

[Chem. Pharm. Bull.]
30(10)3786-3790(1982)

Anodic Pyridination of 2,6-Di-*tert*-butyl-4-methylphenol

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(Received April 2, 1982)

Anodic pyridination of 2,6-di-*tert*-butyl-4-methylphenol (**1**) in acetonitrile gave the corresponding 4-pyridinated cyclohexadienone and the side-chain pyridinated phenol. The yield of the former dienone decreased and that of the latter product increased with increase in the amount of added bases, pyridine and/or 2,6-lutidine. On the other hand, the product distribution in the methoxylation of **1** in methanol or in acetonitrile containing methanol was little affected by the addition of 2,6-lutidine, and 4-methoxylated dienone was the main product.

Keywords—2,6-di-*tert*-butyl-4-methylphenol; controlled potential electrolysis; anodic pyridination; anodic methoxylation; cyclohexadienones

Anodic oxidation of 2,6-di-*tert*-butyl-4-methylphenol (**1**) in acetonitrile with added water¹⁾ or methanol^{1,2)} has been reported to give the corresponding cyclohexadienone (**7b** or **c**) predominantly. The side-chain substituted phenols (**8b** and **c**) are usually formed in smaller amounts. However, in the electrolysis of **1** with an excess of pyridine, the side-chain pyridinated phenol (**8a**) was the major and the sole product isolated.²⁾ No clear explanation could be offered for the marked effects of added nucleophiles on the product distribution. In the electrolysis of a nonionized phenol, though it is generally accepted that a dienone such as **7** is formed by the reaction of a phenoxonium ion of type (**4**) with a particular nucleophile,^{1,3-6)} the sequence of reactions giving a side-chain substituted phenol (**8**),^{1-3,7)} as well as the factors affecting the ratio of nuclear to side-chain substitution, does not seem to be settled completely. We have reinvestigated the anodic pyridination of **1** in acetonitrile in order to find electrolysis conditions which may result in the formation of the pyridinated dienone (**7a**). Such studies were expected to afford further information on the mechanism of anodic side-chain substitution of 4-alkylphenols.

Results and Discussion

In our previous experiments on the pyridination of **1**, the amount of pyridine added to the electrolyte solution was more than 10 times that of the substrate.²⁾ Electrolysis with smaller amounts of pyridine has been found to give the nuclear pyridinated product (**7a**). Table I summarizes the results of controlled potential electrolysis of **1** under various conditions.

Chart 1 shows a summary of anodic substitution pathways of **1** in acetonitrile.^{1,3,4b)} The side-chain substituted phenol (**8**) can be formed through two routes: one involves the steps $5 \rightleftharpoons 3 \rightarrow 6 \rightarrow 8$ and/or $3 \rightleftharpoons 5 \rightarrow 6 \rightarrow 8$ (radical route), and the other involves the steps $3 \rightarrow 4 \rightarrow 8$ (phenoxonium ion route). Formation of **8** in the electrolysis of the phenolate ion (**2**) at a potential < 0.8 V vs. S.C.E. has been shown to take the radical route exclusively.^{4b)} Since the voltammetric peak for the oxidation of **3** to **4** appears near 1.0 V,^{4b,8)} part of the side-chain pyridinated phenol (**8a**) in the present study must be produced *via* the radical route, that is, dimerization⁹⁾ of **3** to **5** will compete with further electron transfer from **3** to give **4** at the potential employed (Table I). The rate constant for the latter reaction increases with the anode potential, whereas that for the dimerization will be unchanged. Thus, the contribution of the radical route to the overall reaction will be reduced by applying a higher electrolysis

