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PREPARATION AND REACTIVITY OF 2,6–DIMETHOXY–4–ALLYLIDENE–2,5–CYCLOHEXADIEN–1–ONE (VINYL QUINONE METHIDE) A NOVEL SYNTHESIS OF SINAPYL ALCOHOL

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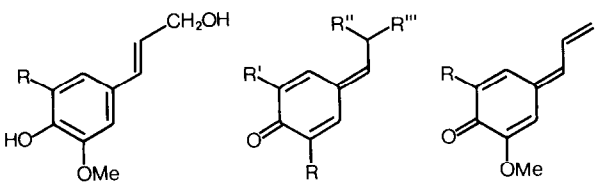
Abstract – Title compound (3b), prepared in concentrated $CHCl_3$ or benzene solution and spectroscopically characterized, is shown to be an useful intermediate for the synthesis of sinapyl alcohol (1b) and its derivatives.

The biosynthesis of lignin is thought to occur by oxidative coupling of coniferyl (1a) and sinapyl (1b) alcohols[1] *via* a quinone methide–type intermediate, such as (2), which successively add hydroxy compounds (alcohols, phenols, acids and sugars). Vinyl quinone methide-type compounds (3), which could be derived from alcohols (1) by dehydration or from the corresponding allyl and propenyl phenols by oxidation, have been observed during the oxidation of eugenol by peroxidase.[2] However, their biological role or their synthetic usefulness has not been recognized so far. The only reported studies[3] are those of Leary[4] who measured, by UV spectrometry, the rate of decay of (3a) and (3b) obtained by flash photolysis of very dilute (10^{-5} M) aqueous solutions of coniferyl (1a) and sinapyl (1b) alcohols. Vinyl quinone methides (3) have been considered not practically available because of their short lifetimes and the extremely low concentrations in which they could be obtained.



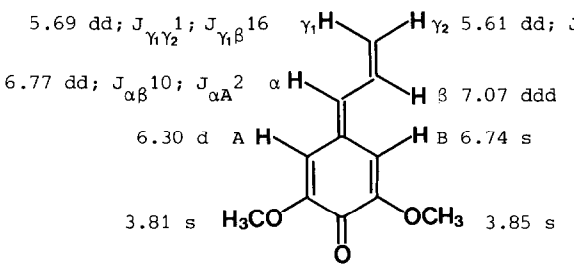
1 2 3

a R=H b R=OMe a R=H b R=OMe

I describe in this paper the synthesis of (3b), in concentrated solution, which makes this reactive intermediate readily available also for multigram scale preparations.

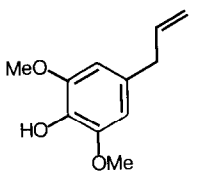
Ag_2O (2.4 g) was added to a solution in $CHCl_3$ of commercially available 2,6–dimethoxy–4–allylphenol (4) (1 g in 20 mL) at room temperature with vigorous stirring. The fast exothermic reaction was complete after 6 minutes (TLC, silica gel, ethyl acetate/hexane 2/1, Rf (4) 0.52, Rf (3b) 0.19) after which the suspension was filtered through Celite. The ^1H NMR of the yellow-orange solution ($CDCl_3$) showed the presence only of the compound (3b), in a pure form[5]

^{1}H NMR, δ vs TMS, J in Hz



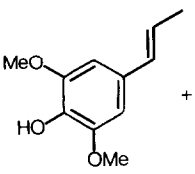
UV $\lambda_{max}^{CHCl_3}$ 285 nm (log ε 4.11)
362 nm (log ε 2.84)

IR ($CHCl_3$) 1633, 1573, 1340
1270, 1110 cm^{-1}



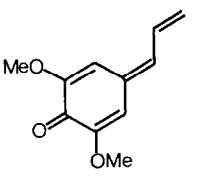
4

Ag_2O
$CHCl_3$
or C_6H_6
6-9 min.



