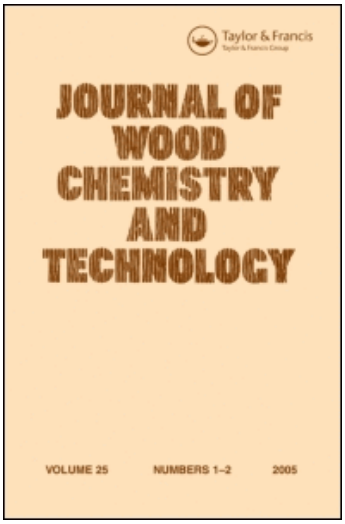

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Lignin Chromophores. III. Syntheses of Hydroxy- and Alkoxystilbenes via Aryl Migration

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LIGNIN CHROMOPHORES, Part III*

Syntheses of Hydroxy- and Alkoxystilbenes via Aryl migration**

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Summary

Stilbenes, representing stilbenoid structures present in residual lignins, have been synthesized by condensation of monochloroacetaldehyde diethylacetal with appropriate phenols and phenol ethers, followed by alkali- or acid-promoted rearrangement of the resulting 1,1-diaryl-2-chloroethanes. It is proposed that the mechanism of these rearrangement steps involves aryl migration with formation of intermediates

* Part II, see Ref. 15

** A preliminary report on the results of this work was presented (by N-O Nilvebrant) at the 1981 International Symposium on Wood and Pulping Chemistry, Stockholm, June 9-12, 1981, Preprints Vol. 5, pp. 96-99.

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of the spiro-cyclohexadienone type. The yields of individual stilbenes vary within wide ranges and are in certain cases moderate. However, the method is competitive due to its simplicity and the availability of the starting materials required.

INTRODUCTION

Numerous studies on the mechanisms of delignification during pulping have revealed that stilbenoid structures are formed as intermediates or as final products representing important potential chromophoric systems in residual lignins (for reviews, see Refs. 1-3). Convenient methods for synthesizing suitable representative models have since been sought in order to study the reactions of these potential chromophoric structures during subsequent bleaching processes (4-6) and during light-induced yellowing of mechanical and chemimechanical pulps (7).

The synthetic methods used hitherto may be divided into two categories. The first includes coupling by some type of condensation between appropriate aromatic aldehydes and either benzylhalogenides [Grignard (8) and Wittig (8-12) syntheses] or aryl-substituted acetic acids [Knoevenagel syntheses, (13-15)]. These methods are particularly suitable for the preparation of "asymmetrical" stilbenes, i. e. stilbenes containing different aromatic moieties and/or a substituent at one or both of the olefinic carbon atoms. However, the synthesis of the condensation partners required for these coupling reactions is often tedious and the overall yields of the final products are low.

The second group of methods start with simple aromatic compounds, in particular phenols or phenol ethers, which are condensed with appropriate aliphatic aldehydes, the latter providing the source of the olefinic part of the final stilbene (16, 17). These methods have the great advantage of employing readily available starting materials. However, when different aromatic condensation partners are used and asymmetrical stilbenes are desired, these methods suffer from the drawback of giving mixtures consisting of one asymmetrical and two symmetrical stilbenes. However, by applying modern chromatographic methods, in particular HPLC, these mixtures can easily be separated into their components, thus affording asymmetrical and symmetrical stilbenes in the same run.

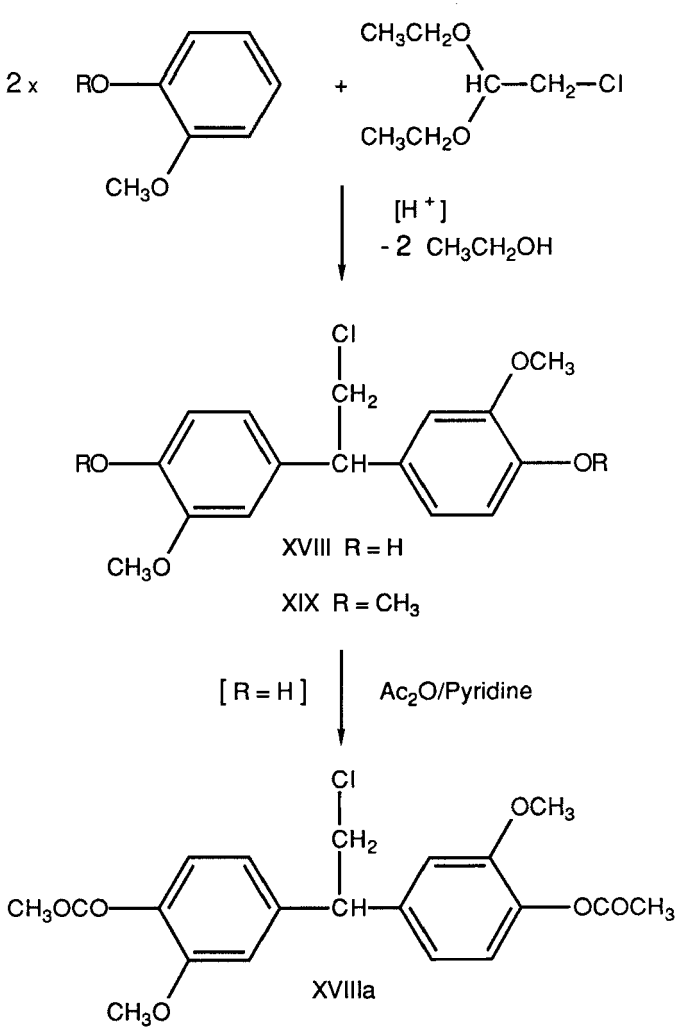


Fig. 1 Acid-catalyzed condensation of monochloroacetaldehyde diethylacetal with guaiacol and veratrole.

The present report describes the synthesis of a variety of stilbenes related to the stilbenoid structures assumed to be present in residual lignins. The method adopted belongs to the second category and comprises acid-catalyzed condensation of monochloroacetaldehyde diethylacetal with various phenols or phenol ethers at low temperature (0 °C) to give the corresponding 1,1-diaryl-2-chloroethane derivative (e.g. XVIII and XIX, Fig. 1).

In the case of the preparation of phenolic stilbenes, this condensation step is followed by an alkali- and heat-promoted rearrangement of the crude condensation product to give the final stilbene (Fig. 2). However, in the case of the preparation of non-phenolic stilbenes, this rearrangement is achieved by heating of the non-phenolic 1,1-diaryl-2-chloroethane intermediate (e.g. XIX, Fig. 3) in acidic solution at higher temperature.

Some phenolic stilbenes, were also prepared by partial or total demethylation of the corresponding methoxy-substituted compounds using boron tribromide. Conversely, some hydroxy-substituted stilbenes were methylated (or ethylated) with diazomethane (or diethylsulfate) to obtain the corresponding alkoxy-substituted stilbenes. The products obtained by demethylation and methylation (or ethylation) were compared with those prepared by condensation and subsequent rearrangement.

