Nucleophilic Substitutions Initiated by Electrochemical Oxidation. II. Substitution of a *tert*-Butyl Group in 2,4,6-Tri-*tert*-butylphenol by Pyridine

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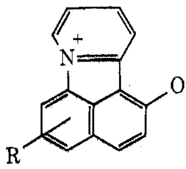
The electrochemical oxidation at controlled potential of 2,4,6-tri-*tert*-butylphenol (2) in the presence of pyridine affords 1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)pyridinium perchlorate (8) and 1-(1,3,5-tri-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-yl)pyridinium perchlorate (9) in a molar ratio of 2:1. Treatment of 8 with 0.1 *N* aqueous base leads to the formation of a novel dark blue phenol betaine (10). The solvatochromic and thermochromic long-wavelength absorption of 10 is shown to be due to an intramolecular charge-transfer band.

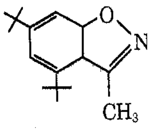
Recently we reported the intramolecular displacement of a *tert*-butyl group by pyridine in derivatives of 8-*tert*-butyl-1-(2-pyridyl)-2-naphthols. The mechanism of this reaction was proposed[1] to be an ECE sequence wherein the nucleophile pyridine attacks carbon atom 8 of the naphthalene moiety after the loss of two electrons and one proton from the starting molecule.

The resulting cationic species eliminated the *tert*-butyl group slowly to form a naphthol perchlorate, which, upon treatment with aqueous base, is converted into a naphthol betaine (1).[1,2]



1

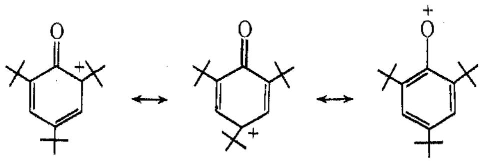
We now report the preparation of a phenol betaine through *intermolecular* nucleophilic displacement of a *tert*-butyl group on 2,4,6-tri-*tert*-butylphenol (2) by pyridine. The electrochemical oxidation of 2,4,6-tri-*tert*-butylphenol in acetonitrile was recently reported to proceed with the exchange of 2 faradays of current per mole of starting material when the base α-lutidine was present in solution. In the presence of the nucleophiles, water, methanol, and acetate ion, the corresponding cyclohexadienone derivatives were isolated in high yields.[3,4] In an earlier note[5] the preparation of 3-methyl-5,7-di-*tert*-butyl-1,2-benzisoxazole (3) through electrochemical oxidation of 2, 4,6-tri-*tert*-butylphenol in acetonitrile was described.



3

Acetonitrile was considered to react as a nucleophile in the course of this reaction with the intermediate 2,4,6-tri-*tert*-butylphenoxylium ion (4).

Pyridine appeared to be a promising nucleophile in these reactions for the electrochemical preparation of substituted arenol betaines.



4

Cyclic voltammetric scans of 2,4,6-tri-*tert*-butylphenol (2) in an anhydrous acetonitrile–tetrabutylammonium perchlorate medium show one irreversible response at +1.46 V. No cathodic response can be detected for 2 if the scan is started at 0.0 V. However, if the scan is begun at a potential corresponding to the diffusion plateau of the oxidation response, a reductive response is observed at −0.10 V. This response can be attributed to the reduction of protons which have been generated through oxidation of 2. Voltammetric scans of 2 in a 1:1 acetonitrile–pyridine mixture using a graphite anode show an irreversible response at +1.26 V, and a broad irreversible response at −1.20 V when the scan is started at a potential corresponding to the diffusion plateau of the oxidation response. Comparison of the peak current of the cyclic voltammetric response of 2 with 9,10-diphenylanthracene showed that at a scan rate of 0.1 V/sec the oxidation response of 2 corresponds to the exchange of approximately two electrons per molecule of starting material. However, coulometric oxidation at a potential corresponding to the diffusion plateau of the oxidation response of 2 proceeded in general with the exchange of approximately four electrons per molecule of substrate. The addition of a base like pyridine or α-lutidine led to a two-electron process for the oxidation response of 2 in these media.

