OXOAMMONIUM SALTS. 4[1] A NEW REAGENT FOR PHENOL COUPLING

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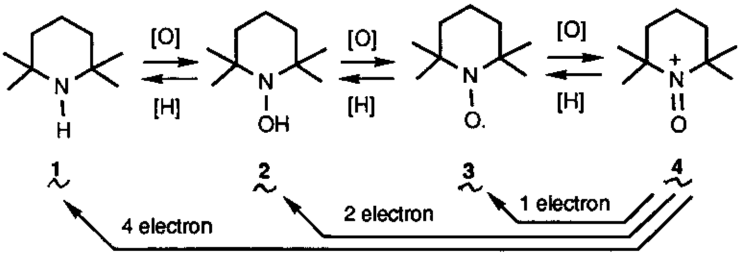
Abstract - Oxoammonium salts, such as 2,2,6,6-tetramethylpiperidine-1-oxonium tetrafluoroborate, oxidatively couple phenols to dihydroxybiphenyls in good yield. Furthermore, these compounds can be used to dehydrogenate tertiary amines to iminium salts and to oxidize certain phenols to quinones.

Organic oxoammonium salts such as 4 can be easily prepared from commercial nitroxide radicals such as TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy) (3) by a one-electron oxidation (Equation 1) or by acid-catalyzed disproportionation.[2] They have been explored recently as selective oxidizing agents for several organic functional groups. Specifically, they have been used to oxidize alcohols to aldehydes or ketones, amines to imines, aldehydes, ketones or nitriles, ketones to alpha diketones, and phenols to quinones. The preparation of the salts, their properties and

Equation 1



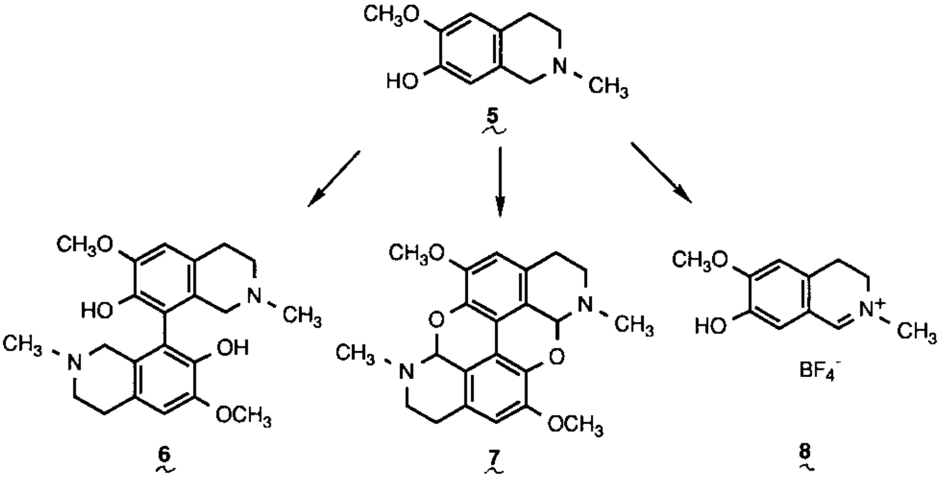
these reactions have been recently summarized.[1-4]

In our search for new applications of these useful materials, we investigated the oxidation of several phenols to determine whether coupling might be produced. Such coupling reactions are important in the biosynthesis of natural materials.[5] While the oxidation of naphthols has been reported to yield quinones, no coupled products were observed.[6]

The phenolic alkaloid corypalline (5) was the model compound for a series of electrochemical phenol coupling studies carried out in our laboratory and summarized several years ago,[7] and it was the first phenol that we studied with the oxoammonium salt (4). A preliminary reaction under neutral conditions revealed the presence of the coupled product (6) but a detailed study was required to completely elucidate the various reactions and obtain good yields of 6.