TABLE I. Results of Controlled Potential Electrolysis of 1^{a)}

Run No.	Amount of 1/mmol	Solvent	Additives ^{b)} (mmol)	Supporting electrolyte ^{c)}	Anode potential ^{d)}	Yield ^{e)} (%)		
						7 ^{f)}	8 ^{g)}	1
1	0.452	MeCN	Py (0.506)	A	0.90	35	37	16
2	0.452	MeCN	Py (0.506)	A	1.00	36	29	12
3	0.452	MeCN	Py (0.506)	A	1.20	52	16	16
4	0.452	MeCN	Py (1.01)	A	1.00	19	36	19
5	0.452	MeCN	Py (2.53)	A	1.00	7	42	21
6	0.452	MeCN	Py (5.06)	A	1.00	5	40	22
7	0.452	MeCN	Py (0.506)	B	1.00	50	23	11
8	0.452	MeCN	Py (0.506), Lut (0.502)	B	1.00	32	35	15
9	0.452	MeCN	Py (0.506), Lut (2.51)	B	1.00	18	54	20
10	0.452	MeCN	Py (0.506), Lut (5.02)	B	1.00	9	60	20
11	0.458	MeCN	MeOH (0.5 ml), Lut (0.465)	B ^{h)}	1.00	46	3 ⁱ⁾	10
12	0.458	MeCN	MeOH (0.5 ml), Lut (2.33)	B ^{h)}	1.00	48	Trace ⁱ⁾	15
13	0.458	MeCN	MeOH (0.5 ml), Lut (4.65)	B ^{h)}	1.00	31	Trace ⁱ⁾	18
14	0.458	MeOH	None	B	1.00	60	6	13
15	0.458	MeOH	Lut (0.465)	B	1.00	79	12	3
16	0.458	MeOH	Lut (0.930)	B	1.00	72	9	4
17	0.458	MeOH	Lut (4.65)	B	1.00	68	22	10

a) Electrolysis was carried out at 0 °C in a one-compartment cell with a glassy carbon plate as the anode and a platinum foil as the cathode; the volume of the electrolyte solution was 40 ml.

b) Py, pyridine; Lut, 2,6-lutidine.

c) A, 0.15 M pyridinium perchlorate; B, 0.15 M 2,6-lutidinium perchlorate.

d) V vs. S.C.E.

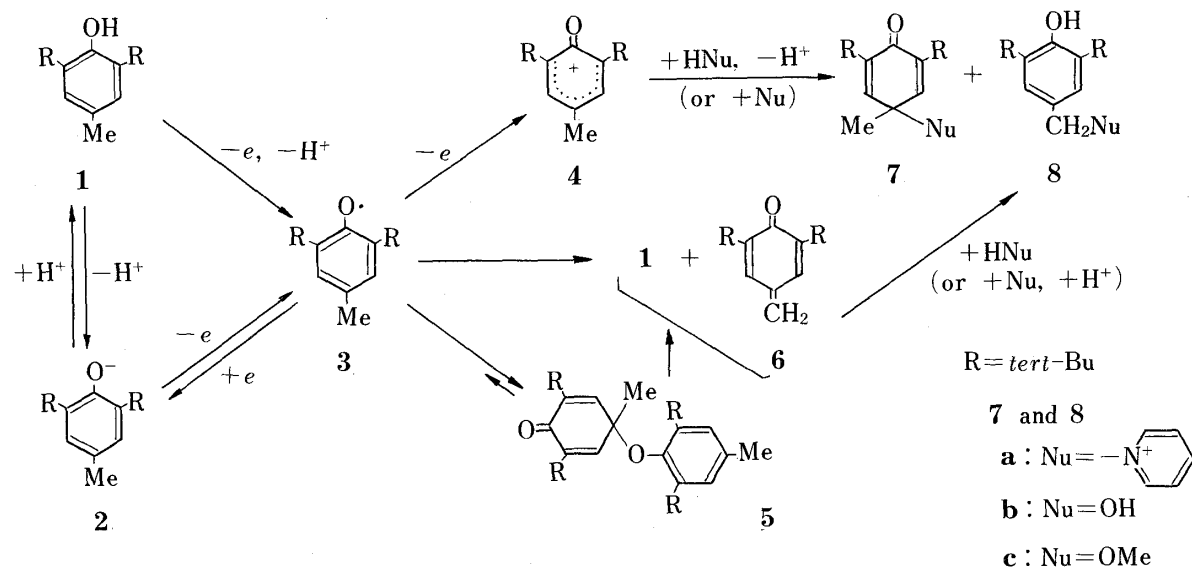
e) Determined by PMR spectroscopy.