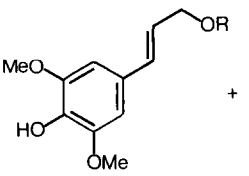
5 + 4

$NaBH_4$
CH_3OH
or H_2O

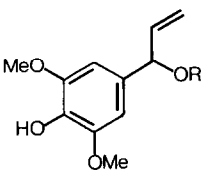


3b

ROH
(PTSA)



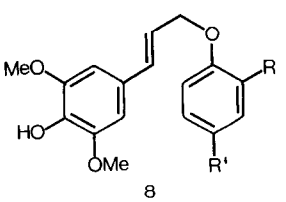
6 +



7

	overall % yield	7/6
a R=CH_3	86	1.2
b R=Et	74	1.7
c R=$PhCH_2$	70	2.6
d R=$PhCH{=}CHCH_2$	80	3.0

ArOH
(Et_3N)

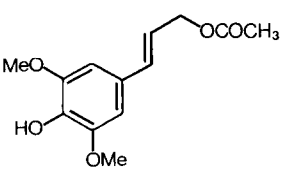


8

	% yield
a R=R'=H	75
b R=H R'=OCH_3	71
c R=H R'=NO_2	20
d R=OCH_3 R'=H	40

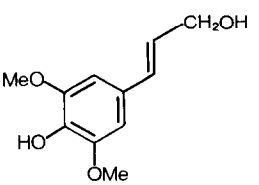
CH_3COOH 35 min. 80%

H_2O
$NaHCO_3$



9

LiAlH$_4$
THF, 30 min.
-10 °C, 100%



1b

In order to verify the value of the vinyl quinone methide (3b) as biological and/or synthetic intermediate for the formation of natural substances it was prepared in benzene solution (0.07 M) and it was reacted with several substrates.

$NaBH_4$ reduction of vinyl quinone methide (3b) (VQM) gave the allylphenol (4) and the propenylphenol (5). The product ratio was found to be dependent on the reaction medium: in CH_3OH a ratio (5):(4) = 2 was found, in $NaHCO_3$ aqueous solution the ratio was 0.7.

VQM reacted readily with alcohols, under acid catalysis (*p*-toluenesulfonic acid, PTSA), to give a mixture of the two isomeric ethers derived from 1-8 (6) and 1-6 (7) addition.[6]

With phenols, in the presence of catalytic amounts of Et_3N, VQM undergoes a regioselective 1-8 addition leading to sinapyl ethers (8).

Attempts to convert VQM (3b) to sinapyl alcohol (1b) by addition of water proved to be unsuccesful. Indeed, the procedure was completely ineffective under either acid or basic conditions due to the fast formation of an unsoluble sawdust-like polymer, while in neutral medium only small amounts of sinapyl alcohol could be detected. Nevertheless, sinapyl alcohol could be obtained in good yield (80%) by first reacting (3b) with acetic acid, in the presence of sodium acetate, for 35 minutes[7] and by subsequently treating sinapyl acetate (9) with $LiAlH_4$ in THF[8] for 30 minutes.

The synthesis thus obtained of sinapyl alcohol is simple and more convenient, in that faster, than Freudenberg synthesis[9] which utilises esterification of sinapic acid and reduction by $LiAlH_4$.

It is well known that compounds such as (4) and (5) are biosynthetically derived from cinnamyl alcohols (1), but "the exact mechanism of this reduction of the alcohol to yield alternatively allylphenols and propenylphenols (*e. g.* isoeugenol) still remains to be determined."[10] The stability of VQM in water deserves further attention. This compound, in neutral or slightly basic aqueous solution, appears to be more stable than sinapyl alcohol itself; VQM rather than sinapyl alcohol is obtained when sinapyl acetate (9) is treated with aqueous $NaHCO_3$.

Moreover, in a one pot experiment, if one dissolves sinapyl acetate in aqueous $NaHCO_3$, the VQM intermediate is readily reduced by $NaBH_4$ to the allyl (4) and propenyl (5) phenols in a 10:7 ratio.

In the light of the above results and of feeding experiments,[11] vinyl quinone methides (3) can be proposed as conceivable biological intermediates in the biosynthesis of allylphenols and propenylphenols from cinnamyl alcohols.

