# Tobacco Smoke Chemistry. 2. Alkyl and Alkenyl Substituted Guaiacols Found in Cigarette Smoke Condensate

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A series of alkyl and alkenyl substituted guaiacols, which comprise a group of biologically and organoleptically active compounds, have been synthesized. Mass spectra and GC retention times for these have been recorded and compared with those obtained for constituents of a weakly acidic fraction of smoke condensate derived from American blend type cigarettes. On the basis of these results, 25 guaiacols have been identified, 18 of which have not been detected in tobacco smoke condensate previously.

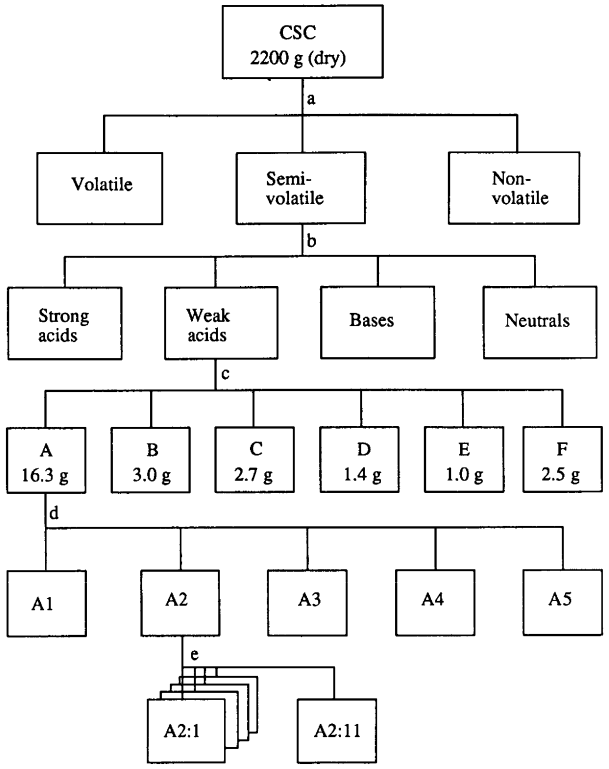
Of the large number of papers published on the composition of tobacco smoke condensate, many demonstrate the presence of guaiacol and of alkyl and alkenyl derivatives thereof. In a review published in 1959, Johnstone and Plimmer[1] reported guaiacol as the sole substance of this kind detected in tobacco smoke. Among the more recent reports disclosing the presence of guaiacol derivatives in tobacco smoke, are those by Rodgman and Cook[2] who in 1964 found eugenol and isoeugenol in Turkish tobacco smoke, Ishiguro *et al.*,[3] who in 1976 identified 4-vinylguaiacol, Schumacher *et al.*[4] who in 1977 reported on 4-methylguaiacol and Newell *et al.*[5] who the following year identified 4-ethylguaiacol. Overviews discussing the contents of the fraction comprising weak acids and phenols from cigarette smoke condensate have also been published, e.g., Snook *et al.*[6] in 1980. These last authors give an idea of the complexity of the fraction and indicate that, in addition to the aforementioned guaiacols, other such compounds are present, but do not identify positional isomers.

Even though minor amounts of guaiacol derivatives have been found in tobacco leaves, most of those present in tobacco smoke condensate probably arise from the pyrolysis of lignin.[7,8] Guaiacols are generally considered to give a 'smoky' or 'spicy' aroma and many of them have been encountered in matter such as commercial smoke condensates,[9] aroma components derived from bacon[10] and matured distilled alcoholic beverages.[11] This group of substances has also been shown to contain biologically active members. Jansson *et al.*[12,13] have recently published a study of sister-chromatid exchanges in human lymphocytes induced by the total weak acid fraction of cigarette smoke condensate (CSC), as well as by subfractions and individual components thereof. The latter group of compounds include several of the easily accessible 4-substituted guaiacols as well as a 5- and a 6-substituted guaiacol.

In an on-going study of CSC, using GC–MS, we have encountered quite a few spectra that correspond to previously unidentified alkyl and alkenyl substituted guaiacols. In view of the fact that very little has been published about the mass spectral behaviour of these substances, reference compounds were needed for the identification of the different positional isomers. Since only some of the 4-substituted guaiacols were commercially available, the remainder of the compounds required were synthesized as described below. A more detailed account for the electron impact induced fragmentation of this group of compounds will be published elsewhere.

