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Electrolytic Oxidation. I. Phenolic Oxidation of *p*-Cresol by Electrolysis (Studies on the Syntheses of Heterocyclic Compounds. CCXXXVII[1])

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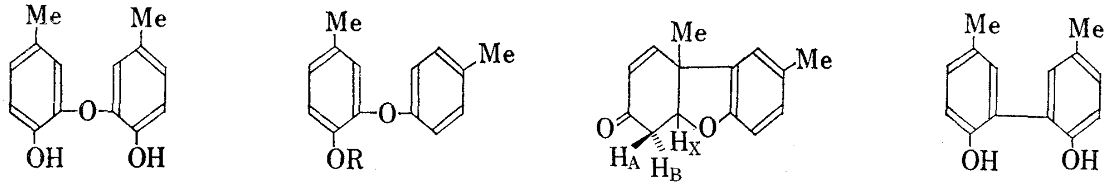
Phenolic oxidation of *p*-cresol in an electric current of 0.0025 A/cm^2 using lead as an electrode and 1 N H_2SO_4 as an electrolyte afforded three compounds, (II), (III), and (IV), which were assigned by spectral elucidation. Furthermore, an authentic sample (III) was synthesized by Ullmann reaction of *p*-cresol with 4-benzyloxy-3-bromotoluene, followed by hydrolysis of V with hydrobromic acid in acetic anhydride.

We have been studying the phenolic oxidative coupling reactions of the 1-substituted isoquinolines in order to synthesize various isoquinoline alkaloids,[3] but syntheses of dauricine[4] type compounds by phenolic oxidative coupling have not yet been achieved. Thus we wish to report phenolic oxidation of *p*-cresol by electrolysis as a model experiment to dauricine type compounds.

Phenolic oxidation of *p*-cresol has hitherto been investigated[5-7] and electrolytic oxidation has been examined only by Bobbit[8] and Fichter,[9] in the latter of which separation of diphenyl ether (I) has been reported.[9]

Electrolytic phenol oxidation of *p*-cresol was achieved by using lead as an electrode and 1 N sulfuric acid as an electrolyte in a current of 0.0025 A/cm.[9] The usual work up involving silicic acid chromatography with chloroform as eluent afforded three compounds (II), (III), and (IV), whose structures were assigned by the following evidence.



I

II : R=H
V : R=CH_2Ph

III

IV

Chart 1

The compound (II), obtained by evaporation of the first eluent, was purified by preparative thin-layer chromatography (TLC) using silica gel to give an oil which showed a hydroxyl band at 3520 cm^{-1} in its infrared spectrum ($CHCl_3$). Nuclear magnetic resonance (NMR) spectrum and TLC[7] were in good accordance with an authentic sample (II), which was obtained

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by Ullmann reaction of 4-benzyloxy-3-bromotoluene with *p*-cresol in the presence of copper powder, potassium carbonate and pyridine, followed by hydrolysis of the resultant compound (V) with 48% hydrobromic acid in acetic anhydride. The NMR spectrum (ppm in CCl_4) revealed two methyl resonances at 2.16 and 2.28 as singlets, respectively, 6.57 (one aromatic proton as singlet) and 6.79 (two aromatic protons as singlet). In addition, there appeared two doublets at 6.82 and 7.08 (J=8.5 cps) and one proton at 4.08 disappeared with deuterium oxide. Furthermore, since the compound (II) was formed as an oil, benzylation of (II) with benzyl chloride in dimethylformamide was carried out to afford the compound (V), identical with an authentic sample on mixed melting point test and infrared (IR) comparison.

The second compound (III), mp 124—125°, which was purified by repeated distillation and recrystallization from *n*-hexane, showed the band of α,β-unsaturated ketone at 1675 cm^{-1} in its IR spectrum ($CHCl_3$). In addition, there appeared no phenolic hydroxyl absorption. The NMR spectrum (ppm in CCl_4) showed the following signals; 1.52 and 2.29 (6H, two methyl groups, singlets), 2.54 and 2.92 (2H, a pair of quartets, $J_{AB}=17.1$; $J_{AX}=3.4$; $J_{BX}=3.0$ cps), 4.58 (1H, multiplet, H_X), 5.76 (1H, olefinic proton, J=10.1 cps), 6.34 (1H, olefinic proton, a pair of doublets, J=10.1; J=1.7 cps), and 6.57 (1H, aromatic proton, doublet, J=8.5 cps). The NMR spectrum of III was superimposable on that of Pummerer's ketone.[10] Thus, mixed melting point test (lit.,[5,6] mp 123—124°) and spectral data support the structure of III.

The third compound (IV), mp 157°, showed a phenolic hydroxyl band at 3560 cm^{-1} in its IR spectrum ($CHCl_3$). The NMR spectrum (ppm in CCl_4) showed the signals, 2.28 (6H, two methyl groups), 6.78 (2H, doublet, J=8.6 cps), 7.04 (2H, a pair of doublets, J=8.6; 2.5 cps), 6.96 (2H, doublet, J=2.5 cps). These spectral data and mp 153—153.5° were identical with those of an authentic sample (IV).[9]

These results as above show that phenolic oxidation of *p*-cresol by electrolysis has proceeded as a result of intermolecular radical reaction as the usual phenolic oxidative coupling using ferric chloride and potassium ferricyanide in case of III and IV.

