# Oxidative Dimerizations of (*E*)- and (*Z*)-Isoeugenol (2-Methoxy-4-propenylphenol) and (*E*)- and (*Z*)-2,6-Dimethoxy-4-propenylphenol [1]

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Reaction of (*E*)-isoeugenol (3) with 1 equiv. of hydrogen peroxide catalysed by peroxidase gives a mixture of dehydrodi-isoeugenol {4-[2,3-dihydro-7-methoxy-3-methyl-5-(*E*)-propenylbenzofuran-2-yl]-2-methoxyphenol} (7a) (65%), *threo*- and *erythro*-1-(4-hydroxy-3-methoxyphenyl)-2-[2-methoxy-4-(*E*)-propenylphenoxy]propan-1-ol (9a) (17%) and (10a) (5%), and isomers of 2,5-bis-(4-hydroxy-3-methoxyphenyl)-3,4-dimethyltetrahydrofuran (13a) (4%) and (14a) (9%) which result from β–5, β–O, and β–β coupling, respectively. Oxidation of (*Z*)-isoeugenol (4) under identical conditions yields products differing only in the propenyl side-chain configurations of compounds (7), (9), and (10): *viz.* (7b) (22%), (9b) (40%), (10b) (13%), (13a) (8%), and (14a) (17%). The tetrahydrofuran dimethyl ethers (13b) and (14b) were identified as the (±)-forms of the lignans galbelgin and veraguensin, respectively. Oxidation of (*E*)-2,6-dimethoxy-4-propenylphenol (5) with 1 equiv. of hydrogen peroxide–peroxidase or potassium ferricyanide affords a 1 : 2 mixture of isomers of 2,5-bis-(4-hydroxy-3,5-dimethoxyphenyl)-3,4-dimethyltetrahydrofuran (13c) and (14c). In identical oxidative treatments, the (*Z*)-phenol (6) gives isomers (13c), (14c), (15c), and (16c) in the ratio 1 : 2 : 2 : 1. The tetrahydrofuran configurations were assigned by reductive degradation experiments involving ring scission and by n.m.r. spectral comparisons with analogous lignans. The β–β coupling of phenols (3)—(5) is remarkably stereospecific and produces exclusively *threo*-compounds, whereas the (*Z*)-phenol (6) gives *threo*- and *erythro*-coupling products in equal amounts. A mechanism is proposed for this coupling which involves the intermediacy of a dimeric ' tail-to-tail ' charge-transfer complex, formed by association of phenoxyl radicals. The feasibility of the alternative ' head-to-tail ' complexes is also discussed. The differences in the probabilities of coupling modes in the oxidations of (*E*)- and (*Z*)-isoeugenol is considered to be due to the characteristics of these intermediate complexes rather than to the differences in free-electron densities.

ENZYME-CATALYSED oxidation of the methoxylated *para*-hydroxycinnamyl alcohols (1) and (2) leads to the formation of coupling products which are of considerable interest for the understanding of the biogenesis of lignins. These reactions are quite complex, as has been demonstrated by the extensive studies of Freudenberg *et al.* on (*E*)-coniferyl alcohol (1), which have resulted in the isolation of about 30 dimeric and oligomeric products.[2] In contrast, the enzymic oxidation of (*E*)-sinapyl alcohol (2) gave the (±)-form of the lignan syringaresinol as the only isolated coupling product.[3] To obtain more information about these processes, the oxidative dimerizations of the readily available γ-deoxy-analogues of the phenols (1) and (2), (*E*)-isoeugenol (3),

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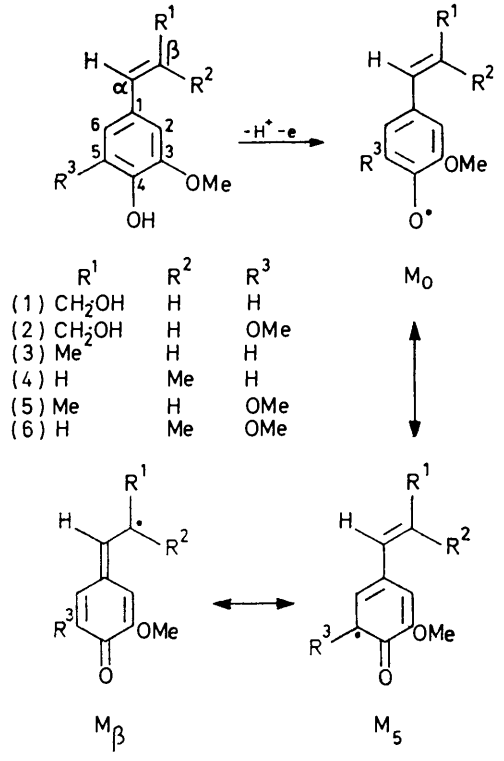
[1] Preliminary communication, K. V. Sarkanen and A. F. A. Wallis, *Chem. Comm.*, 1969, 298.

[2] K. Freudenberg and A. C. Neish, in ' Constitution and Biosynthesis of Lignin,' Springer–Verlag, New York, 1968, pp. 82—92; K. Freudenberg, *Science*, 1965, **148**, 595.

[3] K. Freudenberg and F. Bittner, *Chem. Ber.*, 1950, **83**, 600; K. Freudenberg, R. Kraft, and W. Heimberger, *ibid.*, 1951, **84**, 472.

and (*E*)-2,6-dimethoxy-4-propenylphenol (5), with hydrogen peroxide–peroxidase, were studied. The oxidation products of the (*E*)-phenols (3) and (5) were also compared with those of their (*Z*)-isomers (4) and (6).




SCHEME 1

Phenols (1)—(6) are presumably converted into phenoxyl [radical intermediates by hydrogen peroxide–peroxidase. Of the five mesomeric forms of the (*E*)-coniferyl alcohol radical, only three have been shown to be important in coupling reactions, and are designated $M_0$, $M_5$, and $M_\beta$ in Scheme 1. Six coupling modes for the mesomer are possible (β–β, β–5, β–O, 5–5, 5–O, and O–O), although the O–O coupling is not likely in view of the instability of diaryl peroxides. For the radical derived from the dimethoxyphenols (2), (5), and (6), only β–β and β–O couplings are probable.

*Oxidation of* (E)- *and* (Z)-*Isoeugenol* (3) *and* (4).—Hydrogen peroxide–peroxidase has not been previously applied to isoeugenol, but oxidations by iron(III) chloride [4] as well as with oxygen–laccase [5] have given β–5-coupled dehydrodi-isoeugenol (7a) as the main product. Evidence for β–β coupling in the oxidation of isoeugenol with iron(III) chloride was obtained by the isolation of an arylnaphthalene derivative as one of the products.[6] In addition, β–O-coupled dehydro-dimers have been isolated from the dye-sensitized photo-oxidation [7] and tri-t-butylphenoxyl radical oxidation [8] of isoeugenol.

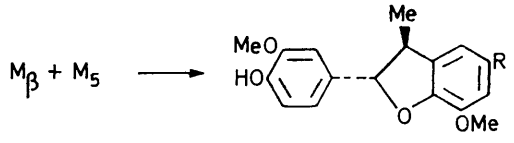
[4] H. Cousin and H. Herissey, *Compt. rend.*, 1908, **147**, 247; H. Erdtman, *Annalen*, 1933, **503**, 283.
[5] H. Cousin and H. Herissey, *Bull. Soc. chim. France*, 1908, **3**, 1070.

