Further elution of the column with benzene gave 851 mg. of an oil which was subjected to another dehydration treatment followed by chromatography to yield an additional 125 mg. of product, m.p. 81–83°, bringing the total yield to 31%. Recrystallization from hexane furnished the analytical sample, m.p. 86–87.5°.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.26; H, 8.03. Found: C, 76.65; H, 8.01.

In an attempt to obtain 3-hydroxystilbestrol (IVb), the above trimethyl ether was subjected to demethylation by heating to 190–200° with three molar equivalents of methylmagnesium iodide, in the manner described previously.[1] The crude product rapidly turned dark and no solid material could be isolated, either by crystallization or by chromatography on alumina.

Chicago 37, Illinois

[Contribution from The Institute of Paper Chemistry]

Studies on Lignin and Related Products. XII.[1] The Synthesis of Lignin Model Compounds Related to Diethylstilbestrol[2]

By Irwin A. Pearl

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Pinacol reduction of propiovanillone yielded α,α′-diethylhydrovanilloin, and this pinacol in the presence of acid underwent rearrangement to the pinacolone 4,4-di-(4-hydroxy-3-methoxyphenyl)-3-hexanone. Sodium and butanol reduction of the pinacolone yielded the pinacolone alcohol 4,4-di-(4-hydroxy-3-methoxyphenyl)-3-hexanol, which was heated with aqueous sulfuric acid to yield the desired 3,3′-dimethoxydiethylstilbestrol by dehydration and retropinacolone rearrangement. 3,3′-Dimethoxydiethylstilbestrol may serve as an excellent intermediate for the preparation of 3,3′-dimethoxyhexestrol and 3,3′-dimethoxydienestrol.

A few years ago[3] 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. More recently, it was demonstrated that except for the 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 such as vanillil (I) and its reduction products.[4] These bis-vanillyl compounds, unfortunately, contained only C_6–C and not the preferred C_6–C_3 groups. Therefore, it was desired to submit lignin model compounds containing C_6–C_3 groups to similar oxidation experiments to determine whether the β- and γ-carbon atoms of the C_6–C_3 groups would be removed. The recently published results of Vanderlinde and co-workers[5] in which 4,4′-dihydroxybenzil (II) and *p*-hydroxybenzoic acid were obtained as products of alkaline oxidation of diethylstilbestrol (III) proved that the β- and γ-carbon atoms were indeed removed by alkaline oxidation of such compounds. Furthermore, these results suggested that guaiacyl or syringyl analogs of diethylstilbestrol would be ideal model compounds for lignin oxidation studies. The present paper reports the synthesis of 3,3′-dimethoxydiethylstilbestrol (IV). This compound will be employed as a model compound for lignin and lignosulfonate oxidation studies.

Most syntheses of III comprise a series of reactions of alkoxyphenyl compounds in which the last step consists of the removal of the alkyl group to liberate the desired 4-hydroxyphenyl derivative. Because of the non-specificity of dealkylation of dialkyl ethers of *o*-dihydroxyphenyl compounds, similar syntheses with alkyl ethers of guaiacyl compounds yield mixtures which can be resolved only with great difficulty. Therefore, a search was made for a synthesis employing free phenolic compounds. After failure in attempts at adapting many well-known procedures for the synthesis of III to the use of free guaiacyl compounds, the elegant procedure of Adler, Gie and von Euler[6] was found to be applicable to these compounds for the synthesis of IV.

Propiovanillone (V), obtained by Fries rearrangement of guaiacol propionate or by oxidation of 1-(4-hydroxy-3-methoxyphenyl)-1-propanol was reduced with alkali and either sodium amalgam or sodium–lead alloy to yield the pinacol, α,α′-diethylhydrovanilloin (VI), which could be isolated in either its *meso*- or *dl*-form. The pinacol VI was rearranged with acid to the pinacolone, 4,4-di-(4-hydroxy-3-methoxyphenyl)-3-hexanone (VII), and this pinacolone was reduced with sodium and butanol to give the pinacolone alcohol, 4,4-di-(4-hydroxy-3-methoxyphenyl)-3-hexanol (VIII). Dehydration and retropinacolone rearrangement of the pinacolone alcohol (VIII) by means of aqueous sulfuric acid yielded the desired 3,3′-dimethoxydiethylstilbestrol (IV) as a mixture of *cis* and *trans* isomers which could not be crystallized. Acetylation of the mixture with acetic anhydride and pyridine gave crystalline 3,3′-dimethoxydiethylstilbestrol diacetate (IX). All phenolic compounds were characterized by acetates. IV may serve as an excellent intermediate for the preparation of two other possible lignin model compounds, namely, 3,3′-dimethoxyhexestrol (X) and 3,3′-dimethoxydienestrol (XI). All of these model compounds may have useful physiological properties.