EXPERIMENTAL

Chemicals

4-n-Propylguaiacol was prepared by hydrogenation of eugenol (H_2, Pd on charcoal as catalyst). Other phenols and phenol ethers used in this work were commercially available from Merck, Darmstadt or Aldrich, Steinheim, Federal Republic of Germany, or from Janssen Chimica, Beerse, Belgium. Monochloroacetaldehyde diethylacetal (1,1-diethoxy-2-chloroethane) (>98%) and potassium *t*-butoxide (>97%) were purchased from Fluka Chemie AG, Switzerland and sodium methoxide (>98%) from Merck. Solvents were of analytical grade or redistilled before use.

General procedure for the synthesis of phenolic stilbenes

One equivalent of each phenol, together with one equivalent of monochloroacetaldehyde diethylacetal, was dissolved in glacial acetic acid and,

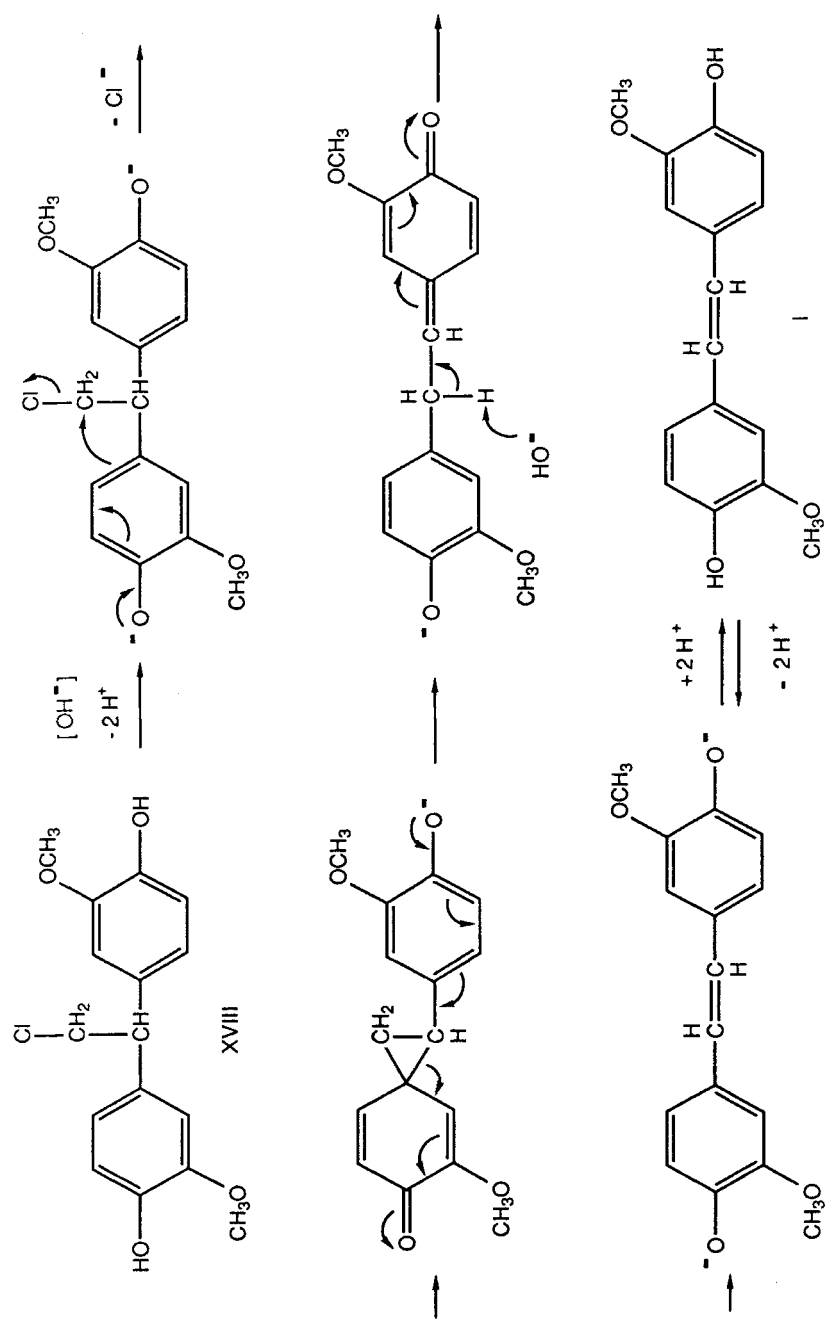


Fig. 2 Alkali- and heat-promoted rearrangement of 1,1-bis-(4-hydroxy-3-methoxyphenyl)-2-chloroethane (XVIII) to give 4,4′-dihydroxy-3,3′-dimethoxystilbene (I).