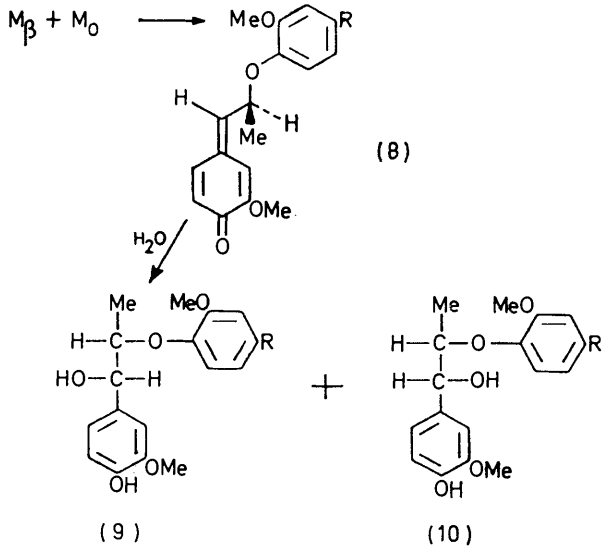
The reaction of both (*E*)- and (*Z*)-isoeugenols (3) and (4) with 1 equiv. of hydrogen peroxide in aqueous acetone containing peroxidase afforded exclusively mixtures of dehydro-dimers which were separated by silica gel chromatography into the compounds listed in the Table. The absence of higher molecular weight products indicates that the oxidation of the isoeugenol monomer is faster than that of its reaction products. Also, the lack of trimers formed through addition of monomer to dehydro-dimeric quinone methide intermediates is in contrast to the oxidation of coniferyl alcohol.[2]

Product analyses of peroxidase-catalysed oxidative dimerizations of (*E*)- and (*Z*)-isoeugenol (3) and (4)

| Coupling mode | Products | Yield (%) from (*E*)-Isoeugenol | Yield (%) from (*Z*)-Isoeugenol |
|---|---|---|---|
| β–5 | Aryldihydrobenzofurans (7a) and (7b) | 65 (7a) | 22 (7b) |
| β–O | *threo*-β-Aryl ethers (9a) and (9b) | 17 (9a) | 40 (9b) |
| | *erythro*-β-Aryl ethers (10a) and (10b) | 5 (10a) | 13 (10b) |
| β–β | Tetrahydrofuran (13a) | 4 | 8 |
| | Tetrahydrofuran (14a) | 9 | 17 |

The aryldihydrobenzofuran (7b) gave the same dihydro-compound (7c) as dehydrodi-isoeugenol (7a)




SCHEME 2

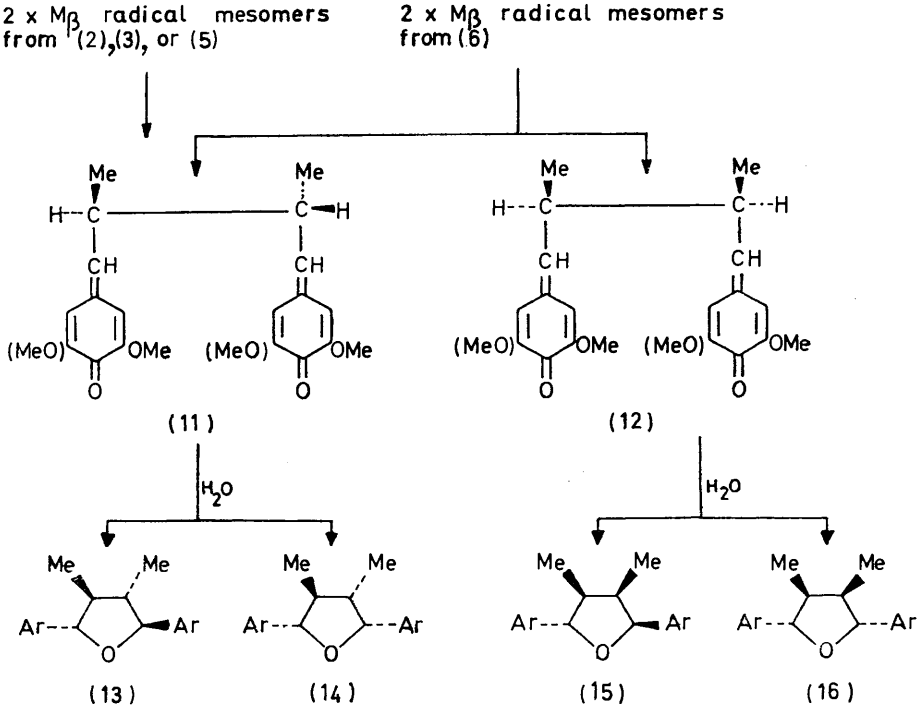
a; R = (*E*)-propenyl. b; R = (*Z*)-propenyl. c; R = Pr$^n$

upon catalytic hydrogenation, and thus dehydro-dimers (7a) and (7b) differ only in the configuration of their

[6] B. Lindberg, *Svensk Papperstidn.*, 1953, **56**, 6.
[7] K. Eskins, C. Glass, W. Rohwedder, R. Kleiman, and J. Sloneker, *Tetrahedron Letters*, 1972, 861.
[8] I. J. Miller, *Tetrahedron Letters*, 1972, 4955.

propenyl side chains. The lack of isomerization of the propenyl groups during the oxidation of phenols (3) and (4) means that the (*E*)- and (*Z*)-radical intermediates behave as discrete entities.[1,8]

The *threo*- and *erythro*-isomers of C(β)-aryl ethers (9) and (10) were not separated by chromatography but were studied as mixtures of isomers. The original propenyl side-chain configuration is again maintained in these compounds; the n.m.r. spectrum of the mixtures (9a) and (10a), and (9b) and (10b) exhibited a doublet at δ 1·87 and a quartet at 1·90 which are assigned to the (10). If the most stable rotamer of intermediate (8) is assumed to be that where the C(β)–O bond lies in the plane of the quinone methide group as shown, then the preponderance of the *threo*-isomer is due to the preferential attack of water on C(β) from the side remote from the C(γ)-methyl group. That the ratio of isomers (9) and (10) is due to kinetic control rather than equilibration in the slightly acidic reaction medium (pH 6·3) was demonstrated by the failure of the *erythro*-isomer (10c) to equilibrate even at pH 4·0. Isolation of the C(β)-aryl ethers (9b) and (10b) in 40% yield by oxidation




a; Ar = 4-HO-3-MeO·$C_6H_3$ b; Ar = 3,4-$(MeO)_2C_6H_3$
c; Ar = 4-HO-3,5-$(MeO)_2C_6H_2$ d; Ar = 3,4,5-$(MeO)_3C_6H_2$

SCHEME 3

methyl protons of (*E*)- and (*Z*)-propenyl systems, respectively. Oxidation of these dihydro-compounds with 2,3-dichloro-5,6-dicyanobenzoquinone in dioxan [9] led to the ketone (17), which on reduction with sodium borohydride yielded largely (*ca.* 95%) the *erythro*-C(β)-ether (10c). The known preference for the formation of the *erythro*-C(β)-ethers on borohydride reduction of ketones analogous to (17) [10] allows the assignment of structure (10) to the *erythro*-isomer.

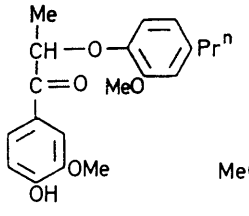
The C(β)-aryl ethers (9) and (10) arise in the isoeugenol oxidations by β–O coupling to give the quinone methide dehydro-dimer (8) (Scheme 2). Addition of water from the solvent on the reactive quinone methide system affords a 3 : 1 ratio of *threo*- and *erythro*-isomers (9) and of (*Z*)-isoeugenol provides a convenient one-step route to these important lignin model compounds, which have previously been available only by a multi-step synthesis.[10]

The tetrahydrofurans (13a) and (14a) were isolated from the oxidation products of both (*E*)- and (*Z*)-isoeugenol. Of the six possible stereoisomers of the tetrahydrofurans, only two are formed in these reactions. Their dimethyl ethers were identical in spectral properties with the naturally occurring lignans (—)-galbelgin (13b) [11,12] and (+)-veraguensin (14b).[12] However, the optically inactive synthetic compounds had (predictably) lower m.p.s than the optically active (13b) and (14b). Compounds (13) and (14) provide the first examples of tetrahydrofuranoid lignans to be synthesized by oxidative coupling techniques.

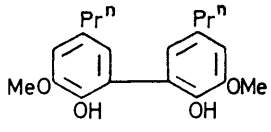
[9] E. Alder, H.-D. Becker, T. Ishihara, and A. Stamvik, *Holzforschung*, 1966, **20**, 3.
[10] E. Alder, S. Delin, and G. E. Miksche, *Acta Chem. Scand.*, 1966, **20**, 1035.
[11] A. J. Birch, B. Milligan, E. Smith, and R. N. Speake, *J. Chem. Soc.*, 1958, 4771.
[12] N. S. Crossley and C. Djerassi, *J. Chem. Soc.*, 1962, 1459.