## Procedure and discussion

The guaiacols were obtained from CSC, which was generated by smoking 100000 commercial plain cigarettes of American blend type (23 mg tar, 11 mg CO and 1.8 mg nicotine) and collecting the condensate using a procedure described previously.[14,15] The CSC was distilled *in vacuo* employing carbon dioxide as the carrier gas[16] to give a volatile, a semivolatile and a non-volatile fraction. Subsequent fractionation of the semivolatiles by liquid–liquid extraction,[17] using, consecutively, 1 M aqueous solutions of sodium hydrogen carbonate, sodium hydroxide and hydrochloric acid, furnished four dichloromethane soluble fractions, see Scheme 1. The weak acids, extractable with sodium hydroxide, were subjected to flash chromatography[18] on silica gel utilizing a stepwise gradient to give six main subfractions, which were examined by GC–MS. The first fraction (A), which contained a complex mixture of




*Scheme 1.* (a) Distillation; (b) Liquid–liquid extraction; (c) Silica-gel chromatography; (d) Silica-gel chromatography; (e) HPLC, CN column.

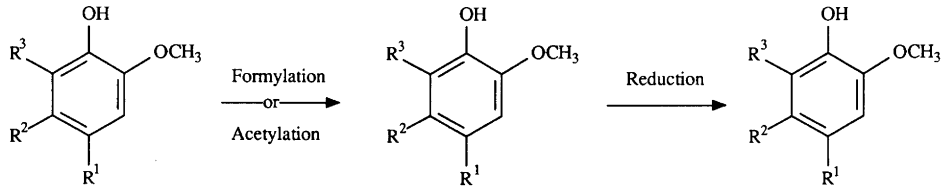
phenolic compounds, was further separated into five subfractions (A1–A5). GC–MS analyses showed the presence of guaiacol-type compounds mainly in fraction A2 but to some extent also in fraction A1. Since the GC resolution of fraction A2 was, in some parts, inadequate, part of the material was further separated by HPLC, see Scheme 1.

The mass spectra corresponding to the alkyl- or alkenyl-guaiacols found showed these compounds to have a molecular weight of 166 or less in all cases but one, thereby limiting their side-chains to three carbons. Since the 4-substituted derivatives, containing a methyl or an ethyl substituent, were quantitatively predominant, and the amounts of 3-substituted derivatives were negligible, we focused our synthetic efforts on the preparation of the 4-, 5- and 6-monosubstituted derivatives and of the disubstituted derivatives containing one alkyl group in the 4-position and one in the 5- or 6-position.

*Syntheses of reference compounds.* Since the main purpose of these syntheses was to obtain reference compounds, conventional synthetic steps were used throughout and no efforts were made to optimize the yields. Scheme 2 shows the combinations of formylations/acetylations and reductions used to obtain most of the disubstituted guaiacols. As expected, the formylation of 5-methylguaiacol (**2**) led to substitution in both the 4- and the 6-positions. These isomers were separated by column chromatography and reduced to 4,5-dimethyl- (**6**) and 5,6-dimethyl-guaiacol (**8**), respectively.

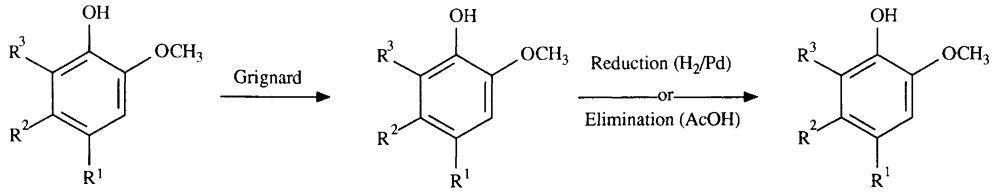
As is evident from Scheme 3, we used the commercially available isomers of hydroxy(methoxy)benzaldehydes and, in one case, a corresponding acetophenone to obtain some of the required monosubstituted alkyl and alkenyl derivatives. The carbonyl compounds were subjected to a Grignard reaction followed by either hydrogenolysis or elimination of the newly generated hydroxy group.

3-Substituted guaiacols are difficult to obtain by the routes described above. 3-Methylguaiacol was therefore




| | $R^1$ | $R^2$ | $R^3$ | | $R^1$ | $R^2$ | $R^3$ | | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | **1** | H | CHO | H | **2** | H | $CH_3$ | H |
| | | | | **3** | H | H | CHO | **4** | H | H | $CH_3$ |
| **2** | H | $CH_3$ | H | **5** | CHO | $CH_3$ | H | **6** | $CH_3$ | $CH_3$ | H |
| **2** | H | $CH_3$ | H | **7** | H | $CH_3$ | CHO | **8** | H | $CH_3$ | $CH_3$ |
| **2** | H | $CH_3$ | H | **9** | $CH_3CO$ | $CH_3$ | H | **10** | $CH_3CH_2$ | $CH_3$ | H |
| **11** | $CH_3$ | H | H | **12** | $CH_3$ | H | CHO | **13** | $CH_3$ | H | $CH_3$ |
| **14** | $CH_3CH_2$ | H | H | **15** | $CH_3CH_2$ | H | CHO | **16** | $CH_3CH_2$ | H | $CH_3$ |

