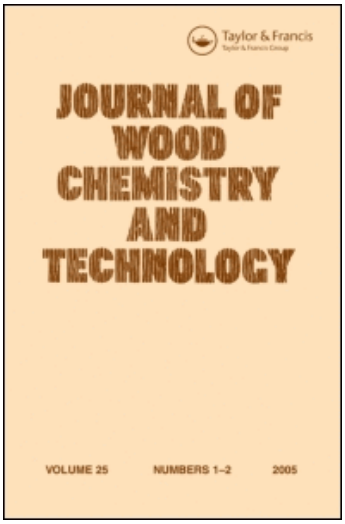


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# Stereochemical Aspects Op Addition Reactions Involving Lignin Model Quinone Methides

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# STEREOCHEMICAL ASPECTS OF ADDITION REACTIONS INVOLVING LIGNIN MODEL QUINONE METHIDES

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## ABSTRACT

Primary amines, similarly to anthrahydroquinone and anthranol, added to the quinone methide from a lignin model, guaiacylglycerol-β-guaiacyl ether, give predominantly the threo-adduct. The configurations were assigned from proton and C-13 NMR spectra of cyclic tetrahydro-1,3-oxazine derivatives, and were compared with configurations of 1,3-dioxanes determined similarly. The predominance of erythro-stereochemistry from reactions of organic acids with this quinone methide is explained by solvation effects.

## INTRODUCTION

Quinone methides are reactive compounds and probable intermediates in alkaline reactions of lignin.[1] They are also thought to be critical intermediates in the anthrahydroquinone (AHQ) catalyzed delignification of wood.[2,3] Addition reactions of quinone methides 1-3 can occur in either basic, neutral or mildly acidic media. However, the degree of stereospecificity and the

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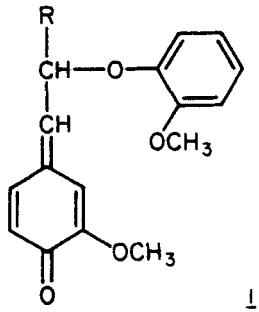
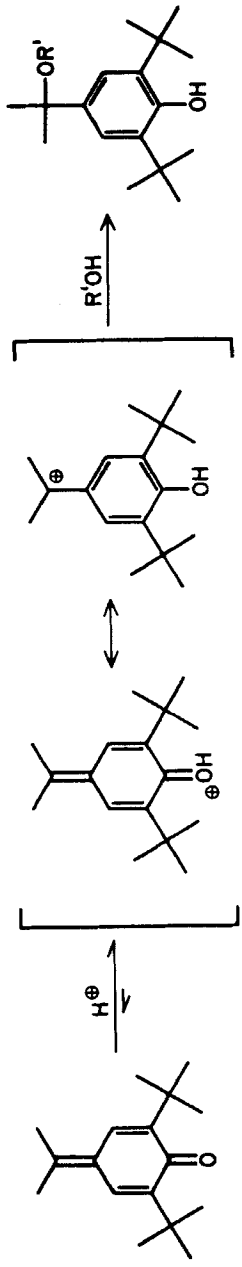
predominant product isomer appear to depend on the reaction conditions. For example, in a study of the reactions of quinone methide 1 with organic acids, Nakatsubo concluded[4] that nucleophiles react with quinone methide 1 to give predominantly the erythro-isomer.[5] In contrast, alkaline addition of AHQ or anthranol to quinone methide 1 or 2 gives exclusively the threo-adduct.[6-9]



1 R = $CH_2OH$
2 R = $CH_3$
3 R = H

Acid catalyzed addition of alcohols to the quinone methide 2,6-di-t-butyl-4-isopropylenequinone 4[10] probably involves addition of the alcohol not to the quinone methide 4 as such but to the benzylic carbonium ion 5 formed by protonation of the quinone methide, Scheme 1.

The mechanism is not as clearly defined at pH 3-7 in aqueous solution. Ivnas and Lindgren[11] provided a good example of the two different kinds of mechanisms by comparing the sulfonation of vanillyl and veratryl alcohols. Vanillyl alcohol (4-hydroxy-3-methoxybenzyl alcohol) can form either a quinone methide or a benzyl carbonium ion and is rapidly sulfonated in base or acid while veratryl alcohol (3,4-dimethoxybenzyl alcohol), which cannot form a quinone methide, is sulfonated rapidly only in acid. A kinetic study[12] of the reaction between mercaptoacetic acid and vanillyl alcohol over a pH range of 2 to 6 also indicated a duality in mechanisms. Formation of the quinone methide was

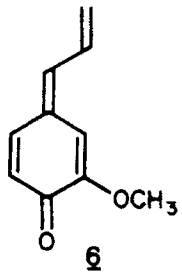



4 5

SCHEME 1

postulated to be rate determining at pH 5 whereas at lower pH it was not determined whether the reaction was $S_N1$ (via a carbonium ion) or $S_N2$.