The mechanism of formation of (13a) and (14a) may be understood as initial coupling of two $M_\beta$ mesomers, formed from oxidation of either (*E*)- or (*Z*)-isoeugenol, to the *threo*-bisquinone methide (11) (Scheme 3). Addition of water to one quinone methide system affords two isomeric monoquinone methides, and subsequent internal cyclization of the C(α) hydroxy-group onto the remaining quinone methide (with *trans*-methyl and quinone methide stereochemistry) leads to the tetrahydrofurans (13a) and (14a). The 1 : 2 ratio of (13a) and (14a) reflects a steric preference of water addition to bisquinone methide (11). The remarkable stereospecificity of the β–β couplings to give *threo*-bisquinone methides is discussed later.

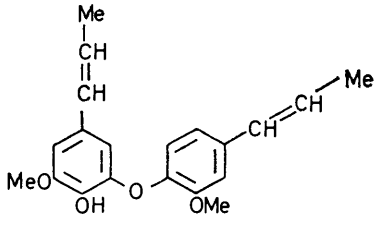
To estimate the product compositions shown in the Table, the aryldihydrobenzofurans (7a) and (7b), which have $R_F$ values greater than those of the other components, were first removed by silica gel chromatography. The remaining mixture was acetylated, and the product examined by n.m.r. spectroscopy. The ratio of the n.m.r. signals due to the propenyl methyl groups of (9) and (10) to the total methyl signals permits an estimation of the C(β)-ethers and tetrahydrofurans. Also, the ratio of the C(α)-aliphatic acetoxy-signals for the acetates of (9) (at δ 2·02) and (10) (at 2·10) to the aromatic acetoxy-signal (at 2·27) gave an additional mode of analysis, and the proportions of the *threo*- and *erythro*-isomers (9) and (10). Finally, the ratio of the tetrahydrofurans (13) and (14) follows from inspection of the methyl and benzylic proton signals of the separated mixture.




(17)




(18)




(19)

Specific efforts were made to isolate 5–5-coupled dehydro-dimers from the product mixtures, because Freudenberg and Renner [13] have presented tentative evidence for the formation of analogous compounds from coniferyl alcohol. To this end, the oxidation mixtures were hydrogenated and examined by t.l.c., but no spot corresponding to the tetrahydro-derivative (18) was observed. In addition, no evidence for the existence of the diaryl ether (19), which would result from 5–O coupling, could be obtained. Thus the radical mesomer $M_\beta$ is a participant in all couplings leading to dimer formation.

*Oxidation of* (E)- *and* (Z)-2,6-*Dimethoxy*-4-*propenylphenol* (5) *and* (6).—Richtzenhain [14] obtained an oily product from oxidation of the phenols (5) and (6) (stereochemistry not specified) with laccase–oxygen, which was not characterized. Treatment of (5) and (6) with iron(III) chloride [15] has given as major products C(β)-aryl ethers analogous to compounds (9) and (10) which are formed by β–O coupling.

Reaction of phenols (5) and (6) with equivalent amounts of either hydrogen peroxide–peroxidase or potassium ferricyanide in aqueous acetone yielded in every case a mixture of β–β-coupled compounds. The product from the (*E*)-phenol (5) was a 1 : 2 mixture of tetrahydrofurans (13c) and (14c). However, the oxidative coupling of the (*Z*)-isomer gave besides (13c) and (14c) the tetrahydrofurans (15c) and (16c). Isomers (13c), (14c), and (15c) were isolated by silica gel chromatography, and compound (16c) was obtained as its dimethyl ether (16d). The n.m.r. spectra of tetrahydrofurans (13c), (14c), and (16d) were similar to those of the lignans galbelgin (13b),[11,12] veraguensin (14b),[12] and and galgravin (16b).[12,16,17] To ascertain by chemical means the stereochemistry of the methyl groups at C-3 and C-4, reactions involving the scission of the tetrahydrofuran ring were carried out.

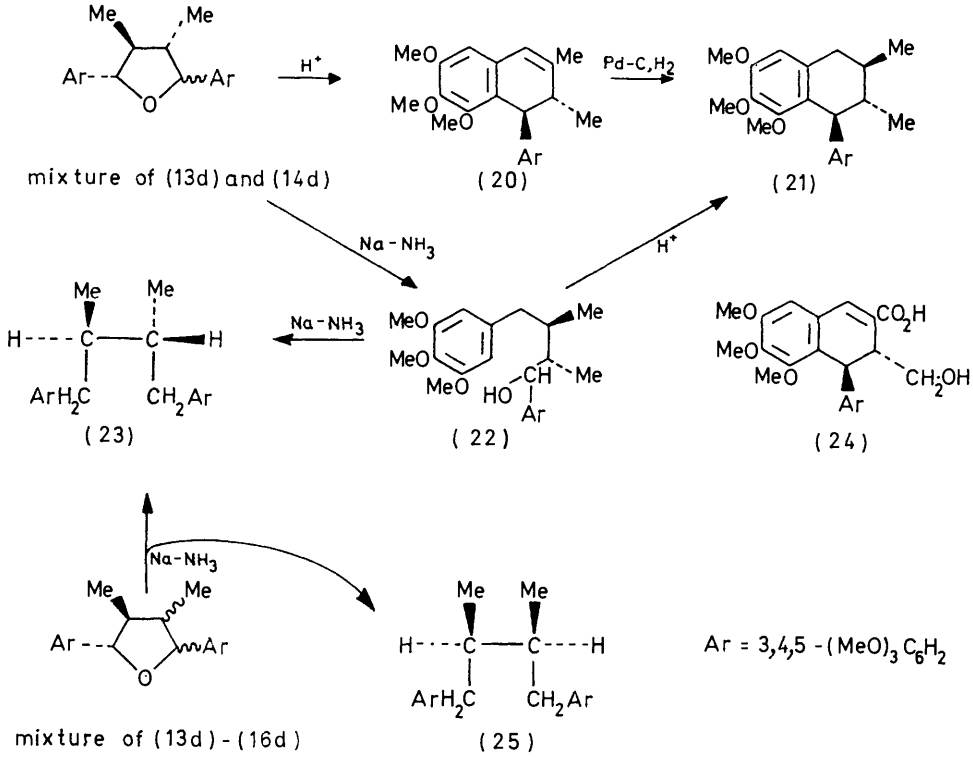
Reaction of the methylated oxidation product from the (*E*)-phenol (5) [(13d) and (14d)] with acetic acid–perchloric acid gave, after filtration through silica gel, the dihydronaphthalene (20) [18] (Scheme 4). The *trans*-nature of C-1 and C-2 aryl and methyl substituents in (20) follows from similar acid-catalysed transformations of the lignans (13b),[11] (14b),[12] and (16b).[16] In addition, the dibenzylic proton signal at δ 4·08 in the n.m.r. spectrum of compound (20) is a broad singlet similar to that of the dimethyl ether of the *trans*-dihydronaphthalene lignan thomasic acid (24).[18,19] Catalytic hydrogenation of (20) with 5% Pd–C in ethanol gave the tetralin derivative (21),[18] the *trans,trans*-configuration of which follows from that obtained in a similar reaction in the 3,4-dimethoxyphenyl series.[11]

On reduction with sodium in liquid ammonia,[11,12] the mixture of (13d) and (14d) yielded the dihydroguaiaretic acid derivative (23). When a shorter reaction time was used, (13d) and (14d) were reduced to the dihydro-compound (22), which without isolation cyclized on treatment with acid to give the tetralin (21). This

[13] K. Freudenberg and K. C. Renner, *Chem. Ber.*, 1965, **98**, 1879.
[14] H. Richtzenhain, *Chem. Ber.*, 1948, **81**, 260.
[15] A. F. A. Wallis, *Austral. J. Chem.*, 1973, **26**, 585.
[16] J. G. Blears and R. D. Haworth, *J. Chem. Soc.*, 1958, 1985.
[17] G. K. Hughes and E. Ritchie, *Austral. J. Chem.*, 1954, **7**, 104.
[18] A. F. A. Wallis, *Tetrahedron Letters*, 1968, 5287.
[19] M. K. Seikel, F. D. Hostettler, and D. B. Johnson, *Tetrahedron*, 1968, **24**, 1475; F. D. Hostettler and M. K. Seikel, *ibid.*, 1969, **25**, 2325.

establishes that the methyl groups in (13d) and (14d) are *trans*-oriented, and confirms the n.m.r. assignment of tetrahydrofurans (13c) and (14c) as the oxidation products of the (*E*)-phenol (5). The possibility of the other isomer (28c) with *trans*-C-2 and C-3 methyl groups being an oxidation product of phenol (5) may be eliminated by n.m.r. spectral analysis. In the n.m.r. spectrum of isomer (28c), both methyl groups would appear at high field as in the all-*cis*-isomer (26b),[20] in which the methyl groups are shielded by the adjacent *cis*-aryl functions. Isomer (14c) exhibits only one high-field (6), had two separate n.m.r. doublets for both the methyl and benzylic protons and is distinct from (14c). Its structure is thus that of the *trans,cis,cis*-isomer. The isomer (15c) represents the first tetrahydrofuranoid lignan analogue of this stereochemistry to be described. The ratio of isomers (13c) : (14c) : (15c) : (16c) formed in the oxidation of phenol (6) as estimated by integration of the methyl group n.m.r. signals was 1 : 2 : 2 : 1.