*Scheme 2.*




| | R¹ | R² | R³ | | R¹ | R² | R³ | | R¹ | R² | R³ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | H | CHO | H | **17** | H | $CH_3CHOH$ | H | **18** | H | $CH_3CH_2$ | H |
| | | | | **19** | H | $CH_3CH_2CHOH$ | H | **20** | H | $CH_3CH_2CH_2$ | H |
| | | | | | | | | **21** | H | $CH_3CH{=}CH$ | H |
| **3** | H | H | CHO | **22** | H | H | $CH_3CHOH$ | **23** | H | H | $CH_3CH_2$ |
| | | | | **24** | H | H | $CH_3CH_2CHOH$ | **25** | H | H | $CH_3CH_2CH_2$ |
| | | | | | | | | **26** | H | H | $CH_3CH{=}CH$ |
| **27** | CHO | H | H | **28** | $CH_3(CH_2)_2CHOH$ | H | H | **29** | $CH_3CH_2CH_2CH_2$ | H | H |
| | | | | | | | | **30** | $CH_3CH_2CH{=}CH$ | H | H |
| **31** | $COCH_3$ | H | H | **32** | $(CH_3)_2COH$ | H | H | **33** | $(CH_3)_2CH$ | H | H |

*Scheme 3.*

prepared by partial methylation of 3-methylcathechol, and the mixture of 3- and 6-methylguaiacol obtained was separated by column chromatography. The 6-substituted isomer was identified by comparison with 6-methylguaiacol (**4**), obtained from *o*-vanillin (**3**) as shown in Scheme 2, and 3-methylguaiacol was identified by its NMR spectrum. 3-Ethylguaiacol was prepared, in rather low yield, from 2-ethylphenol by *ortho* nitration followed by methylation of the hydroxy group and reduction of the nitro group to an amino group, which was converted into a hydroxy group by a diazotation reaction. 3,5-Dimethylguaiacol was prepared from 2,4-dimethylphenol in an analogous fashion. 6-Vinylguaiacol was conveniently obtained by treating *o*-vanillin (**3**) with trimethylsilylmethylmagnesium chloride,[19] a reaction which could be effected without prior protection of the hydroxy group.

*Guaiacols found in CSC.* GC retention times and mass spectral data obtained from our reference compounds were used to identify constituents of the different fractions detailed in Scheme 1. The results are presented in Table 1, which gives the names, molecular weights and GC retention times, relative to 2,6-dimethylphenol, of the compounds, and the fraction in which they were identified by their mass spectra. Also given are the mass spectral data of the reference. The reason for giving these spectral data, rather than those actually obtained for the constituents of the CSC fractions, relates to the difficulty of obtaining mass spectra of single compounds in all cases, cf. Table 1, note *f*. In order to confirm our interpretations of the poorly resolved spectral data, we monitored the abundance of the most prominent single ions over several scans with the aim of establishing which ions derive from the compound of interest and their abundance. Although these complications make the interpretation of the spectral data more difficult, we feel that they, when coupled with coinciding GC retention times, provide adequate evidence for the presence in CSC of the compounds detailed in Table 1.

Of the 25 compounds given in Table 1, 18 have, to our knowledge, not been reported as constituents of CSC previously. Although no effort was made to determine the amount of the different guaiacols, the concentration of the major constitutents could be estimated from the abundance of the more prominent peaks in the total fraction of weak acids (Scheme 1). Guaiacol itself was the major product, followed by the 4-substituted derivatives. If the abundance of guaiacol was arbitrarily given the value 100, those for 4-methyl-, 4-ethyl-, 4-propyl-, 4-vinylguaiacol and isoeugenol (*trans*) were found to be 32, 14, 0.7, 38 and 19, respectively. The other compounds of Table 1 were either present in amounts too small to be detected or their GC retention time coincided with those of other weak acids, which made even an estimate rather meaningless. Apart from those substituted in the 4-position, none of the compounds under consideration seemed to reach a relative abundance of 1.

## Experimental

*General methods.* $^1H$ NMR spectra were recorded in $CDCl_3$ at 300 MHz on a Varian XL-300 instrument using $SiMe_4$ as an internal standard. Mass spectra (70 eV) were

*Table 1.* Alkyl and alkenyl substituted guaiacols found in cigarette smoke condensate.