Reactions of water, alcohols or acids with quinone methides that are more appropriate lignin models have been examined.[13-16] The rate of disappearance of the vinylogous quinone methide 6 passes through a minimum at pH 5 in aqueous solution.[13] For aliphatic alcohols and organic acids in low polarity solvents (e.g., hexane) the rate of disappearance of a variety of quinone methides follows first-order kinetics with respect to the quinone methide and second-order kinetics with respect to the alcohol or acid. The reaction was 1.5 order with regard to water. The rates were qualitatively dependent on the pKa of the acid or alcohol.[14] Additions of water to the quinone methide structure were postulated[15] to proceed via the carbonium ion at low pH, by direct nucleophilic attack on the quinone methide at high pH, and possibly via a general acid-catalyzed reaction at intermediate pH. In the last case, the extremely high negative entropy of activation and the overall third-order reaction kinetics observed[14] suggested that hydroxy compounds reacted with the quinone methides via a termolecular complex which could allow concerted protonation of the carbonyl group and nucleophilic attack on the benzylic carbon atom. Again the evidence presented[16] suggests that, even under mildly acidic conditions, the quinone methide is the key reactant.

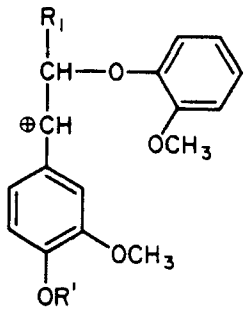



6

7 $R^1 = CH_3$, $R_1 = CH_2OH$

8 $R^1 = CH_3$, $R_1 = CH_3$

9 $R^1 = H$, $R_1 = CH_2OH$



Huckel molecular orbital calculations[8,17] indicate: the high susceptibility of quinone methides to undergo attack by nucleophiles at Cα, the propensity for attack by electrophiles at the 4-oxygen atom (e.g., protonation to give the carbonium ion), the similarity in bond orders (other than the 4-O) in the quinone methide and the corresponding carbonium ion, and the higher charge density at Cα in the carbonium ion. Since the quinone methide and the benzylic carbonium ion have essentially the same shape, the same factors that determine the stereochemistry of the products from quinone methide reactions should govern the stereochemistry in products from carbonium ion reactions but the stereospecificity should be less for the more reactive carbonium ion. Indeed reactions of quinone methides 1 and 2 with anthranol in aqueous base gave the threo-adduct in over 98% yield,[6] but the carbonium ions 7 and 8 generated from the corresponding α-bromoveratryl compounds reacted with the trimethylsilyl ether of anthranol to give predominantly the threo-isomers (66% and 60%, respectively).[8,18]

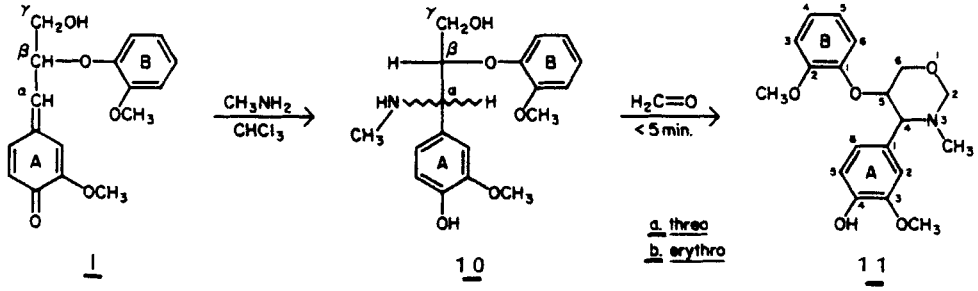
Reaction of quinone methide 1 with water gave results which can be explained in terms of addition to quinone methides or carbonium ions, depending on pH. An approximately 1:1 ratio of threo- and erythro-isomers of guaiacylglycerol-β-guaiacyl ether resulted from the reaction of water with quinone methide 1 in $CHCl_3$ in the presence of catalytic amounts of HCl.[4] Under these conditions the reaction probably proceeded via the less selective carbonium ion 9. The threo-isomer predominated (70%) when the reaction was carried out in aqueous dioxane in the absence of acid.

Attempts to add hydroxide to quinone methides 1-3 (to give α-alcohols with well characterized stereochemistry[19]) were unsuccessful. Quinone methides do undergo nucleophilic addition of primary and secondary amines in high yield,[20] and this reaction has now been utilized to examine the stereochemistry of quinone methide reactions under basic conditions with nucleophiles smaller than AHQ and anthranol.

## RESULTS AND DISCUSSION

A solution of quinone methide 1 in $CHCl_3$ was treated with excess methylamine to give the α-amine adduct 10 in quantitative yield (Scheme 2). Other primary amines, such as isopropylamine, n-propylamine or aniline, and secondary amines, such as dimethylamine, diethylamine, morpholine, or piperidine, (not di-isopropylamine) also reacted with 1 to give corresponding adducts.[8] All adducts were predominantly (over 90%) a single isomer as determined by 270 MHz proton NMR spectroscopy. Parallel reactions carried out with 2 also manifested the same stereospecificity.[8] The predominant isomer was expected to be the threo-adduct based on results of addition of anthranol or AHQ to quinone methides 1 and 2.[6,7] Although the $^1H$ NMR data indicated a single isomer of each amine adduct, it could not be determined whether that isomer was erythro or threo.