When the oxidation of 5 was carried out in CH_3CN-H_2O solution in the presence of $KHCO_3$, the normal coupled product (6) was isolated in 81% yield. When the reaction was carried out in the presence of one equivalent of tetraethylammonium hydroxide, the major products were 6 in 26% yield and the condensed structure (7) in 51% yield. It is strange, however, that the oxidation of 6 to 7 did not proceed under any conditions. In the absence of any added base or acid, the major product was 8 in about 63% yield along with 13% of 6. Compound(8)was not purified but was reduced with $NaBD_4$ to give 1-deutero-5 for identification. In the presence of strong acids such as HBF_4, or in the presence of an excess of strong base, no oxidations took place. Compounds(6)and(7)had been observed previously in our electrochemical studies,[8] and 8 was obtained in very low yield from the catalytic oxidation of corypalline.[8]

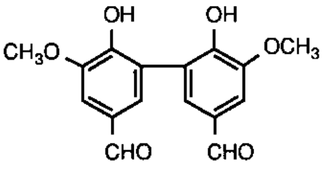
Oxoammonium salts (4) can oxidize by a one electron process and be reduced to a nitroxide (3), by a two electron process with a reduction to a hydroxyamine (2), or by a four electron process with reduction to a piperidine (1) (Equation 1).[3] Thus, the observed reduction product can give some idea of the mechanism in each case.



In the presence of the weak base, $KHCO_3$, the phenol is apparently deprotonated in an equilibrium and is oxidized to give a coupled product. The oxoammonium derived material is the nitroxide, and the reaction appears to be a one electron reaction. In the presence of one equivalent of strong base, tetraethylammonium hydroxide, coupling results, and further oxidation to 7 takes place. This clearly involves the dehydrogenation of the 1,2 C-N bond and addition of the phenol, but the detailed steps in the reaction are not clear. In neutral or near neutral solution, the result is mainly the dehydrogenation product (8), and the hydroxyamine (2) was one of the products. Thus, the reaction appears to be a two electron oxidation. Such amine dehydrogenations have been observed by Semmelhack's group[9] and by Hunter.[10]

Under ideal coupling conditions ($KHCO_3$ in 90:10 CH_3CN-H_2O), vanillin gave dehydrovanillin (**9**) in 85% yield, and 2,4-di-*tert*-butylphenol gave the dimer (**10**) in 72% yield (87% when the added base was lutidine). In the presence of two equivalents of oxoammonium salt, 2,6-di-*tert*-butylphenol gave the dimeric quinone (**11**) in quantitative yield. With smaller amounts of oxoammonium salt, an intermediate, presumably the simple coupled phenol, was observed (chromatographically) from the oxidation of the 2,6-isomer.

The oxidations of 1- and 2-naphthols have been reported,[6] but the products were quinones (1-naphthol gave a mixture of 1,2 and 1,4-naphthoquinones and 2-naphthol gave 1,2-naphthoquinone in 95% yield). We found that



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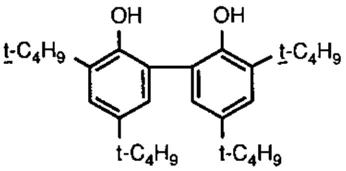

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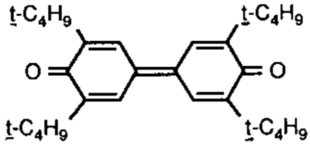

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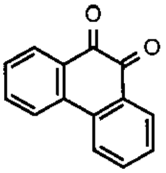

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9-phenanthrol gave 9,10-phenanthroquinone (**12**) in 47% yield (81% when the base was lutidine). For 9-phenanthrol, the product obtained from the oxoammonium salt was the piperidine (**1**), clearly denoting a four electron oxidation.

EXPERIMENTAL SECTION[11]

Oxidation of **5** in Weak Base, $KHCO_3$. Compound(**5**)[12] (195 mg, 1.00 mmol) and $KHCO_3$ (300 mg, 3.00 mmol) were dissolved in 20 ml of H_2O, and a solution of **4** in 5 ml of CH_3CN was added dropwise. The solution was stirred for 20 min, basified with 10% NaOH and washed with ether. The aqueous phase was neutralized with 10% NH_4Cl and extracted with three portions of $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to give 157 mg of **6** as white crystals, mp 234-236° C (lit.,[13] mp 235-237° C). The nitroxide (**3**) was observed by thin-layer chromatography, whereas no hydroxyamine (**2**) was seen.