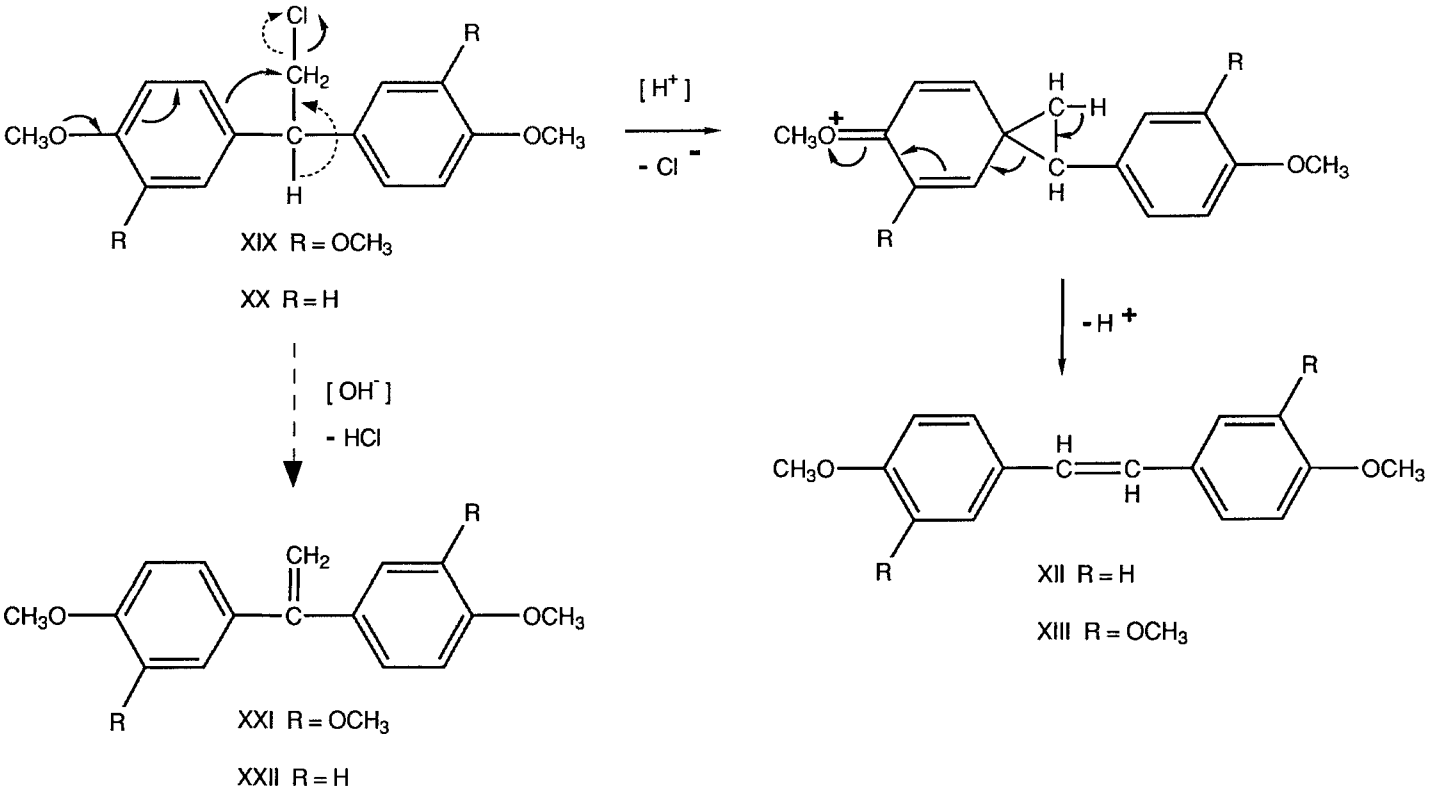


Fig.3 Acid-promoted rearrangement of 1,1-bis-(3.4-dimetoxyphenyl)-2-chloroethane (XIX) and 1,1-bis-(4-methoxyphenyl)-2-chloroethane (XX) to give the corresponding stilbenes XIII and XII and alkali-promoted elimination of hydrogen chloride from XIX and XX to yield the corresponding styrenes XXI and XXII.

while maintaining the temperature at about 0 °C, one equivalent concentrated sulfuric acid in glacial acetic acid was slowly added to the magnetically stirred solution over a 2 h period. The reaction mixture was stirred for a further 4 h at this low temperature, poured onto ice and then repeatedly extracted with diethyl ether. The combined ethereal fractions were washed with water, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give an oil. This crude reaction mixture was emulsified in ethyleneglycol and slowly (over 1 h) added to a refluxed solution of ethyleneglycolate under an atmosphere of argon and with exclusion of light. (The latter solution was prepared by adding five equivalents of sodium methoxide to ethyleneglycol, followed by removal of methanol by distillation.) The resulting mixture was stirred for another hour, allowed to cool, poured onto ice, acidified with dilute sulfuric acid and extracted several times with diethyl ether. [The preparation of hydrophilic stilbenes, such as III and X required prolonged extraction (Soxhlet apparatus)]. After washing with water, drying and filtering, the combined ethereal extract was evaporated to dryness.

Examples of synthesis

4,3′,4′-Trihydroxy-3-methoxystilbene (III): Guaiacol (2.5 g, 20.1 mmol), catechol (2.2 g, 20.0 mmol) and monochloroacetaldehyde diethylacetal (3 g, 19.7 mmol) were dissolved in glacial acetic acid (about 30 ml). The temperature was lowered to 4-8 °C (ice-bath) and a mixture of concentrated sulfuric acid (5 ml) and glacial acetic acid (10 ml) was added dropwise under vigorous stirring during 1 h. The reaction mixture was magnetically stirred for additional 6 h at the low temperature and then poured onto ice and extracted several times with diethyl ether. The isolation of the hydrophilic stilbene was facilated by the use of a Soxhlet liquid-liquid extractor. The extract was dried and the solvent evaporated. Sodium methoxide (5.8 g, 107 mmol) was added to ethyleneglycol (15 ml) and heated to boiling. The crude reaction product was emulsified in ethyleneglycol (30 ml) and the mixture was added dropwise during 1 h to the sodium methoxide solution and stirred for another hour under reflux. The cooled mixture was poured onto ice, immediately acidified with dilute sulfuric acid and extracted as above. The hydroxystilbenes were protected from oxidation by acetylation with an excess of acetic anhydride in pyridine (1:1) at room temperature overnight. The crude product mixture was analysed by TLC [Merck silica gel HF 254, type 60, ethylacetate and light petroleum (1:1)] and fractionated using flash chromatography (see below) with the same eluent. Yield of (IIIa): 0.73 g, (19,2%).

4,4′-Dihydroxy-3,3′,5,5′-tetramethoxystilbene (VII): 2,6-dimethoxyphenol (syringol) (6 g, 39 mmol) and chloroacetaldehyde diethylacetal (3 g, 19.7 mmol) were dissolved in glacial acetic acid (30 ml) and treated as described above. The rearrangement was made under an atmosphere of argon and shielded from daylight; if not protected the mixture turned intensely red-coloured. The crude product mixture was acetylated before separation; yield of pure (VIIa) 30.1%.

Generally, yields after separation and purification vary between 10 and 30%. They can be improved considerably when the rearrangement step (Fig. 2) is performed in dry dimethylformamide (instead of ethyleneglycol), containing potassium *t*-butoxide (3.3 equivalents) as base, at 140 °C for 45 min. The resultant mixture was poured onto ice, acidified with an excess of acetic acid and the crystals formed were filtered, dried and recrystallized from ethanol. In the case of I, an overall yield in excess of 85% was obtained.

The 1,1-diaryl-2-chloroethane intermediate XVIII, formed during the preparation of compound I (Fig. 1), was isolated and purified by column chromatography. Spectroscopic data are reported for the corresponding diacetate (XVIIIa). Intermediate XVIII was converted via base-catalyzed rearrangement into the corresponding stilbene (I) (Fig. 2) in almost quantitative yield.

Before chromatographic separation or storage, the phenolic stilbenes were converted to their acetates by treating the mixture with acetic anhydride and pyridine (1:1) either at 80 °C for 1 h, or at room temperature overnight. If the crude mixture (or product) was discoloured, it was dissolved or suspended in acetic anhydride, catalytic amounts of sodium acetate added and the mixture refluxed for a few minutes. Zinc dust was added in excess and the heating continued until the colour had disappeared (reductive acetylation). The mixture was filtered and the residue washed with acetic acid. After hydrolysis of the acetic anhydride, the filtrate and the combined washings were poured onto crushed ice and the phenolic stilbenes were repeatedly extracted with diethyl ether. The combined ethereal extracts were washed with a saturated $NaHCO_3$ solution and then with water, dried, filtered and evaporated under reduced pressure.

Phenolic stilbenes were recovered from the corresponding acetates in yields usually in excess of 90% by refluxing with an excess of lithium

aluminium hydride in dry tetrahydrofuran and an atmosphere of argon. After approximately 3 h, ethylacetate and then water was slowly added and the reaction mixture was acidified with 2 M H_2SO_4, extracted and dried.

Instead of the two-step procedure, described above, a one-step synthesis comprising acid-catalyzed condensation and acid-promoted rearrangement may be used (see also preparation of non-phenolic stilbenes, below). However, the yields obtained when the latter synthetic variant is used are usually lower.

Demethylations

Some phenolic stilbenes were also prepared from the corresponding methoxy-substituted compounds by partial or complete demethylation with BBr_3 (18). Thus, III, VIII and X were obtained from I, II or III and I, respectively. The stilbene was dissolved in dry CH_2Cl_2 and BBr_3 (1.1 equivalent/methoxyl group to be removed) added to the solution at -80 °C in an atmosphere of argon using a dry syringe. The mixture was allowed to reach room temperature overnight and was then hydrolysed by addition of water, after which the reaction products were extracted.

