When the MeOH solution of the neutral covalent adduct (λ_{max} 268 nm) reacts with methoxide ion, two subsequent UV spectrophotometric changes are detected. At first an absorbance decrease for the adduct is observed together with an increase in the 310–320-nm range where 1 absorbs. At the end of this primary process the UV spectrum is very similar to that observed at the end of the primary interaction between 1 and methoxide ion (Figure 1). The following spectrophotometric change is identical with that reported in Figure 2, and corresponds to the eventual formation of the substitution product 2.

The reversible covalent "solvation" of C=N bonds of nitrogen heteroaromatic compounds,[10] and notably of quinazoline compounds,[8] has been well described in water and has also been reported in other protic solvents, such as alcohols. No reference has been given so far to the possible role of covalent "solvation" adducts in the course of nucleophilic aromatic substitution, if exception is made for the reaction of 6,7-dihalogenopteridines with H_2O.[11] However, in the latter reaction the site of attachment of the OH group in the neutral covalent adduct (C-4) is different from the site involved in the hydroxy dehalogenation reaction (C-7). The formation and the isolation of a neutral covalent adduct under nonacidic conditions is not common. A well-known example is given by the reaction of 4-(trimethylammonium)quinazoline in water.[12] The latter substrate is similar to 1 because of the presence of a substituent with strong electron-withdrawing power and relatively poor leaving group ability.

Experimental Section

Melting points are uncorrected. UV spectra were recorded on a Cary Model 219 instrument. ^{1}H NMR spectra were obtained with a Bruker WP 80 SY instrument, unless otherwise stated. Mass spectra were obtained with a Kratos MS 80 spectrometer.

4-(Trichloromethyl)quinazoline (1) was prepared according to a method similar to that reported for the preparation of 2-(tribromomethyl)quinoline.[13] A 2.16 N solution of Cl_2 in AcOH (22 mL, 24 mmol) was added in 10 min to 70 mL of an AcOH solution of 4-methylquinazoline (1 g, 7 mmol) and anhydrous sodium acetate (3.6 g, 44 mmol) kept at 70 °C. The reaction mixture was further heated at 90–95 °C for a few minutes, and again at 70 °C for 30 min. The cold reaction mixture was poured into ice water, and the resulting solid was collected by filtration and purified by chromatography (silica gel, benzene) to give 1.4 g of a yellowish product: mp (petroleum ether 40–70 °C) 91–91.5 °C; ^{1}H NMR (CD_3OD) δ 7.7–8.3 (m, 3 H, H6–H8), 8.83 (two multiplets, 1 H, H-5), 9.33 (s, 1 H, H-2); UV (MeOH) λ_{max} 315 (ϵ 3950), 233 nm (ϵ 29 160); mass spectrum, calcd for $C_9H_5N_2Cl_3$ (M^+, $^{35}Cl_3$) m/e 245.952 05, found 245.9517; yield 82%.

Reaction of 4-(Trichloromethyl)quinazoline (1) with Methoxide Ion. Compound 1 (0.2 g, 0.81 mmol) was dissolved in 10 mL of MeOH, and 1.18 mmol of sodium methoxide was added at 25 °C. The TLC analysis (silica gel, benzene–ethyl acetate 1:1) showed that after 10 min the concentration of 1 had decreased and two compounds had formed with R_f values 0.32 and 0.06, respectively. However, after 5 h only the compound with R_f 0.32 was present, whereas the substrate and the compound with R_f 0.06, corresponding (TLC) to the covalent adduct 4 were absent.

The reaction mixture was neutralized with HCl and poured into water. The resulting solution was continuously extracted with ether for 16 h. The ether solution was dried. Removal of the solvent left a yellow oily residue (125 mg) that was identified as 4-methoxyquinazoline[14] (yield 97%).

Covalent Adduct between 1 and MeOH. CF_3COOH (0.50 mL, 6.5 mmol) was added at room temperature to a methanol solution of 1 (0.30 g, 1.2 mmol in 15 mL). The reaction was followed by TLC (silica gel, benzene–ethyl acetate 1:1). After 2 h, when compound 1 was absent and one product only was detected, the reaction mixture was poured into 100 mL of water containing 6.5 mmol of NaOH to yield a white solid. The ether solution of the latter was mixed with the ether extract (a TLC analysis showed the presence of 1 in both the ether solutions), and the resulting solution was washed with water and dried. The residue, after evaporation, was subjected to column chromatography (silica gel, benzene–ethyl acetate 1:1). After the elution of compound 1 (0.2 g), the covalent adduct was collected (95 mg): mp (washed with petroleum ether 40–70 °C) 110–111 °C; ^{1}H NMR (CD_3OD) (see Figure 3e); UV (CH_3OH) λ_{max} 268 nm; mass spectrum, calcd for $C_{10}H_9N_2OCl_3$ (M^+, $^{35}Cl_3$) m/e 277.978 27, found 277.9781; yield 28% (the small yield contrasts with the complete conversion of 1 into 4; this fact is related to the partial return of 4 into 1 during the workup).

