Lignin Chromophores. Part I. Synthesis of Chromophores of the 2,4'- and 4,4'-Dihydroxystilbene Types

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Convenient syntheses of 2,4'- and 4,4'-dihydroxystilbenes (types C and E) and their hydroxymethyl derivatives (types D and F) are described.

The key step of the syntheses is a Knoevenagel condensation of appropriate aromatic aldehydes with suitably substituted arylacetic acids to give stilbenecarboxylic acids and/or their lactones. This step is followed by decarboxylation of the stilbenecarboxylic acids and removal of protecting (acetyl) groups (preparation of types C and E), or by esterification of the stilbenecarboxylic acids or lactones and reduction of the resulting esters with lithium aluminium hydride (preparation of types D and F).

The versatility of the method is shown. The analytical and spectral data for the various products and intermediates are summarised in tables.

During pulping, certain phenolic units in lignins are converted to hydroxystilbene structures. These may represent intermediates during the various pulping processes [1-3] or constitute potential chromophoric systems in the resulting pulps [1,4,5] and spent liquors.[6-8] Thus, phenolic units of the phenylcoumaran type (A, see Fig. 1) give 2,4'-dihydroxystilbene structures (C [9,10] and D [2]), and phenolic units of the 1,2-diarylpropane-1,3-diol type (B) yield 4,4'-dihydroxystilbene structures (E [11,12] and F). It has been suggested that these reactions in alkaline media proceed via intermediate methylene quinones (G and H)[1,4,9] and in acidic media via intermediate carbonium ions (I and J).[1,2,13] Elimination of the terminal hydroxy-

methyl group from these two types of intermediates gives stilbene structures which are unsubstituted at the olefinic carbon atoms (C and E).[1,4-13] Loss of their β-proton affords intermediate stilbene structures, substituted at one of the olefinic carbon atoms by a hydroxymethyl group (D and F).[2,13]

For studies of the reactions of the 2,4'- and 4,4'-dihydroxystilbene type structures (C − F) during pulping, bleaching and ageing representative models were needed.

Previously,[6,14] hydroxystilbenes have been synthesised by heating tris-hydroxyaryl-trithianes in the presence of heavy metals (Fe, Cu). The trithianes required can be prepared by treating the appropriate aromatic hydroxyaldehyde with an excess of hydrogen sulfide in acidic solution.[15] However, owing to various side reactions, in particular polymerisations, during the heat treatment of the trithianes, the yields obtainable by this desulfurisation method are usually low. Moreover, the desulfurisation method can only be used for the preparation of symmetrically substituted stilbenes.

The synthesis of asymmetrically substituted stilbenes entails the coupling of two different moieties by some type of condensation after protection of the phenolic hydroxyl groups. Grignard syntheses [16] and Wittig syntheses [16-22] have been used to achieve condensation between free,[18] benzylated,[16,21] acetylated,[16,22] methylated,[20] methoxymethylated,[21] or trimethylsilylated,[19] phenolic benzylhalogenides and aromatic aldehydes. These methods afford low overall yields of hydroxystilbenes, unsubstituted at the olefinic carbon atoms.

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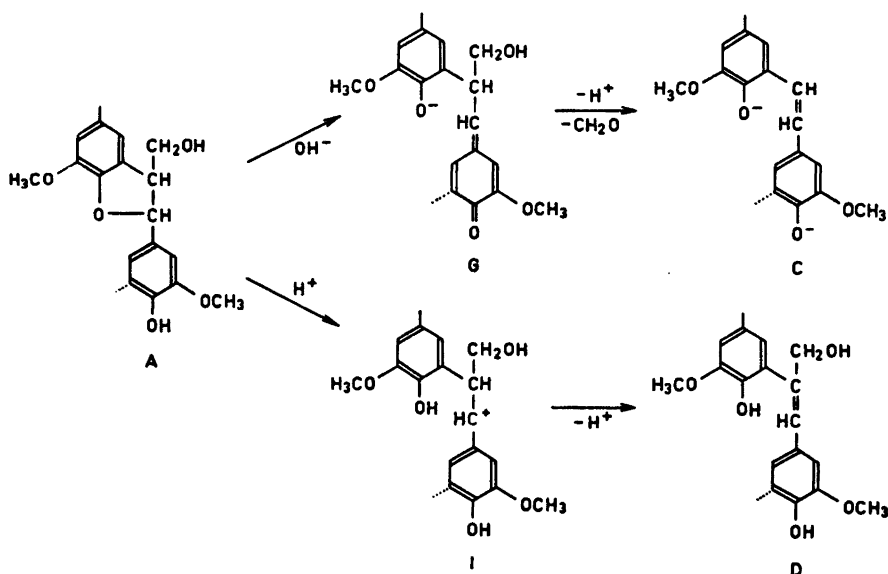** Present address: Medical University of South Carolina, Charleston, U.S.A.

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Fig. 1.

In the present communication, a convenient route of preparation for representatives of all four structural types (C−F) is described (see Scheme 1). The procedure involves:

Scheme 1.

(1) Knoevenagel condensation of appropriate aromatic aldehydes with suitably substituted arylacetic acids to give stilbenecarboxylic acids or their lactones.[23-25]

(2) Decarboxylation of the stilbenecarboxylic acids [26,27] followed by

(3) Removal of protecting (acetyl) groups (preparation of types C and E)

(4) Alternative to (2): Esterification of the stilbenecarboxylic acids and conversion of lactones into methyl esters, followed by

(5) Lithium aluminium hydride reduction (preparation of types D and F).

By choosing appropriate reactants for the condensations and using the above reaction sequences, a wide variety of symmetrical and asymmetrical phenolic and non-phenolic stilbenes and hydroxymethyl-substituted stilbenes, differing in their patterns of aromatic substitution, could be synthesised. The various steps (1−5) in the preparation of some typical representatives (4,4′- and 2,4′-dihydroxystilbenes of types C−F) are described in the experimental section.