| Compound | MW | Rel.R[a] | Fraction[b] | Mass spectrum [*m/z* (%)] |
|---|---|---|---|---|
| Guaiacol[d] | 124 | 0.956 | A2 | 125 (8), 124 (92), 110 (7), 109 (100), 81 (41), 65 (5), 63 (4), 53 (12), 52 (8), 51 (6) |
| 3-Methylguaiacol[c,e] | 138 | 1.022 | A | [g] |
| 4-Methylguaiacol[d] | 138 | 1.042 | A2 | 139 (8), 138 (100), 137 (8), 123 (88), 95 (27), 77 (15), 67 (15), 65 (8), 55 (14), 51 (9) |
| 5-Methylguaiacol[c,e] | 138 | 1.030 | A2 | [g] |
| 6-Methylguaiacol[c,e] | 138 | 0.967 | A1 | [g] |
| 4-Vinylguaiacol[d] | 150 | 1.243 | A2 | 151 (12), 150 (100), 135 (71), 107 (26), 79 (8), 78 (8), 77 (23), 53 (8), 52 (7), 51 (10) |
| 6-Vinylguaiacol[c,e] | 150 | 1.196 | A1 | [g] |
| 4-Ethylguaiacol[d] | 152 | 1.101 | A2 | 152 (41), 138 (9), 137 (100), 122 (10), 94 (6), 91 (8), 77 (8), 65 (6), 53 (6), 51 (6) |
| 5-Ethylguaiacol[c,e] | 152 | 1.105 | A2 | [g] |
| 6-Ethylguaiacol[c,e] | 152 | 1.108 | A1 | [g] |
| 3,5-Dimethylguaiacol[c,e] | 152 | 1.097 | A2[f] | [g] |
| 4,5-Dimethylguaiacol[c,e] | 152 | 1.157 | A2 | [g] |
| 4,6-Dimethylguaiacol[c,e] | 152 | 1.049 | A1 | [g] |
| 5,6-Dimethylguaiacol[c,e] | 152 | 1.076 | A1[f] | [g] |
| Eugenol[d] | 164 | 1.219 | A2 | 164 (100), 149 (31), 137 (18), 133 (13), 131 (20), 121 (11), 103 (16), 91 (13), 77 (18), 55 (13) |
| Isoeugenol (*cis*)[d] | 164 | 1.290 | A2 | 165 (10), 164 (100), 149 (29), 133 (10), 131 (14), 121 (10), 103 (12), 91 (10), 77 (13), 55 (10) |
| Isoeugenol (*trans*)[d] | 164 | 1.360 | A2 | 165 (9), 164 (100), 149 (29), 133 (9), 131 (13), 121 (8), 103 (11), 91 (9), 77 (11), 55 (8) |
| 5-Propenylguaiacol (*trans*)[c,e] | 164 | 1.378 | A2[f] | [g] |
| 6-Propenylguaiacol (*trans*)[c,e] | 164 | 1.311 | A1[f] | [g] |
| 4-Propylguaiacol[d,e] | 166 | 1.172 | A2 | 167 (2), 166 (22), 138 (8), 137 (100), 122 (8), 94 (5), 77 (5), 65 (3), 55 (2), 51 (3) |
| 5-Propylguaiacol[c,e] | 166 | 1.179 | A2 | [g] |
| 4-Isopropylguaiacol[c,e] | 166 | 1.123 | A2:10 | [g] |
| 4-Ethyl-5-methylguaiacol[c,e] | 166 | 1.203 | A2:10 | [g] |
| 4-Ethyl-6-methylguaiacol[c,e] | 166 | 1.107 | A2:11 | [g] |
| 4-Butylguaiacol[c,e] | 180 | 1.247 | A2 | [g] |

[a]GC retention time relative to 2,6-dimethylphenol on a Supelcowax 10 fused silica column. [b]Refers to Scheme 1. [c]Identified by comparison with a synthesized reference. [d]Identified by comparison with a commercially available compound. [e]Presence in CSC not previously demonstrated. [f]Incompletely resolved GC peak. [g]Mass spectrum identical with that of the synthesized reference, see Experimental.

measured on Kratus MS 50 and MS 25 mass spectrometers; intensities of ions (*m/z* 40 to *M*+1) are given as a percentage of the base peak.

*Chromatography.* Gas chromatography was performed on a Hewlett–Packard model 5880 A instrument, equipped with a flame-ionisation detector. The relative retention times were measured on a Supelcowax 10 fused silica column (0.32 mm i.d., 60 m) programmed from 60 to 250 °C at 2 K $min^{-1}$ using helium as the carrier gas. Merck Kieselgel 60 (230–400 mesh) was used for column chromatography. HPLC was performed on a Varian 5000 instrument, equipped with Waters Differential Refractometer R401 and Pharmacia Dual Path Monitor UV-2 (254 nm).

*Preparation of cigarette smoke condensate fractions.* The CSC was prepared from 100000 plain cigarettes of American blend type (23 mg tar, 11 mg CO and 1.8 mg nicotine per cigarette). The cigarettes were smoked according to a standard procedure[14] using a Borgwaldt automatic smoking machine (Type R 09.012, Heinr. Borgwaldt, Hamburg, F.R.G.). The CSC was condensed in an Elmenhorst trap cooled with solid $CO_2$–ethanol.[15] The CSC was distilled *in vacuo* with carbon dioxide as the carrier gas[16] to give three fractions–volatiles, semivolatiles and non-volatiles. The semivolatiles were divided into four dichloromethane-soluble fractions–acids, weak acids, bases and neutrals–utilising an extraction procedure described earlier.[17] Portions (8–9 g) of the weak acids were subjected to flash chromatography[18] on silica gel. The column was eluted with 1300 ml batches of 6 different mixtures of cyclohexane, ethyl acetate and methanol (6:1:0; 3:1:0; 1:1:0; 1:3:0; 0:3:1; 0:0:1). The eluate was collected in 25 ml tubes and, after TLC evaluation, combined into 6 fractions, A–F. Fraction A contained, according to GC–MS, most of the alkylphenols and alkylguaiacols and was further fractionated (silica gel, chloroform containing 2 % ethyl acetate) as shown in Scheme 1 and the subfractions combined according to results obtained by TLC and GC. Subfraction A2, which, according to GC–MS, contained most of the guaia-

col derivatives, was further fractionated by HPLC (CN-column, methanol–water 1:1 until eugenol had been eluted, then methanol for 5 min).