Stereochemistry can be determined from $^1H$-$^1H$ coupling constants in 6-membered ring derivatives such as tetrahydro-1,3-oxazines (e.g., 11). Coupling constants are dependent, in part, on the dihedral angles between the coupled protons,[21,22] and, for an ideal chair conformation, protons on adjacent carbons are oriented either axial-axial (with a 180° dihedral angle and J ~ 10 Hz), axial-equatorial (60°, J ~ 3 Hz) or equatorial-equatorial (60°, J ~ 3 Hz). The dihedral angles implied by the coupling constants in the $^1H$ NMR spectra of 11 (Fig. 1, Table 1) allow an




1 10 11

SCHEME 2

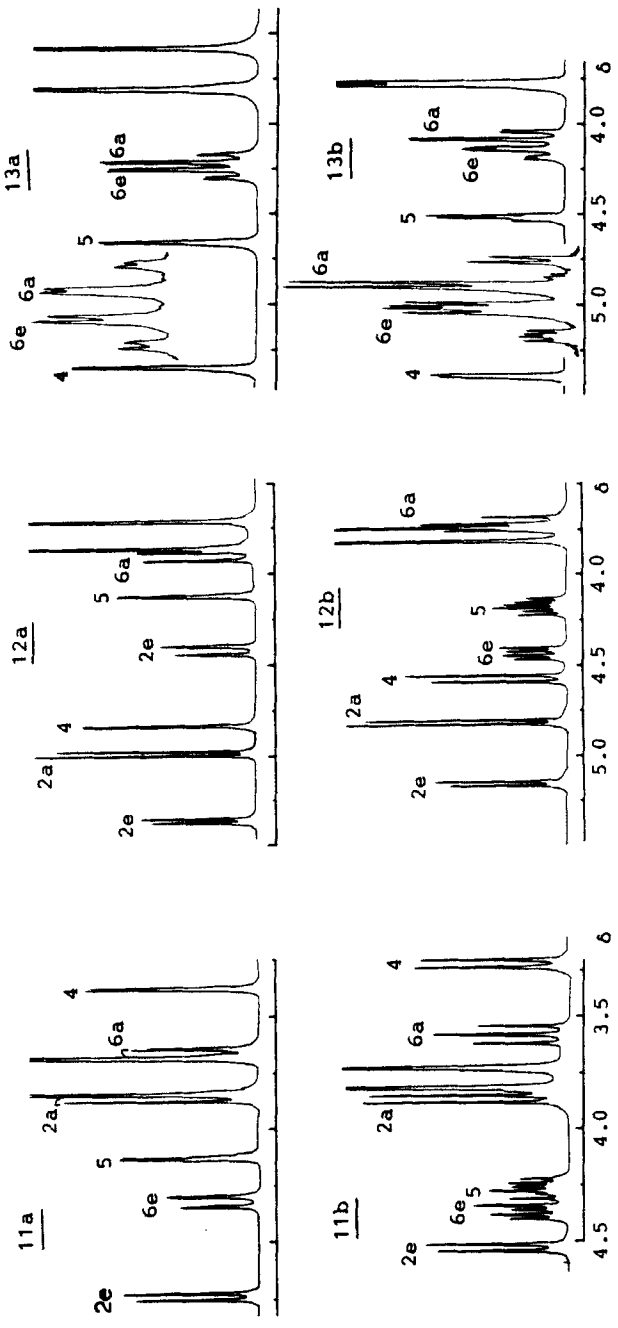
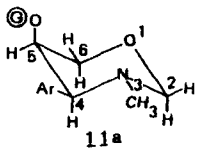
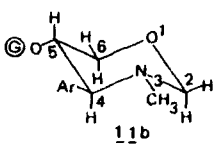


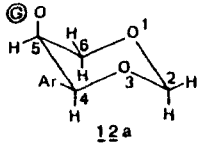

FIGURE 1. Partial $^{1}H$ NMR spectra of 11, 12 and 13 in $CDCl_3$.

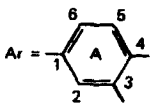
TABLE 1[f]

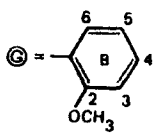
Proton NMR Data for Compounds 11, 12, and 13