Yields, m.p. and elemental analyses of the intermediates and final products are given in Tables 1−6; the NMR-data are summarised in Tables 7−12. The final products were also characterised by mass spectra. Molecular ions
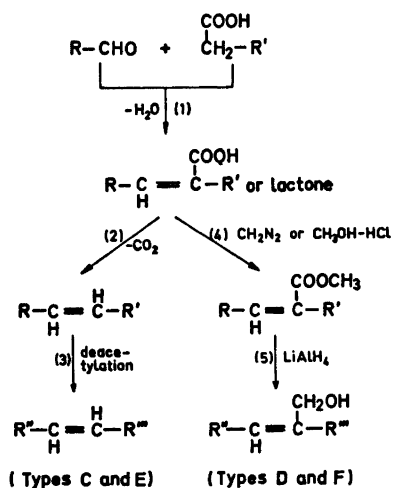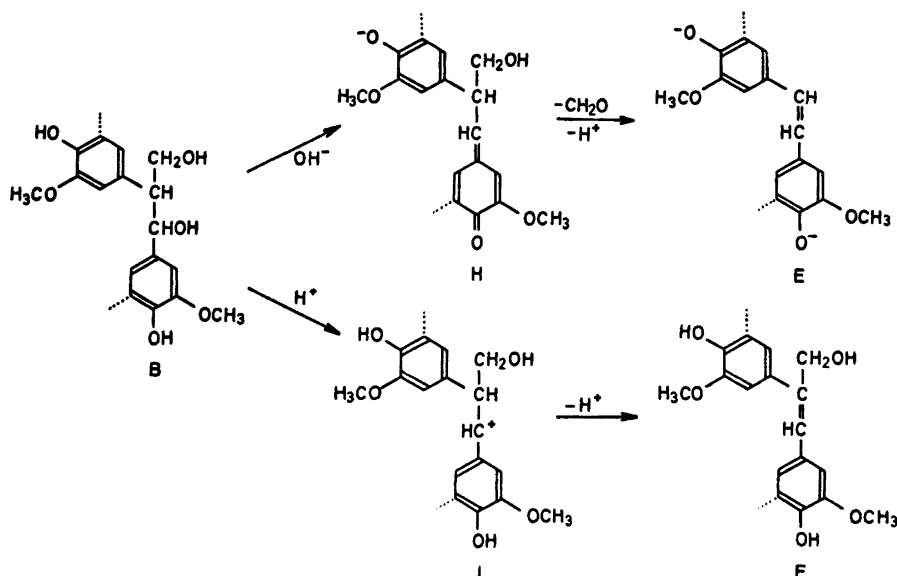
Fig. 2.

Table 1. Stilbenecarboxylic acids.

Compound	Yield %	M.p. °C	Elemental analyses C Calc.	Found	H Calc.	Found	O Calc.	Found
Ia	59.8	205 – 207	69.23	69.07	5.13	5.18	25.64	25.53
IIa [44]	25.7	228 – 233	71.83	71.76	5.63	5.55	22.53	22.65
IIIa	65.7	216 – 218	63.00	63.03	5.00	5.10	32.00	31.92
IVa	49.8	178 – 180	64.51	64.70	5.38	5.55	30.11	30.00
Va	32.5	180 – 190	66.28	66.31	5.81	5.90	27.91	27.69
VIa	59.0	225 – 227	64.04	64.10	4.49	4.55	31.46	31.23
VIIa	39.4	232 – 238	66.67	66.54	5.26	5.4	28.07	27.93
VIIIa	42.2	217 – 220	62.69	62.58	5.47	5.62	31.84	31.78
IXa	53.2	228 – 229	69.23	69.25	5.13	5.12	25.64	25.68
Xa	51.3	179 – 182	63.00	63.02	5.00	5.08	32.00	31.89
XIa	51.0	188 – 191	64.51	64.70	5.38	5.55	30.11	30.00

Table 2. Lactones.

Compound	Yield %	M.p. °C	Elemental analyses C Calc.	Found	H Calc.	Found	O Calc.	Found
XIV	15.4	157 – 158	76.19	76.19	4.77	4.81	19.05	19.15
XV	21.1	145 – 147	69.23	69.72	5.13	5.20	25.64	25.28
XVI	21.7	160 – 161	67.06	67.11	4.71	4.81	28.23	28.18
XVII	58.5	148 – 150	69.68	69.65	4.52	4.39	25.80	25.69
XVIII	71.8	149 – 153	67.80	67.70	5.08	5.10	27.12	27.24

Table 3. Hydroxystilbene acetates.

Compound	Yield %	M.p. °C	Elemental analyses C Calc.	Found	H Calc.	Found	O Calc.	Found
Ib	48.8	141 − 147	76.12	76.22	5.79	6.01	17.91	17.85
IIIb [6]	58.5	227 − 229	67.42	67.38	5.62	5.68	26.96	27.01
IVb	53.6	130 − 132	69.52	70.02	6.09	6.10	24.37	23.81
IXb	62.8	109 − 110	76.13	76.44	5.96	5.62	17.89	17.35
Xb [22]	55.0	138 − 139	67.43	76.72	5.61	5.77	26.95	26.72
XIb	53.2	103 − 104	69.51	69.40	6.09	6.03	24.38	24.46

Table 4. Hydroxystilbenes.

Compound	Yield %	M.p. °C	Elemental analyses C Calc.	Found	H Calc.	Found	O Calc.	Found
Ic [45]	96	130 − 131	79.65	79.57	6.19	6.27	14.16	14.12
IIIc [6,14]	98	215 − 216	70.59	70.45	5.88	5.83	23.53	23.63
Xc [21,22]	100	134 − 135	70.59	70.24	5.88	5.81	23.53	23.44

Table 5. Stilbenecarboxylic acid methyl esters.

