

Synthesis of some Model Compounds for Thiolignin

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A series of model compounds for thiolignin was synthesized. Vanillyl alcohol and thiophenol were found to form vanillyl phenyl sulfide by elimination of water even at room temperature on irradiation with sunlight, or alternatively on moderate heating in the presence of aluminium sulfate or hydrogen ions. Similar reactions were carried out with other substances, including *isoeugenol* and thiophenol, and cinnamyl alcohol and *p*-thiocresol or thioglycolic acid. As a side reaction there also occurred addition of the mercaptan to the ethylenic bond. The ethylenic bond in cinnamyl cresyl sulfide reacted very slowly with soda-alkaline permanganate solution.

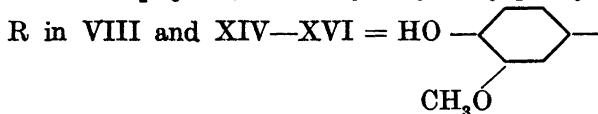
The present work is a continuation of our studies on cinnamyl phenyl sulfide as a model substance for thiolignin¹. Table I gives a survey of the syntheses carried out.

Table I. Syntheses of thiolignin models.

Reagents	Method ^{a)}	time	Reaction product	Yield mole %
Cinnamyl alcohol(I) + <i>p</i> -thiocresol(II)	Pressure heating with aluminium sulfate (1)	17.5 h	Cinnamyl- <i>p</i> -cresyl-sulfide(III) + IV or V	29
Vanillyl alcohol(VI) + thiophenol(VII)	Photosynthesis (2a)	270 days	Vanillyl phenyl sulfide(VIII ^{d)})	91
—→—	Pressure heating with aluminium sulfate ¹ (2b) ^{b,e)}	17 h	—→—	36
I + thioglycolic acid(IX)	Pressure heating with aluminium sulfate (3a) ^{b)}	17 h	S-cinnamylthioglycolic acid(X)	45—51
—→—	Boiling in C ₆ H ₆ with piperidine as catalyst (3b)	36 h	X + XI or XII	15
<i>Isoeugenol</i> (XIII) + VII	Pressure heating (4a) ^{b)}	18.3 h	XIV and XV	79
XVI ^{c)} + VII	Pressure heating with aluminium sulfate(4b) ^{b)}	17 h	XIV	59

^{a)} The numbers in parentheses signify paragraphs in the experim. part. ^{b)} In a sealed glass tube. ^{c)} Kindly supplied by Prof. E. Adler. ^{d)} Is soluble in alkali. The phenyl carbamic acid ester was prepared. ^{e)} Boiling of vanillyl alcohol and thiophenol with HCl as catalyst yielded an amorphous mass containing only 3.5 % S, and molecular weights in 2 chromatographic fractions of 323 and 1069, respectively.

- III. $(p)\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{S}\cdot\text{CH}_2\cdot\text{CH}:\text{CH}\cdot\text{C}_6\text{H}_5$
 IV. $\text{C}_6\text{H}_5\cdot\text{CH}(\text{CH}_2\cdot\text{CH}_2\text{OH})\cdot\text{S}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3(p)$; γ -(*p*-methyl-thiophenoxy)- γ -phenyl-propanol
 V. $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}(\text{CH}_2\text{OH})\cdot\text{S}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3(p)$; β -(*p*-methyl-thiophenoxy)- γ -phenyl-propanol
 VIII. $\text{R}\cdot\text{CH}_2\cdot\text{S}\cdot\text{C}_6\text{H}_5$
 X. $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\cdot\text{S}\cdot\text{CH}_2\cdot\text{COOH}$
 XI. $\text{C}_6\text{H}_5\cdot\text{CH}(\text{CH}_2\cdot\text{CH}_2\text{OH})\cdot\text{S}\cdot\text{CH}_2\cdot\text{COOH}$; S-(α -phenyl- γ -hydroxy-propyl)-thioglycolic acid
 XII. $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}(\text{CH}_2\text{OH})\cdot\text{S}\cdot\text{CH}_2\cdot\text{COOH}$; S-(β -phenyl- β' -hydroxy-*isopropyl*)-thioglycolic acid
 XIV. $\text{R}\cdot\text{CH}(\text{S}\cdot\text{C}_6\text{H}_5)\cdot\text{CH}_2\cdot\text{CH}_3$; 1-thiophenoxy-1-(3-methoxy-4-hydroxy-phenyl)-propane
 XV. $\text{R}\cdot\text{CH}_2\cdot\text{CH}(\text{S}\cdot\text{C}_6\text{H}_5)\cdot\text{CH}_3$; 2-thiophenoxy-1-(3-methoxy-4-hydroxy-phenyl)-propane
 XVI. $\text{R}\cdot\text{CHOH}\cdot\text{C}_2\text{H}_5$; α -(3-methoxy-4-hydroxy-phenyl)-propanol



