[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Studies on Lignin and Related Products. XIII.[1] Oxidations of Lignin Model Compounds and their Significance to Lignin Structure[2]

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RECEIVED JULY 9, 1956

Alkaline cupric oxide and alkaline nitrobenzene oxidation of lignin model compounds such as 5-substituted vanillils and bis-vanillyl compounds with 2-carbon side chains in the α- and α -positions yielded the same compounds that are obtained from analogous oxidations of coniferous lignosulfonate materials. Thus, the occurrence of all monomolecular and bimolecular guaiacyl compounds in such coniferous lignosulfonate oxidation mixtures can be accounted for by assuming for a portion of the lignin complex α-α linkages between two C_6–C_3 structural units. The syntheses of 3,3′-dimethoxydienestrol and 3,3′-dimethoxyhexesterol diacetate are recorded.

A few years ago the possibility of the presence in at least a part of the complex lignin structure of a linkage between the α-carbon atoms of two C_6–C_3 units was suggested,[3] and the hypothesis was supported more recently when it was demonstrated that except for compounds having carbon chains in the 5-position of the guaiacyl group, the compounds formed in alkaline cupric oxide oxidations of lignosulfonate materials actually could be prepared by similar oxidation of bis-vanillyl compounds containing two C_6–C units linked through their α-carbon atoms.[4] Unfortunately, these bis-vanillyl compounds contained only C_6–C units without 5-carbon chain substitution. The present paper presents the results of a continuing study on the alkaline nitrobenzene and alkaline cupric oxide oxidations of lignin model compounds with two C_6–C units linked through their α-carbon atoms and containing 5-carbon side chains and with two C_6–C_3 units linked through their α-carbon atoms. The first group of model compounds comprises 5-allylvanillil, 5,5′-diallylvanillil, 5-propenylvanillil and 5,5′-dipropenylvanillil.[5] The second group comprises 3,3′-dimethoxydiethylstilbestrol,[6] 3,3′-dimethoxyhexestrol and 3,3′-dimethoxydienestrol. These oxidations are compared with similar oxidations of coniferous lignosulfonate materials.

Cupric oxide and oxidation of 5-allylvanillil under conditions reported earlier[4] and isolation of reaction products by means of chromatography yielded products with and without the 5-carbon side chain. Much of the original 5-allylvanillil was recovered as its isomer, 5-propenylvanillil, under the conditions of the experiment. Other compounds isolated and identified were vanillil, 5-propenylvanillovanillone, 5-allylvanillil, 5-propenylvanillic acid, 5-carboxymethylvanillil, 5-carboxyvanillil, 5-carboxyvanillic acid and vanillic acid. Almost identical results were obtained with 5-propenylvanillil, and similar results were obtained with 5,5′-diallylvanillil and 5,5′-dipropenylvanillil except that in the case of the bis-substituted compounds, the yields of unsubstituted guaiacyl compounds were much less.

Thus, no aldehydes were formed from the unsaturated side chains under the cupric oxide oxidation conditions employed, and the state of oxidation of the starting materials precluded aldehyde formation at the α-carbon positions under oxidizing conditions. Therefore, it is apparent that the products of oxidation of these model compounds are very similar to those obtained from lignosulfonate materials under analogous conditions. Alkaline nitrobenzene oxidation of these compounds gave, in addition to the compounds noted above, 5-formylvanillovanillone, and an unidentified carbonyl compound, probably 5-formylvanillil, indicating that bis-vanillyl compounds with 5-carbon substitution can account for all of the types of compounds isolated from alkaline cupric oxide and alkaline nitrobenzene oxidations of lignosulfonate materials. In order to determine whether the β- and γ-carbon atoms of similar guaiacyl compounds with C_6–C_3 units linked through their α-carbon atoms would be removed under these oxidizing conditions to yield the same reaction products, three such compounds were oxidized under both alkaline nitrobenzene and alkaline cupric oxide conditions.