*Syntheses of reference compounds.* Since conventional synthetic steps were used throughout and no attempts were made to optimize the yields, we give only a general description of the steps involved in the syntheses (Schemes 2 and 3) followed by spectroscopic data for the alkyl substituted guaiacols. $^1$H NMR and mass spectra from isolated intermediates confirmed the structures proposed.

In Scheme 2, the acyl groups were reduced to alkyl groups either by catalytic hydrogenation or by Clemmensen reduction. In order to obtain dialkyl substituted guaiacols by this route, we started with a suitable monoalkylated guaiacol and carried out a Reimer–Tiemann formylation or a Friedel–Crafts acylation. After the product(s) had been isolated, the reduction was performed as mentioned above.

4,5-Dimethyl- (**6**) and 5,6-dimethyl-guaiacol (**8**) are described as typical examples of the synthetic route shown in Scheme 2. 5-Methylguaiacol (**2**) was dissolved in ethanol and formylated according to the Reimer–Tiemann method with chloroform in the presence of an excess of sodium hydroxide. The reaction mixture was acidified (conc. HCl), diluted with water, extracted with dichloromethane, and dried and the solvent was evaporated. The residue was purified by column chromatography (silica gel; cyclohexane–ethyl acetate 2:1) The fractions containing **5** and **7** (Scheme 2) were pooled separately and reduced by catalytic hydrogenation (Pd–C, ethanol) to the alkylguaiacols **6** and **8** which could be used as references without any further purification.

*4,5-Dimethylguaiacol* (**6**): $^1$H NMR: δ 6.72 (s, 1 H), 6.65 (s, 1 H), 5.37 (br s, 1 H), 3.85 (s, 3 H), 2.19 (s, 3 H), 2.17 (s, 3 H). MS [*m/z* (%)]: 153 (9), 152 (100), 151 (9), 138 (7), 137 (88), 109 (29), 91 (7), 79 (7), 77 (7), 53 (6).

*5,6-Dimethylguaiacol* (**8**): $^1$H NMR: δ 6.64 (d, 1 H), 6.62 (d, 1 H), 5.69 (s, 1 H), 3.86 (s, 3 H), 2.21 (s, 3 H), 2.18 (s, 3 H). [*m/z* (%)]: 153 (7), 152 (82), 151 (5), 138 (9), 137 (100), 109 (12), 94 (5), 91 (8), 77 (5), 65 (4).

*5-Methylguaiacol* (**2**) (Scheme 2) was obtained from commercially available isovanillin (**1**) by catalytic hydrogenation and showed $^1$H NMR: δ 6.77 (d, 1 H), 6.76 (d, 1 H), 6.65 (m, 1 H), 5.54 (s, 1 H), 3.87 (s, 3 H), 2.27 (s, 3 H). MS [*m/z* (%)]: 139 (8), 138 (93), 124 (7), 123 (100), 95 (24), 77 (11), 67 (12), 66 (6), 65 (6), 55 (11).

*6-Methylguaiacol* (**4**) was prepared from commercially available *o*-vanillin (**3**) as described above. $^1$H NMR: δ 6.84–6.70 (m, 3 H), 5.69 (s, 1 H), 3.88 (s, 3 H), 2.26 (s, 3 H). MS [*m/z* (%)]: 138 (81), 124 (11), 123 (100), 95 (16), 77 (21), 67 (13), 66 (9), 65 (9), 55 (8), 51 (11).

*4-Ethyl-5-methylguaiacol* (**10**). 5-Methylguaiacol (**2**) was acetylated using acetyl chloride and aluminium chloride in carbon disulfide (16 h, ambient temperature). The reaction mixture was diluted with water and extracted with dichloromethane. Since the product was partly *O*-acetylated, the ester function was hydrolysed with sodium hydroxide in aqueous methanol (30 min, ambient temperature), and the reaction mixture was diluted, acidified and extracted with dichloromethane. After the solvent had been evaporated the crude product was purified by column chromatography (cyclohexane–ethyl acetate 2:1) followed by catalytic hydrogenation to give **10** which showed $^1$H NMR: δ 6.72 (s, 1 H), 6.67 (s, 1 H), 5.38 (br s, 1 H), 3.87 (s, 3 H), 2.55 (q, 2 H), 2.21 (s, 3 H), 1.18 (t, 3 H). MS [*m/z* (%)]: 167 (4), 166 (41), 152 (9), 151 (100), 137 (9), 136 (6), 108 (5), 91 (7), 79 (6), 77 (7).