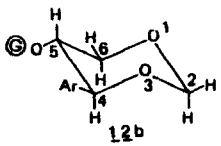

11a

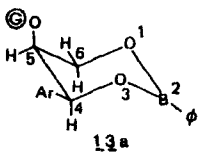

11b

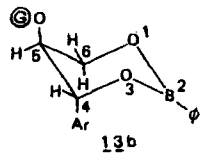

12a


Ar =


G =


12b


13a


13b

| Compound | 11a | | 11b | | 12a | | 12b | | 13a[g] | | 13b[g] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Solv. | C | A | C | A | C | A | C | A | C | A | C | A |
| H-2e | 4.73[d] | 4.58[d] | 4.53[d] | 4.48[d] | 5.38[d] | 5.20[d] | 5.16[d] | 5.07[d] | - | - | - | - |
| H-2a | 3.86[d] | 3.93[d] | 3.86[d] | 3.82[d] | 5.00[d] | 5.00[d] | 4.82[d] | 4.82[d] | - | - | - | - |
| H-4 | 3.38[d] | 3.57[d] | 3.27[d] | 3.21[d] | 4.85[d] | 4.95[d] | 4.58[d] | 4.51[d] | 5.35[d] | 5.55[d] | 5.39[bd] | 5.41[dd] |
| H-5 | 4.12[m] | 4.41[m] | 4.27[m] | (4.23- | 4.14[m] | 4.39[m] | 4.19[ddd] | 4.22[ddd] | 4.67[ddd] | 4.94[m] | 4.52[ddd] | 4.74[ddd] |
| H-6e | 4.31[bd] | 4.21[bd] | 4.37[dd] | 4.36[m]) | 4.43[ddd] | 4.30[ddd] | 4.44[ddd] | 4.37[ddd] | 4.28[dd] | 4.43[dd] | 4.16[ddd] | 4.17[ddd] |
| H-6a | 3.66[dd] | 3.74[dd] | 3.58[dd] | 3.43[dd] | 3.92[dd] | 4.01[dd] | 3.73[dd] | 3.64[dd] | 4.20[dd] | 4.33[dd] | 4.08[dd] | 4.07[dd] |
| $J_{2e2a}$ | 8.1 | 8.5 | 8.1 | 8.5 | 6.2 | 6.2 | 6.3 | 6.2 | - | - | - | - |
| $J_{45}$ | 2.4 | 2.6 | 8.6 | 7.9 | 1.7 | 1.7 | 9.0 | 9.0 | 2.0 | 1.8 | 2.5 | 2.4 |
| $J_{56e}$ | <1 | <1 | 5.1 | p | 1.2 | 1 | 5.0 | 5.0 | 2.6 | 1.6 | 3.7 | 2.9 |
| $J_{56a}$ | 1.3 | 1.5 | 9.9 | 9.9 | 1.3 | 1.3 | 9.9 | 9.9 | 2.0 | 2.2 | 2.6 | 2.6 |
| $J_{6e6a}$ | 12.3 | 12.5 | 10.7 | 9.9 | 12.3 | 12.5 | 11.0 | 10.7 | 12.3 | 12.5 | 12.3 | 12.5 |
| $J_{2e6e}$ | h | h | h | h | 1 | 1 | h | h | - | - | - | - |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $J_{46e}$ | - | - | - | - | - | - | - | - | - | - | 1.7 | 1.8 |
| N-$CH_3$ | 2.10 | 2.12 | 2.05 | 2.00 | - | - | - | - | - | - | - | - |
| OMe | 3.68 | 3.78 | 3.72 | 3.72 | 3.72 | 3.75 | 3.75 | 3.75 | 3.59 | 3.65 | 3.77 | 3.81 |
| OMe | 3.84 | 3.79 | 3.81 | 3.78 | 3.87 | 3.81 | 3.82 | 3.79 | 3.81 | 3.83 | 3.77 | 3.82 |
| PhOH | 5.1[n] | ? | 5.63[bs] | ? | 5.62[bs] | 7.46[bs] | 5.64[bs] | 7.57[s] | 5.88[bs] | ? | 5.73[bs] | ? |
| A2 | 7.35[d] | 7.34[d] | j | 7.02[d] | 7.26[d] | 7.23[d] | 7.00[d] | 7.06[d] | 7.17[d] | 7.02[d] | protons | |
| A5 | i | 6.73[d] | j | 6.77[d] | k | 6.74[d] | 6.87[d] | 6.77[d] | 6.89[d] | 6.84[d] | unresolved, | |
| A6 | i | 6.93[dd] | j | 6.90[dd] | k | 6.91[dd] | 7.02[dd] | 6.95[dd] | 6.94[dd] | 7.07[dd] | (6.80- | (6.87- |
| $J_{56}$ | - | 8.2 | - | 8.1 | - | 8.1 | 8.1 | 8.1 | 8.1 | 8.1 | 7.04[m]) | 7.04[m]) |
| $J_{26}$ | 1.5 | 1.8 | - | 1.8 | 1.5 | 1.8 | 2.0 | 1.8 | 1.8 | 1.8 | | |
| B3 | 6.81[dd] | | 6.76 | (6.83- | 6.82[dd] | (6.81- | 6.79[dd] | (6.82- | 6.89[l] | (6.89- | | |
| B4 | i | (6.66- | j | 6.85[m]) | k | 6.91[m]) | 6.88[ddd] | 6.90[m]) | (6.71- | 6.91[m]) | | |
| B5 | 6.74[ddd] | 6.93[m]) | 6.68[ddd] | 6.67[ddd] | 6.72[dt] | 6.71[dt] | 6.70[dt] | (6.61- | 6.79[m]) | (6.73- | | |
| B6 | 6.53[dd] | | 6.42[dd] | 6.56[dd] | 6.48[dd] | 6.62[dd] | 6.48[dd] | 6.71[m]) | 5.55[dd] | (6.75[m]) | | |
| $J_{34}$ | 8.1 | - | 8.1 | 8.1 | 8.0 | - | 8.1 | - | - | - | | |
| $J_{35}$ | 1.8 | - | 1.7 | 1.5 | 1.7 | 1.8 | 1.7 | - | - | - | | |
| $J_{45}$ | 8.1 | - | 8 | 8 | 8 | 7 | 8.1 | - | - | - | | |
| $J_{46}$ | 1.5 | - | 1.6 | 1.5 | 1.7 | 1.7 | 1.5 | - | 1.7 | - | | |
| $J_{56}$ | 8.1 | - | 8.0 | 8.1 | 8.0 | 8.0 | 7.9 | - | 8 | - | | |

[f] All shifts relative to TMS; s,d,t, have normal meanings, m = multiple, b = broad. C = $CDCl_3$, A = acetone-$d_6$.
[g] Phenyl protons, δ 7.3-7.5 (m, 3H), 7.9 (dd, 1H, J = 8.1, 1.5).
[h] Weak coupling observed from line broadening and line shape.
[i] Overlapping peaks in range 6.86-6.93[m].
[j] Overlapping peaks in range 6.82-6.97[m].
[k] Overlapping peaks in range 6.86-6.97[m].
[l] Hidden among other aromatics.
[n] Extremely broad, visible in integral only.
[p] Since H-5 and H-6 overlap, this coupling constant cannot be determined.

