The Chemistry of Reactive Lignin Intermediates. Part 3.[1] Products of Addition of Methanol and Water to Vinyl-substituted Quinone Methides

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The isomeric ethers 2,6-dimethyl-4-(1-methoxyprop-2-enyl)phenol and 2,6-dimethyl-4-(3-methoxyprop-1-enyl)-phenol and the corresponding isomeric alcohols have been isolated from the reactions of 4-allylidene-2,6-dimethyl-cyclohexa-2,5-dienone (1a) with methanol and water. The isomer ratios for the reactions in acidic, neutral, and basic solution are reported, together with rate data for the reactions in methanol.

ONE addition product is observed when hydroxy-compounds (alcohols, water, carboxylic acids, etc.) react with simple quinone methides like 2,6-dimethyl-4-methylenecyclohexa-2,5-dienone.[2] In contrast, a mixture of two isomeric products is expected when these compounds add to vinyl-substituted quinone methides

a; R' = Me, R = Me
b; R' = Me, R = H

SCHEME

like 4-allylidene-2,6-dimethylcyclohexa-2,5-dienone (1a) (see Scheme).[1,3] This paper reports the isolation and

[1] Part 2, J. A. Hemmingson and G. J. Leary, J.C.S. Perkin II, 1975, 1584.
[2] L. J. Filar and S. Winstein, Tetrahedron Letters, 1960, 9.
[3] L. K. Dyall and S. Winstein, J. Amer. Chem. Soc., 1972, 94, 2196.
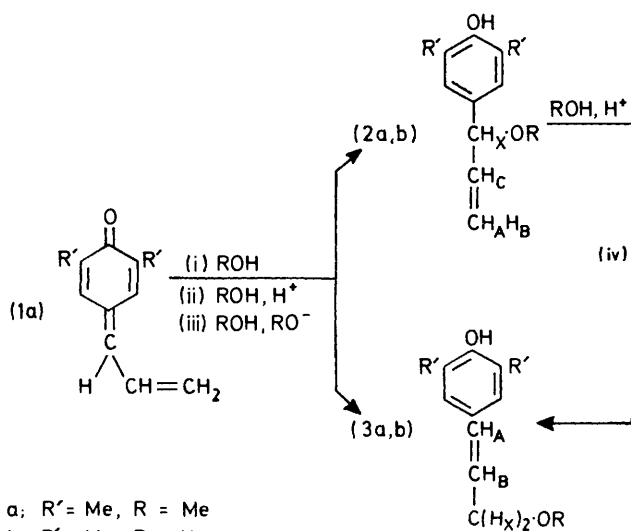
identification of the products of the reactions of compound (1a) with methanol and with water. Product ratios for reactions in acidic, neutral, and basic solution are discussed in terms of mechanisms of addition.

EXPERIMENTAL

U.v., mass, and n.m.r. spectra were recorded on Beckman Acta CV, A.E.I. MS30, and Varian EM 360 instruments, respectively, and a Pye Unicam GCV instrument was used for g.l.c. analyses.

Non-aqueous solvents were purified by standard methods and water was doubly distilled and purged with nitrogen. 4-Allyl-2,6-dimethylphenol was prepared from 2,6-dimethylphenol by Claisen rearrangement of the allyl ether.[4] 4-Allylidene-2,6-dimethylcyclohexa-2,5-dienone (1a) was prepared by oxidation [alkaline hexacyanoferrate(III)] of 4-allyl-2,6-dimethylphenol in hexane solution,[5] and stored in this solvent;[3] m/e 160 (100%, M^+), 145 (100), 117 (50), and 91 (50); λ_{max} 338 in MeOH, 350 nm in H_2O (lit.,[2] 338 nm in MeOH); δ (CCl_4) 2.00br (6 H, s, 2 CH_3), 5.58br (1 H, d, vinylic, J 9.0 Hz), 5.65br (1 H, d, vinylic, J 17.0 Hz), 6.53 (1 H, d, vinylic, J 11.6 Hz), 6.77—7.39 (1 H, m, vinylic), 6.87br (1 H, s, ring H), and 7.38br (1 H, s, ring H) (cf. ref. 3).