Macroelectrolyses have been performed on a gram scale at potentials corresponding to the diffusion plateau of the oxidation response of 2. The oxidations were continued until the current had decayed to approximately 5% of its original value.

When the oxidation of 2 was performed in an anhydrous acetonitrile–sodium perchlorate medium at room temperature, 2,6-di-*tert*-butyl-*p*-benzoquinone (5) and *tert*-butylacetamide (6) were isolated from the reaction mixture in approximately 80 and 39% yield, respectively. Approximately 4–5 faradays were exchanged per mole of starting material. It was found that the nature of the isolated products depended on the acetonitrile used. In cases where acetonitrile from Burdick and Jackson was used as a solvent, 2-methyl-5,7-di-*tert*-butylbenzoxazole (7) was isolated in approximately 2% yield from the reaction mixture

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[1] G. Popp, *J. Org. Chem.*, **37**, 3058 (1972).

[2] D. L. Fields and T. H. Regan, *J. Org. Chem.*, **36**, 2986 (1971).

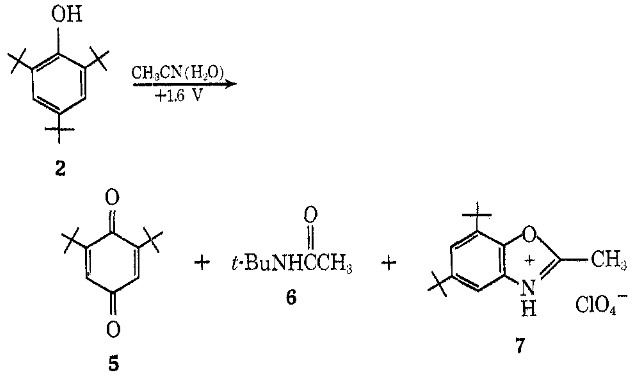
[3] V. D. Parker and A. Ronlán, *J. Electroanal. Chem.*, **30**, 502 (1971).

[4] A. Ronlán and V. D. Parker, *J. Chem. Soc. C*, 3214 (1971).

[5] A. B. Suttie, *Tetrahedron Lett.*, 953 (1969).

as its perchlorate salt, in addition to **5** and **6** (Scheme I). The oxidation proceeded in these cases with the exchange of approximately 2–3 faradays per mole of **2**.

SCHEME I

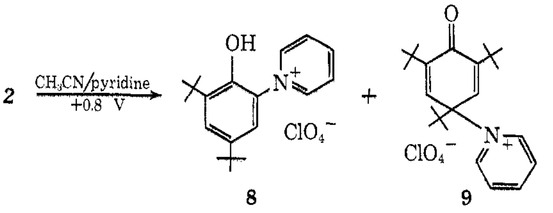


Thus far we have not been able to determine the reasons for the formation of the benzoxazole **7** in acetonitrile from Burdick and Jackson. Although it contained approximately the same amounts of water by Karl Fischer titration) and acid impurities as acetonitrile from Burdick and Jackson, acetonitrile, X-488 from Eastman Organic Chemicals, in no case competed effectively with traces of water to form the benzoxazole, even when solvent and supporting electrolyte were dried carefully before use and the reaction was carried out in an atmosphere of dry nitrogen.

Cyclic voltammetric studies together with coulometric experiments and product characterization of macroelectrolyses have shown that **2** in aprotic solvents is oxidized in a two-electron process to a cationic species that can react with nucleophiles present in solution.[3–5] With water as nucleophile, 2,4,6-tri-*tert*-butyl-4-hydroxycyclohexadienone is formed, which decomposes in the presence of acids to give the corresponding 2,6-di-*tert*-butylhydroquinone. This, in turn, is further oxidized to 2,6-di-*tert*-butyl-*p*-benzoquinone. The leaving group of the acid-catalyzed decomposition of the cyclohexadienone derivative is *tert*-butyl cation, which reacts under these conditions with acetonitrile and water in a Ritter reaction[6] to give *tert*-butylacetamide (**6**). The electrochemical oxidation of 8-*tert*-butyl-1-(2-pyridyl)naphthalenes in the presence of pyridine has shown earlier[1] that vinylogs of *tert*-butylcyclohexadienones are also stable only in basic media. Since carbon atoms 2, 4, and 6 of compound **2** are sterically hindered toward attack by a nucleophile, the choice of base becomes decisive for the course of the reaction. Ronlán and Parker[3,4] have shown that sterically hindered bases like α-lutidine act strictly as proton acceptors, whereas nucleophiles like water, methanol, or acetate ion attack preferentially carbon atom 4 of compound **2**. Although HMO calculations have predicted[4] an even distribution of the positive charge of the phenoxylium ion between carbon atoms 2, 4, and 6, so far there has been no case reported where product arises from attack by the nucleophile in the 2 position. We have observed that pyridine as nucleophile attacks the phenoxylium ion intermediate in the 2 and 4 position to give **8** and **9** in approximately the same product distribution, as predicted by the theory.[4]