*4,6-Dimethylguaiacol* (**13**) was obtained by formylation of 4-methylguaiacol (**11**) followed by a Clemmensen reduction with amalgamated zinc and hydrochloric acid. In this case the crude product was purified by column chromatography (cyclohexane–ethyl acetate 3:1). $^1$H NMR: δ 6.58 (br s, 1 H), 6.56 (br s, 1 H), 5.52 (s, 1 H), 3.87 (s, 3 H), 2.27 (s, 3 H), 2.24 (s, 3 H). MS [*m/z* (%)]: 153 (10), 152 (100), 138 (15), 137 (91), 109 (21), 91 (12), 81 (10), 79 (12), 77 (11), 65 (10).

*4-Ethyl-6-methylguaiacol* (**16**) was prepared as described for **13** starting with 4-ethylguaiacol (**14**). $^1$H NMR: δ 6.60 (br s, 1 H), 6.58 (br s, 1 H), 5.54 (br s, 1 H), 3.89 (s, 3 H), 2.57 (q, 2 H), 2.25 (s, 3 H), 1.23 (t, 3 H). MS [*m/z* (%)]: 167 (5), 166 (48), 152 (14), 151 (100), 137 (7), 136 (6), 123 (4), 91 (5), 79 (4), 77 (5).

In Scheme 3 a Grignard reagent was used directly on the commercially available vanillin derivatives **1**, **3** and **27** without protecting the hydroxy group. The resulting α-hydroxy alkylguaiacols were, after work-up, either reduced to the corresponding alkyl derivative by catalytic hydrogenolysis (Pd–C, ethanol) or dehydrated in acetic acid to the alkenyl derivative. In all cases the substances were about 90 % pure according to GC and they where used as references without further purification.

*5-Propylguaiacol* (**20**). Isovanillin (**1**) was added to an ethereal solution of ethylmagnesium iodide. After 3 h reflux the solution was acidified with dilute hydrochloric acid and the two phases were separated. The aqueous phase was extracted with diethyl ether. The combined ether phases were dried and evaporated and the residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate 2:1). The fractions containing the α-hydroxy compound (**19**) were collected and converted by catalytic hydrogenolysis into **20** which showed $^1$H NMR: δ 6.80 (d, 1 H), 6.80 (d, 1 H), 6.66 (dd, 1 H), 5.60 (br s, 1 H), 3.87 (s, 3 H), 2.50

(t, 2 H), 1.61 (sextet, 2 H), 0.93 (t, 3 H). MS [*m/z* (%)]: 167 (3), 166 (24), 138 (8), 137 (100), 122 (7), 109 (3), 94 (5), 77 (4), 65 (3), 51 (3).

*5-(1-Propenyl)guaiacol* (**21**) was prepared by boiling **19** for 3 h in glacial acetic acid. The reaction mixture was diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate to remove the acetic acid, and dried and the solvent was evaporated. Both the *cis* and *trans* isomers were formed in a 1:20 ratio as evidenced by both GC and NMR spectroscopy. $^1$H NMR (*trans* isomer): δ 6.96 (br s, 1 H), 6.79 (m, 2 H), 6.20 (dq, 1 H), 6.09 (dq, 1 H), 5.56 (s, 1 H), 3.88 (s, 3 H), 1.86 (dd, 3 H). MS (*trans* isomer) [*m/z* (%)]: 165 (10), 164 (100), 150 (7), 149 (72), 131 (7), 121 (10), 103 (15), 91 (15), 77 (19), 55 (18).

*5-Ethylguaiacol* (**18**) was prepared as described above starting with **1** and methylmagnesium iodide. $^1$H NMR: δ 6.80 (d, 1 H), 6.78 (d, 1 H), 6.68 (dd, 1 H), 5.56 (s, 1 H), 3.86 (s, 3 H), 2.56 (q, 2 H), 1.20 (t, 3 H). MS [*m/z* (%)]: 152 (46), 138 (8), 137 (100), 122 (8), 109 (6), 94 (6), 91 (9), 79 (5), 77 (7), 43 (15).

*6-Ethyl-* (**23**), *6-propyl-* (**25**) and *6-(1-propenyl)guaiacol* (**26**) were prepared from *o*-vanillin (**3**) as described for the corresponding 5-substituted guaiacols (Scheme 3). Dehydration, however, was slower and the α-hydroxy compound had to be boiled in acetic acid for 12 h in order to obtain 6-(1-propenyl)guaiacol.