f) 7a for run Nos. 1–10, and 7c for run Nos. 11–17.

g) 8a for run Nos. 1–10, and 8c for run Nos. 11–17.

h) 0.3 M.

i) Formation of tarry materials was observed.



potential, as reflected by the increase in the yield of 7a (Table I, run Nos. 1–3).

Vermillon and Pearl have suggested the processes shown in Chart 2 for the formation of 8 via the phenoxonium ion route.^{3,10} The effects of 2,6-lutidine, a hindered base, on the product distribution (run Nos. 7–10) could be explained as the result of competition between the two steps, 4 → 7a and 4 → 6. 2,6-Lutidine will act as a base to accelerate the latter step, but not as a nucleophile to give a dienone.^{11,12} The effects of pyridine on the product

distribution (run Nos. 2 and 4—6), however, are not compatible with such an explanation. The step $4 \rightarrow 7a$ as well as the step $4 \rightarrow 6$ will be enhanced by increasing the amount of pyridine, and the $[7a]/[8a]$ product ratio should be independent of pyridine concentration.

If it is assumed that in acetonitrile-pyridine and/or 2,6-lutidine system the equilibrium $4 + B \rightleftharpoons 6 + BH^+$ (equilibrium constant, K) is rapidly established as compared to the reactions $4 \rightarrow 7a$ (rate constant, k_7) and $6 \rightarrow 8a$ (rate constant, k_8) and that the formations of $7a$ and $8a$ are first-order with respect to pyridine, the product ratio is given by the equation:

$$\begin{aligned} [7a]/[8a] &= k_7 [\text{pyridine}] [BH^+]/k_8 K [\text{pyridine}] [B] \\ &= k_7 [BH^+]/k_8 K [B] \end{aligned}$$

where B and BH^+ denote total base in the system and its conjugate acid, respectively. Since $[BH^+]$ will be nearly equal to the concentration of supporting electrolyte (pyridinium perchlorate or 2,6-lutidinium perchlorate) and can be regarded as constant under the present experimental conditions, the equation predicts that the product ratio decreases with increase in the amount of added base. It has been suggested that proton abstraction from the α position of an alkylaromatic radical cation by a base should be very fast.¹³⁾ Similarly, deprotonation of the cation (4) may be a fast process.

The effects of 2,6-lutidine on the methoxylation of **1** were not remarkable (run Nos. 11—17), in contrast to the effects on the pyridination, and the dienone (**7c**) was the major product. Combination of at least three factors can make the step $4 \rightarrow 7c$ favored over the deprotonation of **4** to **6**. Attack of methanol at the foot of the methyl group of **4** will be subject to less steric hindrance than attack of pyridine at the same position. The basicity of 2,6-lutidine will be reduced in methanol or in acetonitrile containing methanol, compared to that in nominally dry acetonitrile, because of hydrogen-bonding of methanol to the base. Similar effects of water on the activity of hydroxide ion in acetonitrile have been suggested in the anodic oxidation of the phenolate ion (**2**).^{4b)} Finally, the same hydrogen-bonding may act as a general-base catalysis process in the step $4 \rightarrow 7c$.

It has been suggested that the reaction of a nucleophile with the *o*-quinone methide derived from 2,4-di-*tert*-butyl-6-methylphenol by copper-amine catalyzed autoxidation is highly selective: methanol adds to the ring carbon atom of the methylene while pyridine attacks the exocyclic carbon atom.¹⁴⁾ Thus, another explanation for the results of run Nos. 11—17 might be that the quinone methide (**6**) is also formed preferentially in the presence of excess amounts of 2,6-lutidine (*e.g.* run No. 17), but the reaction of **6** with methanol gives **7c** as the major product. Such a possibility, however, can be ruled out because electrolysis of **2** in methanol at 0.5 V predominantly affords the side-chain substituted products, which must be formed *via* the quinone methide (**6**).¹⁵⁾

In summary, the present results support the intermediacy of the quinone methide (**6**) in the side-chain substitution of the phenoxonium ion (**4**).