Registry No. 1, 99356-81-7; 4-methoxyquinazoline, 16347-95-8; 4-methylquinazoline, 700-46-9.

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Dimethyl Benzoquinone-2,5-dicarboxylate

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Of the three possible isomeric dimethyl benzoquinonedicarboxylates, only the 2,3-isomer has been described in the literature.[1] We now report the synthesis and characterization of the 2,5-isomer.

Results and Discussion

Dimethyl 1,4-dioxocyclohexane-2,5-dicarboxylate (2), which is commercially available (Aldrich), exists exclusively in the enol form. The strong hydrogen bonding between the enol and the ester carbonyl function, shown by the lack of a hydroxyl absorption in the infrared spectrum, results in a planar structure, as proven by X-ray crystal structure determination.[2] Hydrogen bonding is the reason for the extreme reaction conditions necessary to transesterify this diester.[3]

This hydrogen bonding also results in remarkable resistance to oxidation. Although many oxidation methods were investigated on this compound, only activated manganese dioxide[4] in toluene cleanly oxidized this material. However, curiously only the hydroquinone derivative, dimethyl hydroquinone-2,5-dicarboxylate (3), was the product. This compound also shows a weak absorption for the hydroxyl group in the infrared spectrum. The lowered frequency, 3250 cm^{-1}, is indicative of intramolecular chelation with the carbonyl group, whose absorption frequency is also remarkably low (1680 cm^{-1}).

Again numerous oxidation procedures were attempted in order to further oxidize this hydroquinone derivative to the desired dimethyl benzoquinone-2,5-dicarboxylate (1). Among these methods were the following: nitrogen oxides, lead tetraacetate, persulfate, ceric ammonium nitrate, etc., which all resulted in decomposition or no re-

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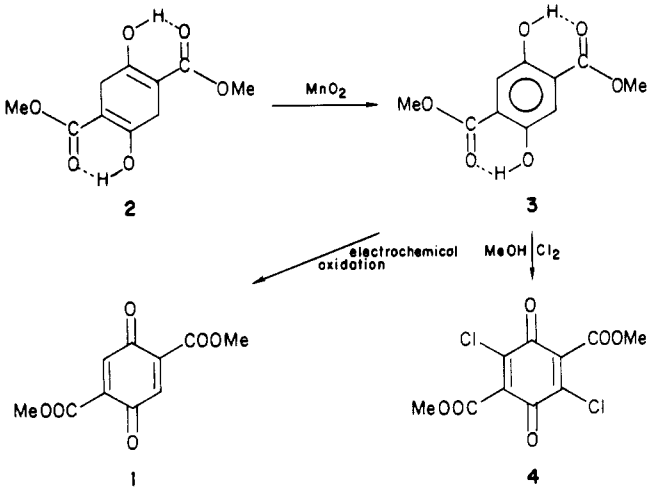
Table I. Reduction Potentials and CT Absorption Maxima with Donors for the Electrophilic Benzoquinones

benzoquinone derivative	E_p[a],V	CT-absorption maxima of EDA complexes[b], λ_{max} (ϵ)			
		HMB	DEA	ECZ	TTF
2,5-dicarbomethoxy (1)	−0.6	–	–	385 (500)	363 (23200), 340 (29000)
2,3-dicarbomethoxy (6)	−0.6	–	–	380 (300)	365 (23200), 336 (29000)
2,5-dichloro-3,6-dicarbomethoxy (4)	−0.3	374 (4700)	425 (3600)	380 (4600)	364 (26600), 340 (29600)

[a] Reduction potentials measured by cyclic voltammetry in acetonitrile at room temperature. [b] Ultraviolet spectra measured in dichloromethane at room temperature: [benzoquinone] = 10^{-4} M, [donor] = 10^{-3} M; donors: HMB = hexamethylbenzene, DEA = *N,N*-diethylaniline, ECZ = *N*-ethylcarbazole, TTF = tetrathiofulvalene, λ_{max} in nm, ϵ = absorbance.

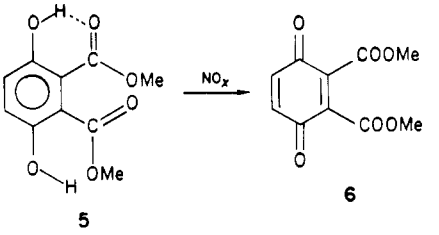
action. Oxidation of the hydroquinone derivative **3** with chlorine gas in methanol at room temperature proceeds



to dimethyl 2,5-dichlorobenzoquinone-3,6-dicarboxylate (**4**) as already reported.[5] We postulate that the strong hydrogen bonding in dimethyl hydroquinone-2,5-dicarboxylate (**3**) is the cause for its reluctance to react with oxidants. Finally, recourse was had to electrochemical oxidation to synthesize **1**.