General procedure for the synthesis of non-phenolic stilbenes

Alkoxy-substituted stilbenes were prepared by condensing monochloroacetaldehyde diethylacetal with the appropriate aryl alkyl ether(s) under conditions similar to those applied in the synthesis of phenolic stilbenes. After slow addition of the monochloroacetaldehyde diethylacetal solution at about 0 °C, the reaction mixture was allowed to reach room temperature over night, poured onto ice and extracted. However, instead of a subsequent alkali-promoted rearrangement (see Fig. 2), the introductory condensation step was followed by an acid-catalyzed rearrangement at a higher temperature (Fig. 3). This was performed after evaporation of the condensation mixture by refluxing the residue in ethyleneglycol which results in the formation of the desired alkoxy-substituted stilbenes.

Condensation of monochloroacetaldehyde diethylacetal with arylalkyl ethers in acidic media may take place in the para- and the ortho-position(s) relative to alkoxy group(s), affording a mixture of 1,1-diaryl-2-

chloroethane isomers. However, the para-isomers strongly dominate and the resulting p,p'-alkoxystilbenes can be easily separated from their ortho-isomers. Thus, 3,3',4,4'-tetramethoxystilbene (XIX) was obtained in this way in a yield of 64%.

Etherifications

Compounds VI, IX, XI, XIII and XV were prepared by partial or complete methylation of the appropriate compounds I, II, V, I or III and VII, respectively, using a solution of diazomethane in diethyl ether which contained a small amount of methanol as catalyst. The diazomethane solution was prepared by addition of 60 % KOH to N-nitroso-N-methyl-p-toluene-sulfonamide in diethyleneglycol monoethylether/diethyl ether (2:1). The reactant was transferred to the ether solution using a slow stream of nitrogen (19).

Compound XIV was obtained by reacting Ia, dissolved in a mixture of water, ethanol and 1,2-dimethoxyethane, with diethylsulfate and alkali, while maintaining the pH of the solution constant at 13 using an autotitrator. After 12 h, the reaction was terminated by addition of 2 M sulfuric acid and the reaction mixture extracted with dichloromethane. Drying of the organic layer ($MgSO_4$) and evaporation of the solvent gave crude XIV.

Stilbenes were usually obtained only in their trans-configuration. The corresponding cis-forms of Ia, IIIa, VIIa and Xa were prepared by several hours irradiation of the trans-forms in a $CHCl_3$ solution using a high pressure mercury lamp.

Product separation

Reactions were monitored and crude product mixtures analysed by thin-layer chromatography (TLC) using silica gel plates (Merck HF 254, type 60). The following solvents and solvent systems were used: chloroform, dichloromethane, chloroform : ethanol (95 : 5) and mixtures of ethyl acetate (from 20 to 100%) and light petroleum (40-60 °C). Compounds were visualized by UV irradiation or by spraying with 70% sulfuric acid and heating the plates at 110 °C for 5-10 min.

HPLC was adopted for good chromatographic separation. Straight phase (SP) separations of the acetylated stilbenes were performed using a Spectra Physics 8000 liquid chromatograph, equipped with a UV detector (ACS, HPLC Monitor® {Applied Chromatograpic Systems, England}), or an Altex model 420, fitted with a Beckman 165 variable wave length detector. The column (4.6 x 250 mm) packed with Licrosorb Si 100 (Merck), 5μ, was eluted with ethyl acetate and light petroleum using gradients between 10 and 50% (1%/min), and peaks were detected at 254 or 280 nm. In more recent experiments, a Philips PU 4002 Liquid Chromatograph equipped with a PU 4021 Diode-array UV/VIS detector was used for ready differentiation between stilbenes, aryl styrenes and quinone impurities.

Reversed phase (RP) chromatography using an Altex 332 liquid chromatograph, equipped with a LKB 2138 UVICORD S detector (280 nm) and an ultraphere ODS 5μ column (4.6 x 250 mm) was preferred for separation of phenolic stilbenes. The stilbenes were eluted with aceto-nitrile and water using gradients between 20 and 70% (1%/min), both solvents containing 0.1% acetic acid.

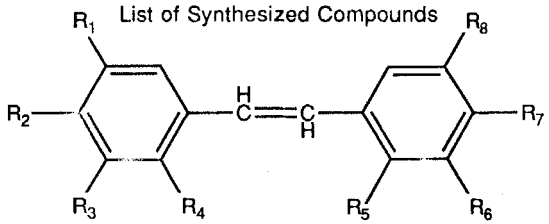
Large scale separations of the stilbene acetates were performed using the flash chromatography technique (20) on Merck Silica 60, 230-400 mesh, with dichloromethane or ethyl acetate : light petroleum (e.g. 35 : 65) as eluants. Intricate separation problems were solved by adopting Merck Lobar column size B and the Altex gradient system equipped with preparative pumpheads.

When maximum separation power was required, repetitive injections were performed into a column packed with Nucleosil® Si 50, 5μ, by the use of an autoinjector (Waters WISP 710 B or a Reodyne 7125 injector operated by compressed air and connected to a syringe pump for refilling of the loop) and a programmable fraction collector (Gilson peak collector).

Product identification

Samples for mass spectroscopy were introduced via direct inlet or GC. Most stilbene acetates could be separated by gas chromatography. Thus, a Hewlett-Packard 5710A instrument, equipped with a 15 m, SE-30 bonded phase fused silica capillary column and temperature programmed from 120 °C to 300 °C was used to introduce samples to a mass spectrometer. Helium served as carrier gas. Peaks were also detected by a FID and the