Reactions at 20 °C.—(a) In methanol. A solution of the quinone methide (1a) in hexane was added to methanol to give solutions which were 0.5—1.5 × 10⁻⁴ mol dm⁻³ in quinone methide and 3—10% v/v in hexane. Acidic solutions were prepared by adding a small volume of methanolic perchloric or hydrochloric acid to the quinone methide solution, and were 4.7 × 10⁻⁵—1.0 × 10⁻⁴ mol dm⁻³ in acid. Basic solutions were prepared by adding

[4] D. S. Tarbell and J. F. Kincaid, J. Amer. Chem. Soc., 1940, 62, 728.
[5] C. D. Cook and B. E. Norcross, J. Amer. Chem. Soc., 1956, 78, 3797.

sodium methoxide and were 6.8×10^{-4}—3.4×10^{-3} mol dm^{-3} in base. Reaction times were determined from spectrophotometric measurements of reaction rates.

(b) *In water.* Aqueous solutions of the quinone methide were prepared by adding a solution of the quinone methide in hexane to water and removing the hexane by evaporation at ambient temperature and reduced pressure. Carbon dioxide was excluded. Acidic and basic solutions were prepared as described for methanol. Acidic solutions were 1.6—3.2×10^{-4} mol dm^{-3} in acid and basic solutions 4.6×10^{-3} mol dm^{-3} in base.

Isolation of Products.—(a) *From methanol.* Neutral reaction mixtures were concentrated to dryness at reduced pressure and ambient temperature. Basic solutions were neutralized with ammonium chloride and acidic solutions with aqueous ammonia before evaporation. The individual products were isolated by preparative layer chromatography (p.l.c.) (ether–hexane 9 : 11).

(b) *From water.* Neutral and acidic reaction mixtures were extracted with an equal volume of chloroform. Basic reaction mixtures were neutralised with dilute acid and ammonium chloride before extraction. The chloroform extracts were concentrated to dryness and the individual products were isolated by p.l.c. (ether–hexane 7 : 3).

Analysis of the Isomer Ratios of the Products from Methanol and from Water.—Method A (g.l.c.). Methanol reaction mixtures were concentrated to dryness and the products were redissolved in ether for g.l.c. analysis on 3% OV-1 at 170 °C. Relative response factors for the products (2a)

complete, Y is the increase in absorbance after isomerization has taken place, and $a = \varepsilon_3/\varepsilon_2$, *i.e.* the extinction coefficient ratio of the two isomers, determined by isomerizing pure (2a) to (3a), and (2b) to (3b), in solution. Each isomerization was carried out by adding a small volume of either perchloric or hydrochloric acid solution to the reaction mixture. This method of analysis was quantitative for the reactions in methanol, but not for the reactions in water, because of the presence of an additional absorbance at $\lambda_{max.}$ for (3b) (see Results).

Kinetic Runs in Methanol.—The rates for reactions (i)—(iv) (see Scheme) were determined spectrophotometrically, by recording the disappearance of (1a) at 340 nm [reactions (i)—(iii)], or the appearance of (3a) at 270 nm [reaction (iv)]. First-order rate constants were determined from the equations $kt = 2.303 \log (A_0 - A_\infty)/(A_t - A_\infty)$ for addition runs and $kt = 2.303 \log (A_\infty - A_0)/(A_\infty - A_t)$ for isomerization runs, where A is the absorbance of the solution at 340 and 270 nm, respectively. Kinetic plots were linear for at least three half-lives.

RESULTS AND DISCUSSION

Two products, (2a) and (3a) were isolated from the reactions of the quinone methide (1a) with acidic, neutral, or basic methanolic solution; three products including (2b) and (3b) were isolated from the corresponding reactions of (1a) with water. Spectral data for (2a and b) and (3a and b) are shown in Table 1.