The tetrahydrofurans (13c) and (14c), which are oxidation products of the (*E*)-phenol (5), are analogous to those formed from stereospecific β–β coupling to the




SCHEME 4

methyl group, and in (13c) both methyl groups have normal n.m.r. δ values.

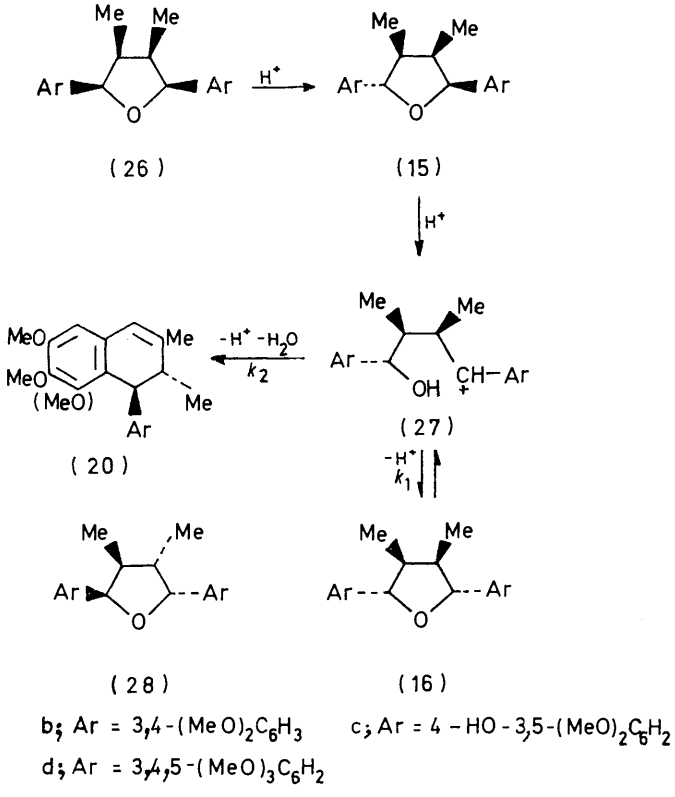
Reduction of the dimethyl ethers (13d)—(16d) of the oxidation mixture from the (*Z*)-phenol (6) with sodium in liquid ammonia gave a mixture of compounds (23) and (25) which we could not resolve by adsorption chromatography or fractional crystallization. However the n.m.r. spectrum of the mixture exhibited two singlets at δ 6·8 and 6·35 in a 1 : 1 ratio, to which the aromatic protons of the *threo*- and *erythro*-isomers (23) and (25), respectively, are assigned. Hence the (*Z*)-phenol (5) on oxidation gives equal amounts of *threo*- and *erythro*-β–β coupling products.

Of the six possible tetrahydrofuran isomers, only (14) and (15) contain both *trans*- and *cis*-methyl and aryl functions. These may be expected to have two separate methyl n.m.r. signals owing to the shielding effect of the adjacent *cis*-aryl system. Isomer (15c), which was isolated from the oxidation mixture of the (*Z*)-phenol *threo*-bisquinone methide (11) (Scheme 3). However, combination of the incipient $M_\beta$ radical mesomers from the (*Z*)-phenol (6) gives rise to equal amounts of *threo*- and *erythro*-bisquinone methides (11) and (12). Addition of water to one quinone methide group in (12) and cyclization of the resulting benzyl alcohol on to the other quinone methide gives rise to the tetrahydrofurans (15c) and (16c), which possess *cis*-methyl groups. The stereochemistry of the β–β coupling process is discussed later.

Isomerization of the tetrahydrofuran (15d) to (16d) was accomplished by treatment with 5% perchloric acid in acetic acid for 30 min at 20°, conditions similar to those used for converting (26b) into (16b).[16] However, the yield of compound (16d) (35% of the crude mixture) was much less than that of (16b) (42% of pure material). Conversely, the yield of the condensed product (20) from (15d) (50% of the mixture) was greater than that of the

[20] F. G. King and J. G. Wilson, *J. Chem. Soc.*, 1964, 4011.

corresponding compound from (26b). The pathways of the acid-catalysed conversion of the tetrahydrofurans (15d) and (26b) are depicted in Scheme 5. When




SCHEME 5

Ar = 3,4,5-trimethoxyphenyl, the rate of condensation ($k_2$) is greater than the rate of formation of (16d) ($k_1$). However, when Ar = 3,4-dimethoxyphenyl, $k_1 > k_2$. This may be rationalized in terms of the greater activation of the aromatic nucleus of (15d) to electrophilic substitution of the benzyl carbonium ion (27) than that of (15b).[21]

*Stereochemistry of β–β Oxidative Coupling of Phenols* (1)—(6).—Coupling of $M_\beta$ radical mesomers derived from β-substituted 4-vinylphenols may occur in two ways to give initially *threo*- or *erythro*-bisquinone methides, *e.g.* (11) or (12), as depicted in Scheme 3 for the radicals from phenols (3)—(6). In previous cases of β–β coupling of 4-vinylphenol derivatives, only *threo*-products have been obtained. For example, pinoresinol [22] and epipinoresinol [23] have been isolated from the oxidation mixture of (*E*)-coniferyl alcohol (1). Analogously, dilactones were obtained by the iron(III) chloride oxidations of (*E*)-ferulic [24] and (*E*)-sinapic [25] acids. Oxidation of (*E*)-sinapyl alcohol (2) with oxygen catalysed by copper(II) sulphate has given the *threo*-dehydro-dimer syringaresinol in 89% yield.[26] In addition, Chapman *et al.*[27] have found only a *threo*-β–β-coupled product from the oxidation of a 2-propenylphenol derivative.

The tetrahydrofurans (13) and (14) obtained from oxidation of phenols (3)—(5) in this study also arise from *threo*-coupling of $M_\beta$ mesomers. The total absence of *erythro*-coupled products observed in this and earlier work is remarkable. No rationalization of this stereospecificity could be obtained by inspection of molecular models and consideration of the interactions incurred upon approach of $M_\beta$ radical mesomers to form C(β) linkages. However, it is explicable if it is assumed that bond formation between the C(β) atoms is preceded by the formation of a short-lived dimeric intermediate in which the aromatic rings are in close association (Scheme 6). This intermediate is best understood as a charge-transfer complex between the aromatic rings, with their planes parallel and aligned in a ' tail-to-tail ' manner, as in the form (29a) derived from (*E*)-isoeugenol radicals. A similar complex has been proposed for the dimer of 2,6-di-t-butoxyphenoxy-radicals.[28] If it is assumed that the aromatic rings in intermediate (29) are displaced from each other as in the charge-transfer complex of crystalline quinhydrone,[29] it may be seen in configuration (29b) that there is a staggered arrangement of substituents about the C(β) atoms, which permits their close approach. This situation is favourable for the series of electron shifts shown in (29a) to occur, resulting in the formation of dimer (11) with a *threo*-configuration. In the configuration (29c), which would give rise to an *erythro*-dimer, severe interactions due to an eclipsed arrangement of substituents about the C(β) atoms would be incurred as they approach within bonding distance. This would impede the formation of an *erythro*-dimer, and thus the configuration (29b), leading to the *threo*-dimer (11), represents a sterically more favourable situation. Likewise, the exclusive formation of *threo*-β–β-coupled compounds from (*Z*)-isoeugenol radicals may be considered as arising from the sterically favoured intermediate complex (30).