List of Synthesized Compounds



I $R_1 = R_6 = OCH_3$, $R_2 = R_7 = OH$, $R_3 = R_4 = R_5 = R_8 = H$

II $R_1 = R_6 = R_8 = OCH_3$, $R_2 = R_7 = OH$, $R_3 = R_4 = R_5 = H$

III $R_1 = OCH_3$, $R_2 = R_6 = R_7 = OH$, $R_3 = R_4 = R_5 = R_8 = H$

IV $R_1 = R_6 = OCH_3$, $R_2 = R_5 = OH$, $R_8 = CH_2CH_2CH_3$, $R_3 = R_4 = R_7 = H$

V $R_1 = R_6 = OCH_3$, $R_2 = R_5 = H$, $R_8 = CH_3$, $R_3 = R_4 = R_7 = H$

VI $R_1 = R_6 = R_7 = OCH_3$, $R_2 = OH$, $R_3 = R_4 = R_5 = R_8 = H$

VII $R_1 = R_3 = R_6 = R_8 = OCH_3$, $R_2 = R_7 = OH$, $R_4 = R_5 = H$

VIII $R_1 = R_3 = OCH_3$, $R_2 = R_6 = R_7 = H$, $R_4 = R_5 = R_8 = H$

IX $R_1 = R_3 = R_6 = R_7 = OCH_3$, $R_2 = OH$, $R_4 = R_5 = R_8 = H$

X $R_1 = R_2 = R_6 = R_7 = OH$, $R_3 = R_4 = R_5 = R_8 = H$

XI $R_1 = R_2 = OH$, $R_6 = R_7 = OCH_3$, $R_3 = R_4 = R_5 = R_8 = H$

XII $R_2 = R_7 = OCH_3$, $R_1 = R_3 = R_4 = R_5 = R_6 = R_8 = H$

XIII $R_1 = R_2 = R_6 = R_7 = OCH_3$, $R_3 = R_4 = R_5 = R_8 = H$

XIV $R_1 = R_6 = OCH_3$, $R_2 = R_7 = OCH_2CH_3$, $R_3 = R_4 = R_5 = R_8 = H$

XV $R_1 = R_2 = R_3 = R_6 = R_7 = R_8 = OCH_3$, $R_4 = R_5 = H$

XVI $R_1 = R_8 = CH_3$, $R_3 = R_6 = OCH_3$, $R_2 = R_4 = R_5 = R_7 = H$

XVII $R_1 = R_8 = CH_2CH_2CH_3$, $R_3 = R_6 = OCH_3$, $R_2 = R_4 = R_5 = R_7 = H$

Compounds XVIII - XXII, see Fig. 1-3

peak areas were measured using a Trivector 2000 Chromatography Data System.

Different mass spectrometers were employed; LKB 9000 (direct inlet only), Finnigan 3200 F instrument with data system 6000, Finnigan 4000 and Finnigan INCOS 50 and an ion energy of 70 eV, or 40 eV when indicated.

In addition, ^{1}H NMR and ^{13}C NMR spectroscopy were used to confirm the structure of the synthesized compounds. Unless otherwise stated, NMR spectra were recorded using deuterio- chloroform ($CDCl_3$) as solvent and tetramethylsilane (TMS) as internal standard. The following instruments were used: Varian R-12 (60 MHz), Varian CFT-20 (80 MHz), Brucker WP-200 (200 MHz) or Brucker 400 (400 MHz). Chemical shifts are given in ppm downfield from TMS. In some instances (XVIa and XVIIa), decoupling experiments facilitated the assignment of particular signals.

Spectroscopic Data

4,4′-Dihydroxy-3,3′-dimethoxystilbene (I)

MS (LKB 9000) {40 eV}, m/e (rel. int.): 272 (M, 100), 257 (3), 239 (4), 211 (14), 207 (34), 197 (9), 196 (7), 169 (10), 168 (7), 157 (10), 149 (15), 131 (8), 123 (11), 109 (17).

^{1}H NMR (Brucker 200 MHz): 3.95 [s, 6H, OCH_3], 5.62 [s, 2H, OH], 6.88-7.02 [m, 8H, ar and olefin].

4,4′-Diacetoxy-3,3′-dimethoxystilbene (Ia)

MS (Finnigan 3200) {40 eV}, m/e (rel. int.): 356 (M,6), 314 (M-42, 15), 272 (100), 257 (2), 211 (13), 169 (12).

^{1}H NMR (Brucker 200 MHz): 2.28 [s, 6H, OAc], 3.86 [s, 6H, OCH_3], 6.95-7.09 [m, 8H, ar and ol].

^{13}C NMR (Varian 80 MHz): [trans] 20.6 ($CO\underline{C}H_3$), 55.9 (OCH_3), 110.3 (C-2), 119.3 (C-6), 123.0 (C-5), 128.5 (C–α), 136.2 (C-1), 139.5 (C-4), 151.3 (C-3), 169.0 (CO).

[cis] 20.6 ($CO\underline{C}H_3$), 55.9 (OCH_3), 112.9 (C-2), 121.9 (C-6), 122.7 (C-5), 129.9 (C–α), 135.8 (C-1), 139.0 (C-4), 150.8 (C-3), 169.0 (CO).

4,4′-Dihydroxy-3,3′,5′-trimethoxystilbene (II)
MS (INCOS 50) m/e (rel. int.): 302 (M, 100), 287 (6), 272 (13), 259 (21), 255 (25), 227 (37), 137 (42), 115 (44).

4,4′-Diacetoxy-3,3′,5′-trimethoxystilbene (IIa)
MS (Finnigan 3200) m/e (rel. int.): 386 (M, <1), 344 (M-42, 16), 302 (M-42-42, 100), 272 (3), 255 (1), 227 (1).
^{1}H NMR (Varian 80 MHz): 2.29 [s, 6H, OAc], 3.86 [s, 9H, OCH_3], 6.52-7.10 [m, 7H, ar + ol].

4,3′,4′-Trihydroxy-3-methoxystilbene (III)
^{1}H NMR (Varian 60 MHz): 3.86 [s, 3H, OCH_3], 4.75 [s, OH], 6.47-7.23 [m, ar + ol].

4,3′,4′-Triacetoxy-3-methoxystilbene (IIIa)
MS (Finnigan 4000) m/e (rel. int.): 384 (M, 2), 342 (M-42, 12), 300 (M-42-42, 53), 258 (M-42-42-42, 100), 207 (2), 197 (6), 169 (3), 141 (7).
^{1}H NMR (Varian 80 MHz): 2.26, 2.28, 2.30 [3xs, 3x3H, OAc], 3.84 [s, 3H, OCH_3], 6.87-7.25 [m, 8H, ar + ol].
^{13}C NMR (Varian 80 MHz): [trans] 20.6 ($CO\underline{C}H_3$), 55.8 (OCH_3), 110.3 (C-2, gua), 119.3 (C-6, gua), 123.0 (C-5, gua), 123.7 (C-5, cat), 124.7 (C-6, cat), 127.2 (C–α, cat), 127.5 (C-2, cat), 129.3 (C–α, gua), 136.0 (C-1, cat), 136.2 (C-1, gua), 139.6 (C-4, gua), 141.5 (C-4, cat), 142.4 (C-3, cat), 151.3 (C-3, gua), 168.2 (CO, cat), 168.9 (CO, gua).
[cis] 20.6 ($CO\underline{C}H_3$), 55.7 (OCH_3), 112.8 (C-2, gua), 121.7 (C-6, gua), 122.8 (C-5, gua), 123.3 (C-2, cat), 123.7 (C-5, cat), 127.2 (C-6, cat), 128.6 (C–α, cat), 130.8 (C–α, gua), 135.3 (C-1, gua), 136.0 (C-1, cat), 139.1 (C-4, gua), 141.2 (C-4, cat), 142.1 (C-3, cat), 150.8 (C-3, gua), 168.1 (CO, cat), 168.9 (CO, gua).

2, 4′-Dihydroxy-3,3′-′dimethoxy-5-propylstilbene (IV)
MS (INCOS 50) m/e (rel. int.): 314 (M, 14), 285 (4), 253 (8), 239 (100), 225 (4), 195 (30), 179 (12), 165 (15), 161 (9), 151 (12), 150 (11), 145 (28), 137 (81).

2,4′-Diacetoxy-3,3′-dimethoxy-5-propylstilbene (IVa)
MS (INCOS 50) m/e (rel. int.): 398 (M, 28), 356 (M-42, 58), 315 (21), 314 (M-42-42, 100), 285 (30), 253 (25), 239 (10), 225 (21), 181 (22), 165 (43), 150 (50).