Cupric oxide oxidation of 3,3′-dimethoxydiethylstilbestrol yielded a mixture of compounds similar to that obtained from a corresponding lignosulfonate oxidation except that no 5-substituted guaiacyl compounds were obtained. Vanillin, vanillic acid, acetovanillone, vanillil and vanillovanillone were identified in the oxidation products. It should be noted that this representative C_6–C_3 dimer yielded acetovanillone as one of the products of oxidation, and it is possible to account for this end-product of oxidation without assuming an aldol configuration for the side chain in the C_6–C_3 structure of lignin with subsequent reverse aldol under alkaline conditions to yield acetovanillone and formaldehyde.[7] It is entirely possible, however, that an aldol configuration is formed as an intermediate in the oxidation of the instant C_6–C_3 dimer when its α-α carbon linkage is broken.

Nitrobenzene oxidation of 3,3′-dimethoxydiethylstilbestrol gave essentially the same compounds as the chief products of oxidation. Paper chromatography indicated even the same minor products. Similar results were obtained when 3,3′-dimethoxydienestrol and 3,3′-dimethoxyhexestrol were oxidized with nitrobenzene although in the latter case all yields were a little lower. Vanderlinde and co-workers[8] recently reported the alkaline

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[1] For paper XII of this series, see THIS JOURNAL, **78**, 4433 (1956).

[2] Presented before the Division of Cellulose Chemistry at its Lignin Symposium at the 130th Meeting of the American Chemical Society, Atlantic City, New Jersey, September 16 to 21, 1956.

[3] I. A. Pearl and E. E. Dickey, THIS JOURNAL, **74**, 614 (1952).

[4] I. A. Pearl and D. L. Beyer, *ibid.*, **76**, 2224 (1954).

[5] I. A. Pearl, *ibid.*, **77**, 2826 (1955).

[6] I. A. Pearl, *ibid.*, **78**, 4433 (1956).

[7] A. v. Wacek and K. Kratzl, *J. Polymer Sci.*, **3**, 539 (1948).

[8] R. E. Vanderlinde, F. D. Vasington and W. W. Westerfeld, THIS JOURNAL, **77**, 1176 (1955).

oxidation of diethylstilbestrol to yield 4,4′-dihydroxybenzil and *p*-hydroxybenzoic acid, and demonstrated the formation of dienestrol as an intermediate in this oxidation. These authors proved that the β- and γ-carbon atoms of two C_6–C_3 units linked through their α-carbon atoms were indeed removed by alkaline oxidation.

Thus, these model compound oxidations indicate that the occurrence of all of the guaiacyl compounds isolated to date from alkaline cupric oxide and alkaline nitrobenzene oxidations of coniferous lignosulfonate materials can be accounted for by assuming for a portion of the lignin complex α-α linkages between two C_6–C_3 structural units.

Experimental

All melting points are uncorrected, ultraviolet spectral data are for solutions in 95% ethanol (concentration, 0.02 g. per liter), and R_f values are given for the system butanol–2% aqueous ammonia at 20°.

Starting Materials.—The allyl- and propenyl-vanillil derivatives and the diacetate of 3,3′-dimethoxydiethylstilbestrol are products whose syntheses have been described earlier.[5,6]

3,3′-Dimethoxyhexestrol (α,α′-**Diethylbivanillyl**).—3,3′-Dimethoxydiethylstilbestrol diacetate (5 g.) was dissolved in 25 ml. of ethanol, treated with 50 ml. of 10% sodium hydroxide solution and boiled under reflux for 8 hours. The mixture was diluted with 100 ml. of water, treated with a few pellets of sodium hydroxide, and distilled until all ethanol was removed, maintaining the volume constant with water. The alkaline solution was acidified with sulfur dioxide and extracted with ether. The ether was removed under reduced pressure at room temperature, and the oily 3,3′-dimethoxydiethylstilbestrol was dissolved in 250 ml. of hot absolute ethanol, treated with one g. of 10% palladium on charcoal catalyst, and hydrogenated at an initial pressure of 50 p.s.i. One mole of hydrogen was absorbed. The catalyst was filtered, and the ethanolic solution was concentrated and cooled to give a quantitative yield of 3,3′-dimethoxyhexestrol as colorless needles melting at 158–159° which, upon recrystallization from methanol, melted at 160–160.5° and gave the following maxima in its ultraviolet absorption spectrum: λ_{max} 230 mμ, ε 16470; λ_{max} 282 mμ, ε 7130.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.64; H, 7.89.

Acetylation with acetic anhydride in pyridine and recrystallization of the product twice from ethanol yielded white crystals of 3,3′-dimethoxyhexestrol diacetate melting at 178–179° and giving the ultraviolet absorption maximum, λ_{max} 280 mμ, ε 5850.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.57; H, 7.31.