In the syringyl series, oxidation of the (*E*)-phenol (5) to give *threo*-coupled products may involve an intermediate analogous to (29b). However, the oxidation of the (*Z*)-isomer (6), which gives both *threo*- and *erythro*-products, is best envisaged as a random ' direct-collision ' process of intermediate (*Z*)-$M_\beta$ radical mesomers. Presumably some factor is operative which prevents the formation of an intermediate complex. In view of the stereospecificity in the β–β oxidative coupling of phenols (1)—(5), we are unable to find a satisfactory interpretation for the anomalous oxidative behaviour of the (*Z*)-phenol (6).

[21] B. Ericsson, B. Nist, and K. V. Sarkanen, in ' Lignin Structure and Reactions,' Advances in Chemistry Series, No. 59, American Chemical Society, Washington D.C., 1966, p. 59.
[22] K. Freudenberg and D. Rasenak, *Chem. Ber.*, 1953, **86**, 755.
[23] K. Freudenberg and B. Lehmann, *Chem. Ber.*, 1960, **93**, 1354.
[24] H. Erdtman, *Svensk kem. Tidskr.*, 1935, **47**, 223; N. J. Cartwright and R. D. Haworth, *J. Chem. Soc.*, 1944, 535.
[25] K. Freudenberg and H. Schraube, *Chem. Ber.*, 1955, **88**, 16.
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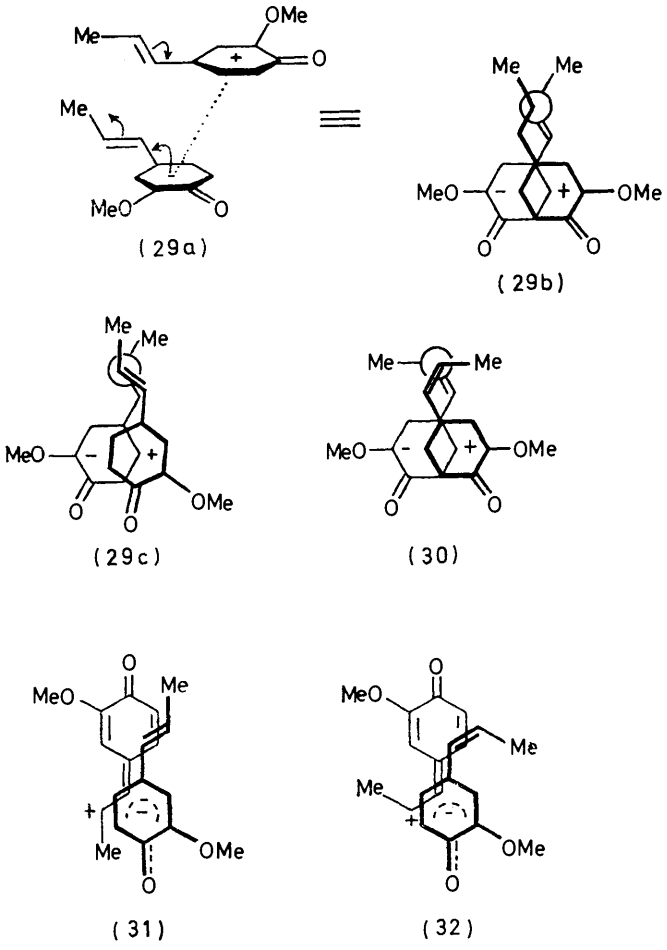
The observations made in this study may have some relevance to the biogenesis of lignans. Most naturally




SCHEME 6 Postulated intermediates in the couplings of (*E*)- and (*Z*)-isoeugenol radicals

occurring *para*-propenylphenols are encountered in their (*E*)-forms, and most lignans possess *threo*-configurations about their β–β bonds.[30] It is possible that the (*E*)-phenols are the precursors of *threo*-lignans, whereas (*Z*)-phenols may give rise to both *threo*- and *erythro*-lignans.

*Relative Probabilities of Coupling Modes of Isoeugenol Radicals.*—The difference in coupling of the (*E*)- and (*Z*)-radicals of isoeugenol is demonstrated by the yields of dimers which result from differing coupling modes (Table). Whereas the dominant coupling for radicals from (*E*)-isoeugenol is β–5 (65%), that for the (*Z*)-isomer is β–O (53%).

It has been proposed that coupling of phenoxyl radicals occurs fastest at the positions of highest free-electron densities, except where there is steric hindrance to their approach.[31] An estimation of these densities in the radical derived from (*E*)-coniferyl alcohol (1) by e.s.r. measurements[32] and quantum mechanical calculations[33] has been attempted. It is questionable, however, whether this approach will be applicable to isoeugenol and related phenols. First, it does not seem reasonable that the free-electron densities in (*E*)- and (*Z*)-isoeugenol radicals would be sufficiently different to account for the observed differences in respective coupling modes. Secondly, if bond formation in coupling is preceded by the formation of dimeric complexes such as (29) and (30), the electron densities in monomeric radicals can hardly be pertinent.

Thus it may be of value to consider speculatively the steric effects upon coupling that may arise from the geometry of hypothetical dimeric intermediates. In addition to the ' tail-to-tail ' complex (29) postulated to account for the stereospecificity of β–β coupling, additional ' head-to-tail ' complex intermediates (31) and (32) may be invoked to account for the β–5 and β–O coupling modes of the (*E*)- and (*Z*)-phenols respectively. Formulae (31) and (32) each represent one of two principal mesomeric forms where the negative charge remains in the aromatic ring and the positive charge at C(β). The favoured β–5 coupling for the (*E*)-complex (31) may be due to the steric hindrance experienced between the C(γ) methyl and the oxygen atom in the approach of C(β) to the oxygen in β–O coupling. Conversely, the relative preference for β–O coupling for the (*Z*)-complex (32) may be because of the reduced steric hindrance involved in the approach of C(β) to the oxygen atom for this coupling mode. From the ' tail-to-tail ' complex (29), β–β, 5–O, and 5–5 coupling modes are possible. Of these three modes, only β–β coupling is operative, probably for steric reasons. However, in the oxidative coupling reactions of guaiacols with a saturated *para*-substituent where the possibility of coupling through C(β) is precluded, the 5–O and 5–5 modes predominate.[34]

## EXPERIMENTAL

M.p.s were determined with a Fisher–Johns apparatus. I.r. spectra, for carbon disulphide solutions, were obtained using a Perkin-Elmer 257 spectrometer. N.m.r. spectra were recorded with a Varian A-60 instrument for deuteriochloroform solutions using tetramethylsilane as an internal reference. Elemental analyses were carried out by Alfred Bernhard Microanalytical Laboratories, Elbach, West Germany. Silica gel for column chromatography was Davison grade 200 × 325.

(E)- *and* (Z)-*Isoeugenols* (*2-Methoxy-4-propenylphenols*) (3) *and* (4).—A commercial sample (Aldrich) containing the (*E*)- and (*Z*)-isomers in the ratio 2 : 1 was fractionally distilled at 0·5 mmHg (50 cm spinning-band column).

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The isomers (3) and (4) were obtained gas-chromatographically pure, and had spectral properties identical with those reported.[35]

*Hydrogen Peroxide–Peroxidase Oxidation of* (E)-*Isoeugenol* (3).—The phenol (3) (5·0 g) was dissolved in acetone–water (5 : 8; 325 ml) containing horseradish peroxidase (10 mg; Calbiochem; RZ *ca.* 6), and 3·14% hydrogen peroxide (17·4 ml; 1·05 equiv.) was added to the stirred solution at 20° during 45 min. A yellow colour due to quinone methide structures became evident, and after addition of 5 ml of oxidant, crystalline material began to separate. Stirring was continued for a further 15 min, finally at 0°, to give, after filtration and washing with aqueous acetone, white crystals (3·1 g), m.p. 124—129°. Recrystallization from ethanol afforded dehydrodi-isoeugenol (7a) as needles, m.p. 132—133° (lit.,[4] 132—133°). The oxidation mother liquor was freed of acetone by distillation under reduced pressure, and the organic material extracted with ether and dried. Evaporation of the solvent gave an oil (0·04 g) which displayed three spots on t.l.c. Adsorption of the oil on silica gel (200 g) in 50% hexane–benzene, and elution with 5% ether–benzene yielded more compound (7a) (320 mg), m.p. 131—133°. Elution with 8% ether–benzene gave a solid (80 mg) which crystallized from ether to give r-2,t-5-*bis*-(4-*hydroxy*-3-*methoxyphenyl*)-t-3,c-4-*dimethyltetrahydrofuran* (13a), m.p. 168—172°, δ 1·50 (6H, d, *J* 5·9 Hz, 2 × Me), 1·8 (2H, m, 3-, 4-H), 3·90 (6H, s, 2 × OMe), 4·65 (2H, d, *J* 9 Hz, 2-, 5-H), 5·70 (2H, s, 2 × OH), and 6·90—6·98 (6H, m, ArH) (Found: C, 69·7; H, 7·2. $C_{20}H_{24}O_5$ requires C, 69·7; H, 7·0%). Methylation with diazomethane gave the *dimethyl ether* (13b), m.p. 124—128° (methanol), $\nu_{max.}$ 1270, 1239, 1160, 1141, 1136, 1037, and 802 $cm^{-1}$, δ 1·05 (6H, d, *J* 6·3 Hz, 2 × Me), 1·8 (2H, m, 3-, 4-H), 3·87 and 3·90 (each s, 6H, 2 × OMe), 4·67 (2H, d, *J* 9 Hz, 2-, 5-H), and 6·90—7·03 (6H, m, ArH) (Found: C, 70·9; H, 7·7. $C_{22}H_{28}O_5$ requires C, 70·9; H, 7·6%). Compound (13b) is (±)-galbelgin, and has n.m.r. data identical with those of (−)-galbelgin [12] [lit.,[11] for (−)-galbelgin, m.p. 138°].