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(1) For paper XI of this series, see *Tappi*, **39**, 171 (1956).

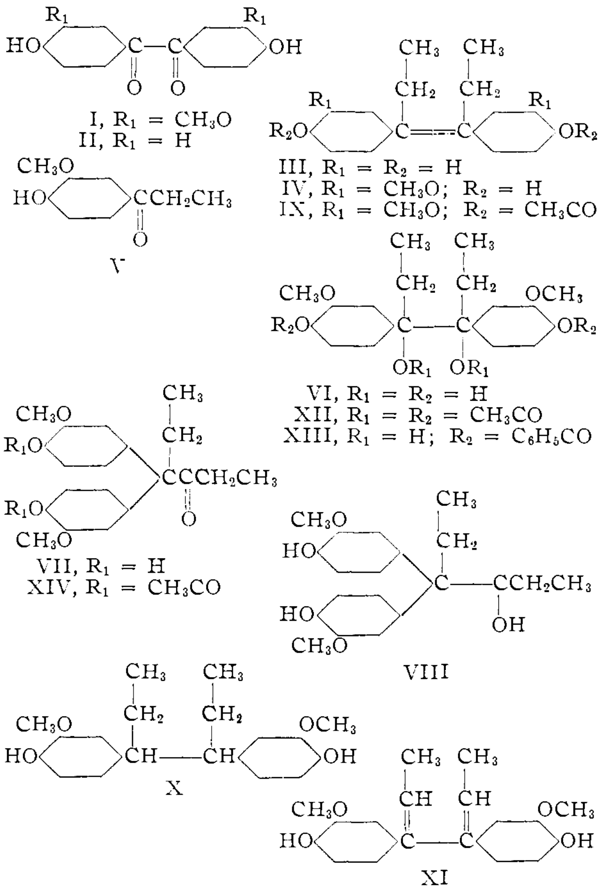
(2) Presented before the Division of Organic Chemistry at the 129th Meeting of the American Chemical Society, Dallas, Texas, April 8 to 13, 1956.

(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) R. E. Vanderlinde, F. D. Vasington and W. W. Westerfeld, *ibid.*, **77**, 4176 (1955).

(6) E. Adler, G. J. Gie and H. von Euler, Swedish Patent 115,816 (Feb. 12. 1946); U. S. Patent 2.421.402 (June 3, 1947).



I, $R_1 = CH_3O$
II, $R_1 = H$

III, $R_1 = R_2 = H$
IV, $R_1 = CH_3O$; $R_2 = H$
IX, $R_1 = CH_3O$; $R_2 = CH_3CO$

V

VI, $R_1 = R_2 = H$
XII, $R_1 = R_2 = CH_3CO$
XIII, $R_1 = H$; $R_2 = C_6H_5CO$

VII, $R_1 = H$
XIV, $R_1 = CH_3CO$

VIII

X

XI

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°.

Propiovanillone (V).—Grignard reaction of vanillin and ethylmagnesium bromide yielded 1-(4-hydroxy-3-methoxyphenyl)-1-propanol,[7] R_f 0.79. A mixture of 18 g. (0.1 mole) of 1-(4-hydroxy-3-methoxyphenyl)-1-propanol and 40 g. (1.0 mole) of sodium hydroxide in 1000 ml. of water was heated to 60° and treated at one time with mechanical stirring with a solution of 34 g. (0.2 mole) of silver nitrate in 500 ml. of water at 60°. After initial reaction, the mixture was heated to boiling under reflux for one hour and filtered hot. The metallic silver precipitate was washed with warm water. The combined filtrate and washings were acidified with sulfur dioxide and extracted with ether, and the ether was dried and distilled to leave 16 g. of heavy oil which crystallized on standing. Recrystallization from petroleum ether (b.r. 30–60°) yielded colorless needles of propiovanillone melting at 62–63° and not depressing the melting point of a mixture with authentic propiovanillone prepared by Fries rearrangement of guaiacol propionate with aluminum chloride in nitrobenzene.[8] The R_f is 0.67.