TABLE 1

Spectral data for products (2a and b) and (3a and b)

Product	$\lambda_{max.}$/nm	m/e (%)	δ(CDCl$_3$; Me$_4$Si)
(2a)	276 †	192 (50, M^+), 177 (30), 165 (50), 161 (100), 145 (60), 117 (50), 91 (50)	2.23 (6 H, s, 2 CH$_3$), 3.30 (3 H, s, CH$_3$O), 4.50 (d, H$_X$, J_{CX} 6.4 Hz), 4.75br (1 H, s, OH, D$_2$O exch.), 5.18br (d, H$_B$, J_{BC} 9.5 Hz), 5.20br (d, H$_A$, J_{AC} 17.4 Hz), 5.96 (m, H$_C$), 6.93 (2 H, s, ArH)
(3a)	268	192 (77, M^+), 177 (40), 165 (23), 161 (100), 145 (77), 117 (40), 91 (50)	2.22 (6 H, s, 2 CH$_3$), 3.35 (3 H, s, CH$_3$O), 4.05 (d, 2H$_X$, J_{AX} + J_{BX} 5.4 Hz), 4.82br (1 H, s, OH, D$_2$O exch.), 6.09 (m, H$_B$), 6.49 (d, H$_A$, J_{AB} 16.0 Hz), 7.01 (2 H, s, ArH)
(2b)	272 †	Me$_3$Si deriv. 322 (50, M^+), 307 (100), 295 (33), 233 (50), 217 (33)	1.87br (1 H, s, OH, D$_2$O exch.), 2.21 (6 H, s, 2 CH$_3$), 4.73br (1 H, s, ArOH, D$_2$O exch.), 5.05 (d, H$_X$, J_{CX} 6.0 Hz), 5.18br (d, H$_B$, J_{BC} 9.5 Hz), 5.29br (d, H$_A$, J_{AC} 17.0 Hz), 6.05 (m, H$_C$), 6.96 (2 H, s, ArH)
(3b)	264	Me$_3$Si deriv. 322 (56, M^+), 307 (100), 295 (10), 233 (66), 217 (50)	1.67br (1 H, s, OH, D$_2$O exch.), 2.23 (6 H, s, 2 CH$_3$), 4.29 (d, 2H$_X$, J_{AX} + J_{BX} 5.0 Hz), 4.77br (1 H, s, ArOH, D$_2$O exch.), 6.18 (m, H$_B$), 6.54 (d, H$_A$, J_{AB} 15.9 Hz), 7.04 (2 H, s, ArH)

† $\varepsilon_{3a}/\varepsilon_{2a}$ 14.48 ± 0.58 (270 nm); $\varepsilon_{3b}/\varepsilon_{2b}$ 11.64 ± 0.69 (264 nm).

and (3a) were determined by using standards with known concentration ratios. For water reaction mixtures, the dry product mixture was treated with hexamethyldisilazane–chlorotrimethylsilane in pyridine and the resulting trimethylsilyl ethers were dissolved in carbon tetrachloride for g.l.c. analysis on 3% OV-1 at 190 °C. Relative response factors were determined as above. This procedure was necessary as the free alcohols (2b) and (3b) were not completely stable under these column conditions.

Method B (u.v. spectrophotometry). This method utilized the acid-catalysed isomerization of the product (2) to the product (3) with >99% conversion (see Results). Isomer ratios were calculated by using the equation $c_2/c_3 = [Y/(1 - a^{-1})]/X - [Y/a(1 - a^{-1})]$, where c_2/c_3 is the concentration ratio of the isomers (2) and (3), X is the absorbance at the absorption maximum of (3) when addition is

The mass spectral data for products (2a) and (3a) showed parent ions of the same mass, corresponding to methanol addition products of (1a). The two compounds gave similar fragmentation patterns, with loss of a methoxy-group predominating and differing significantly only in the relative intensity of the fragment m/e 165. The u.v. spectral data were consistent with (2a) and (3a) being an isomeric pair, with (3a) being more highly conjugated than (2a). The differences between $\lambda_{max.}$ values and extinction coefficients were similar to those observed for isomeric pairs like 1-phenylprop-2-en-1-ol and 3-phenylprop-2-en-1-ol [6] and the $\lambda_{max.}$ value

[6] H. L. Goering and R. E. Dilgren, *J. Amer. Chem. Soc.*, 1959, **81**, 2556; 1960, **82**, 5744.