Further elution with 8% ether–benzene yielded r-2,c-5-*bis*-(4-*hydroxy*-3-*methoxyphenyl*)-t-3,c-4-*dimethyltetrahydrofuran* (14a) as an oil (140 mg), δ 0·65 (3H, d, *J* 6·5 Hz, 2-Me), 1·05 (3H, d, *J* 6·3 Hz, 3-Me), 1·6—2·5 (2H, m, 3-, 4-H), 3·82 and 3·87 (each 3H, s, OMe), 4·42 (1H, d, *J* 8·6 Hz, 2-H), 5·13 (1H, d, *J* 8·2 Hz, 5-H), 5·8 (2H, s, 2 × OH), and 6·89—7·10 (6H, m, ArH) (Found: C, 69·7; H, 7·1. $C_{20}H_{24}O_5$ requires C, 69·7; H, 7·0%). Methylation with diazomethane gave the *dimethyl ether* (14b), m.p. 121—123° (ether), $\nu_{max.}$ 1270, 1240, 1163, 1140, 1037, and 807 $cm^{-1}$, δ 0·67 (3H, d, *J* 6·6 Hz, 4-Me), 1·07 (3H, d, *J* 6·2 Hz, 3-Me), 1·6—2·5 (2H, m, 3-, 4-H), 3·85, 3·87, 3·88, and 3·90 (each 3H, s, OMe), 4·44 (1H, d, *J* 8·6 Hz, 2-H), 5·13 (1H, d, *J* 8·1 Hz, 5-H), and 6·87—7·11 (6H, m, ArH) (Found: C, 71·1; H, 7·7. $C_{22}H_{28}O_5$ requires C, 70·9; H, 7·6%). Isomer (14b) is (±)-veraguensin, and exhibits identical i.r. and n.m.r. characteristics to (+)-veraguensin [12] [lit.,[12] for (+)-veraguensin, m.p. 128—129°].

Finally, elution with 10% ether–benzene afforded a 3 : 1 mixture of *threo*- and *erythro*-isomers of 1-(4-hydroxy-3-methoxyphenyl)-2-[2-methoxy-4-(*E*)-propenylphenoxy]-propan-1-ol (9a) and (10a) (670 mg), δ 1·15 (3H, d, *J* 6 Hz, 3-Me), 1·87 [3H, d, *J* 5 Hz, (*E*)-vinyl Me], 3·85—3·90 (6H, OMe), 4·64 (d, *J* 8 Hz, *threo*-1-H), and 6·8—6·95 (6H, m, ArH) (Found: C, 69·7; H, 7·1. $C_{20}H_{24}O_5$ requires C, 69·7; H, 7·0%).

The product composition (Table) was obtained by acetylation of the mixture of compounds (9a), (10a), (13a), and (14a) with acetic anhydride–pyridine, and examination of the n.m.r. spectrum of the acetylated material.

*Hydrogen Peroxide–Peroxidase Oxidation of* (Z)-*Isoeugenol* (4).—Hydrogen peroxide (3·14%; 7·0 ml, 1·05 equiv.) was added during 30 min at 20° to a stirred solution of (*Z*)-isoeugenol (2·0 g) in acetone–water (5 : 8; 130 ml) containing peroxidase (10 mg). After stirring for an additional 15 min, the acetone was evaporated off at 20 mmHg, and the organic material was extracted with ether. The resulting oil (2·15 g) showed three spots on t.l.c., and was adsorbed on silica gel (200 g) in 50% hexane–benzene. Elution with 5% ether–benzene gave 2,3-*dihydro*-2-(4-*hydroxy*-3-*methoxyphenyl*)-7-*methoxy*-trans-3-*methyl*-5-(Z)-*propenylbenzofuran* (7b) (440 mg), which crystallized from ethyl acetate–hexane in needle clusters, m.p. 83—84°, δ 1·38 (3H, d, *J* 6·8 Hz, 3-Me), 1·93 [3H, q, *J* 7 and 1·8 Hz, (*Z*)-vinyl Me], 3·48 (1H, q, 3-H), 3·87 and 3·90 (each 3H, s, OMe), 5·14 (1H, d, *J* 9·2 Hz, 2-H), 5·72 (1H, s, OH), 5·44—6·6 (2H, m, CH=CH), 6·79 (s, 2H, 4-, 6-H), and 6·94—7·01 (3H, m, 2-aryl) (Found: C, 73·5; H, 6·9. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%).

Elution with 8% ether–benzene gave the tetrahydrofuran (13a) (95 mg), m.p. 168—172° (ether), identical with compound (13a) isolated from the oxidation mixture of the (*E*)-isomer (3). Further elution with 8% ether–benzene yielded isomer (14a) as an oil (170 mg), identical (spectral properties) with that isolated from the oxidation of phenol (3).

Elution with 10% ether–benzene gave a 3 : 1 mixture of the *threo*- and *erythro*-isomers of 1-(4-hydroxy-3-methoxyphenyl)-2-[2-methoxy-4-(*Z*)-propenylphenoxy]propan-1-ol (9b) and (10b) (820 mg), δ 1·17 (3H, d, *J* 6·2 Hz, 3-Me), 1·90 (3H, q, *J* 8 Hz, *threo*-1-H), and 6·84—6·95 (6H, m, ArH) (Found: C, 69·6; H, 7·1. Calc. for $C_{20}H_{24}O_5$: C, 69·7; H, 7·0%).

The product analysis (Table) was obtained by examination of the n.m.r. spectrum of the acetylated mixture of (9b), (10b), (13a), and (14a).

*Hydrogenation of the Aryldihydrobenzofuran* (7b).—A solution of compound (7b) (100 mg) in absolute ethanol (20 ml) was hydrogenated at 1 atm over 5% Pd–C (20 mg). After 30 min, filtration, evaporation, and crystallization of the product from hexane gave dihydrodehydrodi-isoeugenol (7c) (90 mg), m.p. 93—94° (lit.,[36] 94°), identical with an authentic sample obtained by catalytic hydrogenation of compound (7a).

*Preparation of the Ketone* (17).—A 3 : 1 mixture of the *threo*- and *erythro*-isomers (9c) and (10c) [prepared by catalytic hydrogenation of either (9a) and (10a) or (9b) and (10b) mixtures] (400 mg) and 2,3-dichloro-5,6-dicyanobenzoquinone (300 mg, 2 equiv.) in dioxan (10 ml) were kept at 20° for 20 h. After removal of the resulting hydroquinone, evaporation at 20 mmHg gave an oil which was adsorbed on silica gel (50 g). Elution with 5% ether–benzene afforded 1-(4-*hydroxy*-3-*methoxyphenyl*)-2-(2-*methoxy*-4-*propylphenoxy*)*propan*-1-*one* (17) as an oil (340 mg), δ 1·68 (3H, d, *J* 7 Hz, 3-Me), 3·82 and 3·85 (each 3H, s, OMe), 5·41 (1H, d, *J* 7 Hz, 2-H), 6·57 (1H, s, OH), 6·6—7·2 (4H, m, 2-aryl 3-, 5-, 6-H and 1-aryl 5-H), and 7·70—7·89 (2H, m, 1-aryl 2-, 6-H) (Found: C, 69·7; H, 7·1. $C_{20}H_{24}O_5$

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[36] G. Aulin-Erdtman, *Svensk kem. Tidskr.*, 1942, **54**. 168.

requires C, 69·7; H, 7·0%). Methylation with diazomethane yielded the *methyl ether*, m.p. 71—72° (needle clusters from methanol), δ 1·68 (3H, d, *J* 7 Hz, 3-Me), 3·82, 3·90, and 3·92 (each 3H, s, OMe), 5·39 (1H, d, *J* 7 Hz, 2-H), 6·63—6·96 (4H, m, 2-aryl 3-, 5-, 6-H and 1-aryl 5-H), and 7·69—7·96 (2H, m, 1-aryl 2-, 6-H) (Found: C, 70·2; H, 7·4. $C_{21}H_{26}O_5$ requires C, 70·4; H, 7·3%).