Compound	Yield %	M.p. °C	Elemental analyses C Calc.	Found	H Calc.	Found	O Calc.	Found
Id	100	124 − 126	69.94	69.59	5.52	5.86	24.54	24.75
IId	76.1	105 − 107	72.48	72.44	6.04	5.99	21.48	21.57
IIId	70.8	126 − 127	63.77	63.69	5.31	5.36	30.92	30.69
IVd	66.5	105 − 108	65.28	65.30	5.70	5.89	29.02	29.13
VId	64.5	94 − 96	64.86	64.69	4.86	4.83	30.28	30.42
VIId	77.2	161 − 164	67.42	67.70	5.62	5.71	26.97	26.92
VIIId	88.5	147 − 149	63.46	63.37	5.77	5.78	30.77	30.77
IXd	95.0	114 − 115	69.94	69.90	5.52	5.59	24.54	24.36
Xd	70.8	94 − 96	63.77	63.86	5.31	5.40	30.92	30.79
XId	78.5	92 − 94	65.30	65.48	5.69	5.62	29.00	28.91
XIId [a]	41.2	112 − 113	65.64	65.51	5.21	5.17	29.15	29.46
XIIId [a]	58.9	152 − 153	64.50	64.46	5.60	5.43	29.89	30.21

[a] Prepared by cleavage of the corresponding lactone with methanolic hydrogen chloride and subsequent acetylation.

and fragmentation patterns were in accordance with the expected data.

No attempts were made to increase the yields by systematic variation of the reaction conditions.

Some of the syntheses were not completed. Nevertheless, the data for the intermediates prepared are included in the tables.

In view of the versatility of this method, the small number of steps involved, the accessibility of the appropriate starting materials and the yields obtainable, the synthetic routes outlined above appear to compete well with those mentioned in the introduction.

The various compounds are assigned roman numerals according to their aromatic substitu-
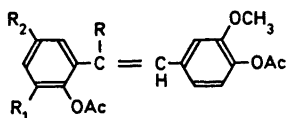
tion pattern as follows:
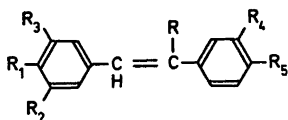
I $R_1 = OAc$, $R_2 = OCH_3$, $R_3 = R_4 = R_5 = H$

II $R_1 = R_2 = OCH_3$, $R_3 = R_4 = R_5 = H$

III $R_1 = R_5 = OAc$, $R_2 = R_4 = OCH_3$, $R_3 = H$

IV $R_1 = OAc$, $R_2 = R_4 = R_5 = OCH_3$, $R_3 = H$

V $R_1 = R_2 = R_4 = R_5 = OCH_3$, $R_3 = H$

VI $R_1 = OAc$, $R_2 = OCH_3$, $R_3 = H$,
$R_4 - R_5 = O-CH_2-O$

VII $R_1 = OAc$, $R_2 = R_3 = OCH_3$, $R_4 = R_5 = H$

VIII $R_1 = OAc$, $R_2 = R_3 = R_4 = R_5 = OCH_3$
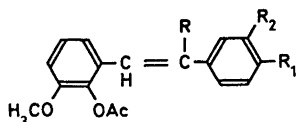
IX $R_1 = R_2 = H$

X $R_1 = OAc$, $R_2 = OCH_3$

XI $R_1 = R_2 = OCH_3$

XII $R_1 = R_2 = H$

XIII $R_1 = OCH_3$, $R_2 = CH_3$

XIV $R_1 = R_2 = H$

XV $R_1 = OAc$, $R_2 = OCH_3$

XVI $R_1 = R_2 = OCH_3$
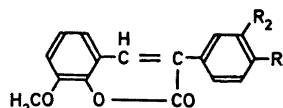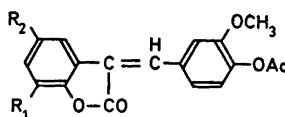
XVII $R_1 = R_2 = H$

XVIII $R_1 = OCH_3$, $R_2 = CH_3$

XIX

The indices used refer to:

a, stilbenecarboxylic acids (R = COOH);

b, stilbenes unsubstituted at the olefinic carbon atoms (R = H);

c, deacetylation products of b (R = H, OH instead of OAc);

d, stilbenecarboxylic acid methyl esters (R = COOCH_3);

e, hydroxymethyl-substituted stilbenes (R = CH_2OH, OH instead of OAc).

EXPERIMENTAL

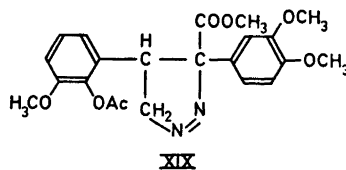Melting points are corrected. Evaporations were carried out under reduced pressure.

Thin-layer chromatography (TLC) was performed using plates coated with a 0.25 mm thick layer of silica gel (Merck HF_{254}, type 60). The following solvent systems were used: chloroform, chloroform containing 5 % ethanol, chloroform containing 5 % ethyl acetate, toluene containing 5 % ethyl acetate, and diisopropyl ether:formic acid:water 90:7:3. Spots were visualised by exposure to iodine vapour or by spraying with a 3 % solution of vanillin in conc. sulfuric acid followed by heating at 110 °C for 5 − 10 min.

Column chromatography was accomplished using silica gel (Merck 0.05 − 0.5 mm, 70 − 325 mesh, ASTM) or silicic acid (Mallinckrodt, 100 mesh); solvent systems: chloroform containing 5 % ethyl acetate or toluene containing 5 % ethyl acetate. The separations were followed by TLC.

NMR-spectrometry. The NMR-spectra were run on a Perkin-Elmer R-12 spectrometer using CDCl_3, CD_3OD or (CD_3)_2SO as solvents. Chemical shifts are given in δ (ppm downfield from tetramethylsilane, internal standard).

The mass spectra were recorded on a Perkin-Elmer 270 instrument at 70 eV using the direct inlet system. The temperature of the probe heater was 60 °C.

Table 6. Hydroxymethylstilbenes.