2,4´-Diacetoxy-3,3´-dimethoxy-5-methylstilbene (Va)
MS (Finnigan 3200) m/e (rel. int.): 370 (M, 21), 328 (M-42, 38), 314 (3), 286 (M-42-42, 100), 272 (12), 255 (10), 211 (9), 197 (6), 182 (9), 165 (11), 162 (8).
^{1}H NMR (Varian 80 MHz): 2.24 [s, 3H, CH_3], 2.30 [s, 6H, OAc], 3.82, 3.85 [2xs, 6H, OCH_3], 6.69, 6.74 [2xd, 2H, ol], 6.85-7.11 [m, 5H, ar].

4-Hydroxy-3,3´,4´-trimethoxystilbene (VI)
MS (INCOS 50) m/e (rel. int.): 286 (M, 100), 271 (32), 211 (19), 181 (17), 165 (26), 152 (22), 139 (22), 128 (38), 115 (28).
^{1}H NMR (Varian 80 MHz): 3.82 [s, 6H, OCH_3], 3.88 [s, 3H, OCH_3], 5.6 [s, broad, 1H, OH], 6.70-7.05 [m, 8H, ar + ol].

4-Acetoxy-3,3´,4´-trimethoxystilbene (VIa)
MS (Finnigan 4000) m/e (rel. int.): 328 (M, 28), 287 (14), 286 (M-42, 100), 271 (20), 255 (3), 211 (6), 181 (6), 165 (7), 152 (7), 139 (8).

4,4´-Dihydroxy-3,3´,5,5´-tetramethoxystilbene (VII)
MS (LKB 9000) {40 eV}, m/e (rel. int.): 332 (M, 100), 316 (4), 301 (5), 286 (9), 285 (8), 284 (6), 271 (5), 257 (9), 153 (11), 151 (9), 137 (14).
^{1}H NMR (Varian 60 MHz): 3.89 [s, 12H, OCH_3], 5.48 [s, 2H, OH], 6.68 [s, 4H, ar], 6.82 [s, 2H, ol].

4,4´-Diacetoxy-3,3´,5,5´-tetramethoxystilbene (VIIa)
MS (LKB 9000) m/e (rel. int.): 416 (M, 14), 374 (M-42, 74), 332 (M-42-42, 100), 317 (4), 289 (6), 257 (9), 182 (11), 167 (9).
^{1}H NMR (Brucker 200 MHz): 2.35, 2.38, 2.38 [3xs, 6H, OAc], 3.79-3.89 [m, 12H, OCH_3], 6.78-7.48 [m, 6H, ar + ol].
^{13}C NMR (Varian 80 MHz): [trans] 20.4 ($CO\underline{C}H_3$), 56.2 (OCH_3), 103.2 (C-2, C-6), 123 (C–α), 128.5 (C-4), 136.3 (C-1), 152.3 (C-3, C-5), 168.6 (CO) {tentative assignments}
[cis] 20.4 ($CO\underline{C}H_3$), 56.2 (OCH_3), 105.8 (C-2, C-6), 124 (C–α), 128.5 (C-4), 135.3 (C-1), 152.3 (C-3, C-5), 168.6 (CO) {shifts obtained from the isomeric mixture}.

4,3´,4´-Triacetoxy-3,5-dimethoxystilbene (VIIIa)
MS (Finnigan 3200) {40 eV} m/e (rel. int.): 414 (M, 18), 372 (M-42, 35), 330 (M-42-42, 60), 288 (M-42-42-42, 100), 273 (4), 255 (11), 245 (9), 241 (12), 213(16).

^1H NMR (Brucker 200 MHz): 2.17-2.35 [m, 9H, OAc], 3.67, 3.88 [2xs, 6H, OCH_3] 6.47-7.35 [m, 5H, ar + ol].

4-Hydroxy-3,5,3′,4′-tetramethoxystilbene (IX)
MS (INCOS 50) m/e (rel. int.): 316 (M, 100), 301 (25), 281 (3), 241 (11), 227 (7), 213 (11), 211 (9), 198 (16), 181 (20), 169 (13).
^1H NMR (Varian 60 MHz): 3.80 [s, 3H, OCH_3], 3.85 [s, 9H, OCH_3], 5.5 [s, 1H, OH], 6.70 [s, 2H], 6.84 [s, 2H], 6.85-7.10 [m, 3H].

4-Acetoxy-3,5,3′,4′-tetramethoxystilbene (IXa)
MS (INCOS 50) m/e (rel. int.): 358 (M, 20), 317 (21), 316 (M-42, 100), 301 (M-28), 225 (6), 213 (8), 209 (5), 181 (15), 171 (11), 165 (40), 115 (38).
^1H NMR (Brucker 200 MHz): 2.34 [s, 3H, OAc], 3.87 [s, 6H, OCH_3], 3.90 [s, 3H, OCH_3], 3.95 [s, 3H, OCH_3], 6.74-7.06 [m, 7H, ar + ol].
^{13}C NMR (Brucker 200 MHz): 20.5 ($CO\underline{C}H_3$), 55.9 (OCH_3), 56.0 (OCH_3) 56.1 (OCH_3) 102.9 (C-2 and C-6, syr), 108.8 (C-2, ver), 111.3 (C-5, ver), 120.0 (C-6, ver), 126.6 (C–α), 128.8 (C–α and C-4, syr), 130.2 (C-1, ver), 136.0 (C-1, syr), 149.1 (C-3 or C-4, ver), 149.2 (C-3 and C-4, ver), 152.3 (C-3 and C-5, syr), 168.8 (CO).

3,4,3′,4′-Tetrahydroxystilbene (X)
MS (LKB 9000) m/e (rel. int.): 244 (M, 100), 242 (51), 229 (3), 226 (7), 225 (7), 220 (3), 213 (11), 209 (9), 205 (17), 197 (54), 183 (30) 169 (7), 110 (30).
^1H NMR (Varian 60 MHz) {in CD_3OD}: 4.75 [s broad, OH], 6.75 [s, 6H, ar], 6.95 [s, 2H, ol].

3,4,3′,4′-Tetraacetoxystilbene (Xa)
MS (Finnigan 3200) {40 eV} m/e (rel. int.): 412 (M, 3), 370 (M-42, 12), 328 (M-42-42, 37), 286 (M-42-42-42, 55), 244 (M-42-42-42-42, 100), 225 (10), 197 (25), 169 (12), 141 (10).
^1H NMR (Brucker 200 MHz): 2.26, 2.28 [2xs, 2x6H, OAc], 6.96-7.43 [m, 8H, ar + ol].
^{13}C NMR (Varian 80 MHz): [trans] 20.6 ($CO\underline{C}H_3$), 121.1 (C-2), 123.6 (C-5), 124.8 (C-6), 128.2 (C–α), 135.9 (C-1), 141.6 (C-4), 142.4 (C-3), 168.1 (CO).
[cis] 20.6 ($CO\underline{C}H_3$), 123.4 (C-2), 123.6 (C-5), 127.2 (C-6), 129.3 (C–α), 135.9 (C-1), 141.4 (C-4), 142.0 (C-3), 168.1 (CO).