Perhaps the most interesting observation made was the readiness with which vanillyl phenyl sulfide (VIII) was formed in 91 % yield by elimination of water from vanillyl alcohol and thiophenol, even at room temperature, by photosynthesis.

Attempts to add thioglycolic acid to the double bond of S-cinnamyl thioglycolic acid in acetone solution with piperidine as catalyst failed.

Of the pure crystalline substances synthesized III and VIII are, as far as we know, new ones. Of the liquid reaction products, which are possibly mixtures of isomers, IV, V, XI, XII, XIV and XV have also not been reported hitherto. X has been synthesized by Holmberg² but by another method than that employed by us. It can be mentioned in this connection that Freudenberg recently has prepared S-vanillyl thioglycolic acid from vanillyl alcohol and thioglycolic acid using boron fluoride as catalyst³.

Ultraviolet and infrared spectra. The absorption spectrum in ultraviolet of cinnamyl-*p*-cresylsulfide (Fig. 1) shows a single maximum at about 255 $m\mu$, very similar to that of cinnamyl phenyl sulfide¹, S-cinnamylthioglycolic acid (Fig. 2, H, D), allyl phenyl sulfide and cinnamyl disulfide¹, but distinctly different from that of vanillyl phenyl sulfide (Fig. 2, V), 2-methyl thiocoumarane¹ and the addition products of *isoeugenol* and thiophenol (Fig. 3). The addition product (XI or XII) of cinnamyl alcohol and thioglycolic acid shows an UV spectrum (Fig. 4) clearly differing from that of S-cinnamyl thioglycolic acid (Fig. 2). The IR spectrum (Fig. 5) lacks the absorption band of the ethylenic bond at 960 cm^{-1} . The band at 1710 cm^{-1} is very probably due to the valence oscillations of the C:O group of the carboxyl grouping. The valence oscillations of the alcoholic hydroxyl group should occur between 2.6 and 3.0 μ . For instance, the addition product of cinnamyl alcohol and thiophenol¹

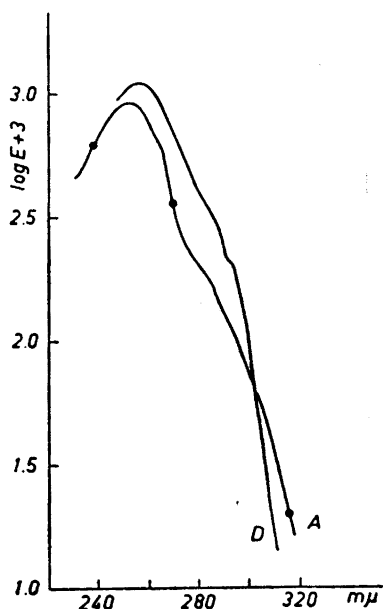


Fig. 1. UV spectrum of cinnamyl-*p*-cresyl sulfide. D = in dioxan. A = in 0.5 N alcoholic sodium hydroxide solution.

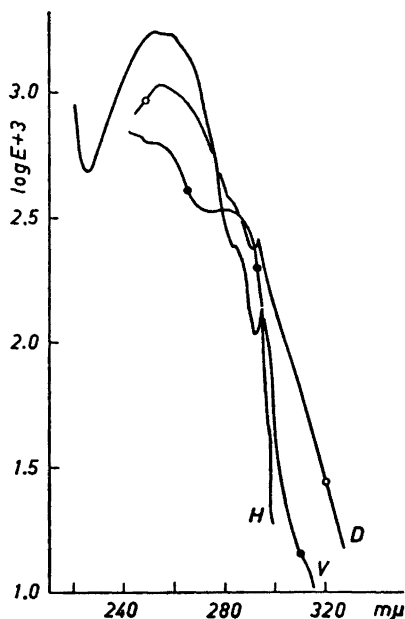


Fig. 2. UV spectrum of vanillyl phenyl sulfide and of *S*-cinnamyl thioglycolic acid. V = vanillyl phenyl sulfide in dioxan. H = *S*-cinnamyl thioglycolic acid in hexane. D = the same in dioxan.

absorbs at 2.9 μ . In Fig. 5 this bond is very broad, indicating association or hydrogen bonding⁴.