Reaction of 1-(4-hydroxy-3-methoxyphenyl)-1-propanol with alkaline copper solutions failed to yield V.

α,α′-Diethylhydrovanilloin (VI).—A solution of 100 g. of V and 50 g. of sodium hydroxide in 400 ml. of water was treated with 700 g. of 3% sodium amalgam, stirred 8 hours, and allowed to stand overnight. The dark solution was acidified with sulfur dioxide while maintaining the temperature below 30° by means of outside cooling. On further cooling, the viscous, semi-solid precipitate solidified completely. The solid was washed with water several times by decantation and then dissolved in 1000 ml. of warm benzene. The benzene solution was washed with water and then boiled under a water-separatory head to remove all moisture. On cooling, the benzene solution yielded 24 g. of granular crystals of VI melting at 188–190°. Repeated concentration under reduced pressure of the benzene filtrate and cooling gave additional yields of VI as granular crystals melting from 167–174° to 190–191°. The total yield was 78 g. All crystals appeared to be pure by paper chromatographic methods with R_f 0.91 (R_f 0.83 in 10:3:3 butanol–pyridine–water), and upon repeated crystallization from toluene all batches yielded crystals of VI melting at 190–191°, and having an ultraviolet absorption spectrum with the following maxima: λ_{max} 229 mμ, ε 13690; λ_{max} 280 mμ, ε 5260.

Anal. Calcd. for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.27; H, 7.26.

If the original benzene solution was poured into petroleum ether and allowed to stand, crystals were obtained which melted at 65–70° with gas evolution. These crystals possess the same R_f values and ultraviolet absorption spectrum as does VI, and upon recrystallization from toluene also yield VI melting at 190–191°.

VI was also prepared in lower yield by pinacol reduction of V with 10% sodium-lead alloy and alkali by a modification of the procedure of Breivogel.[9] Electrolytic reduction by the previously employed procedure[10] failed to yield the desired product.

Acetylation of VI with acetic anhydride in pyridine, and recrystallization of the product twice from ethanol yielded white crystals of α,α′-diethylhydrovanilloin tetraacetate (XII) melting at 195–196° and giving the following ultraviolet absorption maximum: λ_{max} 276 mμ, ε 5680.

Anal. Calcd. for $C_{28}H_{34}O_{10}$: C, 63.38; H, 6.46. Found: C, 63.27; H, 6.47.

Benzoylation of VI in alkaline solution with benzoyl chloride, and recrystallization of the product from ethanol gave crystals of α,α′-diethylhydrovanilloin dibenzoate (XIII) melting at 223–224° and having the maxima in its ultraviolet absorption spectrum: λ_{max} 228 mμ, ε 42050; λ_{max} 275 mμ, ε 9310.

Anal. Calcd. for $C_{34}H_{34}O_8$: C, 71.56; H, 6.01. Found: C, 71.26; H, 6.01.

4,4-Di-(4-hydroxy-3-methoxyphenyl)-3-hexanone (VII).—A mixture of 50 g. of VI and 800 ml. of 6 *N* sulfuric acid was boiled under reflux 2 hours and allowed to cool. The resulting resinous solid was washed with water several times by decantation. The R_f was 0.82. All attempts at obtaining crystalline VII from this resinous product failed. However, acetylation of this resinous VII with acetic anhydride in pyridine gave a quantitative yield of its diacetate XIV, which was recrystallized from ethanol to colorless crystals melting at 134–135° and having an ultraviolet absorption spectrum with a maximum λ_{max} 279 mμ, ε 5830.