The oxidation of **2** in a 1:1 mixture of acetonitrile (Eastman Organic Chemicals X-488)–pyridine on a graphite electrode at 5–10° yielded initially a mixture of 1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)pyridinium perchlorate (**8**) and 1-(1,3,5-tri-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-yl)pyridinium perchlorate (**9**) in 44 and 23% yield, respectively (Scheme II). In addition, a brown tarry material was isolated from the product mixtures. However, attempts to elucidate the chemical nature of this material were frustrated by its resistance toward further purification. No indication was found for the formation of compounds **5** and **6**. Since the unprotonated form of **8**, the zwitterion **10**, is oxidized further at a potential of +0.46 V, we feel that the tarry material may arise from further oxidation of **10** which had been incompletely protonated during the reaction.

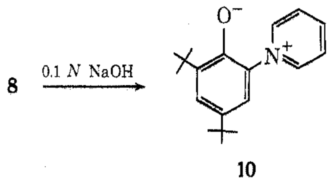
SCHEME II



The detailed mechanism of the overall reaction involves the generation of a phenoxylium ion through the loss of two electrons and one proton from **2**. The question whether deprotonation occurs after the loss of the first (ECE mechanism) or second electron (EEC mechanism) has been discussed in great detail by others[3,4] and our data at present also do not allow differentiation between the two mechanisms. In general, proton transfer reactions are held to be very rapid, and therefore an ECE step appears plausible. However, several cases have been reported where proton transfer from a cationic species appeared to be slow on the time scale of voltammetric experiments.[7–9] We are currently studying the voltammetric oxidation of 5-hydroxy-8-*tert*-butylanthracene, the cation radical of which also deprotonates only slowly.

Compound **8** can be converted easily to the red phenol betaine **10** on treatment with 0.1 *N* aqueous sodium hydroxide (Scheme III). Under these conditions compound **9** remains unchanged.

SCHEME III



The structures of compounds **8**, **9**, and **10** have been confirmed by elemental analysis, ^1H nuclear magnetic resonance spectra, mass spectra, and infrared spectra.

Phenol betaine **10** is a new member of a class of compounds which has been investigated earlier by

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[6] L. Eberson and K. Nyberg, *Acta Chem. Scand.*, **18**, 1567 (1964).

[7] A. M. F. Marcus and M. D. Hawley, *Biochem. Biophys. Acta*, **201**, 1 (1970).

[8] A. Ronlán and V. D. Parker, *Chem. Commun.*, 1567 (1970).

[9] V. D. Parker, *J. Amer. Chem. Soc.*, **91**, 5380 (1969).

Dilthey and Dierichs,[10] Schneider, *et al.*,[11] and in great detail by Dimroth, *et al.*[12] Similarly to Dimroth's experience with phenol betaines, **10** always contained water and it can be obtained in the form of dark blue, water-free crystals only in a high-vacuum system. As soon as the compound is exposed to air the color changes from dark blue to red. Elemental analysis shows that the blue form of **10** is water-free, whereas the red species is a monohydrate. Like other phenol betaines,[13] **10** exhibits remarkable solvatochromic and thermochromic properties.

