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Oxidative Coupling of 4-Substituted 2-Methoxy Phenols Using Methyltributylammonium Permanganate in Dichloromethane.

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Abstract: Dimers of 4-substituted 2-methoxy phenols were prepared using methyltributylammonium permanganate (MTBAP) in dichloromethane. This methodology allows the selective coupling of such compounds preserving other moieties easily oxidized by permanganate anion in aqueous solution.

One of the chemical properties of phenols is their facile oxidation, which can be accomplished with almost any oxidant leading to quinones, or to dimeric, trimeric or polymeric coupling products[1,2]. Not only are these reactions of synthetic importance, but they are also implicated in many biogenetic pathways[3,4,5], including the biosynthesis of lignoids.

More than two hundred of the lignoids recorded in the literature are described to have antibiotic, antihepatotoxic, antioxidant, anti-PAF (platelet activating-factor) antitumoral, calcium antagonistic, cytostatic, cytotoxic and enzyme inhibitor activity[6].

In this work we have studied the oxidative coupling of 4-substituted 2-methoxy phenols using methyltributylammonium permanganate (MTBAP) in dichloromethane. It has been reported[7] that the permanganate anion exhibits a lower oxidizing power in organic solvents compared with in aqueous solution. This behaviour was exploited to effect selective oxidations of phenols bearing other moieties easily oxidized by permanganate anion under other conditions.

This reaction led to the formation of the dimeric products whose structures, in the case of dimers **5**, **6** and **7**, resemble the structures of lignoids.

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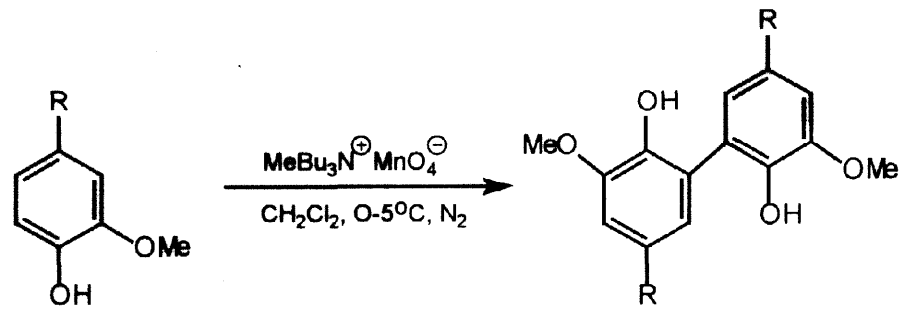
Scheme 1



1 : R = $CH_2CH(O)CH_2$

2 : R = $CH_2CH{=}CH_2$

3 : R = $CH_2CH_2CH_3$

4 : R = CH_3

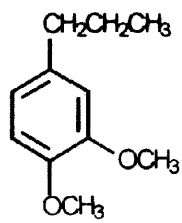
5 (50%)

6 (52%)

7 (55%)

8 (54%)

When the reaction was performed with eugenol[8] **2** or with the epoxide derived of eugenol **1**, the major products isolated were results of the oxidation of phenol, preserving the double bond and epoxide present in the structures of the respective compounds, which could be easily oxidized by permanganate anion in either acidic or basic aqueous solution. The free phenolic OH group plays a major role in this oxidation since no dimeric products were obtained in the reaction of ethers **9** and **10** even when the reaction was kept for a longer period of time, recovering most of the starting material.



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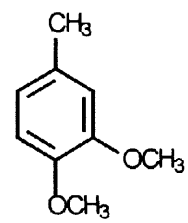

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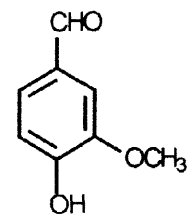

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The presence of a deactivating group in the aromatic ring, as observed for vanilin **11**, acts as expected, inhibitting the oxidation of the phenol.

Since the reactions with permanganate anion are often performed in aqueous medium, to avoid the presence of water the oxidant salt was previously prepared in a two phase system[9], adding an aqueous solution of potassium permanganate into a round bottom flask, equipped with

magnetic stirrer, containing methyltributylammonium chloride in dichloromethane. The anion permanganate was rapidly extracted into the organic phase and the dichloromethane was rotaevaporated without heating.

The oxidant salt, very soluble in dicloromethane, was shown to be stable when stored in the refrigerator over a three days period.