Reactions of the ethylenic bonds. Cinnamyl *p*-cresyl sulfide, like cinnamyl phenyl sulfide¹, decolorized soda-alkaline permanganate solution at room temperature only very slowly, after hours of standing. In contrast, *S*-cinnamyl thioglycolic acid (X), as well as XI and XII, immediately decolorize the reagent. With tetranitromethane cinnamyl-*p*-cresyl sulfide gave a golden yellow color, whereas the compound XIV gave a red color.

EXPERIMENTAL

1. *Cinnamyl-p-cresyl sulfide.* The synthesis was almost completely analogous to the synthesis of cinnamyl phenyl sulfide¹, 0.990 g of aluminium oxide being used, however, for 0.044 mole of cinnamyl alcohol and 0.043 mole of *p*-thiocresol. The sulfide obtained was recrystallized from 99 % ethanol, yield 3.001 g, m. p. 67–68°C. (Found: C 80.20; H 7.01; S 13.14. Calc. for C₁₆H₁₆S: C 79.95; H 6.71; S 13.34). UV spectrum Fig. 1. From the mother liquors a main fraction was isolated by chromatography in about the same way as in the synthesis of cinnamyl phenyl sulfide¹. (Found: S 12.09. Calc. for C₁₆H₁₆SO: S 12.41).

2. *Vanillyl phenyl sulfide.* a) *Photosynthesis.* Vanillyl alcohol was prepared by catalytic hydrogenation of vanillin according to Ref.⁵ Yield 72 mole %.

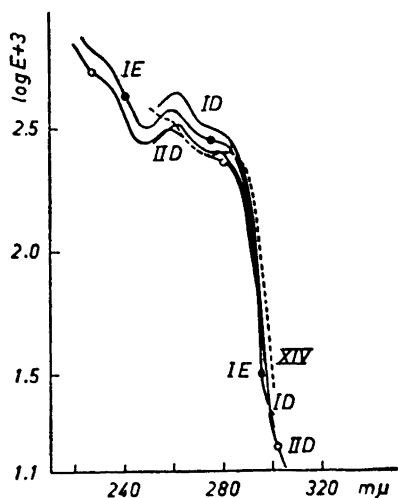


Fig. 3. UV spectrum of addition product (XIV or XV) of isoeugenol and thiophenol (4a). I D = first chromatographic fraction in dioxan, I E = the same in ethanol. II D = second chromatographic fraction in dioxan, II E = the same in ethanol. XIV = XV in dioxan.

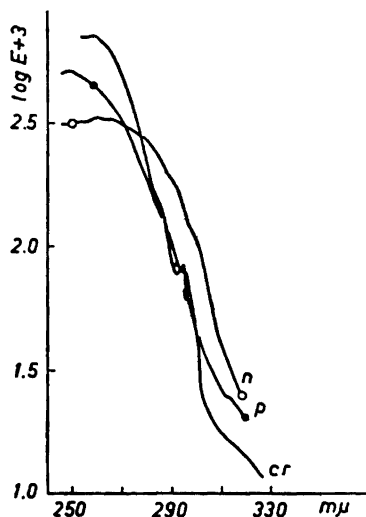


Fig. 4. UV spectra of addition products XI and XII of cinnamyl alcohol and thioglycolic acid. cr = crude, p = chromatographically purified acids. n = neutral product from 3 b.

1.54 g (0.010 mole) vanillyl alcohol and 1.100 g (0.010 mole) thiophenol were mixed in a glass test tube sealed with a rubber stopper. The tube was allowed to stand in a sunny window from December to the end of August. The reaction product was recrystallized from 99 % ethanol. Yield 2.239 g with m.p. 87–90.5°. Part of the material was chromatographed on aluminium oxide (Brockmann) previously washed with 2 N hydrochloric acid and with water, and dried 24 h at 150°, in about the same way as in the synthesis of cinnamyl phenyl sulfide¹, benzene being used instead of carbon tetrachloride, however. The sulfide thus purified melted at 91.5–92°. (Found: C 68.23; H 5.76; S 12.92; mol. weight (Beckmann, cryosec.) 239. Calc. for $C_{14}H_{14}SO_2$: C 68.26; H 5.73; S 13.02; mol. weight 246). UV spectrum Fig. 2, V.