Spectroscopic analysis of **10** in solvents of different polarities, according to Kosower's[14] and Dimroth's[13,15] proposals, shows that the long-wavelength absorption is due to an intramolecular charge-transfer band. The temperature sensitivity[16] of this charge-transfer band of **10** in diethyl ether has been determined to be $d\tilde{\nu}_{\max}/d(1/T) = 8.62 \times 10^{-3}\ \mathrm{cm}^{-1}\ {}^\circ\mathrm{K}$.

To our knowledge, phenol betaines so far have been prepared only through reaction of pyrylium salts with aminophenols.[11-13] Since this method excludes the preparation of phenol betaines with an unsubstituted pyridine moiety, it appears that the chemical and electrochemical methods complement each other ideally. Further work on the scope and limitation of these electrochemical reactions is in progress and will be reported elsewhere.

Experimental Section

Apparatus.—Cyclic voltammetric experiments were performed in a conventional three-electrode cell with an Electrochemistry System Model 170 from the Princeton Applied Research Corp. All potentials are referred to an aqueous saturated sodium chloride calomel reference electrode (ssce). If not mentioned otherwise, all voltammetric scan rates refer to 0.1 V/sec.

Controlled-potential coulometry and preparative oxidations were carried out in conventional two-compartment cells at platinum working electrodes. The potentiostat was either the Model 170 from Princeton Applied Research Corp. or a Model AS100 from Tacussel Electronique.

^{1}H nuclear magnetic resonance spectroscopy was performed with a Varian A-60 instrument, mass spectroscopy was performed with the Hitachi RMS-4 spectrometer, and uv-visible and ir spectra were obtained with the Cary Model 14 and Perkin-Elmer Model 137 instruments, respectively.

Materials.—2,4,6-Tri-*tert*-butylphenol (TTBP) (Aldrich T4940-9) was purified by recrystallization from hot isopropyl alcohol, mp 129–130°. Acetonitrile (Eastman Organic Chemicals X-488 and Burdick and Jackson) and pyridine (Eastman Organic Chemicals ACS) were dried over 4-Å molecular sieves. Sodium perchlorate (G. F. Smith) and tetrabutylammonium perchlorate (Eastman Organic Chemicals) were used as obtained.

Controlled Potential Oxidation of 2,4,6-TTBP in Acetonitrile–Pyridine.—A 50% acetonitrile–pyridine solution (150 ml) of sodium perchlorate (0.5 *M*) and 2,4,6-TTBP (3.13 g, 1.19 × 10^{-2} mol) was oxidized at 10° at a graphite wool electrode (6 × 6 × 0.6 cm) fitted over a platinum screen maintained at a potential of 0.80 V. The catholyte solution consisted of sodium perchlorate (0.5 *M*) in 50% pyridine–acetonitrile. After 1.3 hr, 2.52 × 10^{-2} faradays (2.1 electrons/molecule) had been passed.

After most of the liquid had evaporated from the reaction mixture, addition of water slowly precipitated a white solid, mp 193–195°. Nmr analysis of this solid (2.9 g) showed it to consist of a 60:40 mixture of **8** and **9**. This solid was extracted into ether–water. The portion that did not dissolve in either was filtered and recrystallized from hot chloroform to yield white needles of **9**. The water layers from this extraction were combined and the water was evaporated, leaving the white solid **7**, which was not purified further. The aqueous filtrate from the reaction mixture was extracted first with ether and then with dichloromethane. The dichloromethane extracts were rinsed with water and evaporated under high vacuum. A mixture (0.256 g) of **8** and **10** precipitated upon the addition of a small volume of water. The overall yields of **8** and **9** were 44 and 23%, respectively.

Compound **8** had ^{1}H nmr spectrum (60 MHz, deuterioacetonitrile) δ 1.33 (9 H, s, *tert*-butyl protons), 1.45 (9 H, s, *tert*-butyl protons), 7.32 (1 H, d, aromatic proton), 7.61 (1 H, d, aromatic proton), 7.9–8.9 (5 H, pyridine protons); ir (KBr pellet) 3400 (broad, s), 2940 (m), 1620 (s), 1450 (m), 1100 (broad, s), 880 (w), 779 (w), 670 cm^{-1} (m).

Anal. Calcd for $C_{19}H_{26}ClNO_5$: C, 59.5; H, 6.8; N, 3.6; Cl, 9.3. Found: C, 58.7; H, 6.2; N, 3.6; Cl, 9.3.