The ortho-ortho pattern of coupling of the dimers prepared was confirmed analyzing the ^{1}H-NMR of compounds **6** and **7** which show a coupling constant (J) for the aromatic hydrogens of 1.8 and 2.1 Hz, respectively, characteristic for hydrogens having a meta relationship. For compound **5** a singlet at 6.81 ppm was observed for both aromatic hydrogens. A good concordance was verified when the ^{13}C-NMR data of the latter compound was compared with the data of the others dimers prepared. This fact lead us to conclude that the signal of the two aromatic hydrogens of the dimer **5** appeared as a singlet, with the same chemical shift, by coincidence.

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7. Bock, H. and Jaculi, D. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 305.
8. **Typical procedure for oxidative coupling of eugenol as representative**: To a solution of eugenol **2** (493 mg, 3 mmol) in dry dichloromethane (5 mL) under nitrogen at 0°C, was added a solution of MTBAP (479 mg, 1.5 mmol) in dichloromethane (10 mL). After 15 minutes water (10 mL) was added into the reaction flask followed by the bubbling of SO_2. The organic layer was separated, washed with a 0,1 **M** solution of HCl (3 x 5 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product obtained was purified by a quick filtration through a short pad of silica using a mixture of hexane/ethyl acetate (3:1 ratio) followed by a flash chromatograpy on silica gel with the same mixture of solvents, yielding 254 mg (52%) of dimer **6**.

9. **Typical procedure for preparation of MTBAP**: To a round bottom flask containing an aqueous solution (75% w/w) of methyltributylammonium chloride (1.258 g, 4 mmol) and dichloromethane (100 mL) was added a solution of potassium permanganate (632 mg, 4 mmol) in water (35 mL). The resulting mixture was stirred for one hour, the phases were separated and the organic layer was dried over anhydrous $MgSO_4$. After filtration, the dichloromethane was removed under reduced pressure and the product, a dark purple solid, was kept under high vacuum for one hour affording 1.277 g (90%) of the oxidant salt.

10. Physical and spectroscopic data for **5** : ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.81 (s, 4H), 6.11 (brs, 2H - OH), 3.92 (s, 6H), 3.19-3.15 (m, 2H), 2.80 (dd, J = 3.95, 4.96 Hz, 2H), 2.86-2.82 (m, 4H), 2.58 (dd, J = 2.67, 4.96 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 147.21, 141.40, 129.06, 124.25, 123.52, 110.10, 56.14, 52.67, 46.91, 38.52; IR (KBr) 3494, 3414, 3056, 1588, 1250 cm^{-1}; MS (m/z, EI): 358 (M^+, 100), 283, 69, 57.

11. Physical and spectroscopic data for **6** : ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.75 (d, J = 1.8 Hz, 2H), 6.72 (d, J = 1,8 Hz, 2H), 6.06-5.91 (m, 2H), 6.03 (brs, 2H - OH), 5.15-5.03 (m, 4H), 3.91 (s, 6H), 3.36 (d, J = 6.9 Hz, 4H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 147.32, 141.01, 137.73, 131.98, 124.47, 123.18, 115.76, 110.75, 56.02, 39.87; IR (KBr) 3341, 3244, 3083, 1632, 1598 cm^{-1}; MS (m/z, EI): 326 (M^+, 100), 297, 253; Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.64; H, 6.74. Found: C, 73.54; H, 6.85.

12. Physical and spectroscopic data for **7** : ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.74 (d, J= 2.1 Hz, 2H), 6.72 (d, J = 2.1 Hz, 2H), 6.02 (brs, 2H - OH), 3.92 (s, 6H), 2.56 (t, J = 7.2 Hz, 4H), 1.72-1.57 (m, 4H), 0.95 (t, J = 7.2 Hz, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 147.23, 140.60, 134.77, 124.53, 123.04, 110.70, 56.02, 37.78, 24.65, 13.75; IR (KBr) 3351, 3261, 3022, 1598 cm^{-1}; MS (m/z, EI): 330 (M^+), 301 (100), 136; Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.75; H, 7.87. Found: C, 72.77; H, 8.12.

13. Physical and spectroscopic data for **8** : ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.75-6.69 (m, 4H), 3.90 (s, 6H), 2.32 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 147.16, 140.42, 129.67, 124.42, 123.48, 111.34, 55.98, 21.03; IR (KBr) 3217, 3022, 1598 cm^{-1}; MS (m/z, EI): 274 (M^+, 100), 241, 227, 199; Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06 ; H, 6.61. Found: C, 70.30; H, 6.60.