unambiguous assignment of the stereochemistry, especially when compared with the related acetal 12 and phenylboronate 13 derivatives. $^{13}C$ NMR chemical shift assignments (Table 2) consistent with these structures, were assigned by comparison with spectral data of related lignin models.[23]

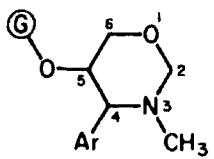
The phenylboronates 13a and 13b were each prepared as previously described.[24] The erythro-isomer 13b existed in solution in the diaxial conformation. Consequently each isomer had $H_4$-$H_5$ and $H_5$-$H_6$ dihedral angles of approximately 60°, resulting in coupling constants so small as to make distinction between isomers by $^1H$ NMR difficult at 90 MHz. However at 270 MHz, the erythro-derivative 13b was clearly distinguished (Fig. 1) by the 1.7 Hz "W-coupling"[25,26] between H-4 and the equatorial 6-proton, H-6e. This assignment agreed with that of Gierer and Noren[19] which was based only on electrophoretic mobilities of boric acid complexes.

The acetal derivatives 12 were prepared under conditions of a modified Prins reaction[27] from guaiacylglycerol-β-guaiacyl ether, paraformaldehyde and boron trifluoride etherate. Isomerization occurred during the reaction but the isomers were separated by thick-layer chromatography. The erythro-acetal 12b was diequatorial, judging by the large $H_4$-$H_5$ and $H_5$-$H_{6a}$ coupling constants in the $^1H$ NMR (Table 1, Fig. 1). Presumably the conformations of the acetals and the phenylboronates differ because of the possibility of additional 1,3-diaxial clashes in the acetals. The corresponding coupling constants for 12a were small. In each isomer protons H-2e and H-6e were unambiguously assigned by the slight broadening due to mutual "W-coupling"[25,26] and their greater chemical shift compared to the axial protons, H-2a and H-6a.[28]

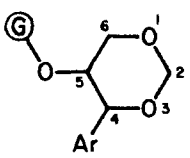
The tetrahydro-1,3-oxazine 11, prepared in >98% yield from the crude adduct 10 (Scheme 2) was over 95% threo. The 5 minute reaction was stereospecific although isomerization to an equilibrium mixture of 70% 11b (erythro) and 30% 11a (threo) occurred after a 20 h period and provided a convenient source of the erythro-isomer. The two isomers separated cleanly by thick-layer

TABLE 2

15 MHz $^{13}C$ NMR Data for 11, 12, and 13 in Acetone-$d_6$

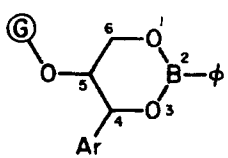


11

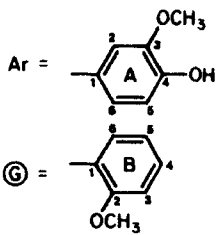


12

a threo
b erythro



13




| | 2 | 4 | 5 | 6 | $OCH_3$'s | N-$CH_3$ | A1 | A2 | A3 | A4 | A5 | A6 | B1 | B2 | B3 | B4 | B5 | B6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 11a | 87.5# | 69.3* | 74.9* | 69.1# | 56.3,56.5 | 37.9 | 131.4 | 114.0 | 147.8 | 146.6 | 114.8 | 121.7 | 151.6 | 148.5 | 114.4 | 122.5 | 122.3 | 117.0 |
| 11b | 87.4* | 73.0* | 76.7* | 70.6* | 56.3,56.4 | 36.8 | 131.5 | 113.1 | 148.1 | 146.9 | 115.2 | 121.5 | 151.8 | 148.6 | 113.9 | 122.7 | 123.3 | 119.1 |
| 12a | 94.5 | 75.2 | 80.8 | 68.7 | 56.4,56.6 | -- | 131.2 | 112.2 | 147.8 | 146.8 | 114.8 | 120.5 | 151.9 | 148.5 | 114.6 | 122.8 | 121.7 | 118.6 |
| 12b | 94.0 | 75.6 | 83.2 | 70.0 | 56.1,56.3 | -- | 131.1 | 112.2 | 147.8 | 147.2 | 115.1 | 121.5 | 151.6 | 148.0 | 113.7 | 123.4 | 121.5 | 118.8 |
| 13a** | -- | 75.2 | 76.6 | 64.2 | 56.4 | -- | 131.9 | 111.7 | 147.5 | 146.7 | 115.1 | 120.2 | 152.2 | 147.8 | 114.4 | 123.7 | 121.6 | 119.7 |
| 13b** | -- | 75.9 | 78.6 | 61.2 | 56.4 | -- | 132.2 | 110.4 | 147.2 | 146.9 | 115.9 | 121.0 | 152.6 | 148.5 | 114.3 | 124.5 | 121.8 | 119.1 |

\# Inverted under $\Delta = 3/4J$ $^1H$-decoupled INEPT conditions.

* Assignment confirmed by SFORD; 87.4$^t$, 73.0$^d$, 76.7$^d$, 70.6$^t$.