3,3′-Dimethoxyhexestrol diacetate was also obtained directly by hydrogenation under the same conditions of 3,3′-dimethoxydiethylstilbestrol diacetate. In this case the saturated compound crystallized during hydrogenation.

3,3′-Dimethoxydienestrol Diacetate [**3,4-Bis-(4-acetoxy-3-methoxyphenyl)-hexa-2,4-diene**].—A mixture of 5 g. of α,α′-diethylhydrovanilloin,[6] 5 g. of acetyl chloride and 50 ml. of acetic anhydride was boiled under reflux 4 hours, and the excess solvents removed under reduced pressure below 40°. The residue was covered with water, and the yellow resinous solid was washed with water several times by decantation and recrystallized twice from ethanol to give the diacetate of 3,3′-dimethoxydienestrol as white needles melting at 147–148° and giving the following maxima in its ultraviolet absorption spectrum: λ_{max} 213 mμ, ε 23000; λ_{max} 240 mμ, ε 14680; λ_{max} 312, mμ, ε 18860.

Anal. Calcd. for $C_{24}H_{26}O_6$: C, 70.23; H, 6.39. Found: C, 70.22; H, 6.40.

The mother liquor from the first recrystallization above was evaporated to dryness under reduced pressure at 20°, and the residue was recrystallized from ethanol to give white needles of the diacetate of 4,4-di-(4-hydroxy-3-methoxyphenyl)-3-hexanone melting at 136–137° and not depressing the melting point of a mixture with authentic 4,4-di-(4-acetoxy-3-methoxyphenyl)-3-hexanone.[6]

General Cupric Oxide Oxidation Procedure. The Oxidation of 5-Allylvanillil.—A mixture of 26 g. of 5-allylvanillil, 80 g. of sodium hydroxide, 223 g. of cupric hydroxide and 1250 g. of water was stirred and heated in a one-gallon stainless steel autoclave at 170° for 3 hours as described earlier.[9] The reaction mixture was filtered and the residue was washed thoroughly with hot water. The combined filtrate and washings were acidified with dilute sulfuric acid and extracted with ether. The ether was extracted successively with 21% sodium bisulfite, 8% sodium bicarbonate and 5% sodium hydroxide solutions, and these solutions acidified and worked up as described in the past to yield 5% of bisulfite-solubles, 25% of bicarbonate-solubles and 70% of alkali-solubles based on the starting material.

Analysis of Alkali-soluble Fraction.—The alkali-soluble fraction was covered with cold acetone, allowed to stand at room temperature 24 hours and filtered. The crystalline residue was recrystallized from methanol to yield white crystals melting at 168–169°, having an R_f 0.45, and not depressing a mixed melting point with authentic 5-propenylvanillil.[5] The acetate was prepared and its melting point and mixed melting point with authentic 5-propenylvanillil diacetate was 152–153°.

The acetone solution was evaporated to dryness. A sample was absorbed on cellulose powder and placed on a cellulose powder column. The column was developed with butanol saturated with 2% aqueous ammonia collecting 60 fractions of effluent. The effluent fractions were monitored by means of paper chromatography and combined to give three groups with the following R_f values: A, 0.45, 0.50, 0.68; B, 0.45; C, 0.19.

The R_f 0.45 material was previously identified as 5-propenylvanillil. Fraction A was dissolved in benzene and chromatographed on acid-washed Magnesol. The chromatogram was developed with 50:1 benzene–ethanol to give two fractions, one of which did not contain the R_f 0.50 product. This fraction was chromatographed in quantity on paper and separated into its two components. The R_f 0.68 material was cut from the chromatogram and eluted with 50% acetone to give white crystals of 5-propenylvanillovanillone melting at 140–141° and having the following maxima in its ultraviolet absorption spectrum: $\lambda_{shoulder}$ 260 mμ, ε 17620; λ_{max} 320 mμ, ε 16200.

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.73; H, 6.01.

The other fraction containing the R_f 0.50 product was chromatographed in the same manner and the R_f 0.50 compound eluted with acetone to give crystals of 5-allylvanillil melting at 178–179° and not depressing a mixed melting point with the starting material.

