinone 20: Synthesis of 2-Bromo-3-(1-pyrrolidinyl)-5-methyl-6-methoxy-1,4-benzoquinone (31) and 2-Bromo-3-(1-pyrrolidinyl)-5-methoxy-6-methyl-1,4-benzoquinone (32). Conversion of 10 to 11. To quinone **20** (71.6 mg, 0.231 mmol) and anhydrous potassium carbonate (95.8 mg, 0.693 mmol) in benzene (2.3 mL) was added pyrrolidine (17.2 mg, 0.242 mmol) with rapid stirring in the dark. TLC (SiO_2, dichloromethane) showed completion of the reaction in 5 min. The reaction mixture was transferred with benzene (4 mL) to a hydrogenation vessel. Hydrogenation (55 psi of H_2, 45 °C, 43 mg of 5% Pd/C) proceeded for 18 h, after which time the catalyst and salts were removed by filtration and washed with benzene, and the combined organic solution was evaporated to a crystalline mass of **10** and **11** (49.7 mg, 97%). Reverse-phase HPLC (25% CH_3CN) showed 98% **10** and 2% **11**. Compound **31** has been isolated in >90% yield by filtration and evaporation in the dark at room temperature after the amine addition step. This compound is best stored at low temperature in the dark and is best used in subsequent reactions without purification. Purification can be achieved by rapid chromatography in the dark (SiO_2, dichloromethane). For **31**: purple crystals; R_f (SiO_2, dichloromethane) 0.15–0.25; NMR δ 1.86 (s, 3 H, CH_3), 1.8 (m, 4 H, $NCH_2CH_2CH_2$), 3.87 (m, 4 H, CH_2NCH_2), 4.08 (s, 3 H, OCH_3); IR (Nujol) 1653, 1616, 1524, 1225, 1166, 1120, 1088, 1013, 820, 750, 725 cm^{-1}; mass spectrum, found m/e 299.0158 (M^+), $C_{12}H_{14}N^{79}BrO_3$ requires m/e 299.0157.

3-Bromo-4-(1-pyrrolidinyl)-5-methoxy-6-methyl-1,2-benzoquinone (33). To dibromoquinone **25** (0.0424 g, 0.137 mmol) and anhydrous potassium carbonate (38 mg, 0.274 mmol) in benzene (0.35 mL) was added pyrrolidine (10.9 mg, 0.154 mmol) in benzene (0.35 mL) with rapid stirring in the dark. After 5 h, the reaction mixture was filtered through a small pipet of silica with benzene and was evaporated in the dark to give **33** as a purple solid (41.9 mg, 102%). This material is best reacted without further manipulation as attempted removal of residual solvent led to substantial decomposition: NMR δ 1.92 (s, 3 H, CH_3), 1.9 (m, 4 H, $NCH_2CH_2CH_2$), 3.80 (s, 3 H, OCH_3), 3.94 (m, 4 H, CH_2NCH_2); IR (neat) 2976, 1672, 1623, 1493, 1441, 1355, 1333, 1255, 1218, 1172, 1096, 972, 913, 888, 870, 810, 769, 747 cm^{-1}; mass spectrum, m/e (relative intensity) 301, 303 (13.0, 12.3; as bromohydroquinone), 288 (25.0), 286 (26.3); found m/e 301.0318 (M^+), $C_{12}H_{16}{}^{79}BrO_3$ requires m/e 301.0314.

2-Bromo-3-(1-pyrrolidinyl)-5-methyl-6-hydroxy-1,4-benzoquinone (35) and 2-Hydroxy-3-methyl-5-(1-pyrrolidinyl)-1,4-benzoquinone (36). (A) From 33. To a stirred solution of dichloromethane (1.0 mL) and boron tribromide

(0.51 g, 2.0 mmol) under argon at −78 °C was added **33** (prepared from 0.290 mmol **25**) in dichloromethane (2.0 mL) dropwise over the course of 5 min. The cooling bath was removed after 10 min, and the mixture was allowed to warm to room temperature over 10.5 h. Water (10 mL) was added dropwise with rapid stirring to give a red mixture which was extracted with dichloromethane (2 × 10 mL). The combined organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried, and evaporated to give **35** and **36** as a red-brown crystalline solid (33.9 mg, 41–56% from **25** depending on degree of debromination; NMR showed ~40% **36** based on integration of ring proton singlet). Characterization data of pure **36** and the controlled conversion of **35** to **36** is reported below.

(B) From 31. Quinone **20** (160 mg, 0.52 mmol) was reacted with pyrrolidine to give **31** as described earlier, and the product was immediately dissolved in dichloromethane (3 mL) under argon. After cooling the solution to −78 °C, boron tribromide (0.80 g, 3.1 mmol) was added dropwise over the course of 1 min with rapid stirring. The cold bath was removed 10 min later, and the reaction mixture was allowed to warm while being stirred in the dark over 15 h. Water (10 mL) was added dropwise with stirring, and the red mixture was partitioned between dichloromethane (8 mL) and 10% $NaHCO_3$ (8 mL). Acidification of the aqueous layer to pH 6 with 10% HCl followed by extraction with dichloromethane gave a combined organic solution which was washed with brine (10 mL) and dried. Evaporation gave **35** and **36** as a red-brown solid (111.0 mg, 75–103% from **20**, depending on the degree of debromination; NMR showed 50% **36** based on integration of ring proton singlet). This mixture was then hydrogenated (50 psi of H_2, Parr shaker, 65 mg of 5% Pd/C) in methanol (5 mL) for 15 h at which time the methanol was removed under a stream of nitrogen, and the residue was stirred under an air atmosphere with dichloromethane (8 mL) and 10% $NaHCO_3$ (8 mL) for 5 h. Filtration, separation of layers, and acidification of the aqueous phase to pH 6–7 gave a red mixture which was extracted with dichloromethane (3 × 5 mL). The combined organic solution was washed with brine (10 mL), dried, and evaporated to give red crystalline **36**: 46.9 mg (44% from dibromoquinone **20**); mp 200–201 °C (sublimed) (lit.[2] mp 196–197 °C); NMR δ 1.87 (s, 3 H, CH_3), 1.96 (m, 4 H, $NCH_2CH_2CH_2$), 3.6 (m, 4 H, CH_2NCH_2), 5.38 (s, 1 H, quinone H); IR (Nujol) 3215, 1650, 1610, 1447, 1420, 1397, 1387, 1339, 1325, 1307, 1248, 1206, 1068, 1046, 910, 816, 807, 799, 736, 727, 710 cm^{-1}; mass spectrum, found *m/e* 207.0890 (M^+), $C_{11}H_{13}NO_3$ requires *m/e* 207.0895.