** In addition peaks for C2,6, C3,5, and C4 in the B-phenyl ring in 9a(9b) were observed at δ 134.6(134.8), 128.2(128.3), 131.3(131.5); C1 of this phenyl ring was not observed, presumably due to quadrupolar broadening by boron. A resonance for C1 of phenylboric acid was also not observed under these conditions.

chromatography. As expected the erythro-compound had large $H_4$-$H_5$ and $H_5$-$H_{6a}$ coupling constants although they were smaller than those of the other derivatives implying a deviation from the ideal chair conformation. The corresponding coupling constants in the threo-isomer 11a were small (1-3 Hz) confirming the equatorial-axial orientation of these protons. Halls et al.[28] determined the influence of the orientation of the non-bonded lone pair of electrons on nitrogen on the differential proton chemical shift of adjacent methylene protons and on geminal coupling constants. On the basis of their results, the observation that the difference in chemical shift between the equatorial and axial 2-protons was large (0.56-0.87 ppm) in compounds 11a and 11b suggests that the lone pair is axial.

The $^1$H NMR spectra of compounds 11-13 showed a marked solvent effect, such as reversing the order of the H-5 and H-6e chemical shifts in 11a and 12a. Also, the aromatic protons in these NMR spectra were often assignable (Table 1). The narrow doublet ($J^4$ = 1.5-1.8 Hz) at low field was assigned to the A-2 proton, the only aromatic proton not vicinally coupled to another aromatic proton (where $J^3$ is approximately 8 Hz). The deshielding is presumably due to steric compression[29] and is complemented by a slight shielding of the respective A-2 carbons in the $^{13}$C NMR when compared with the parent amino alcohol or diol. In each of the compounds 11-13 one proton is shielded. That proton was assigned as the B-6 proton and is most likely shielded by the A ring as can be seen in molecular models. Solvent-dependent conformations are implied by the differences in chemical shift observed in spectra measured in $CDCl_3$ as compared to those in acetone-$d_6$ (Table 1).

The threo-isomer predominated (>90%) in all tetrahydro-1,3-oxazine derivatives (e.g., 11) which were prepared stereospecifically from the crude amine adducts (e.g., 10). Consequently like AHQ and anthranol, amines trap quinone methides 1 with a high degree of stereospecificity for the threo-isomer.

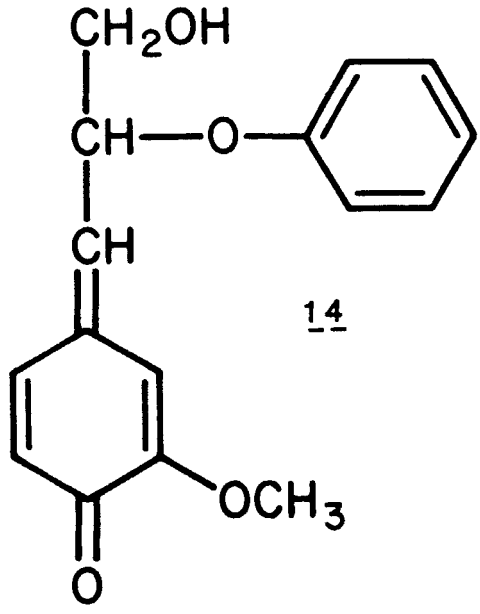
Of all the examples of reactions with quinone methide 1 (trapping by amines, anthranol,[6,7] AHQ,[6,7] water,[4] and organic

acids[4]) only the organic acids give predominantly erythro-stereochemistry. An explanation for this anomaly was sought by reacting acetic acid with quinone methides 1, 2 and 14 in chloroform.[30] Quinone methide 2 lacks the γ-hydroxyl functionality and 14 lacks the ring B methoxyl. Association with acetic acid at these sites could result in a directed attack at the reactive center or in a conformational change of the quinone methide itself.

That the ratio of stereoisomers was similar for reactions of quinone methides 1, 2 and 14 (Table 3) indicated that neither the ring B methoxyl nor the γ-hydroxyl was responsible for the

TABLE 3
Ratio of threo-:erythro-α-acetates from Reaction of Quinone Methides 1, 2 and 14 with Acetic Acid

| QM | % threo | % erythro |
|---|---|---|
| 1 | 29 | 71 |
| 2 | 25 | 75 |
| 14 | 32 | 68 |




14

resultant erythro stereochemistry. Based on these findings, and on subsequent studies on the structure of quinone methides 1-3,[8,9,29] it is suggested that the outcome might simply be attributable to a preferential solvation of the least hindered side of the quinone methide (Fig. 2). The solvating acetic acid molecule is orientated poorly for attack at Cα. The figure also illustrates the possible concomitant carbonyl oxygen protonation suggested by Leary et al.[14] from the observation of termolecular kinetics. Additionally this model is consistent with the observation[4] of increased propensity for the erythro-diastereomer (but lower reaction rates) from more bulky acids.

In summary, it has been shown that even small amine nucleophiles add to the quinone methide 1 with a high degree of stereospecificity for the threo-isomer. For large nucleophiles such as anthrahydroquinone or anthranol, only the threo-isomer is detected. The anomaly of erythro-stereochemistry from reactions of quinone methide 1 with organic acids may be a result of solvation effects.



