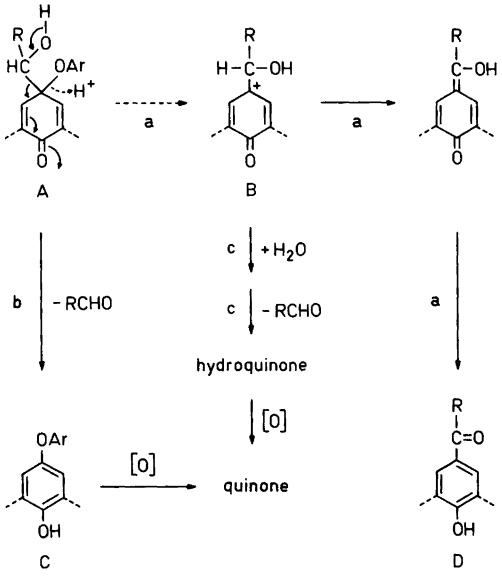
The Cleavage of the 4-(1-Hydroxyalkyl) Side-Chain from a Cyclohexa-2,5-dienone. A Model Reaction for the Biodegradation of Lignin

G. BRUNOW and M. KARHU

Department of Chemistry, University of Helsinki, Vuorikatu 20, SF-00100 Helsinki 10, Finland

In studies concerning the decomposition of lignins by microorganisms it has been shown that phenol oxidizing enzymes are capable of causing cleavage of the bond between an aromatic ring and the alkyl side-chain in some structural units in the lignin macromolecule.[1] These reactions were first discovered during detailed investigations of the biosynthesis of lignin. The side-chain cleavage reaction has been suggested as an explanation for the occurrence of 1,2-diarylpropane units in lignin.[2] It has been assumed that the reaction involves dimerization of phenoxy radicals and subsequent elimination of the side-chain. In the light of later investigations[3] it seems doubtful whether this cleavage leads to any net degradation of the lignin macromolecule. The enzymatic oxidation causes extensive formation of bonds *ortho* to the phenolic hydroxyls and the side-chain cleavage seems to occur only in units were *o*−*o*-coupling is impossible.



Scheme 1.

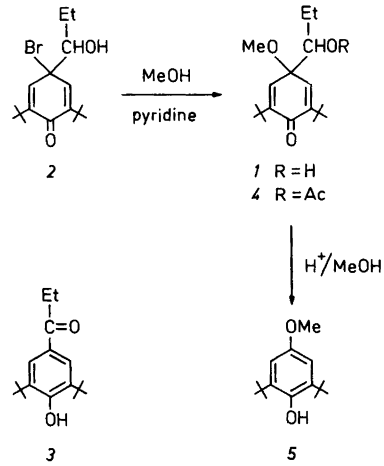
In such units a probable mechanism for this cleavage involves a 4-(1-hydroxyalkyl)-4-substituted cyclohexa-2,5-dienone intermediate A (Scheme 1).[4] Such an intermediate can either react to form a ketone D in what is essentially a disproportionation reaction (reaction a), or eliminate the hydroxylalkyl side-chain in an acid-catalyzed retro-aldol reaction to form a diphenyl ether C (reaction b).

A third possible reaction is attack of water on cation B in reaction a. Subsequent cleavage of the hydroxyalkyl group leads in this case to a hydroquinone (reaction c). Under the oxidative conditions prevailing in a peroxidase catalyzed oxidation both the diphenyl ethers and the hydroquinones will be oxidized to quinones. Ketones and quinones are usually the main products encountered in enzymatic oxidations of phenols of this type.

In order to clarify the role of intermediates of type A in the biosynthesis and biodegradation of lignins, we have undertaken a systematic study of the synthesis and hydrolytic behaviour of compounds of this type. In the present communication we report on the preparation and hydrolysis of the cyclohexadienone *1*, which has some structural features in common with hypothetical intermediates of type A.

Results and discussion. Compound *1* was prepared by treating the bromocyclohexadienone *2* with methanol containing some pyridine at room temperature. The NMR spectrum of the reaction mixture showed that two products were formed: *1* (82 %) and the ketone *3* (18 %). Owing to its instability the quinol ether *1* was characterized as the acetate *4*.

Hydrolysis of *1* in 5 % methanolic sulfuric acid gave a quantitative (TLC) yield of the substituted hydroquinone monomethyl ether *5*. The same result was obtained in chloroform without the acid catalyst but the reaction was much slower. No ketone *3* was formed under either conditions.