Compound	Yield %	M.p. °C	Elemental analyses C Calc.	Found	H Calc.	Found	O Calc.	Found
Ie	49.5	98 − 100	75.00	75.03	6.25	6.31	18.75	18.90
IIe	53.2	83 − 85	75.53	75.38	6.71	6.54	17.76	17.81
IIIe	58.4	147 − 148	67.55	67.45	5.96	6.05	26.49	26.30
IVe	58.6	131 − 134	68.35	68.22	6.33	6.40	25.32	25.31
Ve	72.5	110 − 113	69.09	69.23	6.67	6.85	24.24	24.05
VIIIe diacetate [a]	74.2	amor- phous	64.17	64.26	6.09	6.18	29.73	29.79
IXe	64.6	139 − 141	75.00	75.15	6.25	5.90	18.75	18.98
Xe triacetate [a]	80.0	amor- phous	64.48	64.35	5.63	5.66	29.88	29.98
XIe	52.8	192 − 195	68.35	68.32	6.33	6.31	25.31	25.19
XIIe	73.8	125 − 126	70.60	70.36	5.87	5.97	23.51	23.56
XIIIe triacetate [a]	77.1	amor- phous	65.17	64.86	5.87	6.18	28.94	28.77

[a] Mixture of the *cis-* and *trans*-forms.

Table 7. Stilbenecarboxylic acids.

Compound	Chemical shifts (δ) [a,b] Aromatic and olefinic H	Methoxyl H	Acetyl H
Ia	7.52 − 6.63 (m, 9 H)	3.32 (s, 3 H)	2.18 (s, 3 H)
IIa[44]	7.40 − 6.70 (m, 9 H)	3.78 (s, 6 H)	
IIIa	7.12 − 6.55 (m, 7 H)	3.40 (s, 3 H)	2.23 (s, 3 H)
		3.72 (s, 3 H)	2.28 (s, 3 H)
IVa	7.10 − 6.67 (m, 7 H)	3.42 (s, 3 H)	2.20 (s, 3 H)
		3.67 (s, 3 H)	
		3.77 (s, 3 H)	
Va	7.05 − 6.35 (m, 7 H)	3.30 (s, 6 H)	
		3.70 (s, 6 H)	
VIa [c]	7.11 − 6.57 (m, 7 H)	3.50 (s, 3 H)	2.20 (s, 3 H)
VIIa	7.50 − 6.41 (m, 8 H)	3.40 (s, 6 H)	2.18 (s, 3 H)
VIIIa	7.14 − 6.33 (m, 6 H)	3.48 (s, 6 H)	2.20 (s, 3 H)
		3.65 (s, 3 H)	
		3.75 (s, 3 H)	
IXa	7.45 − 6.10 (m, 9 H)	3.82 (s, 3 H)	2.33 (s, 3 H)
Xa	7.00 − 6.15 (m, 7 H)	3.59 (s, 3 H)	2.22 (s, 3 H)
		3.75 (s, 3 H)	2.32 (s, 3 H)
XIa	7.00 − 6.20 (m, 7 H)	3.68 (s, 3 H)	2.34 (s, 3 H)
		3.77 (s, 3 H)	
		3.84 (s, 3 H)	

[a] Solvent: $(CD_3)_2SO$, except IXa: CD_3OD. [b] The signals of the carboxyl H appear between δ 7.70 and 7.90. [c] The signal of the methylene H appears at δ 6.02.

Table 8. Lactones.

Compound	Chemical shifts (δ) [a] Aromatic and olefinic H	Methoxyl H	Acetyl H	Others
XIV	7.70 − 7.05 (m, 9 H)	3.92 (s, 3 H)		
XV	7.72 − 6.95 (m, 7 H)	3.83 (s, 3 H)	2.30 (s, 3 H)	
		3.92 (s, 3 H)		
XVI	7.63 − 6.72 (m, 7 H)	3.81 (s, 3 H)		
		3.87 (s, 6 H)		
XVII	7.70 − 6.95 (m, 8 H)	3.80 (s, 3 H)	2.30 (s, 3 H)	
XVIII	7.75 − 6.85 (m, 6 H)	3.85 (s, 3 H)	2.28 (s, 3 H)	2.33 (s, 3 H)
		3.92 (s, 3 H)		

[a] Solvent: $CDCl_3$.

Table 9. Hydroxystilbene acetates.

Compound	Chemical shifts (δ) [a] Aromatic and olefinic H	Methoxyl H	Acetyl H
Ib	7.00 (s, 5 H)	3.85 (s, 3 H)	2.30 (s, 3 H)
	7.35 (m, 5 H)		
IIb [46,47]	7.30 − 6.85 (m, 10 H)	3.85 (s, 6 H)	
IIIb *cis*	6.83 (m, 6 H)	3.55 (s, 6 H)	2.27 (s, 6 H)
	6.52 (s, 2 H)		
IIIb *trans* [6]	7.00 (m, 8 H)	3.87 (s, 6 H)	2.30 (s, 6 H)
IXb	7.35 − 6.80 (m, 10 H)	3.78 (s, 3 H)	2.33 (s, 3 H)
Xb *cis*	6.80 (m, 6 H)	3.73 (s, 3 H)	2.18 (s, 3 H)
	6.50 (d, 2 H)	3.45 (s, 3 H)	2.25 (s, 3 H)
Xb *trans* [22]	7.00 (s, 8 H)	3.78 (s, 3 H)	2.28 (s, 3 H)
		3.82 (s, 3 H)	2.32 (s, 3 H)
XIb	7.02 − 6.35 (m, 8 H)	3.78 (s, 6 H)	2.26 (s, 3 H)
		3.52 (s, 3 H)	

[a] Solvent: $CDCl_3$.

Table 10. Hydroxystilbenes.

Compound	Chemical shifts (δ) [a] Phenolic OH	Aromatic and olefinic H	Methoxyl
Ic [45]	∼9 (b, 1 H)	7.80 − 6.66 (m, 10 H)	3.85 (s, 3 H)
IIIc [6,14]	8.95 (s, 2 H)	7.28 − 6.62 (m, 8 H)	3.79 (s, 6 H)
Xc [21,22]	8.85 (s, 2 H)	7.50 − 6.50 (m, 8 H)	3.78 (s, 3 H)
			3.80 (s, 3 H)

[a] Solvent: $(CD_3)_2SO$.

Table 11. Stilbenecarboxylic acid methyl esters.