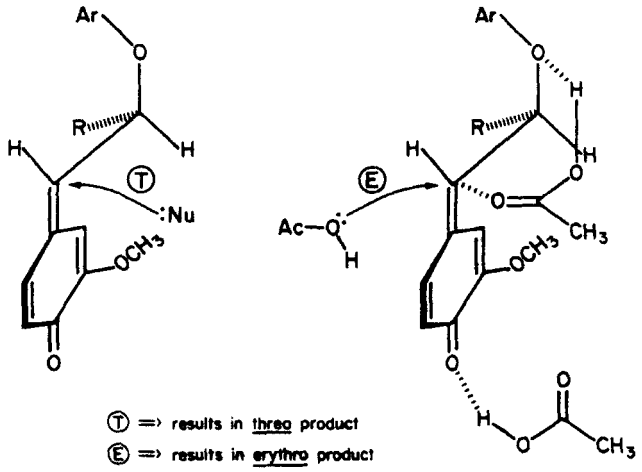



FIGURE 2. Preferential attack on quinone methides 1 and 2 by nucleophiles and by acetic acid.

## EXPERIMENTAL

$^1$H NMR spectra were determined in $CDCl_3$ or acetone-$d_6$ on a Bruker WH270 FT spectrometer with TMS as internal reference. Spectra were run with 16K data points resulting in J values accurate ± 0.4 Hz. Pulsing was generally performed without a pulse delay, often resulting in loss of OH and NH signals, especially in acetone-$d_6$. $^{13}$C NMR spectra were determined in acetone-$d_6$ (plus DMSO-$d_6$ for 10a) on a JEOL FX60 FT spectrometer. Assignment ambiguities were resolved either by single-frequency off-resonance decoupling (SFORD) techniques or by broad-band proton-decoupled $^{13}$C INEPT pulse sequencing using $\Delta = 3/4J$ (inversion of $CH_2$ resonances).[31] Infrared spectra were determined in KBr discs or as films on a Beckman IR-12 spectrometer. Mass spectra (probe, 50 eV) were determined on a Finnigan-MAT 4510 spectrometer.

Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Melting points were determined on a calibrated Thomas-Hoover capillary melting point apparatus. Unless otherwise noted, all products exhibited only one spot on thin-layer chromatography (silica gel, 10-50% ethyl acetate in hexane as developer). When required, compounds were purified by thick layer or column chromatography on silica gel.



Lignin Models: Parent lignin models were synthesized according to literature procedures (ref. 23 and references therein).

Quinone Methides: Quinone methides were prepared by a more convenient method than described previously. Treatment of a solution of the model benzyl alcohol (20-200 mg) in $CHCl_3$ (5-30 ml) with bromotrimethylsilane (2 eq) for 10-60 s produced the benzyl bromides. The solution was shaken with saturated aqueous sodium bicarbonate and the $CHCl_3$ layer (containing the QM) dried over anhydrous $MgSO_4$, filtered, and stored at -78°C until required.

Amine Adducts, General Procedure: A solution of 30-200 mg of the QM in $CHCl_3$ at -78°C was added to a vigorously stirred solution of

the amine (at least 2 eq) in $CHCl_3$ at room temperature under nitrogen. After 2 to 10 minutes the product was poured into a separatory funnel containing saturated sodium bicarbonate and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to give an oil in greater than 98% yield. Reactions involving methylamine were carried out using commercially available 40% aqueous solutions.

1-(4-Hydroxy-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)-propylmethylamine (10). The quinone methide-methylamine adduct 10 was prepared in quantitative yield by the General Procedure and was approximately 92% threo-isomer.

10a (threo): white crystals from EtOAc-hexane, mp 140-140.5°C. Anal. calcd. for $C_{18}H_{23}O_5N$ (mol wt 333.38): C, 64.85; H, 6.95; N, 4.20%. Found C, 64.99; H, 7.02; N, 4.07%. $^1H$ NMR (270 MHz, acetone-$d_6$) δ 2.22 (s, 3H, N-$CH_3$), 3.47 (dd, 1H, $J_{\gamma1\gamma2}$ = 11.8, $J_{\gamma1\beta}$ = 4.4, $H_{\gamma1}$), 3.66 (dd, 1H, $J_{\gamma2\gamma1}$ = 11.8, $J_{\gamma2\beta}$ = 3.7, $H_{\gamma2}$), 3.80 (s, 3H, methoxyl), 3.85 (s, 3H, methoxyl), 3.85 (d, 1H, $J_{\alpha\beta}$ = 7.7, Hα), 4.20 (ddd, 1H, $J_{\beta\alpha}$ = 7.7, $J_{\beta\gamma1}$ = 4.4, $J_{\beta\gamma2}$ = 3.7, Hβ), 6.78 (d, 1H, $J_{56}$ = 8.0, $A_5$), 6.81-7.00 (m, 4H, B ring protons), 7.09 (d, 1H, $J_{26}$ = 1.6, $A_2$), 7.13 (dd, 1H, $J_{65}$ = 8.0, $J_{62}$ = 1.6, $A_6$). $^{13}C$ NMR (15 MHz, acetone-$d_6$ + DMSO-$d_6$ to increase solubility) δ 34.3 (N-$CH_3$), 56.3 (methoxyls), 61.8 (Cγ), 66.2 (Cα), 86.4 (Cβ); 132.3, 112.9, 148.5, 146.9, 115.7, 121.8 (A-1 to A-6, respectively); 151.4, 149.4, 113.6, 122.6, 121.8, 118.6 (B1 to B-6, respectively). IR (KBr disc) 3430m (OH), 3325m $cm^{-1}$ (NH). M/S, m/e 333 ($M^+$, not observed), 167(53), 166(100), 151(4), 137(2), 124(4), 109(4).