Oxidation of **5** With One Equivalent of Strong Base (Tetraethylammonium Hydroxide. Compound(**5**)(195 mg, 1.00 mmol) was dissolved in 20 ml of CH_3CN, and 1.00 mmol (360 μl of a 40% aqueous solution) was added. A solution of **4** (267 mg, 1.10 mmol) in 5 ml of CH_3CN was added dropwise. The solution was stirred for 30 min, concentrated to 5 ml, acidified with 10% HCl and washed with $CHCl_3$. The aqueous phase was basified to pH 12 with 10% NaOH and extracted with three portions of $CHCl_3$. The $CHCl_3$ solutions were dried (Na_2SO_4) and evaporated to give 76 mg (51% corrected for starting material) of **7**, mp 217-220° C (lit.,[8] mp 217-220° C). The above aqueous phase was then neutralized with solid NH_4Cl and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and evaporated. The residue was chromatographed by preparative tlc (CH_3OH: conc. NH_4OH, 98:2) to give 41 mg of starting material and 39 mg of **6** (25% corrected).

Oxidation of 5 in Neutral Solution. Compound(**5**)(39 mg, 0.20 mmol) was suspended in 2 ml of CH_3CN, and a solution of 4 (49 mg, 0.20 mmol) in 4 ml of CH_3CN was added dropwise. The solution was stirred for 30 min and concentrated to a small volume. The mixture was separated by preparative tlc (CH_3OH: conc. NH_4OH, 97:3 on silica gel). The major product (**8**) had an R_f of 0.05 and was isolated as 22 mg of red solid, mp 137-140° C;[14] ^1H nmr (D_2O) δ 8.36 (1H, s, C_1H), 6.82 and 6.79 (2H, singlets, C_5H and C_8H), 3.75 (3H, s, OCH_3), 3.72 (2H, t, J=8.1, C_3H), 3.48 (3H, s, NCH_3), 2.95 (2H, t, J=8.1, C_4H). Compound(**8**)was reduced with $NaBD_4$ to give 1-deutero-**5**, mp 168-169° C, identical with non-deuterated **5** except for the peak at δ 3.29 which had only one hydrogen.

Oxidation of Vanillin. Vanillin (152 mg, 1.00 mmol) was dissolved in 20 ml of CH_3CN, and a solution of $KHCO_3$ (300 mg, 3.00 mmol) in 5 ml of H_2O was added (the $KHCO_3$ partially precipitated). Oxidant (**4**) (365 mg, 1.50 mmol) in 10 ml of CH_3CN was added dropwise, and the mixture was stirred for 30 min. The solution was concentrated to about 5 ml, and 10 ml of H_2O was added. The mixture was shaken with $CHCl_3$ for a few min whereupon a white precipitate formed. The solid was collected by filtration to give 127 mg (85%) of dehydrovanillin (**9**), mp 305-307° C (lit.,[15] mp 303-305° C).

Oxidation of 2,4-Di-tert-butylphenol. 2,4-Di-*tert*-butylphenol (206 mg, 1.00 mmol) was dissolved in 10 ml of CH_2Cl_2, and 130 μl of 2,6-lutidine (1.10 mmol) was added. Oxidant (**4**) (267 mg, 1.10 mmol) dissolved in 20 ml of CH_2Cl_2 was added dropwise, and the solution was stirred for 30 min. The solution was washed with 0.1 M HCl, dried (Na_2SO_4), evaporated and separated on a silica gel column to give 177 mg (87%) of **10**, mp 195-197° C (lit.,[16] mp 194-195° C).

Oxidation of 2,6-Di-tert-butylphenol. 2,6-Di-*tert*-butylphenol (103 mg, 0.50 mmol) was dissolved in 10 ml of CH_3CN, and a solution of $KHCO_3$ (150 mg, 1.50 mmol) in 5 ml of H_2O was added. Oxidant (**4**) (267 mg, 1.10 mmol) in 10 ml of CH_3CN was added dropwise, and the solution was stirred for 60 min. Red needles formed during the reaction and were collected by filtration to give 101 mg (100%) of **11**, mp 247-248° C (lit.,[17] mp 245-248° C).

Oxidation of 9-Phenanthrol. 9-Phenanthrol (194 mg, 1.00 mmol) and 2,6-lutidine (117 μl, 1.00 mmol) were dissolved in 10 ml of CH_2Cl_2, and a solution of oxidant (**4**) (267 mg, 1.10 mmol) in 20 ml of CH_2Cl_2 was added. The mixture was stirred for 30 min, extracted with 0.1 M HCl, dried (sat. NaCl followed by Na_2SO_4) and evaporated. The residue was separated on a silica gel column with 20:80 ethyl acetate: petroleum ether to give 169 mg (81 %) of 9,10-phenanthroquinone, mp 205-207° C (lit.,[18] mp 205-207° C).

ACKNOWLEDGMENT

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