Experimental

Materials—Phenol (**1**) was recrystallized from methanol-water. Pyridinium and 2,6-lutidinium perchlorates were recrystallized from methanol-ether and stored over phosphorus pentoxide under reduced pressure. Acetonitrile was purified as described previously.²⁾

Apparatus—Controlled potential electrolysis was carried out in an undivided cylindrical cell (diameter, 35 mm; height, 75 mm) using a Hokuto Denko HA-104 potentiostat-galvanostat connected with a Hokuto Denko HF-201 coulometer and a Toa Dempa EPR-108 electronic recorder. A glassy carbon plate, a platinum foil, and an S.C.E. separated by an agar bridge were used as the anode, cathode, and reference electrode, respectively. Proton magnetic resonance (PMR) spectra were obtained with Hitachi RMU-6E and R-20A spectrometers.

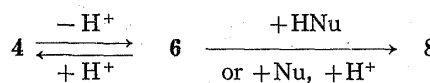


Chart 2

Determination of the Product Distribution—Electrolyses were carried out at 0°C in an ice-water bath. Stock solutions of the phenol (**1**), pyridine, and 2,6-lutidine were prepared, both in acetonitrile and in methanol. Typical examples of the procedure are described below.

(a) Pyridination: In the electrolysis cell were placed the stock solutions of **1** (10.0 ml, which contains 99.7 mg of **1**) and pyridine (1.0 ml, which contains 40.2 mg of the base), 1.0 g of pyridinium perchlorate, and the necessary amount of acetonitrile to make the volume 40 ml (*cf.* run No. 2 in Table I). The mixture was subjected to electrolysis at 1.0 V *vs.* S.C.E. until 87.0 C of electricity, which corresponded to 2 F per mol of **1**, had been consumed. The solution after electrolysis was evaporated to dryness under reduced pressure in a round-bottomed flask and the residue was washed with chilled water (2 × 5 ml) on a sintered glass filter. The remaining solids, both on the filter and attached to the wall of the flask, were dissolved in acetonitrile (5–10 ml). To this solution was added a stock solution of maleic acid in acetonitrile (5.0 ml, which contains 19.9 mg of the acid), and about half of the resulting mixture was taken out and evaporated to dryness under reduced pressure. The residue was dissolved in acetonitrile-*d*₃ (0.5–1 ml) and the solution, after two drops of D₂O and a small amount of SiMe₄ had been added, was subjected to PMR spectroscopy. The yields of **7a**, **8a**, and **1** were determined by comparing the intensities of the signals due to the ring protons of the corresponding compounds with that of the signal due to the vinyl protons of maleic acid.¹⁶⁾

(b) Methoxylation: The phenol (**1**) was electrolyzed similarly in acetonitrile containing methanol or in methanol. The 2,6-lutidine and lutidinium perchlorate system was employed. The solution after electrolysis was evaporated to dryness under reduced pressure, and the residue was extracted with warm benzene (5 × 20 ml). The combined extracts were evaporated to dryness under reduced pressure. The residue was treated by essentially the same procedure as described in (a), and the yields of **7c**, **8c**, and **1** were determined by PMR spectroscopy (solvent, methanol-*d*₄).¹⁷⁾