Compound	Chemical shifts (δ) [a] Aromatic and olefinic H	Carbomethoxyl H	Methoxyl H	Acetyl H
Id	7.80 − 6.52 (m, 9 H)	3.78 (s, 3 H)	3.32 (s, 3 H)	2.22 (s, 3 H)
IId	7.70 − 6.40 (m, 9 H)	3.78 (s, 3 H)	3.35 (s, 3 H) 3.75 (s, 3 H)	
IIId	7.78 − 6.42 (m, 7 H)	3.80 (s, 3 H)	3.40 (s, 3 H) 3.70 (s, 3 H)	2.21 (s, 3 H) 2.27 (s, 3 H)
IVd	7.70 − 6.45 (m, 7 H)	3.80 (s, 3 H)	3.40 (s, 3 H) 3.75 (s, 6 H)	2.15 (s, 3 H)
Vd	7.33 − 6.52 (m, 7 H)	3.85 (s, 3 H)	3.48 (s, 3 H) 3.80 (s, 9 H)	
VId [b]	7.72 − 6.65 (m, 7 H)	3.78 (s, 3 H)	3.50 (s, 3 H)	2.23 (s, 3 H)
VIId	7.72 − 6.70 (m, 8 H)	3.70 (s, 3 H)	3.70 (s, 6 H)	2.28 (s, 3 H)
VIIId	7.70 − 6.35 (m, 6 H)	3.85 (s, 3 H)	3.48 (s, 6 H) 3.75 (s, 6 H)	2.25 (s, 3 H)
IXd	7.80 − 6.27 (m, 9 H)	3.77 (s, 3 H)	3.77 (s, 3 H)	2.33 (s, 3 H)
Xd	7.78 − 6.67 (m, 7 H)	3.75 (s, 3 H)	3.59 (s, 3 H) 3.75 (s, 3 H)	2.26 (s, 3 H) 2.33 (s, 3 H)
XId	7.73 − 6.22 (m, 7 H)	3.84 (s, 3 H)	3.66 (s, 3 H) 3.78 (s, 6 H)	2.18 (s, 3 H)
XIId	7.47 − 6.60 (m, 8 H)	3.72 (s, 3 H)	3.35 (s, 3 H)	2.09 (s, 3 H) 2.20 (s, 3 H)
XIIId [c]	7.73 − 6.42 (m, 6 H)	3.76 (s, 3 H)	3.39 (s, 3 H) 3.66 (s, 3 H)	2.19 (s, 3 H) 2.23 (s, 3 H)

[a] Solvent: $CDCl_3$. [b] Methylene H: 5.93 (s, 2 H). [c] Methyl H: 2.06 (s, 3 H).

Preparation of condensation reactants

o-Vanillin acetate by acetylation of *o*-vanillin (20 g) with acetic anhydride (30 ml) in pyridine (30 ml); yield 20 g, 78 %. Recrystallisation from isopropanol gave a product melting at 74 − 75 °C (lit.[28] 76 °C).

Syringaldehyde acetate from syringaldehyde (5 g) by acetylation with acetic anhydride (5 ml) in pyridine (5 ml); yield 5.9 g, 96 %. Recrystallisation from chloroform/hexane yielded the pure acetate, m.p. 115 − 117 °C (lit.[28] 114 °C).

4-Acetoxy-3-methoxyphenylacetic acid (homovanillic acid acetate) was prepared by oxidation of eugenol acetate (m.p. 23 − 28 °C, lit.[29] 27 °C) with potassium permanganate according to Ref. 30 with slight modifications. Total yield: 3.28 g, 94 %. After recrystallisation from glacial acetic acid, the acid melted at 137 − 138.5 °C, lit.[31] 139 − 140 °C.

3,4-Methylenedioxyphenylacetic acid (homopiperonalic acid) was analogously prepared from safrole. Yield 46 %, m.p. 125 − 127 °C (lit.[32] 127 − 128 °C).

6-Hydroxymethyl-4-methylguaiacol was obtained by reacting 4-methylguaiacol (creosol) with formaldehyde (300 ml, 3.7 mol) in a 5 % aqueous solution of sodium hydroxide according to Ref. 33. The colourless prisms (m.p. 50 − 51.5 °C) were recrystallised from ligroin; yield 24 %. Starting material (44 %) was recovered and *bis*-(2-hydroxy-3-methoxy-5-methylphenyl)-methane, m.p. 128 − 129 °C, was obtained in a low yield (4 %) from the fraction distilling at about 200 °C/5 mmHg.

2-Hydroxy-3-methoxy-5-methylphenylacetonitrile. 6-Hydroxymethyl-4-methylguaiacol (9.2 g, 0.055 mol) and sodium cyanide (5.5 g, 0.112 mol) were dissolved in anhydrous methanol and refluxed for 7 h (*cf.* Ref. 34). After removal of methanol the residue was dissolved in water and the solution neutralised with carbon dioxide. The nitrile precipitated in the form of brownish crystals (yield 7.45 g, 77 %) which were contaminated with a small amount of the above-mentioned diphenylmethane derivative and of a cyclic trimeric condensation product.[35] Recrystallisation from benzene-petroleum ether gave the pure nitrile; m.p. 62.5 − 63.5 °C). (Found: C 67.51; H 6.18; O 18.27; N 8.02. $C_{10}H_{11}O_2N$ (177.11) requires: C 67.80; H 6.21; O 18.08; N 7.91.) δ 6.80 − 6.53 (d, 2 H, arom. H); 6.58 (s, 1 H, phenol. H); 3.83 (s, 3 H, arom. OCH_3); 3.67 (s, 2 H, methylene H); 2.27 (s, 3 H, arom. CH_3).

Table 12. Hydroxymethylstilbenes.