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The clean side-chain elimination observed in *1* on alcoholysis shows that ketone formation (reaction a) is not an important reaction for compounds of this type. When the leaving group in the reaction a is an aroxyl group the likelihood of this reaction would be somewhat greater but still probably unimportant since compound *2*, where the leaving group is bromide ion, only gives 18 % ketone on alcoholysis. Recently we have reported the formation of diphenyl ethers in the reactions of the quinol bromide *2* with phenols.[5] However, attempts to synthesize the corresponding 4-aroxy-4-(1-hydroxypropyl)-2,5-cyclohexadienones failed.

The ketones of type D which are frequently observed as main products in oxidations of phenolic benzyl alcohols are probably formed by some other mechanism such as direct transfer of hydrogen between phenoxy radicals.[6]

Experimental. For general remarks, see the previous paper.[7]

4-(1-Hydroxypropyl)-4-methoxy-2,6-di-t-butylcyclohexa-2,5-dienone (1). 4-Bromo-4-(1-hydroxypropyl)-2,6-di-*t*-butylcyclohexa-2,5-dienone[7] (340 mg) was dissolved in a mixture of methanol (20 ml) and pyridine (0.5 ml) and the solution left to stand at room temperature for 6 h. The reaction mixture was then poured into ice water (50 ml) and extracted with light petroleum. Washing (water) of the combined extracts, drying ($MgSO_4$), and evaporation of the solvent under vacuum at room temperature afforded 220 mg of a crude product which according to the ^1H NMR spectrum contained the title compound (82 %) and the ketone *3*[7] (18 %). Preparative TLC (cyclohexaneethylacetate 11:1) gave 106 mg (36 %) of the dienone *1* as a viscous oil. ^1H NMR ($CDCl_3$): δ 6.58 and 6.28 [1H, d (W long-range coupling), $J = 3$ Hz, CH=C], 3.73–3.55 (1H, m, C*H*OH), 3.18 (3H, s, OCH_3), 2.98 (1H, broad s, OH), 1.45–0.96 (5H, m, CH_2CH_3) and 1.28 (18H, s, *t*-Bu). IR (film): 1660, 1640 and 1615 cm^{-1}.

As satisfactory elemental analysis was not obtained for *1* the compound (140 mg) was acetylated with acetic anhydride-pyridine to yield, after purification by preparative TLC (cyclohexane-ethyl acetate 15:1) and recrystallization from light petroleum, 70 mg (44 %) of the acetate *4* as crystals, m.p. 66–67 °C. ^1H NMR ($CDCl_3$): δ 6.42 (2H, s, CH=C), 4.95 (1H, dd, $J = 3$ and 10 Hz, CHOAc), 3.18 (3H, s, OCH_3), 1.97 (3H, s, OAc), 1.85–1.45 (2H, m, CH_2CH_3), 1.27 (18H, s, *t*-Bu) and 0.85 (3H, t, $J = 7$ Hz, CH_2CH_3). IR (KBr): 1740, 1665, 1640 and 1620 cm^{-1}. (Found: C 71.41; H 9.46. Calc. for $C_{20}H_{32}O_4$: C 71.39; H 9.59).

Reaction of the dienone (1). (a) *In methanolic sulfuric acid.* A solution of the dienone *1* (73 mg) in 5 % (v/v) methanolic sulfuric acid (10 ml) was stirred at room temperature for 2 h. TLC showed the disappearance of the starting material and formation of only a single product. Isolation as above gave the crude product as a yellowish solid which was recrystallized from light petroleum to afford 45 mg (76 %) of 4-methoxy-2,6-di-*t*-butylphenol *5* as white crystals, m.p. 105.5–106.5 °C (Lit.[8] m.p. 105–106 °C). ^1H NMR ($CDCl_3$): δ 6.78 (2H, s, Ar–H), 4.77 (1H, s, OH), 3.78 (3H, s, OCH_3) and 1.45 (18H, s, *t*-Bu).

(b) *In chloroform.* The samples of the dienone *1* were stored in chloroform after purification by TLC. One of these solutions was left to stand at room temperature in the dark. After several weeks TLC showed quantitative transformation of the dienone into 4-methoxy-2,6-di-*t*-butylphenol, m.p. 105.5–106.5 °C.

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