*6-Ethylguaiacol* (**23**): $^1$H NMR: δ 6.81–6.70 (m, 3 H), 5.69 (s, 1 H), 3.90 (s, 3 H), 2.69 (q, 2 H), 1.24 (t, 3 H). MS [*m/z* (%)]: 153 (7), 152 (69), 138 (9), 137 (100), 122 (7), 120 (7), 109 (7), 91 (14), 77 (8), 65 (6).

*6-Propylguaiacol* (**25**): $^1$H NMR: δ 6.81–6.70 (m, 3 H), 5.67 (br s, 1 H), 3.89 (s, 3 H), 2.62 (m, 2 H), 1.65 (sextet, 2 H), 0.97 (t, 3 H). MS [*m/z* (%)]: 166 (35), 138 (12), 137 (100), 122 (7), 109 (5), 91 (5), 79 (4), 77 (8), 65 (4), 51 (4).

*6-(1-Propenyl)guaiacol* (**26**): $^1$H NMR (*trans* isomer): δ 7.00 (dd, 1 H), 6.79 (dd, 1 H), 6.73 (dd, 1 H), 6.69 (dd, 1 H), 6.30 (dq, 1 H), 5.83 (s, 1 H), 3.89 (s, 3 H), 1.91 (dd, 3 H). MS (*trans* isomer) [*m/z* (%)]: 165 (10), 164 (100), 149 (23), 133 (7), 132 (7), 131 (19), 121 (17), 103 (14), 91 (10), 77 (12).

4-Butylguaiacol (**29**) was prepared, as described above, from vanillin (**27**) and propylmagnesium iodide. During work-up of the α-hydroxy compound (**28**) dehydration occurred spontaneously to form 4-(1-butenyl)guaiacol (**30**) as a minor product.

*4-Butylguaiacol* (**29**): $^1$H NMR: δ 6.83 (d, 1 H), 6.69 (s, 1 H), 6.68 (d, 1 H), 5.44 (s, 1 H), 3.88 (s, 3 H), 2.54 (dd, 2 H), 1.57 (m, 2 H), 1.35 (sextet, 2 H), 0.93 (t, 3 H). MS [*m/z* (%)]: 181 (2), 180 (21), 138 (11), 137 (100), 123 (2), 122 (5), 94 (3), 91 (2), 77 (3), 51 (2).

4-(1-Butenyl)guaiacol (**30**): $^1$H NMR (*trans* isomer): δ 6.89 (s, 1 H), 6.85 (s, 2 H), 6.31 (d, 1 H), 6.11 (dt, 1 H), 5.55 (s, 1 H), 3.91 (s, 3 H), 2.22 (quintet, 2 H), 1.09 (t, 3 H). MS (*trans* isomer) [*m/z* (%)]: 179 (12), 178 (100), 163 (26), 147 (15), 132 (13), 131 (99), 91 (14), 77 (11), 45 (10).

*4-Isopropylguaiacol* (**33**) was obtained from commercially available 4-hydroxy-3-methoxyacetophenone (**31**) and methylmagnesium iodide. $^1$H NMR: δ 6.85 (d, 1 H), 6.72 (m, 2 H), 5.45 (br s, 1 H), 3.90 (s, 3 H), 2.85 (septet, 1 H), 1.22 (d, 6 H). MS [*m/z* (%)]: 166 (32), 152 (9), 151 (100), 136 (5), 119 (16), 91 (25), 79 (6), 77 (9), 65 (6), 53 (5).

*3,5-Dimethylguaiacol.* 2,4-Dimethylphenol was dissolved in glacial acetic acid and added dropwise to a stirred solution of sodium nitrate in sulfuric acid–acetic acid (1:3). After 3 h the reaction mixture was diluted with water, extracted with dichloromethane and dried, and the solvent evaporated. The crude product subjected to column chromatography (silica gel; cyclohexane–ethyl acetate 5:2). 2,4-Dimethyl-6-nitrophenol was *O*-methylated with dimethyl sulfate and sodium hydroxide in methanol (2 h, 70 °C), diluted with dichloromethane and washed with 1 M sodium hydroxide to remove remaining phenolic compounds. After the organic layer had been dried and evaporated, the nitro group was reduced with stannous chloride and hydrochloric acid in hot ethanol to the corresponding amine. The mixture was diluted with water, washed with diethyl ether, made alkaline, extracted with diethyl ether, and dried. The solvent was evaporated and the resulting amine was diazotized with sodium nitrite in hydrochloric acid (1 h, 5 °C) and added dropwise to boiling water. The reaction mixture was extracted with dichloromethane and the solvent was evaporated, to give 3,5-dimethylguaiacol in very low yield. $^1$H NMR: δ 6.64 (br s, 1 H), 6.53 (br s, 1 H), 5.55 (s, 1 H), 3.78 (s, 3 H), 2.27 (s, 3 H), 2.25 (s, 3 H). MS [*m/z* (%)]: 152 (59), 151 (8), 138 (10), 137 (100), 123 (10), 109 (19), 91 (9), 81 (9), 79 (10), 77 (10).