Fraction C was recrystallized first from methanol and then from acetic acid to give slightly yellow needles of vanillil melting at 228–230° and not depressing the melting point of a mixture with authentic vanillil.[10]

Analysis of Bicarbonate-soluble Fraction.—This fraction contained eight compounds as indicated by paper chromatography. The fraction was chromatographed on a column of cellulose powder as described above, and the eluate was separated into five fractions.

Fraction A, containing materials of R_f 0.43, 0.17, 0.14 and 0.12, was covered with benzene, allowed to stand 24 hours at room temperature, and filtered. The crystalline solid was washed with benzene and recrystallized from benzene to give colorless crystals melting at 152–153° with R_f 0.17 and 10:3:3 butanol–pyridine–water R_f 0.63, and having the ultraviolet absorption maximum λ_{max} 245 mμ, ε 21630. The analysis agrees with 5-propenylvanillic acid and the ultraviolet absorption spectrum is identical with that of 5-propenylvanillic acid[11] although the melting point is higher than that recorded earlier.

It is possible that this compound is the *trans* form and the earlier compound melting at 125–126° is the *cis* form.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.10; H, 5.82.

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[9] I. A. Pearl and D. L. Beyer, *Tappi*, **33**, 544 (1950).

[10] I. A. Pearl, This Journal, **74**, 4260 (1952).

[11] I. A. Pearl and D. L. Beyer, *ibid.*, **74**, 4263 (1952).

The benzene solution was chromatographed on acid-washed Magnesol and developed with 10:1 petroleum ether (b.r. 65–110°)–ethanol to give three bands which were eluted with acetone. The first band contained the R_f 0.17 compound, presumably *trans*-5-propenylvanillic acid. The second band, containing R_f 0.14 and 0.43 material, was chromatographed on paper in quantity, and the paper was cut and eluted with 50% acetone. The R_f 0.14 material was present in just trace amounts. The R_f 0.43 product solidified on standing. It was washed with ether and dried to give crystals melting at 111–112°, which analyzed for 5-propenylvanillil containing 2.5 molecules of water, and had ultraviolet absorption spectrum identical with that of 5-propenylvanillil.[5]

Anal. Calcd. for $C_{19}H_{23}O_{8.5}$: C, 58.91; H, 5.98. Found: C, 58.72; H, 5.97.

The third band yielded crystals melting at 222–223°, but has not been identified as yet. The compound has an R_f 0.12, 10:3:3 butanol–pyridine–water R_f 0.67 and maxima in its ultraviolet absorption spectrum at 242 and 332 mμ.

Fraction B contained only one compound with R_f 0.11 and butanol–pyridine–water R_f 0.39. The product was washed with acetone and dried to give white crystals melting at 246–247° and having the following maxima in its ultraviolet absorption spectrum: λ_{max} 235 mμ, ϵ 26420; λ_{max} 323 mμ, ϵ 18500. Analyses and properties correspond with 5-carboxymethylvanillil.

Anal. Calcd. for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48. Found: C, 60.01; H, 4.64.

Fraction C contained two compounds having R_f's 0.11 (5-carboxymethylvanillil) and 0.06. The fraction was covered with acetone and filtered. The acetone filtrate was chromatographed on paper, and the R_f 0.06 band was eluted with 50% acetone and concentrated under reduced pressure to give colorless crystals of 5-carboxyvanillil hydrate melting at 261–262° and not depressing a mixed melting point with 5-carboxyvanillil prepared by oxidation of 5-propenylvanillil diacetate[5] with potassium permanganate in boiling acetone and hydrolysis of the resulting 5-carboxyvanillil diacetate. The 10:3:3 butanol–pyridine–water R_f is 0.49 and the ultraviolet absorption spectrum has the following maxima: λ_{max} 230 mμ, ϵ 26720; $\lambda_{shoulder}$ 292 mμ, ϵ 14770; λ_{max} 330 mμ, ϵ 18710.

Anal. Calcd. for $C_{17}H_{16}O_9$: C, 56.04; H, 4.43. Found: C, 56.10; H, 4.44.

Fraction D was chromatographed on paper and found to contain only 5-carboxyvanillil melting at 261–262° and vanillil which was crystallized from acetic acid to yield crystals melting at 230–231° which did not depress a mixed melting point with authentic vanillil.

Fraction E was the largest fraction, comprising almost half of the bicarbonate-soluble material. This fraction contained only one product, vanillic acid melting at 208–210° and not depressing a mixed melting point with authentic vanillic acid.