Anal. Calcd. for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.28; H, 6.70.

Essentially the same yields of VII and XIV were obtained by saturating a mixture of 8 g. of VI and 300 ml. of anhydrous ether with dry hydrogen chloride until a clear solution was obtained and removing the ether under reduced pressure. The resulting resinous solid was washed with water.

3,3′-Dimethoxydiethylstilbestrol (IV).—The washed resinous VII obtained above was not isolated, but was covered directly with 750 ml. of *n*-butyl alcohol. The mixture was boiled under a water-separatory head until all water was removed. The resulting clear solution was boiled under reflux and treated over a period of 2.5 hours with 20 g. of sodium metal while maintaining gentle refluxing. Refluxing was continued another hour, and the mixture was allowed to cool. The cool mixture containing considerable crystalline precipitate was extracted with water, and the water extract was distilled under reduced pressure to remove all butanol. The clear water solution was cooled, and exactly neutralized with dilute sulfuric acid. The resinous precipitate which separated was washed with water by decantation to give an almost quantitative yield of the pinacolone alcohol VIII, which was not isolated but which

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(7) P. C. Roberti, R. F. York and W. S. MacGregor, THIS JOURNAL, **72**, 5760 (1950).

(8) C. E. Coulthard, J. Marshall and F. L. Pyman, *J. Chem. Soc.*, 280 (1930).

(9) P. J. Breivogel, U. S. Patent 2,509,127 (May 23, 1950).

(10) I. A. Pearl, THIS JOURNAL, **74**, 4260 (1952).

was covered directly with 1000 ml. of 6 *N* sulfuric acid and boiled under reflux 3 hours. After cooling, the acid solution was decanted from the resinous solid, and the solid washed with water by decantation. The solid was dissolved in benzene, washed first with sodium bicarbonate solution and then with water, and finally dried by boiling under a water-separatory head. The dry benzene solution was concentrated to dryness under reduced pressure to yield 46 g. of IV as a very viscous light yellow oil which would not solidify and which was probably a mixture of *cis* and *trans* isomers. Paper chromatography indicated only one compound with R_f 0.80 (R_f 0.80 in 10:3:3 butanol–pyridine–water). All attempts at recrystallization failed.

Acetylation of the above non-crystalline IV with acetic anhydride in pyridine gave an almost quantitative yield of its diacetate IX as a crystalline solid, which upon recrystallization from methanol yielded fine white needles of IX melting at 194–195° and fluorescing strongly under ultraviolet light. The ultraviolet absorption spectrum showed a maximum $\lambda_{\max}$ 280 mμ, ϵ 7860.

Anal. Calcd. for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.89; H, 6.88.

Attempted reductions of VII with sodium in boiling ethanol yielded only the starting VII.

Propiovanillone Hydrazone.—A mixture of 40 g. of V, 14 g. of 85% hydrazine hydrate and 50 ml. of isopropyl alcohol was boiled under reflux for 8 hours and cooled. The clear solution was concentrated to dryness under reduced pressure and stirred with benzene. The granular precipitate was filtered and recrystallized from benzene to yield 24 g. of propiovanillone hydrazone melting at 109–110° and having the maxima in its ultraviolet absorption spectrum: $\lambda_{\max}$ 272 mμ, ϵ 11900; $\lambda_{\max}$ 214 mμ, ϵ 17250.

Anal. Calcd. for $C_{10}H_{14}O_2N_2$: N, 14.42. Found: N, 14.54.

Oxidation of this hydrazone to the corresponding diazo compound and decomposition by sulfur dioxide in accordance with the procedure of Gyar[11] failed to produce IV.

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

[11] R. G. V. Gyar, British Patent 526,927 (Sept. 27, 1940).