*Sodium Borohydride Reduction of the Ketone* (17).—To a solution of the ketone (17) (300 mg) in ethanol (10 ml), sodium borohydride (30 mg) was added. The mixture was set aside for 4 h, diluted with water, and extracted with ether to give oily erythro-1-(4-*hydroxy*-3-*methoxyphenyl*)-2-(2-*methoxy*-4-*propylphenoxy*)*propan*-1-*ol* (10c) (285 mg), δ 1·17 (3H, d, *J* 6·1 Hz, 3-Me), 3·84 (6H, s, 2 × OMe), 4·34 (1H, q, OH), and 6·67—7·04 p.p.m. (6H, m, ArH) (Found: C, 69·3; H, 7·7. $C_{20}H_{26}O_5$ requires C, 69·3; H, 7·6%), contaminated with *ca.* 5% of the *threo*-isomer (9c). The equilibration of isomer (10c) was not accomplished by treatment with hydrochloric acid in aqueous acetone at pH 4 for 1 h at 20°; compound (10c) was recovered unchanged.

4,4′-*Dipropyl*-6,6′-*biguaiacol* (18).—The dehydro-dimer (18), prepared by hydrogen peroxide–peroxidase oxidation of 4-propylguaiacol,[34] crystallized from ethanol as plates, m.p. 151—152° (lit.,[34] 152°).

(E)- *and* (Z)-2,6-*Dimethoxy*-4-*propenylphenol* (5) *and* (6).—The isomers were obtained gas-chromatographically pure according to the procedure of ref. 15.

*Oxidation of* (E)-2,6-*Dimethoxy*-4-*propenylphenol* (5).—(a) *With hydrogen peroxide–peroxidase.* To a stirred solution of the phenol (5) (2·0 g) in aqueous acetone (50%; 100 ml) containing horseradish peroxidase (10 mg; Calbiochem; RZ *ca.* 0·6), 0·31% hydrogen peroxide (29 ml; 1·05 equiv.) was added during 5 h. After stirring for an additional 5 h, the yellow quinone methide colour was no longer evident. The acetone was evaporated off under reduced pressure and the residue extracted with ether to give an oil (2·12 g) which was adsorbed on silica gel (200 g) and eluted with 15% ether–benzene to give r-2,t-5-*bis*-(4-*hydroxy*-3,5-*dimethoxyphenyl*)-t 3,c-4-*dimethyltetrahydrofuran* (13c) (550 mg) as needles (ether), m.p. 157—159°, δ 1·07 (6H, d, *J* 6·5 Hz, 2 × Me), 1·70 (2H, m, 3-, 4-H), 3·92 (12H, s, 4 × OMe), 4·65 (2H, d, *J* 8·6 Hz, 2-, 5-H), 5·54 (2H, s, 2 × OH), and 6·67 (4H, s, ArH) (Found: C, 65·6; H, 7·2. $C_{22}H_{28}O_7$ requires C, 65·3; H, 7·0%). Methylation with diazomethane yielded the *dimethyl ether* (13d), m.p. 128—129° (ether–hexane), $\nu_{max.}$ 1372, 1354, 1030, 829, and 715 cm$^{-1}$, δ 1·10 (6H, d, *J* 6·5 Hz, 2 × Me), 1·77 (2H, m, 3-, 4-H), 3·84 (12H, s, 4 × OMe), 3·88 (6H, s, 2 × OMe), 4·67 (2H, d, *J* 8·6 Hz, 2-, 5-H), and 6·65 (4H, s, ArH) (Found: C, 66·9; H, 7·6. $C_{24}H_{32}O_7$ requires C, 66·7; H, 7·5%).

Further elution with 15% ether–benzene gave r-2,c-5-*bis*-(4-*hydroxy*-3,5-*dimethoxyphenyl*)-t-3,c-4-*dimethyltetrahydrofuran* (14c) as an oil (760 mg), δ 0·67 (3H, d, *J* 6·4 Hz, 4-Me), 1·08 (3H, d, *J* 6·0 Hz, 3-Me), 1·5—2·5 (2H, m, 3-, 4-H), 3·85 and 3·90 (each 6H, s, 2 × OMe), 4·42 (1H, d, *J* 8·3 Hz, 2-H), 5·11 (1H, d, *J* 8·0 Hz, 5-H), 5·60 (2H, s, 2 × OH), and 6·60 and 6·79 (each 2H, s, ArH) (Found: C, 65·7; H, 7·1. $C_{22}H_{28}O_7$ requires C, 65·3; H, 7·0%). Methylation with diazomethane and crystallization from ether–hexane gave the *dimethyl ether* (14d) as prisms, m.p. 90—91°, $\nu_{max.}$ 1380, 1347, 1055, 1032, 730, and 700 cm$^{-1}$, δ 0·70 (3H, d, *J* 6·5 Hz, 4-Me), 1·12 (3H, d, *J* 5·9 Hz, 3-Me), 1·83 (1H, m, 3-H), 2·24 (1H, m, 4-H), 3·82, 3·84, and 3·87 (each 6H, s, 2 × OMe), 4·43 (1H, d, *J* 8·3 Hz, 2-H), 5·11 (1H, d, *J* 8·0 Hz, 5-H), and 6·59 and 6·76 (each 2H, s, ArH) (Found: C, 66·7; H, 7·6. $C_{24}H_{32}O_7$ requires C, 66·7; H, 7·5%).

The ratio (13c) : (14c), estimated by integration of the methyl n.m.r. signals of the crude mixture, was 1 : 2.

(b) *With potassium ferricyanide.* A solution of the phenol (5) (2·0 g) and potassium ferricyanide (3·4 g; 1 equiv.) in 30% acetone–water (120 ml) was kept under nitrogen at 20° for 7 days. The acetone was evaporated off at 20 mmHg and the organic material was extracted with ether–benzene to give an oil (1·22 g), the n.m.r. spectrum of which showed the presence of (13c) and (14c) in the ratio 1 : 2 (by integration of the methyl and aromatic proton signals). The mixture was separated by column chromatography on silica gel into tetrahydrofurans (13c), m.p. 157—159°, and (14c), as already described.

*Oxidation of* (Z)-2,6-*Dimethoxy*-4-*propenylphenol* (6).—(a) *With hydrogen peroxide–peroxidase.* The phenol (6) (2·0 g) was oxidized with 0·31% hydrogen peroxide catalysed by peroxidase in the same manner as the (*E*)-isomer. The product was an oil (2·27 g), which was adsorbed on silica gel (200 g). Elution with 12% ether–benzene afforded oily r-2,t-5-*bis*-(4-*hydroxy*-3,5-*dimethoxyphenyl*)-t-3,t-4-*dimethyltetrahydrofuran* (15c) (550 mg), δ 0·60 (3H, d, *J* 6·5 Hz, 4-Me), 1·02 (3H, d, *J* 6 Hz, 4-Me), 2·50 (2H, m, 3-, 4-H), 3·82 and 3·84 (each 6H, s, 2 × OMe), 4·66 (1H, d, *J* 8 Hz, 2-H), 5·46 (1H, d, *J* 4 Hz, 5-H), 5·6 (2H, s, 2 × OH), and 6·61 and 6·65 p.p.m. (each 2H, s, ArH) (Found: C, 65·2; H, 6·9. $C_{22}H_{28}O_7$ requires C, 65·3; H, 7·0%). Methylation with diazomethane and crystallization from ether–hexane afforded the *dimethyl ether* (15d) as needle clusters, m.p. 121—122°, $\nu_{max.}$ 1522, 1351, 1070, 981, 828, 725, and 710 cm$^{-1}$, δ 0·64 (3H, d, *J* 6·7 Hz, 4-Me), 1·05 (3H, d, *J* 6·1 Hz, 3-Me), 2·47 (2H, m, 3-, 4-H), 3·85, 3·87, and 3·88 (each 6H, s, 2 × OMe), 4·67 (1H, d, *J* 8·5 Hz, 2-H), 5·48 (1H, d, *J* 4·0 Hz, 3-H), and 6·61 and 6·65 (each 2H, s, ArH) (Found: C, 66·9; H, 7·6. $C_{24}H_{32}O_7$ requires C, 66·7; H, 7·5%).