3,4-Dihydroxy-3′,4′-dimethoxystilbene (XI)
MS (INCOS 50) m/e (rel. int.): 272 (M, 100), 257 (15), 211 (5), 197 (6), 169 (5), 165 (4), 153 (6), 152 (7), 139 (7), 127 (5), 115 (6)
^{1}H NMR (Varian 60 MHz) (in $CDCl_3/CD_3OD$): 3.75 [s, 3H, OCH_3], 3.80 [s, 3H, OCH_3], 4.60 [s, 2H], 6.70-7.08 [m, 8H, ar + ol]

3,4-Diacetoxy-3′,4′-dimethoxystilbene (XIa)
MS (INCOS 50) m/e (rel. int.): 356 (M, 24), 314 (M-42, 49), 273 (33), 272 (M-42-42, 100), 257 (32), 225 (18), 211 (19), 197 (29), 169 (17), 152 (26), 139 (25), 128 (48).
^{1}H NMR (Brucker 200 MHz): 2.29, 2.31[2xs, 6H, OAc], 3.90, 3.94 [2xs, 6H, OCH_3] 6.85-7.35 [m, 8H, ar + ol].
^{13}C NMR (Brucker 400 MHz): 20.7 ($CO\underline{C}H_3$), 55.9 (OCH_3), 56.0 (OCH_3), 108.8 (C-2, ver), 111.3 (C-5, ver), 120.1 (C-6, ver), 120.7 (C-2, cat), 123.5 (C-5, cat), 124.5 (C-6, cat), 125.1 (C–α), 129.7 (C–α), 130.0 (C-1, ver), 136.7 (C-1, cat), 141.0 (C-4, cat), 142.3 (C-3, cat), 149.2 (C-3 or C-4, ver), 149.2 (C-3 or C-4, ver), 168.3 (CO), 168.4 (CO).

4,4'-Dimethoxystilbene (XII)
MS (Finnigan 3200) m/e (rel. int.): 240 (M, 100), 225 (M-15, 50), 210 (4), 197 (5), 182 (22), 211 (50), 183 (40), 165 (64).
^{1}H NMR (Brucker 400 MHz): 3.84 [s, 6H, OCH_3] 6.89-7.46 [m, 10H, ar + ol].

3,4,3′,4′-Tetramethoxystilbene (XIII)
MS (Finnigan 4000) m/e (rel. int.): 300 (M, 100), 285 (M-15, 32), 270 (2), 242 (3), 225 (5), 209 (4), 195 (2), 181 (4), 165 (10), 150 (13).
^{1}H NMR (Brucker 400 MHz): 3.90 [s, 6H, OCH_3], 3.95 [s, 6H, OCH_3], 6.85-7.06 [m, 8H, ar + ol].

4,4′-Diethoxy-3,3′-dimethoxystilbene (XIV)
MS (Finnigan 3200) m/e (rel. int.): 328 (M,100), 299 (M-29, 96), 271 (M-29-29, 28), 239 (12), 221 (22), 211 (50), 183 (40), 181 (46), 165 (64).
^{1}H NMR (Varian 80 MHz): 1.45 [t, 6H, CH_3], 3.90 [s, 6H, OCH_3], 4.09 [q, 4H, CH_2], 6.74-7.01 [m, 8H, ar + ol].

3,4,5,3′,4′,5′-Hexamethoxystilbene (XV)
MS (INCOS 50) m/e (rel. int.): 360 (M, 100), 346 (10), 345 (58), 330 (1), 315 (4),

179 (26), 164 (18), 157 (22), 149 (33).
^1H NMR (Varian 80 MHz): 3.90 [s, 6H, OCH_3], 3.91 [s, 12H, OCH_3], 6.70-7.37 [m, 6H, ar + ol].

2,2´-Diacetoxy-3,3´-dimethoxy-5,5´-dimethylstilbene (XVIa)
MS (Finnigan 3200) m/e (rel. int.): 384 (M, 11), 342 (M-42, 21), 300 (M-42-42, 100), 285 (6), 283 (2), 270 (8), 165 (40), 115 (57).
^1H NMR (Varian 80 MHz): {CD_2Cl_2} [cis] 2.28 [s, 6H, OAc], 2.35 [s, 6H, CH_3], 3.87 [s, 6H, OCH_3], 6.87-7.17 [m, 6H, ar + ol].
^{13}C NMR (Brucker 200 MHz) {CD_3COCD_3}: 18.9 (CH_3), 20.5 ($CO\underline{C}H_3$), 56.5 (OCH_3), 110.9 (C-2), 125.5 (C-6), 128.5 (C–α), 129.2 (C-5), 135.8 (C-1), 151.10 (C-4), 151.8 (C-3), 171.7 (CO).

2,2´-Diacetoxy-3,3´-dimethoxy-5,5´-di-n-propylstilbene (XVIIa)
MS (Finnigan 4000) m/e (rel. int.): 440 (M, 4), 398 (M-42, 29), 356 (M-42-42, 100), 179 (17), 178 (18), 177 (9), 151 (12), 150 (60), 145 (10), 137 (65).
^1H NMR (Brucker 400 MHz): 0.99 [t, 6H, -CH_3], 2.33 [s, 6H, OAc], 2.68 [t, 4H, Ph-CH_2-], 1.62 [m, 4H, -CH_2-], 3.84 [s, 6H, OCH_3], 6.76 [s, 2H, ol], 6.96 [s, 2H, ar], 7.19 [s, 2H, ar].
^{13}C NMR (Brucker 200 MHz): 14.1 (CH_3), 20.7 ($CO\underline{C}H_3$), 24.3 (β-CH_2-), 35.5 (α-CH_2), 56.0 (OCH_3), 113.6 (C-2), 119.9 (C-6), 125.8 (C–α), 129.3 (C-5), 138.0 (C-4 or C-1), 139.3 (C-1 or C-4), 150.2 (C-3), 169.3 (CO).

1,1-bis-(4-Acetoxy-3-methoxyphenyl)-2-chloroethane (XVIIIa)
MS (Finnigan 4000) m/e (rel. int.): 392 (M,1), 352 (2), 350 (M-42, 8), 310 (10), 308 (M-42-42, 30), 301 (4), 272 (3), 259 (100), 229 (6).
^1H NMR (Brucker 200 MHz): 2.30 [s, 6H, OAc], 3.79 [s, 6H, OCH_3], 4.00, 4.04 [d, 2H, CH_2], 4.24, 4.27, 4.31, 4.35 [q, CH], 6.79-7.06 [m, 6H, ar].

1,1-bis-(3,4-Dimethoxyphenyl)-2-chloroethane (XIX)
MS (Finnigan 4000) m/e (rel. int.): 338 (M+2, 4), 336 (M, 22), 302 (1), 300 (7), 288 (3), 287 (100), 257 (10).

1,1-bis-(4-Methoxyphenyl)-2-chloroethane (XX)
MS (Finnigan 4000) m/e (rel. int.): 278 (M+2, 5), 276 (M, 17), 240 (6), 229 (M+2-49, 10), 227 (M-49, 100), 212 (9), 196 (5), 184 (4), 169 (9).