APPLETON, WISCONSIN

[CONTRIBUTION FROM THE CEREAL CROPS SECTION, NORTHERN UTILIZATION RESEARCH BRANCH[1]]

The Structure of NRRL B-512 Dextran. Methylation Studies[2]

BY J. W. VAN CLEVE, W. C. SCHAEFER AND C. E. RIST

RECEIVED MARCH 9, 1956

Fully methylated NRRL B-512 dextran was completely hydrolyzed by heating in an acetic acid solution containing aqueous hydrochloric acid. The resulting mixture of reducing sugars, on passage through a cellulose column, afforded 2,4-di-*O*-methyl-D-glucose, 2,3,4-tri-*O*-methyl-D-glucose and 2,3,4,6-tetra-*O*-methyl-D-glucose in a molecular ratio of 1:21:1. The proportion of 1,6-linked anhydroglucose units and non-reducing end-groups thus indicated agrees closely with the results obtained through periodate oxidation. The isolation and identification of 2,4-di-*O*-methyl-D-glucose in the products of hydrolysis of the methylated polysaccharide proved that NRRL B-512 dextran contains the unusual 1,3-glucosidic linkage and that this linkage occurs at the branch points.

The dextran produced from sucrose by *Leuconostoc mesenteroides* NRRL B-512[3] has recently gained considerable importance through its use in the manufacture of a synthetic blood-volume expander. Related to its effectiveness for such use is the manner in which the clinical material is metabolized in the human body. As a consequence the chemical structure of the native dextran has been of considerable interest.

Early structural information was provided by periodate oxidation studies[4] which showed that 95% of the anhydroglucose units of this polyglucosan are 1,6-linked residues or non-reducing end-groups. The remaining linkages, the nature of which was not defined, have been assumed to be 1,4[4a] although some evidence has indicated the presence of other linkage types[5] in this dextran.

A more definitive approach to the problem of structure is afforded through methylation studies such as are described in the present paper. We have hydrolyzed a fully methylated sample of NRRL B-512 dextran and have resolved the resulting mixture of reducing sugars into its components by passage through a cellulose column. The methylated sugars so isolated were identified through the preparation of crystalline derivatives. Also, from the molar ratio of the isolated reducing sugars, the average length of the unit chain and the limits of its structural possibilities could be ascertained.

Preliminary examination by paper chromatography of the products of hydrolysis of the trimethyldextran revealed, in addition to the methylated sugars, a number of hydrolytic artifacts. A detailed investigation of the nature of these artifacts and the elaboration of quantitative methods for dealing with them were necessary prerequisites for obtaining structurally accurate results from the separation of the reducing sugars on the cellulose column.

Experimental

All melting points are uncorrected and were determined with a Fisher–Johns melting point apparatus.[6] All evaporations were performed at reduced pressure unless otherwise stated.

Materials and Apparatus. (a) **Chromatography.**—For qualitative chromatography Whatman No. 1 filter paper was used, development being performed in the descending manner. Sugars were detected on developed chromato-

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[1] One of the Branches of the Agricultural Research Service, U. S. Department of Agriculture.

[2] Presented at the 125th meeting of the American Chemical Society, Kansas City, Missouri, March 30, 1954.

[3] The dextran used for the present studies was produced by *Leuconostoc mesenteroides* NRRL B-512F as described by A. Jeanes, C. A. Wilham and J. C. Miers, *J. Biol. Chem.*, **176**, 603 (1948). NRRL B-512F is a substrain which in 1950 supplanted the original strain, NRRL B-512, at the Northern Utilization Research Branch. This substrain is the organism which is used industrially. Since 1950 it has been commonly designated (though inexactly) as NRRL B-512 in numerous publications. This common designation is used throughout the present article. *Cf.* THIS JOURNAL, **76**, 5045 (footnote 27) (1954).

[4] (a) A. Jeanes and C. A. Wilham, *ibid.*, **72**, 2655 (1950); (b) J. C. Rankin and A. Jeanes, *ibid.*, **76**, 4435 (1954).

[5] (a) M. Abdel-Akher, J. K. Hamilton, R. Montgomery and F. Smith, *ibid.*, **74**, 4970 (1952); (b) J. W. Sloan, B. H. Alexander, R. L. Lohmar, I. A. Wolff and C. E. Rist, *ibid.*, **76**, 4429 (1954); (c) S. C. Burket and E. H. Melvin, *Science*, **115**, 516 (1952).

[6] The mention in this article of firm names or commercial products does not constitute an endorsement of such firms or products by the U. S. Department of Agriculture.