Isolation of the Dienone (7a)—The electrolysis products **7c**,²⁾ **8a**,¹⁾ and **8c**,^{2,15)} are known compounds and we have authentic samples. Thus, only the procedure for obtaining **7a** is described. The phenol (**1**) (351 mg) was subjected to electrolysis in acetonitrile (40 ml) containing pyridine (225 mg) and 0.3 M 2,6-lutidinium perchlorate at 1.25 V¹⁸⁾ at room temperature until the value of the current fell below 1% of the initial value: 601 C, which corresponded to *ca.* 4F per mol of the substrate, was found to have been consumed. The solution after electrolysis was evaporated to dryness under reduced pressure and the residue was washed successively with ether (5 × 20 ml) and chilled water (3 × 20 ml). The infrared (IR) spectrum of the remaining solid (276 mg) suggested that it was a mixture of **7a** and **8a**, with the former predominating. Recrystallization of the mixture once from chloroform–ether and twice from chloroform gave pale yellow needles. The crystals were dissolved in acetone and then the solvent was removed under reduced pressure. The procedure was repeated three times, and the residue was identified as *N*-(3,5-di-*tert*-butyl-1-methyl-4-oxo-2,5-cyclohexadienyl)pyridinium perchlorate (**7a**); mp 148°C (*dec.*). *Anal.* Calcd for C₂₀H₂₈ClNO₅: C, 60.37; H, 7.09; N, 3.52. Found: C, 60.06; H, 7.14; N, 3.51. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1670, 1645, 1630, 1095. PMR (CDCl₃) δ : 1.25 (18H, s, *tert*-Bu), 2.08 (3H, s, Me), 6.73 (2H, s, ring-H), 7.9–8.9 (5H, m, pyridinium ring-H).

References and Notes

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- 8) The voltammetric peak of **1** appears at *ca.* 1.2 V under these conditions: the phenoxy radical (**3**) is oxidized more easily than the parent phenol.
- 9) It has been suggested that the equilibrium between **3** and **5** is rapidly established and lies well toward **5**, while decomposition of **5** or disproportionation of **3** to give **6** is a relatively slow reaction: E.J. Land and G. Porter, *Trans. Faraday Soc.*, **59**, 2016 (1963); S.A. Weiner and L.R. Mahoney, *J. Am. Chem. Soc.*, **94**, 5029 (1972); R.D. Parnell and K.E. Russell, *J. Chem. Soc., Perkin Trans. 2*, **1974**, 164 and references therein.
- 10) Ronlán and Parker have suggested a seemingly different reaction sequence (*ref.* 1): $4 \rightarrow \text{HO-Ar} + \text{HNu} - \text{H}^+ \rightarrow \text{CH}_2^+ \rightarrow 8$. However, this sequence cannot be regarded as representing a different mechanism from that suggested by Vermillon and Pearl, because the rate-determining steps of both reactions are not defined.
- 11) V.D. Parker and L. Ebersson, *Tetrahedron Lett.*, **1969**, 2839; *idem*, *Acta Chem. Scand.*, **24**, 3542 (1970).
- 12) In the electrolysis of **1** in acetonitrile containing 2,6-lutidine and lutidinium perchlorate but without

- any other added nucleophile, formation of side-chain lutidinated product was recognized though the yield was low.
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 - 15) The phenol (**1**) was electrolyzed at 0.5 V in methanol containing an equimolar amount of sodium methoxide (supporting electrolyte, 0.1 M NaClO₄) until the quantity of electricity corresponding to 2 F per mol of the substrate had been consumed. Formation of **8c** and 2,6-di-*tert*-butyl-4-formylphenol in yields of 63 and 17%, respectively, was found in the solution after electrolysis. The latter phenol was confirmed to be formed in the electrolysis of **8c** under the same conditions.
 - 16) The corresponding signals appeared at $\delta=6.73$, 7.34, 6.94, and 6.35 ppm for **7a**, **8a**, **1**, and maleic acid, respectively.
 - 17) The corresponding signals appeared at $\delta=6.48$, 7.11, 6.83, and 6.27 ppm for **7c**, **8c**, **1**, and maleic acid, respectively.
 - 18) At this potential, part of **8a** is oxidized. Since separation of **7a** from **8a** is rather difficult, further oxidation of **8a** was expected to aid in the isolation of **7a** from the product mixture.