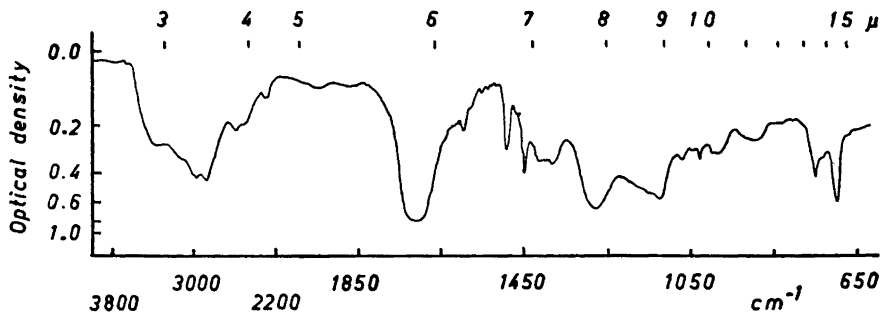


Fig. 5. IR spectrum of addition product of cinnamyl alcohol and thioglycolic acid (3 b).

120.1 mg of vanillyl phenyl sulfide were heated 5 h at 140–145° with 60.1 mg of phenyl isocyanate, moisture being excluded by means of a calcium chloride tube. The phenyl carbamic acid ester formed was recrystallized three times from hot ligroin and then once more from carbon tetrachloride containing 10 % of petrol ether. Yield 86 mg; m. p. 137–138°. (Found: C 68.95; H 5.48; N 3.66; S 8.69. Calc. for $C_{21}H_{19}NSO_3$: C 69.02; H 5.24; N 3.83; S 8.77).

b) *With aluminium sulfate.* The synthesis was analogous to that used in Ref.¹, using 5.932 g of vanillyl alcohol, 4.298 g of thiophenol and 0.350 g of aluminium sulfate. The reaction product was dissolved in ether, washed three times with a sodium hydrogen carbonate solution, which dissolves the bulk of the thiophenol, and finally with water. The isolated neutral substance was recrystallized first from ligroin containing 5 % of chloroform and then from 50 % alcohol. Yield 3.406 g, m. p. 89–91°. 100 mg of the substance was chromatographed on aluminium oxide treated with hydrochloric acid, after which it showed a m. p. of 91.5–92°.

3. *S-Cinnamyl thioglycolic acid.* a) With aluminium sulfate. 3.807 g (0.0413 mole) of thioglycolic acid and 5.545 g (0.0413 mole) of cinnamyl alcohol were heated with 0.343 g anh. aluminium sulfate 17 h at 127°. The reaction product was dissolved in benzene and extracted from the benzene by repeated shaking with 2 N sodium hydroxide. The alkaline layer was acidified with 2 N sulfuric acid and extracted five times with benzene. The final benzene solution was washed with water, dried and evaporated at room temperature. The residue was dried in vacuum over phosphorus pentoxide. The yield varied in the various experiments between 45–51 mole % calculated as S-cinnamyl thioglycolic acid. By recrystallization from ligroin containing 5 % chloroform a crystalline substance with m. p. 78–79° was isolated. UV spectrum Fig. 2. (Found: C 63.46; H 5.88; S 15.35. Calc. for $C_{11}H_{12}SO_3$: C 63.43; H 5.81; S 15.40).

b) With piperidine catalyst, substances XI and XII. 2.530 g (0.0275 mole) of thioglycolic acid, 3.2210 g (0.24 mole) of cinnamyl alcohol and 0.2 ml of piperidine were dissolved in 10 ml of benzene and refluxed 36 h. The acidic reaction products were separated from the neutral ones as described under 3 a. Yield 1.593 g of yellow oil giving a positive Baeyer test, S 14.53 %, UV spectrum Fig. 4, cr. Paper chromatography was carried out on Whatman paper No. 1 with toluene-methanol-water (10:5:5), developing with 0.1 N silver nitrate solution and heating⁶ 15 min at 110°, with 0.5 N permanganate solution in the dark, or with starch solution and iodine-azide solution according to Feigl⁷. Three spots corresponding to R_F 0.92, 0.88 and 0.00 were found. Of these R_F 0.92 was found by a parallel run to correspond to cinnamyl thioglycolic acid.