Analysis of Bisulfite-soluble Fraction.—This relatively small fraction was worked up in the same manner as the bicarbonate-soluble fraction to yield vanillic acid, vanillil, 5-propenylvanillil, 5-carboxymethylvanillil, 5-carboxyvanillil and 5-carboxyvanillic acid.

The total recovery of identified products from this experiment is given in Table I. Because of the high recovery of 5-propenylvanillil under these conditions, the experiment was repeated at 180° for 5 hours and, in this case, the yields of all products, especially vanillil and vanillic acid, increased at the expense of 5-propenylvanillil.

Other Oxidations of Allyl and Propenylvanillil Compounds.—5,5′-Diallylvanillil, 5-propenylvanillil and 5,5′-dipropenylvanillil were oxidized with alkaline cupric oxide under the same conditions, and the reaction products were treated in the same manner to give substantially the same results. Individual yields varied somewhat, and yields of unsubstituted oxidation products were lower. In addition, the bis-allyl and bis-propenyl substituted compounds gave several new unidentified compounds which presumably still have bis-substitution.

TABLE I

PRODUCTS FROM THE ALKALINE CUPRIC OXIDE OXIDATION OF 5-ALLYLVANILLIL

Compound	Yield, %
5-Propenylvanillil	60.4
Vanillic acid	11.7
Vanillil	8.6
5-Propenylvanillovanillone	3.8
5-Carboxymethylvanillil	3.2
5-Propenylvanillic acid	3.0
5-Carboxyvanillil	2.7
5-Allylvanillil	1.4
5-Carboxyvanillic acid	0.7
	95.5

5-Propenylvanillil was oxidized with nitrobenzene and alkali under conditions reported earlier[11] and, after removal of the nitrobenzene, the mixture analyzed as described above. From the bisulfite-soluble fraction, in addition to the other products noted, there was recovered a light yellow crystalline solid melting at 178–179°, with R_f 0.10 and 10:3:3 butanol–pyridine–water R_f 0.85, and not depressing a mixed melting point with 5-formylvanillovanillone.[3] The formation of this compound in the present reaction indicates that the product isolated originally from the oxidation of lignosulfonate material must have the assigned structure.

The other allyl- and propenylvanillil compounds were oxidized by the micro method of Stone and Blundell,[12] and the reaction mixtures analyzed by means of paper chromatography. All products were compared with identical materials isolated in the macro-studies described above.

Cupric Oxide Oxidation of 3,3′-Dimethoxydiethylstilbestrol.—A mixture of 13 g. of 3,3′-dimethoxydiethylstilbestrol diacetate,[6] 40 g. of sodium hydroxide, 625 g. of water and 100 ml. of ethanol was boiled under reflux one hour and then distilled under reduced pressure until all ethanol was removed, maintaining the volume constant with water. The mixture was transferred to a stainless steel stirring autoclave and heated at 170° for 3 hours and processed as described above for 5-allylvanillil. The reaction mixture was analyzed in the same manner employed for similar oxidations of vanillil and its reduction products.[4] The main products of oxidation were vanillil, vanillic acid and acetovanillone, with smaller amounts of vanillin and vanillovanillone. All products were identified by isolation and comparison with authentic samples. A number of other compounds were indicated by paper chromatography, but these have not been isolated and identified as yet.

Other Oxidations of Compounds Related to 3,3′-Dimethoxydiethylstilbestrol.—3,3′-Dimethoxydiethylstilbestrol diacetate, 3,3′-dimethoxydienestrol and 3,3′-dimethoxyhexestrol diacetate were oxidized with alkaline nitrobenzene by the Stone and Blundell procedure, and the oxidation mixtures analyzed by means of paper chromatography and comparison with the results of the large scale cupric oxide oxidation of 3,3′-dimethoxydiethylstilbestrol. All oxidations gave the same products by chromatography, but yields of individual compounds varied in the several experiments. The yields of all products appeared to be a little less in the experiment with 3,3′-dimethoxyhexestrol diacetate.

Acknowledgment.—The author wishes to thank Mr. Harold Willemsen for the analyses and ultraviolet absorption spectra reported in this paper.

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[12] J. E. Stone and M. J. Blundell, *Anal. Chem.*, **23**, 771 (1951).