4-(4-Hydroxy-3-methoxyphenyl)-5-(2-methoxyphenoxy)-3-methyl-tetrahydro-1,3-oxazine (11). The procedure used was similar to that used for the synthesis of a series of oxazolidines related to aromatic "nitrogen mustards".[32] The amino alcohol 10 (50-250 mg) was stirred until dissolved with 2-5 ml of 37% formaldehyde solution (J. T. Baker Chemical Co.). After 5 min, saturated sodium bicarbonate solution (10-20 ml) was added and the product extracted into ether. The organic phase was dried over $MgSO_4$ and

evaporated to a pale yellow oil in quantitative yield. Judging from $^{1}H$ NMR data, the major isomer was clearly the threo-compound (as was therefore the precursor 10). The isomers were separated by column chromatography on silica gel using 30% ethyl acetate in methylene chloride as eluant or by thick-layer chromatography in ethyl acetate-hexane. Additional erythro-11 was obtained by allowing the reaction above to proceed for 20 h, isomerization taking place to give an equilibrium mixture comprising 70% erythro- and 30% threo-compound.

11a (threo): pale yellow oil. $^{1}H$ NMR (Table 1, Fig. 1). $^{13}C$ NMR (Table 2). IR 3420w (broad, OH); no NH. M/S, m/e 345 ($M^{+}$, 10), 302(9), 272(3), 222(21), 195(16), 194(36), 192(9), 179(18), 178(18), 166(28), 165(100), 164(65), 151(32), 150(66), 149(21), 137(16), 135(13), 124(20), 121(21), 109(26).

11b (erythro): pale yellow oil. Anal. calcd for $C_{19}H_{23}O_5N$ (mol wt 345.39): C, 66.07; H, 6.71; N, 4.06. Found: C, 66.26; H, 6.78; N, 3.93. $^{1}H$ NMR (Table 1, Fig. 1). $^{13}C$ NMR (Table 2). IR 3430w (broad, OH); no NH. M/S, m/e 345 ($M^{+}$, 4), 302(5), 272(1), 222(18), 195(12), 194(32), 192(9), 179(18), 178(27), 165(27), 165(100), 164(79), 151(12), 150(68), 149(16), 137(17), 135(12), 124(17), 121(25), 109(29).

4-(4-Hydroxy-3-methoxyphenyl)-5-(2-methoxyphenoxy)-1,3-dioxane (12). Acetals and ketals of guaiacylglycerol-β-guaiacyl ether could not be prepared by conventional methods (e.g., in refluxing benzene with p-toluenesulfonic acid as catalyst in a Dean-Stark apparatus) due to the reverse aldol reaction which occurred under acidic conditions. However, the formaldehyde acetal was prepared in quantitative yield using conditions of a modified Prins reaction,[27] although isomerization occurred. erythro-Guaiacylglycerol-β-guaiacyl ether (91 mg) was dissolved in 5 ml. of $CH_2Cl_2$ and paraformaldehyde (15 mg, 1.8 eq) was added. $BF_3 \cdot Et_2O$ (10 mg = 0.25 eq) was added, and the solution was stirred at room temperature for 2 h. The mixture was transferred to a separatory funnel with $CHCl_3$ and washed with sodium bicarbonate. The solution was dried and evaporated in the normal way yielding 94 mg (over 99%)

of product. Preparative thick-layer chromatography separated the isomers into 64% erythro- and 36% threo-product (as confirmed by $^1$H NMR of the initial reaction product).

12a (threo): white crystalline solid from acetone, mp 111.5-113°C. $^1$H NMR (Table 1, Fig. 1). $^{13}$C NMR (Table 2). IR 3430w (broad, OH). M/S, m/e 332 ($M^+$, 7), 307(1), 272(1), 152(7), 151(28), 150(100), 149(9), 137(8), 121(20), 109(15).

12b (erythro): colorless oil. Anal. calcd for $C_{18}H_{20}O_6$ (mol wt 332.35): C, 65.05; H, 6.07%. Found: C, 65.26; H, 6.20%. $^1$H NMR (Table 1, Fig. 1). $^{13}$C NMR (Table 2). IR 3430m (broad, OH). M/S, m/e 332 ($M^+$, 11), 307(1), 272(1), 152(7), 151(24), 150(100), 149(4), 137(8), 121(18), 109(15).

Phenylboronates: Phenylboronates of guaiacylglycerol-β-guaiacyl ether were prepared as described previously.[26] $^1$H NMR (Table 1, Fig. 1). $^{13}$C NMR (Table 2).

Reactions of Quinone Methides with Acetic Acid: A few drops of glacial acetic acid were added to 20-30 mg of the quinone methide in dry $CHCl_3$. Quinone methide disappearance was monitored by UV spectroscopy and took up to 24 h. The product was extracted into $CHCl_3$, washed with bicarbonate and worked up as usual. The ratios of the erythro- and threo-isomers were determined by 270 MHz $^1$H NMR of the acetylated products.



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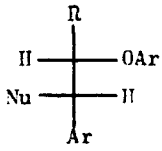


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Nakatsubo's observation of a complete reaction time of about 5 min. However, the rate of addition was markedly increased if the quinone methide solution was not dried.

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