for (3a) was similar to the values for 4-(3-hydroxy-prop-l-enyl)phenol and its 2-methoxy- and 2,6-di-methoxy-derivatives.[7] The n.m.r. data were in accord with structures (2a) and (3a) (see Scheme). The strongly coupled spectrum obtained for (3a) and the value of J for the vinylic protons (16.0 Hz) indicated that this compound was the *trans*-isomer. Further evidence for the suggested structures was the observation of essentially quantitative acid-catalysed isomerization of (2a) to (3a) (see Table 3). A compound with structure (2a) would be expected to undergo essentially complete allylic rearrangement to (3a), owing to the phenyl-to-vinyl conjugation introduced.[8]

The mass spectra of the trimethylsilyl derivatives of the products (2b) and (3b) also showed parent ions having the same mass, corresponding to bistrimethyl-silyl derivatives of water addition products of (1a). The two compounds also had similar fragmentation patterns with loss of a methyl group, characteristic of trimethylsilyl derivatives, predominating, and differing significantly only in the relative intensity of the fragment m/e 295. The u.v. and n.m.r. data and the acid-catalysed isomerization of (2b) to (3b) were entirely analogous to those described above for (2a) and (3a), and were therefore consistent with the assigned structures.

The additional product isolated from water reaction mixtures appears to be a dimer of (1a) with one molecule of water added. However it does not appear to be a product from reactions of (1a) in dilute aqueous solution and therefore its formation will not be discussed in this paper; it is being studied at present. Absorbance by this compound at $\lambda_{max.}$ for (3b) interfered with spectro-scopic determination of isomer ratios in water as noted above.

The products of addition of methanol and water to the quinone methide (1a) in acidic, neutral, and basic solution are thus mixtures of two isomers resulting from both 1,6- and 1,8-addition. Dyall and Winstein[3] also detected two products, which were not identified, from the reaction of (1a) with neutral methanol.

In neutral and in basic solution the isomer ratio did not change with time when addition was complete. In acidic solution, the rate of acid-catalysed isomerization of (2a) to (3a) and (2b) to (3b) was so much less than the rate of addition of methanol or water, that the isomer ratio could be determined when addition was essentially complete, but before significant isomerization had occurred. Rate constants for addition of methanol to the quinone methide (1a) in acidic, neutral, and basic solution, and for acid-catalysed isomerization of (2a) to (3a), are shown in Table 2. The second-order rate constants were obtained from first-order rate constants $(k_2 = k_1/[\text{OH}^-]$ or $k_1/[\text{H}^+])$ and were constant over the two- to three-fold variation in base or acid concentration studied. Isomeric rearrangement of allylic ethers and alcohols is catalysed by acids,[8] and the conversion of 1-phenylprop-2-en-1-ol into 3-phenylprop-2-en-1-ol is

[7] G. Aulin-Erdtman and R. Sandén, *Acta Chem. Scand.*, 1968, **22**, 1187.

thought to occur by an S_N1' mechanism involving the conjugate acid of the alcohol.[6] Electron-releasing sub-stituents, particularly the p-hydroxy-group, as in (2a and b), would favour this mechanism by assisting heterolysis. When a solution of the methyl ether (2a)

TABLE 2

Rate constants for reactions (i)—(iv) in methanol

Reac-tion †	[Acid]/ mol dm⁻³	[Base]/ mol dm⁻³	k_1/s^{-1}	k_2/dm^3 mol⁻¹ s⁻¹
(i)			6.82×10^{-5} (25 °C) ‡	
(ii)	4.7×10^{-5}		$ca.\ 5 \times 10^{-2}$	$ca.\ 10^3$ (20 °C)
(iii)		1.41×10^{-4}	2.55×10^{-3}	
		2.55×10^{-4}	4.79×10^{-3}	$1.84 \pm 0.09 \times 10^1$ (20 °C)
(iv)	5.07×10^{-5}	3.68×10^{-4}	6.72×10^{-3} 3.70×10^{-4}	
	1.01×10^{-4}		7.96×10^{-4}	7.60 ± 0.23 (25 °C)
	1.69×10^{-4}		1.29×10^{-3}	

† See Scheme. ‡ $cf.$ 6.72×10^{-5} s⁻¹ (ref. 3).

was isomerized in an equimolar mixture of methanol and ethanol, a mixture of methyl and ethyl ethers was obtained. This observation was consistent with the proposed mechanism.