Compound **9** had ^{1}H nmr spectrum (60 MHz, acetonitrile) δ 1.11 (9 H, s, protons of *tert*-butyl group on C-4), 1.32 (18 H, s, *tert*-butyl protons), 7.30 (2 H, s, ring proton), 7.0–8.0 (5 H, pyridinium protons); ir 5400 (broad, w), 2930 (m), 1650 (m), 1625 (w), 1600 (w), 1450 (m), 1350 (m), 1090 (broad, s), 684 cm^{-1} (w).

Anal. Calcd for $C_{23}H_{34}ClNO_5$: C, 62.8; H, 7.7; N, 3.2; Cl, 8.3. Found: C, 62.9; H, 7.8; N, 3.1; Cl, 8.3.

Based on these spectral and analytical data, compounds **8** and **9** were assigned the following structure, respectively, 1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)pyridinium perchlorate and 1-(1,3,5-tri-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-yl)pyridinium perchlorate.

Phenol Betaine 10.—The addition of aqueous sodium hydroxide (0.1 *N*) to an aqueous solution of **5** (0.115 g, 0.30 mmol) resulted in the formation of red needles of **7** (0.060 g, 0.20 mmol, 65%) in the monohydrate form. Under high vacuum, the orange-red color changes to dark blue: mass spectrum *m/e* 283 (M$^+$), 268, 252, 241, 240, 80; ir (KBr pellet) 3500 (broad, m), 2990 (s), 1620 (w), 1460 (s), 1440 (s), 1420 (s), 1395 (m), 1340 (m), 1310 (s), 1260 (m), 825 (m), 782 (m), 735 cm^{-1} (m); ^{1}H nmr (60 mHz, deuterioacetonitrile) δ 1.26 (9 H, s, *tert*-butyl protons), 1.37 (9 H, s, *tert*-butyl protons), 7.02 (1 H, d, ring proton), 7.23 (1 H, d, aromatic proton), 7.75–9.00 (5 H, pyridine protons); uv and visible max. (acetonitrile) 532 mμ (ε 3.7 × 10^3), 303 (7.8 × 10^3), 254 (1.5 × 10^4).

Anal. Calcd for $C_{19}H_{25}NO$ (**7**): C, 80.5; H, 8.8; N, 4.9. Found: C, 80.3; H, 9.0; N, 4.9.

Controlled Potential Oxidation of 2,4,6-TTBP in Acetonitrile.—2,4,6-TTBP (1.0 g, 3.85 × 10^{-3} mol), dissolved in an acetonitrile (Eastman Organic Chemicals X-488) solution of sodium perchlorate (0.5 *M*) was oxidized at 1.60 V on a platinum screen. After 0.50 hr, the current had decayed to 2% of the original value and 2.07 × 10^{-2} faradays (5.4 electrons/molecule) had been consumed.

Upon evaporation of the acetonitrile, a yellow solid residue remained and was shaken in water. A pale yellow solid (0.681 g, 3.1 × 10^{-3} *M*, 80%) was filtered and recrystallized from ethanol–water as yellow needles, mp 65.5–66.0° (lit.[17] mp 67.5–68.5°) and identified as 2,6-di-*tert*-butyl-1,4-benzoquinone (**5**). The aqueous filtrate was extracted with dichloromethane. After drying and evaporation of this solvent, a solid (0.171 g, 1.62 × 10^{-3} mol, 39%) was isolated. Recrystallization from hexane afforded white needles, mp 95.0–95.5° (lit.[18] mp 98°), which were identified as *tert*-butylacetamide (**6**).

Registry No.—2, 732-26-3; **8**, 35889-93-1; **9**, 35889-94-2; **10**, 35889-95-3; pyridine, 110-86-1.

Acknowledgments.—We wish to thank Mr. D. P. Maier for supplying the mass spectral data and Mr. R. L. Young for recording and interpreting ^{1}H nuclear magnetic resonance spectra.

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[18] C. Cook, R. Woodworth, and P. Fianu, *J. Amer. Chem. Soc.*, **78**, 4159 (1956).