1,1-bis-(4-Methoxyphenyl)-2-chloroethane (XXI)
MS (Finnigan 4000) m/e (rel. int.): 300 (M, 100), 285 (6), 270 (4), 269 (14), 254 (7), 253 (7), 211 (10), 165 (10), 163 (23).
^{1}H NMR (Brucker 400 MHz): 3.84 [s, 6H, OCH_3], 3.91 [s, 6H, OCH_3], 5.33 [s, 2H, CH_2], 6.83-6.94 [m, 6H, ar].
^{13}C NMR (Brucker 400 MHz): 55.9 (OCH_3), 110.7, 111.5, 112.1, 121.0, 134.5, 148.5, 148.9, 149.5.

1,1-bis-(4-Methoxyphenyl)-ethene (XXII)
MS (Finnigan 3200) m/e (rel. int.): 240 (M, 100), 225 (M-15, 62), 209 (M-15-15, 28), 182 (10), 165 (18), 153 (12).
^{1}H NMR (Brucker 400 MHz): 3.84 [s, 6H, OCH_3], 5.31 [s, 2H, CH_2], 6.86-7.31 [m, 8H, ar].

The abbrevations ar and ol refer to aromatic and olefinic hydrogens and "gua", "ver", "cat" and "syr" refer to guaiacol, veratrol, catechol and syringol moieties, respectively. Index "a" refers to the acetylated derivative.

RESULTS AND DISCUSSION

When monochloroacetaldehyde diethylacetal was condensed with only one phenol, e.g. guaiacol, 2,6-dimethoxyphenol or catechol, the corresponding symmetrical stilbenes I, VII and X were obtained in yields ranging from 20% to >85%. However, when the condensation was performed using equimolar amounts of two phenols, the reaction mixtures obtained after alkaline rearrangement contained, in addition to the corresponding asymmetrical stilbene (Ar_1-Ar_2), both symmetrical stilbenes (Ar_1-Ar_1 and Ar_2-Ar_2). Theoretically, the yield ratio between the asymmetrical and the sum of the symmetrical stilbenes is 1:1. The relative yields obtained in these condensation reactions were determined by HPLC or GC and corresponded roughly to this ratio. The yield of an individual stilbene varied widely depending on the nature of the condensation partner(s) and the reaction conditions employed. No attempt has been made to maximize the yields by varying the reaction conditions or the work-up and separation procedures.

As indicated in the Introduction, this method has the disadvantage of giving two symmetrical stilbenes in addition to the asymmetrical, when only the latter may be desired. However, this is outweighed by the ready availability of the starting materials, by the versatility of the 2-step procedure without isolation of the intermediates and by the facile separation of the components of the reaction mixture. Due to the high temperatures used during the preparations, the synthesized stilbenes were obtained mainly in the thermodynamically more stable trans-forms. Conversion to the corresponding cis-forms was achieved photochemically.

The following mechanism is proposed for this two-step synthesis of phenolic stilbenes: The first step entails acid-catalyzed condensation between monochloroacetaldehyde diethylacetal and two molecules of one particular phenol, e.g. guaiacol (Fig. 1, R = H) (preparation of symmetrical stilbenes) or with one molecule of each of two phenols (preparation of asymmetrical and symmetrical stilbenes) to give 1,1-diaryl-2-chloroethanes (Fig.1). In the second step (Fig. 2), these 1,1-diaryl-2-chloroethanes undergo alkali-promoted aryl migration, involving elimination of chloride ion as leaving group and formation of spirocyclohexadienone intermediates, followed by opening of the spiro ring and proton abstraction from the quinone methide intermediate to give the final products. This mechanism parallels the course of stilbene formation from "condensed" ß-aryl ether structures [1,1-bis(p-hydroxyaryl)ethane-2-O-aryl ether structures], assumed to be present in residual lignins, a reaction which also involves an alkali-promoted aryl migration (21, 22). In the latter case, the phenolate ion functions as leaving group instead of the chloride ion which is operative in the present rearrangement.

Experimental support for this course of reaction was provided by the isolation and identification of the 1,1-diaryl-2-chloroethane intermediate XVIII, following reaction of monochloroacetaldehyde diethylacetal with guaiacol in acidic medium (Fig. 1) and by the smooth conversion of this intermediate into the corresponding phenolic stilbene (I) by treatment with alkali (Fig. 2).

The methylated derivative of XVIII, 1,1-diveratryl-2-chloroethane (XIX), prepared by acid-catalyzed condensation of monochloroacetaldehyde diethylacetal with veratrole, does not afford any noticeable amount of stilbene XIII on treatment with base (potassium *t*-butoxide in dimethylformamide) (Fig. 3). In this case, the alkali-promoted migration of the

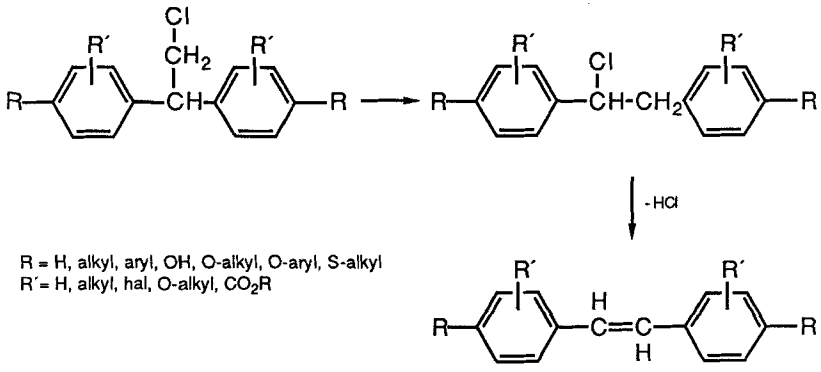


Fig. 4 Alternative mechanism of stilbene formation from 1,1-diaryl-2-chloroethanes *via* mutual exchange of chlorine and one of the aryl moieties to give 1,2-diaryl-1-chloroethane intermediates (proposed by R.H. Sieber, Ref. 17).

aryl groups is blocked by the etherified phenolic hydroxyl groups. Instead, the corresponding 1,1-diarylethene derivative (1,1-diveratrylethene, XXI) was formed by elimination of hydrogen chloride (Fig. 3). An analogous behaviour is shown by 1,1-dianisyl-2-chloroethane (XX) which affords the styrene derivative XXII.

The condensation/rearrangement mechanism applies also to the synthesis of non-phenolic stilbenes. However, in this case, the rearrangement step has to be promoted by the action of acids, due to the absence of electron-donating phenoxide ions in the condensation product. These conditions have been employed in the synthesis of 4,4'-dimethoxystilbene (XII), 3,3', 4,4'-tetramethoxystilbene (XIII) and 3,3', 4,4', 5,5'-hexamethoxystilbene (XV).

An alternative mechanism of stilbene formation from 1,1-diaryl-2-halogenoethanes has been proposed earlier (17). This would proceed *via* a concerted mutual exchange of the halogen atom and one of the aryl residues with formation of a 1,2-diaryl-1-halogenoethane and subsequent elimination of hydrogen chloride from the latter (Fig. 4).

However, in view of the apparent analogy to the aryl migration with elimination of phenolate ions mentioned above, and other aryl partici-

pation reactions of related compounds described in the literature (23, 24), the formulation of the reaction course via intermediates of the spirocyclohexadienone type is strongly preferred.

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