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4. G. Leary, *J.C.S. Perkin II,* 1972, 640. J. A. Hemmingson and G. Leary, *J.C.S. Perkin II,* 1975, 1584.
5. The only reported NMR of a vinyl quinone methide has been described by L. K. Dyall and S. Winstein, *J. Am. Chem. Soc.,* 1972, 94, 2196.
6. All compounds have been characterized by NMR, IR, UV and MS with the exception of the unstable (8c). The yields of isolated compounds refer to (4). Spectroscopic data are given for the compounds (6b) and (7b) as an example. Products were isolated by flash chromatografy. (6b): mp 68°C (cyclohexane), ^1H NMR ($CDCl_3$) (δ vs TMS, J in Hz): 1.20 (t, J=6.6, CH_2-CH_3), 3.53 (q, J=6.6, CH_2-CH_3), 3.87 (s, OCH_3), 4.10 (dd, $J_{\gamma\beta}$=6.0, $J_{\gamma\alpha}$=1, γCH_2), 5.60 (s, OH),

6.17 (dt, $J_{\beta\alpha}$=16, βCH), 6.50 (dd, αCH), 6.63 (s, ArH). λ_{max}^{EtOH} 277 nm (log ε 4.22). MS m/e (rel. int.): 238 (100, M^+). (7b) : oil, ^1H NMR: 1.19 (t, J=6.7, $CH_2-C\underline{H}_3$), 3.46 (q, J=6.7, $C\underline{H}_2-CH_3$), 3.87 (s, OCH_3), 4.63 (d, $J_{\alpha\beta}$=7, αH), 5.20 (m, γCH_2), 5.53 (s, OH , 5.90 (ddd, $J_{\beta cis}$=10, $J_{\beta trans}$=16, βH). λ_{max}^{EtOH} 241 nm (log ε 3.90), 267 sh (3.34). MS m/e: 238 (100, M^+).

7. The benzene solution of vinyl quinone methide (prepared from 4 g of (4) as described above) was filtered in a flask containing 50 ml of CH_3COOH and 8 g of CH_3COONa. When the reaction was complete (35 min.) CH_3COONa was filtered off and the excess of acetic acid was removed under high vacuum. The residual oil was quickly filtered through 30 g of silica gel by eluting with hexane/ethyl acetate 1/1. Evaporation of the solvent left 4.1 g of (9); mp 62 °C (cyclohexane). ^1H NMR ($CDCl_3$, δ vs TMS, J in Hz) : 2.06 (s, $COCH_3$), 3.86 (s, OCH_3), 4.70 (d, $J_{\gamma\beta}$=6, γCH_2), 5.73 (s, OH), 6.17 (dt, $J_{\beta\alpha}$=15, βH), 6.56 (d, αH), 6.65 (s, ArH). λ_{max}^{EtOH} 280 nm (log ε 4.14). IR ν_{max} 1730 cm^{-1}. MS m/e: 252 (100, M^+), 210 (15), 209 (20), 193 (12), 161 (20), 149 (16).
8. A solution of 2 g of (9) in 10 ml of dry THF was added dropwise to a stirred suspension of 0.61 g of $LiAlH_4$ in 10 ml of THF at −10 °C under a nitrogen atmosphere. The solution was stirred at the same temperature for additional 30 minutes; 5 ml of ethyl acetate were added, then 5 ml of wet THF followed by 40 ml of cold water and 30 ml of CH_2Cl_2. The water phase was neutralized with a $KHSO_4$ solution then extracted twice with CH_2Cl_2. To the organic layers, dried over Na_2SO_4, 50 ml of toluene were added and the solution was concentrated under vacuum to 30 ml keeping the temperature below 10 °C. Sinapyl alcohol was crystallized letting the toluene solution to exchange hexane vapours in a close container in the cold. Even when an oil was obtained the alcohol was very pure and the yield quantitative.
9. K. Freudenberg and H. H. Hübner, *Chem. Ber.*, 1952, 85, 1181.
10. J. B. Harborne in *Biosynthesis* Vol. 5, ed. J. D. Bu'Lock, The Chemical Society, London, 1977, p. 45.
11. A feeding experiment concerning step (1a)→eugenol has been reported. The results entirely fit this hypothesis: [γ-$^{14}C^3H_2OH$]coniferin was incorporated into eugenol without change of the ^3H: ^{14}C ratio. This demonstrates that both hydrogen atoms, linked directly to C-1 of the cinnamyl alcohol, are retained during the reduction to allylphenols and proves that these alcohols are immediate precursor in this conversion. M. Klischies, J. Stöckigt and M. H. Zenk, *J. C. S. Chem. Comm.*, 1975, 879.

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