On chromatography on a Whatman cellulose column (32 × 2.5 cm) washed with 350 ml of the toluene-methanol-water-mixture described, 0.288 g of the substance was applied, dissolved in 4 ml chloroform, and the chromatogram was developed with the solvent mixture. The substance separated into one fraction which could be eluted with the toluene mixture, and another, which was eluted with ether-ethanol 1:1. The first fraction was a partially crystallized oil, from which S-cinnamyl thioglycolic acid with m.p. 74–76° (undepressed on admixture of acid from synthesis 3 a) could be prepared through crystallization from ligroin. The second fraction was a yellow oil, which was dried 3 days in vacuum over P_2O_5 ; yield 0.148 g, UV spectrum Fig. 4 p. R_F -value 0.00 with the toluene mixture. (Found: C 57.50; H 5.59; S 13.67; mol.weight (Childs) 294. Calc. for $C_{11}H_{14}SO_3$: C 58.38; H 6.24; S 14.17; mol.weight 226). IR spectrum Fig. 5. The product gave a S-benzyl thiuronium salt with m. p. 150–152°.

A sample of the neutral product was purified by chromatography on aluminium oxide in benzene solution and elution with benzene containing increasing amounts (5–50 %) of ethanol. S 9.65 %. UV spectrum Fig. 4, n.

4. *Synthesis of XIV and XV.* a) From isoeugenol. 4.785 g (0.0291 mole) of thiophenol were heated in a sealed glass tube 18.3 h at 127°. The yield of reaction products soluble in 2 N sodium hydroxide was 6.623 g. 4.025 g were dissolved in 15 ml of carbon tetrachloride and separated into two fractions by chromatography on 21.7 g of aluminium oxide treated with hydrochloric acid by elution with carbon tetrachloride containing 0.10 and finally 25 % ethanol. Both fractions gave a red colour with tetranitromethan. The first fraction, a light yellow oil, was obtained mainly with pure carbon tetrachloride. Yield 2.008 g, UV spectrum Fig. 3, 1D and 1E. (Found: C 69.56; H 6.86; S 11.52; mol.weight (Beckmann, cryosc.) 265. Calc. for $C_{16}H_{18}SO_2$: C 70.04; H 6.61; S 11.69; mol.weight 274).

Acetylation according to Ref.¹ (synthesis 1 a): reaction product a yellow oil. (Found: CH_3CO 13.23 %. Calc. for $\text{C}_{16}\text{H}_{17}\text{SO}_2 \cdot \text{COCH}_3$: CH_3CO 13.60). Phenyl carbamic ester was prepared by heating 85 mg of the fraction with a 20 mole % excess of phenyl isocyanate. The excess of reagent was removed by digestion with ligroin. The liquid reaction product was dissolved in hot ligroin containing 5 % chloroform and cooled. Only a few mg were obtained of a crystalline product, melting after recrystallization at 95–98°, the greater part remaining liquid.

The second fraction was also a light yellow oil. Yield 1.843 g, UV spectra Fig. 3, II D and II E. (Found: C 69.76; H 6.50; S 11.74; mol. weight 276. Calc. for $\text{C}_{16}\text{H}_{18}\text{SO}_2$: see above!)

The following derivatives were prepared in a manner corresponding to the first fraction: 315.3 mg were acetylated, giving a light yellow oil. (Found: CH_3CO 13.11.) Phenyl carbamic ester, m. p. 94–96°, undepressed on admixture of the corresponding derivative from the first fraction.

b) From XVI. 0.605 g (0.0033 mole) of α -(3-methoxy-4-hydroxy-phenyl)-propanol (XVI), 1.795 g thiophenol and some anhydrous aluminium sulfate were heated 17 h at 127° in a sealed glass tube. A liquid reaction product, obviously 1-thiophenoxy-1-(3-methoxy-4-hydroxy-phenyl)-propane (XIII) was isolated chromatographically as described under 4 a. Yield 0.539 g; UV spectrum Fig. 3, XIV. (Found: S 11.43. Calc. for $\text{C}_{16}\text{H}_{18}\text{SO}_2$: S 11.69.)

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