Compound	Chemical shifts (δ) [a] Aromatic and olefinic H	Methylene H [e]	Methoxyl H	Solvent
Ie	7.25 – 6.53 (m) (9 H)	4.38 (s) (2 H)	3.38 (s) (3 H)	CDCl$_3$
IIe	7.22 – 6.40 (m) (9 H)	4.38 (s) (2 H)	3.40 (s) (3 H) 3.78 (s) (3 H)	CDCl$_3$
IIIc	6.75 – 6.25 (m) (7 H)	4.35 (s) (2 H)	3.38 (s) (3 H) 3.63 (s) (3 H)	(CD$_3$)$_2$SO
IVe	6.72 – 6.35 (m) (7 H)	4.20 (s) (2 H)	3.40 (s) (3 H) 3.65 (s) (3 H) 3.73 (s) (3 H)	(CD$_3$)$_2$SO
Ve	6.91 – 6.45 (m) (7 H)	4.45 (s) (2 H)	3.55 (s) (3 H) 3.80 (s) (3 H) 3.85 (s) (3 H) 3.92 (s) (3 H)	CDCl$_3$
VIe [b]	7.15 – 6.35 (m) (7 H)	4.32 (s) (2 H)	3.50 (s) (3 H)	CDCl$_3$
VIIIe diacetate [c]	7.09 – 6.20 (m) (6 H)	5.15, 4.87 (2s) (2 H)	3.98 – 3.43 (8s) (12 H)	CDCl$_3$
IXe	7.20 – 6.30 (m) (9 H)	4.45 (s) (2 H)	3.72 (s) (3 H)	CDCl$_3$
Xe triacetate [c]	7.13 – 6.28 (m) (7 H)	4.92, 4.83 (2s) (2 H)	3.57 (s) (3 H) 3.78 (s) (3 H)	CDCl$_3$
XIIe	7.25 – 6.45 (m) (8 H)	4.30 (s) (2 H)	3.37 (s) (3 H)	CD$_3$OD
XIIIe [d]	6.90 – 6.45 (m) (6 H)	4.34 (s) (2 H)	3.42 (s) (3 H) 3.80 (s) (3 H)	CDCl$_3$

[a] Acetates prepared from the hydroxymethylstilbenes, listed in this table, exhibit signals for the aliphatic acetyl H at δ 2.05 and for the aromatic acetyl H between δ 2.22 and 2.31. [b] The signal of the methylene H appears at δ 5.90. [c] Mixture of *cis-* and *trans*-forms. [d] Methyl H: 2.18 (s, 3 H). [e] The signals of the methylene protons were relatively broad indicating weak allylic coupling to the olefinic proton.

2-Hydroxy-3-methoxy-5-methylphenylacetic acid. The acetonitrile described above (4.6 g, 0.027 mol) was dissolved in conc. hydrochloric acid (1 l) and kept at room temperature for 2 days. The solution was extracted with chloroform and the combined chloroform extracts were extracted with water and dried. Evaporation gave colourless needles which were recrystallised from chloroform/hexane, m.p. 120 – 123 °C; yield 2.73 g, 56 %. [Found: C 61.66; H 5.80; O 32.62. C$_{10}$H$_{12}$O$_4$ (196.10) requires: C 61.22; H 6.12; O 32.65.] δ 8.05 (b, 1 H); 6.60 (s, 2 H); 3.85 (s, 3 H); 3.64 (s, 2 H); 2.25 (s, 3 H).

Heating the 2-hydroxyphenylacetic acid in glacial acetic acid afforded the corresponding lactone; m.p. 98 – 99 °C. [Found: C 67.33; H 5.52; O 27.03. C$_{10}$H$_{10}$O$_3$ (178.10) requires: C 67.44; H 5.61; O 26.96.] δ 6.66 (s, 2 H); 3.86 (s, 3 H); 3.62 (s, 2 H); 2.30 (s, 3 H).

Condensation (1)

trans-4,4′-Diacetoxy-3,3′-dimethoxystilbene-α-carboxylic acid (IIIa). A mixture of homovanillic acid acetate (6.82 g, 0.0304 mol), vanillin acetate (7.65 g, 0.0395 mol) and triethyl-

amine (7.8 ml) in acetic anhydride (76 ml) was refluxed for 45 min. The bulk of acetic anhydride and of triethylamine was then removed by distillation under reduced pressure. The residue was repeatedly washed with water and brought to crystallisation by addition of ethanol. From the combined aqueous washing liquors an additional amount of stilbenecarboxylic acid crystallised and was added to the bulk of the material. Recrystallisation from ethanol gave the pure compound IIIa as yellowish crystals.

trans-2,4′-Diacetoxy-3,3′-dimethoxystilbene-α′-carboxylic acid (Xa) was prepared analogously by heating homovanillic acid acetate (6.82 g, 0.0395 mol) and *o*-vanillin acetate (7.65 g, 0.0395 mol) in acetic anhydride (76 ml) and triethylamine (7.8 ml) under reflux for 30 min. After removal of acetic anhydride and triethylamine by distillation under reduced pressure, the residue was dissolved in chloroform and the chloroform solution was extracted several times first with water and then with a saturated solution of sodium bicarbonate. From the combined bicarbonate extracts the stilbenecarboxylic acid (Xa) was obtained in the usual way. Recrystallisation from isopropanol gave the pure compound (6.25 g, 51.3 %, yellowish crystals).

3-(4-Acetoxy-3-methoxyphenyl)-8-methoxy-coumarin (XV), formed by lactonisation from compound Xa, was isolated from the remaining chloroform solution. After extraction with sodium bisulfite (removal of the excess of *o*-vanillin acetate), extraction with water, drying (Na_2SO_4) and evaporation, a dark oil was obtained which crystallised on addition of isopropanol. Yield 1.0 g (8.2 %). Recrystallisation from isopropanol gave the pure lactone XV; colourless needles.

Prolongation of the reaction time to 2 h increased the yield of lactone to 22 %.

When 2-acetoxyphenylacetic acids and aromatic aldehydes were refluxed under similar conditions (preparation of type D stilbenes), lactonisation of the starting acids prevented condensation. Conversion of the 2-hydroxyphenylacetic acids into their piperidinium salts enabled condensation but the resulting 2-hydroxystilbene-α-carboxylic acid piperidides underwent extensive lactonisation yielding the corresponding five-membered stilbene lactones (*cf.* Ref. 36).

3-(4-Acetoxy-3-methoxy-benzylidene)-coumaran-2-one (XVII). *o*-Hydroxyphenylacetic acid (3.8 g, 0.025 mol) was dissolved in piperidine (30 ml) and the solvent was removed by distillation under reduced pressure. Large prisms of the *piperidinium salt of o-hydroxyphenylacetic acid* were obtained which after recrystallisation from benzene melted at 104–105 °C; yield 5.2 g (90.5 %) (Found: C 66.1; H 8.3; O 20.1; N 5.7. Calc. for $C_{13}H_{19}O_3N$: C 65.82; H 8.17; O 20.25; N 5.91).