The oxidation potential of dimethyl hydroquinone-2,5-dicarboxylate (**3**) was measured by cyclic voltammetry in acetonitrile as 1.17 V, which is not excessively high. Preparative electrochemical oxidation of **3** was then performed at a platinum anode in a three-compartment cell equipped with an SCE reference electrode and a graphite cathode at 1.5 V. The solvent was aqueous acetonitrile with tetramethylammonium tetrafluoroborate as supporting electrolyte. In the absence of a base, a mixture of products is obtained, but in the presence of 1.5 equiv of 2,6-di-*tert*-butylpyridine the oxidation proceeds smoothly to give **1** in low yield (10%). Despite reported instability of related compounds,[1,6,7] **1**, once formed, is reasonably stable.

Dimethyl benzoquinone-2,3-dicarboxylate (**6**), a reference compound, was prepared by oxidation[1] with nitrogen oxides from the corresponding hydroquinone derivative **5**. This oxidation proceeds smoothly. A molecular model shows that molecule **5** is planar and that only one carbonyl group is hydrogen bonded. Two carbonyl absorptions are observed in the infrared spectrum, one at 1726 cm^{-1} for the free carbonyl group and one at 1680 cm^{-1} for the chelated one.



In order to characterize the electron-accepting character of dimethyl benzoquinonedicarboxylates, we measured the reduction potentials of the 2,5-isomer **1**, the 2,3-isomer **6**, and the dichloro derivative **4**, and also the CT-absorption maxima of their EDA complexes with different donors. These data are summarized in Table I. The reduction potentials showed that dimethyl 2,5-dichlorobenzoquinone-3,6-dicarboxylate (**4**) is more electrophilic than **1** and **6**, which are equal within the experimental error, despite the presumed planarity of **1**. The information obtained from the EDA complexes with such donors as *N,N*-diethylaniline, hexamethylbenzene, *N*-ethylcarbazole, and tetrathiofulvalene was in agreement, namely, that the dichloro derivative **4** is more electrophilic than either **1** or **6**. The electrophilicity of **1** was not especially great, in keeping with the ease of oxidation of the corresponding hydroquinone in cyclic voltammetry.

Experimental Section

General Methods. Melting points are uncorrected and determined on a Mel-Temp melting point apparatus. Nuclear magnetic resonance spectra were recorded on a Varian EM-360 instrument, infrared spectra on a Perkin-Elmer Model 983 spectrometer; and ultraviolet spectra on a Perkin-Elmer Model 552 spectrometer. Chemical analyses were performed by Micanal, Tucson, AZ.

Cyclic voltammetry was carried out on a Bioanalytical Systems potentiostat in conjunction with a BAS cyclic voltammograph CV-1B with a scan rate of 50 mV/s in aqueous acetonitrile vs. $Ag/AgNO_3$.

The preparative electrochemical oxidations were carried out on an ECO 551 potentiostat and a Par 379 digital coulometer. The electrolysis cell was a three compartment H-type cell with medium porosity glass frits as cell-dividers, equipped with a magnetic stirrer, a $Ag/AgNO_3$ (0.1 M in acetonitrile) electrode as a reference electrode, a graphite cathode, and a platinum electrode.

Acetonitrile was purified by distillation. Activated manganese dioxide was prepared from potassium permanganate and manganous chloride.[4]

Dimethyl Hydroquinone-2,5-dicarboxylate (3). Dimethyl 1,4-dioxocyclohexane-2,5-dicarboxylate (Aldrich) (2.5 g, 20 mmol) was dissolved in 60 mL of refluxing toluene. Activated manganese dioxide (10 g, excess) was added, and the mixture was refluxed for an additional 30 min and filtered hot. The solids were washed with hot toluene. These green crystals were recrystallized from

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benzene and dried: mp 173 °C, yield 40%; NMR (Me_2SO-d_6) 7.3 (s, 1 H), 3.9 (s, 3 H) ppm; IR (KBr) 3250, 1680, 1500, 1440, 1330, 1200, 1100, 960 cm^{-1}. Anal. Calcd: C, 53.10; H, 4.46. Found: C, 53.04; H, 4.45.