The kinetically controlled product ratios for addition of methanol and of water to the quinone methide (1a) in acidic, neutral, and basic solution (Table 3) show that in

TABLE 3

Isomer ratios of the products of addition of methanol and of water to the quinone methide (1a)

Reaction †	[(2a)]/[(3a)] Method A	Method B	[(2b)]/[(3b)] Method A
(i)	2.23 ± 0.13	2.22 ± 0.13	2.66 ± 0.16
(ii)	5.75 ± 0.52	6.02 ± 0.36	3.37 ± 0.27
(iii)	4.28 ± 0.25	4.53 ± 0.27	11.4 ± 1.14
(iv)	<0.01		<0.01

† See Scheme.

each case a higher proportion of the thermodynamically less stable isomer (2a or b) was formed. In a previous paper,[1] three mechanisms were proposed to account for the pH dependence of the kinetics of addition of water to 4-allylidene-2-methoxycyclohexa-2,5-dienone; these mechanisms are applicable to the reactions in acidic, neutral, and basic solution reported here.

As there is little information in the literature on product ratios for nucleophilic addition to extended conjugated systems, the addition of methoxide and hydroxide ions to the quinone methide (1a) is of par-ticular interest. The higher proportion of (2a and b) suggests that electron deficiency at the reactive carbon atom is not the controlling factor in determining the position of addition, as the terminal carbon atom in this case would be the most electron-deficient.[8] Solvation and entropy factors could favour the transition state for the 1,6-product, which has a less dispersed charge than

[8] C. K. Ingold, ' Structure and Mechanism in Organic Chem-istry,' 2nd edn., Bell, London, 1969, pp. 849, 861.

that for the 1,8-product, and which retains free rotation about the 6,7-bond.[9] Dyall and Winstein [3] also found 1,6-addition to be favoured (ratio 1.7 : 1) in the reaction of tetrahydroaluminate ion with (1a).

In acidic solution, the proposed mechanism involves formation of an allylic carbocation and combination of this intermediate with available nucleophilic species. In this case, the higher proportion of (2a and b) suggests that the product ratio is determined by the charge distribution of the carbocation, as the nucleophiles are small and weak and steric hindrance to combination would be low.[10,11] In each case the isomer ratio is lowest for neutral solution, for which a mechanism involving concerted nucleophilic attack and proton transfer by solvent molecules is suggested.

Implications for Lignin Biosynthesis.—The mobility of the ether linkage of (2a) and the alcohol linkage of (2b)

in acidic solution has an interesting implication for lignin biosynthesis, in that, if vinyl quinone methides were involved,[12] their 1,6-addition products with hydroxy-compounds could provide a mobile linkage in the probably weakly acidic lignification medium, and substitution by other nucleophilic species present could accompany any isomerization. This might allow the formation of linkages with compounds that were less able to compete for addition to the quinone methide at the time of its formation, but were subsequently in a more favourable environment for capturing a carbo-cation. The quinone methides thought by Freudenberg and Harkin [13,14] to be involved in lignin biosynthesis are without vinyl conjugation and can form only the 1,6-addition product. The mobility of the linkage in these compounds is therefore also of interest.

[9] J. F. Bunnett, in ' Techniques of Chemistry,' ed. A. Weissberger, Wiley, New York, 1974, 3rd edn., vol. VI, part I, pp. 375, 425.

[10] R. H. deWolfe and W. G. Young, *Chem. Rev.,* 1956, **56**, 797.

[11] M. Andrac and C. Prevost, *Bull. Soc. chim. France,* 1964, 2284.

[12] I. J. Miller and G. J. Smith, *Austral. J. Chem.,* 1975, **28**, 825.

[13] K. Freudenberg and A. C. Neish, ' Constitution and Biosynthesis of Lignin,' Springer–Verlag, New York, 1968, p. 93.

[14] J. M. Harkin, in ' Oxidative Coupling of Phenols,' eds. W. I. Taylor and A. R. Battersby, Dekker, New York, 1967, p. 285.