Further elution with 12% ether–benzene gave no pure isomers, although it was evident from the n.m.r. spectra of successive fractions that the isomers were eluted from the column in the order (15c) > (13c) > (14c) ~ (16c). The final fractions (650 mg) containing isomers (14c) and (16c) in the ratio 2 : 1, were combined and methylated with diazomethane. After seeding with authentic material, crystals separated from a hexane solution of t-3,t-4-*dimethyl*-r-2,c-5-*bis*-(3,4,5-*trimethoxyphenyl*)*tetrahydrofuran* (16d), m.p. 90—90·5°, $\nu_{max.}$ 1381, 1070, 1040, 800, and 789 cm$^{-1}$, δ 1·08 (6H, d, *J* 6·3 Hz, 2 × Me), 2·36 (2H, m, 3-, 4-H), 3·85 (18H, s, 6 × OMe), 4·55 (2H, d, *J* 5·9 Hz, 2-, 5-H), and 6·68 (4H, s, ArH) (Found: C, 66·6; H, 7·5. $C_{24}H_{32}O_7$ requires C, 66·7; H, 7·5%).

Integration of the methyl proton n.m.r. signals of the crude product showed a 1 : 2 : 2 : 1 ratio [(13c) : (14c) : (15c) : (16c)].

(b) *With potassium ferricyanide.* The (*Z*)-phenol (6) (2·0 g) when oxidized with potassium ferricyanide [like the (*E*)-phenol (5)] gave an oily mixture with the same n.m.r. spectral and t.l.c. characteristics as the oxidation mixture in (a). Silica gel chromatography again allowed the isolation of isomer (15c).

trans-1,2-*Dihydro*-6,7,8-*trimethoxy*-2,3-*dimethyl*-1-(3,4,5-*trimethoxyphenyl*)*naphthalene* (20).—A mixture of tetrahydrofurans (13d) and (14d) (300 mg) [obtained by methylation (diazomethane) of the oxidation product of phenol

(5)] was dissolved in acetic acid (5 ml) containing 60% perchloric acid (0·5 ml) and was kept at 20° for 4 h. After neutralization with N-sodium hydroxide, the organic material was extracted with dichloromethane and filtered through a column of neutral alumina in the same solvent. Evaporation of the solvent and crystallization from ether gave the dihydronaphthalene (20) as *plates* (180 mg), m.p. 105—106°, δ 1·08 (3H, d, *J* 1·5 Hz, 3-Me), 2·1—2·5 (1H, m, 2-H), 3·60 (3H, s, 8-OMe), 3·73, 3·85, and 3·87 (each 3H, s, OMe), 3·77 (6H, s, 2 × OMe), 4·08br (1H, s, 1-H), 6·10 (1H, d, *J* 1·5 Hz, 4-H), 6·33 (2H, s, 1-aryl), and 6·43 (1H, s, 5-H) (Found: C, 69·7; H, 7·4. $C_{24}H_{30}O_6$ requires C, 69·6; H, 7·3%).

*1,2,3,4-Tetrahydro-6,7,8-trimethoxy-t-2,c-3-dimethyl-r-1-(3,4,5-trimethoxyphenyl)naphthalene* (21).—The dihydronaphthalene (20) (200 mg) in absolute ethanol (20 ml) containing 5% Pd–C (20 mg) was hydrogenated at 1 atm for 3 h. Filtration and evaporation gave a solid (195 mg), m.p. 127—131°, which on crystallization from ether gave the tetralin (21) as *fine needles*, m.p. 133—134°, δ 1·05 (6H, d, *J* 5 Hz, 2-, 3-Me), 1·2—1·7 (2H, m, 2-, 3-H), 2·62 (2H, d, *J* 6 Hz, 4-H), 3·20 (3H, s, 8-OMe), 3·72, 3·79, and 3·84 (each 3H, s, OMe), 3·77 (6H, s, 2 × OMe), 6·40 (1H, s, 5-H), and 6·31 (2H, s, 1-aryl) (Found: C, 69·1; H, 7·7. $C_{24}H_{32}O_6$ requires C, 69·2; H, 7·7%).

*Reduction of the Tetrahydrofurans* (13d) *and* (14d) *with Sodium in Liquid Ammonia.*—(*a*) A mixture of isomers (13d) and (14d) (150 mg), prepared from the (*E*)-phenol (5), in ethylene glycol dimethyl ether (10 ml) and liquid ammonia (25 ml) was stirred during the addition of sodium (25 mg). After 5 min, methanol (1 ml) and water (1 ml) were added, and the ammonia was allowed to evaporate. The product, isolated by extraction with dichloromethane, was an oil (143 mg), which was kept for 16 h in ethanol (20 ml) containing hydrochloric acid (10N; 1 ml). The mixture was diluted with water and extracted with dichloromethane to give the tetralin (21) (75 mg), m.p. 133—134° (ether), identical (n.m.r. spectral data and mixed m.p.) with an authentic sample.

(*b*) The mixture of isomers (13d) and (14d) (200 mg) in ethylene glycol dimethyl ether (20 ml) and liquid ammonia (25 ml) was similarly treated with sodium (90 mg). After 10 min, the reaction was arrested by addition of water (2 ml), and the ammonia was evaporated off. Water (200 ml) was added, and the resulting crystalline material (185 mg), m.p. 120—124° was filtered off. Two recrystallizations from methanol yielded (2RS,3SR)-1,4-*bis*-(3,4,5-*trimethoxyphenyl*)-2,3-*dimethylbutane* (23) (145 mg), m.p. 129—130°, δ 0·87 (6H, d, *J* 6 Hz, 2 × Me), 1·5—2·0 (2H, m, 2-, 3-H), 2·48 (4H, d, *J* 11 Hz, 1-, 4-H), 3·77 (12H, s, 4 × OMe), 3·80 (6H, s, 2 × OMe), and 6·28 (4H, s, ArH) (Found: C, 68·9; H, 8·1. $C_{24}H_{34}O_6$ requires C, 68·9; H, 8·2%).

*Reduction of Tetrahydrofurans* (13d)—(16d) *with Sodium in Liquid Ammonia.*—The mixture of tetrahydrofurans (13d)—(16d) (200 mg) derived from the oxidation mixture of the (*Z*)-phenol (6), in ethylene glycol dimethyl ether (10 ml) and liquid ammonia (25 ml) was stirred during the addition of sodium (100 mg). After 10 min, methanol (2 ml) and water (2 ml) were added, and the ammonia was allowed to evaporate. Isolation of the organic material with dichloromethane yielded an oil (180 mg), which exhibited one t.l.c. spot and was not resolved by silica gel column chromatography. The n.m.r. spectrum exhibited singlets at δ 6·28 and 6·35 of equal intensity, assigned to the aromatic protons of isomers (23) and (25), respectively.

*Acid-catalysed Isomerization of the Tetrahydrofuran* (15d).—Isomer (15d) (250 mg) in 5% perchloric acid–acetic acid was kept at 20° for 30 min. The mixture was neutralized with sodium hydroxide and the organic material was extracted with ether to give an oil (232 mg). The composition of the oil, obtained by integration of the aromatic proton n.m.r. signals, was (20) (50%), (16d) (35%), and (15d) (15%). Adsorption of the oil on silica gel (30 g) and elution with 5% ether–benzene gave the dihydronaphthalene (20) (110 mg), which crystallized from ether, m.p. and mixed m.p. 105—106°. Elution with 8% ether–benzene gave, successively, starting material (15d) (20 mg), and isomer (16d) (41 mg), which crystallized from ether–hexane as plates, m.p. 90—90·5°.

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