*3-Ethylguaiacol* was prepared from 2-ethylphenol, as described above. 3-Ethylguaiacol showed $^1$H NMR: δ 6.97 (dd, 1 H), 6.82 (dd, 1 H), 6.75 (br dd, 1 H), 5.59 (br s, 1 H), 3.81 (s, 3 H), 2.69 (br q, 2 H), 1.25 (t, 3 H). MS [*m/z* (%)]: 153 (8), 152 (100), 137 (73), 119 (11), 109 (27), 91 (30), 81 (8), 79 (10), 77 (11), 65 (8).

*3-Methylguaiacol.* 3-Methylcatechol (20 mmol), tetrabutylammonium hydrogen sulfate (20 mmol) and sodium hydroxide (40 mmol) were dissolved in water (20 ml) and a solution of methyl iodide (40 mmol) in dichloromethane (20 ml) was added. After being vigorously stirred for 1 h, the organic phase was separated and washed with dilute hydrochloric acid. The solvent was evaporated, and the

solid residue was triturated with boiling diethyl ether. The crude extract contained 6-methylguaiacol (**4**) as the main product, together with the target compound. Column chromatography (silica gel; cyclohexane–ethyl acetate 3:1) gave pure 3-methylguaiacol showing $^1$H NMR: δ 6.92 (dd, 1 H), 6.83 (dd, 1 H), 6.72 (br dd, 1 H), 5.64 (s, 1 H), 3.82 (s, 3 H), 2.32 (s, 3 H). MS [*m/z* (%)]: 138 (78), 124 (7), 123 (100), 95 (15), 77 (17), 67 (11), 66 (6), 65 (7), 51 (7), 41 (6).

*6-Vinylguaiacol* was prepared by reaction of *o*-vanillin (**3**) with trimethylsilylmethylmagnesium chloride[20] in anhydrous diethyl ether followed by treatment with thionyl chloride.[18] The residue was purified by column chromatography (Sephadex LH 20; ethanol). $^1$H NMR: δ 7.09 (dd, 1 H), 7.01 (dd, 1 H), 6.82 (dd, 1 H), 6.76 (dd, 1 H), 5.89 (s, 1 H), 5.80 (dd, 1 H), 5.30 (dd, 1 H), 3.89 (s, 3 H). MS [*m/z* (%)]: 151 (10), 150 (100), 135 (19), 131 (8), 121 (8), 120 (9), 107 (37), 79 (8), 78 (5), 77 (13).

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## References

1. Johnstone, R. A. W. and Plimmer, J. R. *Chem. Rev. 59* (1959) 885.
2. Rodgman, A. and Cook, L. C. *Tob. Sci. 8* (1964) 161.
3. Ishiguro, S., Sato, S., Sugawara, S. and Kaburaki Y. *Agric. Biol. Chem. 40* (1976) 977.
4. Schumacher, J. N., Green, C. R., Best, F. N. and Newell, M. P. *J. Agric. Food Chem. 25* (1977) 310.
5. Newell, M. P., Heckman, R. A., Moates, R. F., Green, C. R., Best, F. W. and Schumacher, J. N. *Tob. Sci. 22* (1978) 6.
6. Snook, M. E., Fortson, P. J. and Chortyk, O. T. *Tob. Sci. 30* (1980) 78.
7. Evans, R. J., Milne, T. A. and Soltys, M. N. *J. Anal. Appl. Pyrolysis 9* (1986) 207.
8. Schlotzhauer, W. S. and Chortyk, O. T. *J. Anal. Appl. Pyrolysis 12* (1987) 193.
9. Kim, K., Kurata, T. and Fujimaki, M. *Agric. Biol. Chem. 38* (1974) 53.
10. Shu, C. and Mookherjee, B. D. *J. Agric. Food Chem. 33* (1985) 1107.
11. Lehtonen, M. *J. Assoc. Off. Anal. Chem. 66* (1983) 62.
12. Jansson, T., Curvall, M., Hedin, A. and Enzell, C. R. *Mutat. Res. 169* (1986) 129.
13. Jansson, T., Curvall, M., Hedin, A. and Enzell, C. R. *Mutat. Res. 206* (1988) 17.
14. *Coresta Information Bulletin 1* (1969) 24.
15. Elmenhorst, H. *Beitr. Tabaksforsch. 3* (1965) 101.
16. Enzell, C. R., Kimland, B. and Rosengren, A. *Acta Chem. Scand. 24* (1970) 1462.
17. Curvall, M., Enzell, C. R., Jansson, T., Pettersson, B. and Thelestam, M. *J. Toxicol. Environ. Health 14* (1984) 163.
18. Still, W. C., Kahn, M. and Mitra, A. *J. Org. Chem. 43* (1978) 2923.
19. Peterson, D. J. *J. Org. Chem. 33* (1968) 780.
20. Chan, T. H. and Chang, E. *J. Org. Chem. 39* (1974) 3264.

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