2-Methyl-3-hydroxy-5-(1-pyrrolidinyl)-1,4-benzoquinone (37). To aminoquinone **11** (7.8 mg, 0.035 mmol) in dichloromethane (1.5 mL) at −78 °C under argon and with stirring was added boron tribromide (0.020 mL, 0.21 mmol). The cold bath was removed 10 min later, and the mixture was allowed to warm to room temperature. After 3.5 h the reaction was quenched by dropwise addition of water (10 mL). The mixture was extracted with dichloromethane (8 mL), and the aqueous phase was basified to pH 6 with 10% $NaHCO_3$. Extraction with dichloromethane (2 × 7 mL) was again performed, and the combined organic phase was washed with brine, dried, and evaporated to give **37** as a purple solid (4.6 mg, 64%) after chromatography: R_f (SiO_2, ether) 0.45; NMR δ 1.92 (s, 3 H, CH_3), 1.9 (m, 4 H, $NCH_2CH_2CH_2$), 3.6 (m, 4 H, CH_2NCH_2), 5.32 (s, 1 H, quinone H); IR (neat) 3165, 2941, 1667, 1597, 1577, 1567, 1451, 1379, 1330, 1318, 1300, 1229, 1185, 1155, 1139, 1104, 1044, 997, 821, 806, 754 cm^{-1}; mass spectrum, found *m/e* 207.0895 (M^+), $C_{11}H_{13}NO_3$ requires *m/e* 207.0895.

3-Methyl-4-methoxy-5-(1-pyrrolidinyl)-1,2-benzoquinone (38). Quinone **25** (172.1 mg, 0.555 mmol) was hydrogenated (50 psi of H_2, Parr shaker, 43 mg of 10% Pd/C) in methanol (10 mL) for 29 h after which time the solution was filtered and evaporated to give **30** as an amber oil (85 mg, 100%; R_f 0.15, dichloromethane/SiO_2), which decomposes in air. Anhydrous sodium sulfate (1.5 g), ether (8 mL), and pyrrolidine (55.6 μL, 0.666 mmol) were then added with rapid stirring. Argentous oxide (772 mg, 3.33 mmol) was added in one portion, and after 12 min the mixture was filtered. The salts were washed with ether, and the combined organic solution was evaporated to give **38** as red crystals: 99.3 mg (86%); R_f (SiO_2, CH_3CN) 0.21; NMR δ 1.8 (m, 4 H, $NCH_2CH_2CH_2$), 1.97 (s, 3 H, CH_3), 3.62 (m, 4 H, CH_2NCH_2), 3.77 (s, 3 H, OCH_3), 5.41 (s, 1 H, quinone H); IR (neat) 2979, 1672, 1610, 1529, 1456, 1418, 1381, 1330, 1312, 1305, 1218, 1176, 1006, 984, 891, 820, 754 cm^{-1}; mass spectrum, found *m/e* 221.1042, 223.1197 (M^+, M + 2), $C_{12}H_{15}NO_3$ requires *m/e* 221.1052, $C_{12}H_{17}NO_3$ (hydroquinone) requires *m/e* 223.1208.

2-Hydroxy-3-methyl-5-(1-pyrrolidinyl)-1,4-benzoquinone (36) from 38. Aminoquinone **38** (7.3 mg, 0.033 mmol) could be converted to **36** (3.3 mg, 48%) by the same procedure used to convert **11** to **37**.

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Synthesis and Stereochemistry of 3,5-Bis(carbomethoxy)-2,6-diphenyltetrahydro-4*H*-thiopyran-4-ones and Derivatives

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3,5-Bis(carbomethoxy)-2,6-diphenyl-4*H*-thiopyran-4-one (**2**) and its 5,6-*trans*-dihydro derivative **14** were synthesized by dehydrogenation with active manganese dioxide in refluxing chloroform of the corresponding diastereoisomeric mixture of *cis*- and *trans*-2,6-diphenyltetrahydro compounds **5** and **6**. The latter were prepared by the addition of hydrogen sulfide to dimethyl dibenzalacetonedicarboxylate (**4**). The stereochemistry and the reaction with *N*-chlorosuccinimide (NCS) of the diastereoisomers **5** and **6** and their corresponding sulfoxides **11** and **8** are elucidated. NCS reacted at the active methylene position in preference to the sulfide or sulfoxide function.

In connection with our interest in the synthesis of tetraphenyl-$\Delta^{4,4'}$-4*H*-heterobipyrans (**1**, X and Y = O and S),[1,2] we desired an efficient synthesis of the hitherto unknown 3,5-bis(carbomethoxy)-2,6-diphenyl-4*H*-thiopyran-4-one

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