The piperidinium salt (10.85 g, 0.457 mol) and vanillin acetate (11.45 g, 0.590 mol) were refluxed in acetic anhydride (50 ml) containing piperidine (1.6 ml) for 3 h. After removal of acetic anhydride by distillation, ice-water was added to the residue and the resulting oil was separated from the aqueous layer. Addition of ethanol brought about crystallisation. Repeated recrystallisation from the same solvent gave the pure coumaranone XVII; yield 8.3 g (58.5 %), yellowish crystals.

The reaction is likely to proceed as follows: piperidinium salt → piperidide → stilbenecarboxylic acid piperidide → coumaranone. This view is supported by the following results: Refluxing the piperidinium salt (0.5 g) in acetic anhydride (5 ml) for 1 h gave the piperidide; yield 0.4 g, m.p. 114–115 °C. Addition of vanillin acetate to a solution of the piperidide in acetic anhydride containing piperidine and refluxing the mixture for 2 h afforded coumaranone XVII. Finally, the piperidide of XIIa in the deacetylated form (Found: C 70.9; H 6.5; O 18.1; N 4.0. $C_{21}H_{23}O_4N$ requires: C 71.40; H 6.51; O 18.12; N 3.96) (250 mg) was converted into the coumaranone XVII by heating in acetic anhydride (3 ml) under reflux for 4 h. After removal of acetic anhydride and addition of ice to the residue, XVII was obtained as an oil which crystallised on standing; yield 216

mg (98.5 %); m.p. 148–150 °C (see Table 2).

The preparation of the piperidinium salt, its conversion into the piperidide and the condensation to the coumaranone XVII could be conveniently performed in one step with essentially the same result. Thus, addition of vanillin acetate to a solution of *o*-hydroxyphenylacetic acid and piperidine in acetic anhydride and refluxing the mixture for 2 h afforded XVII. The working-up was carried out as described above; yield 58 %.

3-(4-Acetoxy-3-methoxybenzylidene)-5-methyl-7-methoxycoumaran-2-one (XVIII) was similarly prepared from 2-hydroxy-3-methoxy-5-methylphenylacetic acid (see above) (0.795 g, 0.004 mol), piperidine (6.5 ml), vanillin acetate (0.84 g, 0.0043 mol) and acetic anhydride (9 ml). The product crystallised on addition of ethanol and was purified by recrystallisation from isopropanol; yellowish plates.

Decarboxylation (2)

trans-4,4'-Diacetoxy-3,3'-dimethoxystilbene (IIIb).[6] Stilbenecarboxylic acid IIIa (13.5 g, 0.034 mol) and hydroquinone (250 mg) were dissolved in freshly distilled quinoline (140 ml). Copper chromite [37] (250 mg) was added and the mixture was heated under reflux for 30 min in a steady stream of nitrogen passing through. After the decarboxylation, the quinoline solution was concentrated to about 25 ml by evaporation under reduced nitrogen pressure. The partially deacetylated product was reacetylated by addition of acetic anhydride (30 ml) and keeping the mixture overnight. After the usual working-up, an oil was obtained which crystallised on addition of isopropanol. The stilbene was purified by recrystallisation from toluene (yield 55.8 %). About the same yield of the *trans*-stilbene (58.3 %) and a minor amount of the amorphous *cis*-isomer (10.0 %) were obtained (see Table 3), when the acetylation mixture was separated on a silicic acid column.

trans-2,4'-Diacetoxy-3,3'-dimethoxystilbene (Xb)[22] was similarly prepared from stilbenecarboxylic acid Xa (6.0 g, 0.015 mol), hydroquinone (120 mg) and copper chromite (120 mg). After reacetylation and the usual working-up, an oil was obtained which was fractionated by chromatography on a silicic acid column. *trans*-Stilbene Xb (2.93 g, 54.9 %), the amorphous *cis*-isomer (about 100 mg, ∼2 %), and lactone XV (0.6 g, 12 %) were isolated. *trans*-Stilbene Xb and lactone XV were further purified by recrystallisation from isopropanol.

Deacetylation (3)

trans-4,4'-Dihydroxy-3,3'-dimethoxystilbene (IIIc).[6,14] The *trans*-form of IIIb (0.59 g, 0.0015 mol) was dissolved in tetrahydrofuran in an atmosphere of nitrogen and the solution was

dropped to a cooled suspension of lithium aluminium hydride (0.47 g, 0.012 mol) in the same solvent (100 ml). After 15 min, the excess of lithium aluminium hydride was decomposed by addition of ethyl acetate saturated with water. Hydrochloric acid (2 M) was added until all the precipitate was dissolved and the solution was extracted repeatedly with ethyl acetate. The combined extracts were washed with water until neutral, dried and evaporated. The stilbene was recrystallised from ethanol.

trans-2,4'-Dihydroxy-3,3'-dimethoxystilbene (Xc)[21,22] was prepared from the corresponding diacetate (Xb, 182 mg) by addition of sodium (30 mg) to a solution in ethanol (10 ml). Neutralisation (CO_2) and evaporation of the solvent gave a residue which was dissolved in chloroform. The chloroform solution was extracted with water, dried (Na_2SO_4) and evaporated. The product was recrystallised from ethanol.

On exposure to air, the phenolic stilbenes undergo slow autoxidation with discoloration. The impurities can be removed by recrystallisation from ethanol containing small amounts of sodium borohydride.

In the preparation of phenolic hydroxymethyl-substituted stilbenes (types D and F), the reduction of the stilbenecarboxylic acid methyl ester group by lithium aluminium hydride (see below) is, of course, accompanied by the removal of acetyl groups. Thus, no extra deacetylation step is needed.