Dimethyl Benzoquinone-2,5-dicarboxylate (1). Dimethyl hydroquinone-2,5-dicarboxylate (**3**) (300 mg, 1.3 mmol) was oxidized in aqueous acetonitrile containing 1.5 equiv of 2,6-di-*tert*-butylpyridine with tetramethylammonium tetrafluoroborate as supporting electrolyte at 1.5 V vs. $Ag/AgNO_3$. After the anodic current dropped to a negligible value, the acetonitrile was evaporated at room temperature which dissolved the organic products and 2,6-di-*tert*-butylpyridinium salts, and the remaining solids were extracted with dichloromethane. Addition of ether precipitated the salts. After rotary evaporation of the filtrate and recrystallization from a dichloromethane/ether mixture at low temperature, orange crystals were obtained: mp 130 °C (yield 30 mg, 10%); NMR ($CDCl_3$) 7.05 (s, 2 H), 3.8 (s, 6 H) ppm; IR (KBr) 3055, 1712, 1666, 1436, 1350, 1271 cm^{-1}; UV (CH_2Cl_2) λ_{max} 255 (3000) nm. Anal. Calcd: C, 53.38; H, 3.60. Found: C, 53.28; H, 3.47.

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Synthesis of the Enantiomers of Nornicotine

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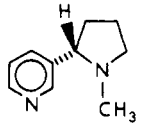
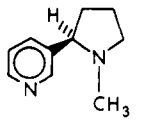
In the last few years, significant effort has been expended toward the preparation of the enantiomers of nicotine, **1** and **2**, often with the concomitant goal of high



1, (S)-(-)-nicotine

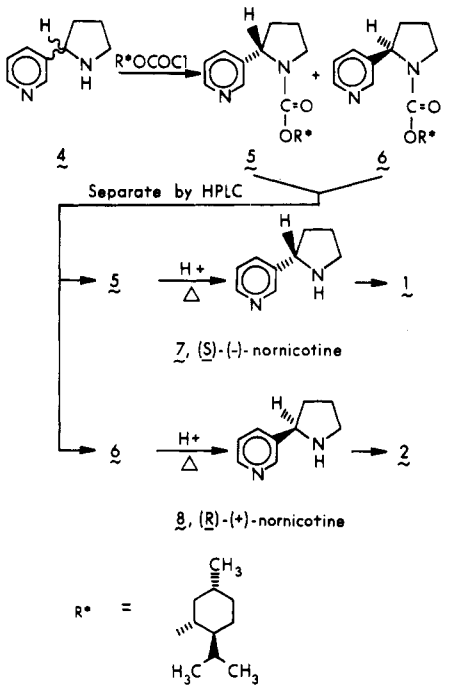


2, (R)-(+)-nicotine

tritium incorporation and high optical purity.[1-4] The preparation of optically pure (*S*)-[^{3}H]nicotine of moderate incorporation (ca. 5–10 Ci/mmol) by tritium reduction of optically pure cotinine dibromide (**3**) has recently been reported.[1] (*R,S*)-[*N-methyl*-^{3}H]Nicotine of high specific activity (>20 Ci/mmol), prepared by the reaction of [^{3}H]iodomethane with (*R,S*)-nornicotine is now available commercially.[5]

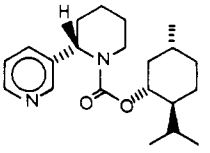
Based on the successful transformation of (*R,S*)-nornicotine to (*R,S*)-[*N-methyl*-^{3}H]nicotine having high specific activity via methylation with [^{3}H]iodomethane,[5,6] we focused our attention toward the development of a general procedure for the preparation of the enantiomers of nornicotine (**7** and **8**).[3] Our successful strategy is illustrated in Scheme I. It depends on the preparative scale formation, separation, and purification of the diastereomeric urethanes **5** and **6**, followed by the hydrolysis of these optically pure urethane diastereomers into their corresponding nornicotine enantiomers **7** and **8** *without* racemization.

Scheme I

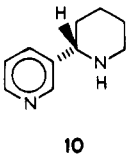


The preparation of mixture **5** + **6** from (*R,S*)-nornicotine (**4**) was straightforward and proceeded in high yields by treatment of (*R,S*)-nornicotine[6] with optically pure (–)-menthyl chloroformate. Following much experimentation, we found that the *N'*-(menthoxycarbonyl)nornicotine diastereomers **5** and **6** could be best separated (base-line separation) on a preparative scale using a Whatman Partisil 10, Magnum 20 column with a hexane/acetone/triethylamine (89:11:3) solvent mixture and standard high performance liquid chromatography (HPLC) techniques, as described in detail in the Experimental Section. The HPLC separations were followed by capillary GC analysis and fractions containing urethanes of >99.8% purity were combined for subsequent acid hydrolysis.

Rather than experiment with various hydrolysis conditions with the precious optically active *N'*-(menthoxycarbonyl)nornicotine, we prepared the analogous urethanes **9**[7] from commercially available, optically active (*S*)-(–)-



9



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