Experimental[11]

Oxidation of *p*-Cresol by Electrode Reaction——a) A mixture of 10.8 g of *p*-cresol and 150 ml of 1 N H_2SO_4 aq. solution was stirred at room temperature during 21.5 hr using lead as an electrode under the condition of 0.0025 amp/cm^2 and 3.5 volt. After the electrolysis, the reaction mixture was extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 9.3 g of a reddish-brown oil, whose distillation *in vacuo* recovered 7 g of *p*-cresol. In this case, 4.5 g of a black brown syrup remained as a residue, which was chromatographed on silicic acid using $CHCl_3$ as solvent gave the three fractions.

Evaporation of the first eluate afforded a pale reddish-orange oil, whose purification by fractional distillation resulted in failure. Therefore, attempt to purify the above oil by preparative thin-layer chromatography on silica gel afforded 65 mg of 4-methyl-2-(4-methylphenoxy)phenol (II) as a pale yellow oil, whose IR and NMR data were identical with those of an authentic sample (II) described later.

The second eluate was evaporated to give a residue which was purified by column chromatography on silicic acid repeatedly. Furthermore, recrystallization from *n*-hexane gave 113 mg of colorless needles, mp 124—125°, whose IR in $CHCl_3$ and NMR in CCl_4 were superimposable on those of an authentic sample, namely, Pummerer's ketone (III).

The third eluate was evaporated to give a residue which was separated as crystals under inspection on thin-layer chromatograpy. Recrystallization from *n*-hexane afforded 187 mg of colorless needles, which were identical with an authentic sample by mixed melting point test and IR comparison. IR cm^{-1} ($CHCl_3$): ν_{OH}3560. NMR (ppm in CCl_4): 2.28 (6H, two singlets, C_4-CH_3, $C_{4'}$-CH_3); 6.78 (2H, doublet, J=8.6 cps, C_6-H, $C_{6'}$-H), 7.04 (2H, a pair of doublets, J=8.6 cps, J=2.5 cps, C_5-H, $C_{5'}$-H), 6.96 (2H, doublet, J=2.5 cps, C_3-H, $C_{3'}$-H).

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[11] Melting points were determined on a Yanagimoto micro-melting point apparatus (MP-S2) and were not corrected. NMR spectra were run on a Hitachi H-60 and Varian A-60 spectrometers using carbon tetrachloride as solvent and tetramethylsilane as an internal reference.

b) A mixture of 15 g of *p*-cresol and 200 ml of 1 N H_2SO_4 aq. solution was oxidized by the same electrolysis as above for 38.5 hr. Treatment of the reaction mixture gave 15.6 g of an oil, whose distillation recovered 7.7 g of *p*-cresol. The residue (7.9 g) was extracted with hot *n*-hexane. Removal of the extract afforded a pale yellow oil, which was chromatographed on silica gel using benzene.

Evaporation of the first eluate gave 376 mg of II and the second fraction gave 343 mg of Pummerer's ketone (III). Finally, 1.25 g of IV was obtained from the third eluate.

4-Benzyloxy-3-bromotoluene——A mixture of 2.5 g of 3-bromo-4-hydroxytoluene,[5] 2.5 g of benzyl chloride, 2 g of anhyd. K_2CO_3, and 15 ml of dimethylformamide was heated under reflux for 1 hr with stirring. After the reaction the usual work up afforded 3.5 g (97.1%) of colorless oil, bp 174—176° (5 mmHg). *Anal.* Calcd. for $C_{14}H_{13}OBr$: C, 60.67; H, 4.73. Found: C, 60.29; H, 4.92.

4-Benzyloxy-3-(4-methylphenoxy)toluene (V)——a) A mixture of 30 g of the above toluene 11.7 g of *p*-cresol, 11 g of copper powder, 10 g of anhyd. K_2CO_3, and 15 ml of pyridine was mildly refluxed for 8 hr. After the reaction mixture had been admixed with benzene, the resultant extract was filtered, washed with 3% HCl, 5% NaOH aq. solution and then water, and dried over Na_2SO_4. Evaporation of the solvent afforded a reddish-brown oil, whose silica gel chromatography using $CHCl_3$ as an eluent afforded the crude crystals. Recrystallization from *n*-hexane afforded 16 g (52.7%) of the compound (V) as colorless needles, mp 76—78°. *Anal.* Calcd. for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.73; H, 6.83.

b) A mixture of 45 mg of II, 30 mg of benzyl chloride, 250 mg of K_2CO_3, and 1 ml of dimethylformamide was gently refluxed for 1.5 hr. After the reaction mixture was extracted with benzene, the benzene extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a reddish orange oil, whose purification by Al_2O_3-chromatography using benzene as solvent afforded the compound (V) as colorless needles, mp 76—78°, which were identical with the above sample (V) on admixed melting point test and spectral camparison.

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