Esterification (4):

(a) starting from stilbene-carboxylic acids

4,4'-Diacetoxy-3,3'-dimethoxystilbene-α-carboxylic acid methyl ester (IIId). To a saturated solution of the stilbenecarboxylic acid IIIa (5.6 g, 0.014 mol) in dioxane (100 ml) an ethereal solution of diazomethane (about 0.02 mol) was dropped slowly. The mixture was kept at room temperature for 16 h. After removal of the solvents by distillation under reduced pressure, a yellowish oil was obtained which crystallised on standing. Recrystallisation from toluene gave the pure compound IIId.

The use of a larger excess of diazomethane lowered the yield owing to addition of the methylating reagent across the olefinic double bond. In one instance (esterification of XIa) the resulting 3,4-diarylpyrazoline derivative (XIX) was isolated, purified and identified by elemental analyses and NMR; m.p. 105–107 °C. (Found: C 61.7; H 5.6; O 25.8; N 6.6. $C_{22}H_{24}O_7N_2$ requires: C 61.68; H 5.60; O 26.16; N 6.54.) δ 6.97–6.55 (m, 6 H); 6.00–5.82 (1 q, 1 H); 5.05–4.57 (1 q, 1 H); 4.65–4.45 (1 q, 1 H (AMX spectrum) 3.75 (s, 3 H); 3.68 (s, 3 H); 3.62 (s, 6 H); 2.42 (s, 3 H).

2,4'-Diacetoxy-3,3'-dimethoxystilbene-α'-carboxylic acid methyl ester (Xd) was similarly prepared by treatment of stilbenecarboxylic acid

Xa with diazomethane. The ester crystallised from the oily reaction product on prolonged standing in the refrigerator. Recrystallisation from toluene gave the pure compound. In addition to the ester, the oily reaction product contained the corresponding lactone (XV) and some other by-products not further characterised (TLC).

(b) starting from stilbene lactones

The yields of methyl esters were high except those of 2-acetoxystilbene-α-carboxylic acid methyl esters (XIId and XIIId) which had to be prepared be refluxing the corresponding stilbene lactones in an excess of methanolic hydrogen chloride.

2,4'-Diacetoxy-3'-methoxystilbene-α-carboxylic acid methyl ester (XIId). 3-(4-Acetoxy-3-methoxybenzylidene)-coumaran-2-one (XVII) (1.6 g) was dissolved in a 0.5 % solution of hydrogen chloride in anhydrous methanol (150 ml) and the solution was refluxed for 90 min.

After removal of the solvent and hydrogen chloride by evaporation, the residual oil was separated by preparative TLC and the fraction containing the deacetylated methyl ester was acetylated with acetic anhydride in pyridine. The resulting diacetyl compound XIId was purified by recrystallisation from ethanol.

2,4'-Diacetoxy-3,3'-dimethoxy-5-methylstilbene-α-carboxylic acid methyl ester (XIIId) was prepared analogously by refluxing a solution of 3-(4-acetoxy-3-methoxybenzylidene)-5-methyl-7-methoxycoumaran-2-one (XVIII, 0.818 g) in 1 % methanolic hydrogen chloride (75 ml) for 2.5 h. The product was worked up and purified as described for the preceding compound. Starting material (315 mg, 38.5 %) was also isolated.

Lithium aluminium hydride reduction (5)

The conversion of stilbenecarboxylic acid methyl esters into hydroxymethyl stilbenes was performed following the procedure described for the reduction of ferulic acid ethyl ester [38] and of acetylferulic acid methyl ester [39] to coniferyl alcohol with some modifications.

4,4'-Dihydroxy-3,3'-dimethoxy-α-hydroxymethylstilbene (IIIe). To a cooled suspension of lithium aluminium hydride (2.66 g, 0.07 mol) in anhydrous tetrahydrofurane (200 ml) a solution of 4,4'-diacetoxy-3,3'-dimethoxystilbene-α-carboxylic acid methyl ester (IIId, 4.1 g, 0.01 mol) in tetrahydrofurane (100 ml) was added at 0 °C in a nitrogen atmosphere during 20 min. The reduction was allowed to continue for 4 h at 0 °C with vigorous stirring and was followed by TLC.

Excess of lithium aluminium hydride was decomposed by addition of ethyl acetate satu-

rated with water. After dissolution of the precipitate by acidification with 2 M hydrochloric acid, the solution was extracted with ethyl acetate. Evaporation of the combined and dried (Na_2SO_4) extracts gave a colourless viscous oil which crystallised on standing. Recrystallisation from toluene yielded pure compound IIIe.

2,4'-Dihydroxy-3'-methoxy-α-hydroxymethyl stilbene (XIIe) was prepared similarly from 2,4'-diacetoxy-3'-methoxystilbene-α-carboxylic acid methyl ester (XIId). Recrystallisation from ether − petroleum ether gave the pure compound. An additional amount was isolated from the combined mother liquors by preparative column chromatography.

2,4'-Dihydroxy-3,3'-dimethoxy-5-methyl-α-hydroxymethylstilbene (XIIIe) was prepared in a similar manner from 2,4'-diacetoxy-3,3'-dimethoxy-5-methylstilbene-α-carboxylic acid methyl ester (XIIId).

The phenolic hydroxymethylstilbenes were stable, provided air (oxygen) and moisture were excluded.

Direct reductions of stilbene lactones with lithium aluminium hydride [40] (*cf.*, however, Ref. 41), aluminium hydride [42] and borohydride [43] resulted in complex mixtures consisting mainly of products formed by alkaline or reductive cleavage of the lactone ring with concomitant or subsequent reduction of the stilbene double bond (NMR).

Thus, compound XVII, when treated with sodium borohydride in ethanol-chloroform-water (7:4:1) at room temperature, afforded a mixture of products which was separated by chromatography on a column of silica gel yielding a main component, melting at 118 − 119 °C. This compound was acetylated with acetic anhydride in pyridine and identified as 2,4'-diacetoxy-3'-methoxy-α-acetoxymethylbibenzyl (XIIe, OAc instead of OH, $-CH_2-CH_2-$ instead of $-CH=CH-$). δ 7.43 − 6.43 (m, 7 H); 4.20 (d, 2 H); 3.60 (s, 3 H); 3.75 − 3.40 (m, 1 H); 2.89 (d, 2 H); 2.20 (s, 6 H); 1.89 (s, 3 H).

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