

of residual liquid which was taken up in absolute alcohol. Addition to this solution of 5 cc. of a saturated alcoholic solution of picric acid gave a yellow precipitate (m. p. 130–134°) which, after two recrystallizations from absolute alcohol, melted at 147–148°, undepressed when mixed with an authentic sample of morpholine picrate.¹²

Thioformylmorpholine.¹³—A solution of formylmorpholine¹⁴ (34.5 g., 0.30 mole) in benzene (500 cc.) was rapidly stirred as phosphorus pentasulfide (133 g., 0.60 mole) was added portionwise during fifteen minutes. The mixture warmed spontaneously to about 45°. Stirring was continued for one hour and the mixture was allowed to stand at room temperature for two days. The mixture was heated to boiling and filtered hot, the benzene removed under vacuum from the filtrate, and the residue leached with 50 cc. of boiling absolute alcohol. The chilled alcoholic filtrate, on standing overnight, deposited colorless crystals (9.0 g., 23% yield, m. p. 65–68°) which melted at 67.5–68.5° after recrystallization first from ethanol and then from Skellysolve C.

Anal. Calcd. for C₅H₉NOS: N, 10.69; S, 24.43. Found: N, 10.49; S, 24.75.

Alkaline Hydrolysis of (C₅H₈NOS)₂.—A mixture of (C₅H₈NOS)₂ (1.3 g.) and alcoholic potassium hydroxide (7 g. of potassium hydroxide in 21 g. of absolute alcohol) was refluxed three hours and then diluted with an equal volume of water. A slight amount of suspended material was removed by filtration, the filtrate was chilled, and then acidified with hydrochloric acid. The acidic solution was extracted five times with 50-cc. portions of ether, the solvent removed from the combined extract and the residue stirred well with water (5 cc.). This mixture was filtered and the filtrate allowed to evaporate spontaneously, yielding colorless crystals, m. p. 98–100°, undepressed when mixed with an authentic sample of oxalic acid dihydrate.

Oxalodimorpholide.—A mixture of morpholine (89 g., 1.00 mole) and ethyl oxalate (73 g., 0.50 mole) was placed in a 1-liter round-bottomed flask fitted with a six-inch

helices-packed column topped by a still head and downward condenser. The mixture was slowly distilled, the alcohol of reaction being removed as it was formed (only about two-thirds of the theoretical amount was obtained). The still-residue crystallized on cooling and was pressed out on a filter and washed with Skellysolve B. The dry material (m. p. 169–175°) weighed 60 g. (53% yield) and melted at 184–185° after two recrystallizations from acetone.

Anal. Calcd. for C₁₀H₁₆N₂O₄: C, 52.63; H, 7.01; N, 12.28. Found: C, 52.69; H, 6.97; N, 12.31.

Dithiooxalodimorpholide (from Oxalodimorpholide).—A finely ground mixture of oxalodimorpholide (5.7 g., 0.025 mole) and phosphorus pentasulfide (3.4 g., 0.021 mole) was placed in a 50-cc. round-bottomed flask containing a thermometer whose bulb was in the solid mixture. The flask was heated in an oil-bath to 110°, at which temperature a vigorous reaction started and the internal temperature rose rapidly to 250°. The flask was cooled and its cinder-like contents were ground in a mortar and then leached with 1500 cc. of boiling absolute alcohol. The chilled alcoholic filtrate deposited colorless crystals (1.4 g., 22% yield, m. p. 249–250.5°) which after recrystallization from benzene melted at 252–253°, undepressed when mixed with a sample of the material obtained from diisobutylene.

Treatment of oxalodimorpholide with phosphorus pentasulfide and potassium sulfide in xylene¹⁵ failed to give the desired product.

Summary

When the morpholine modification of the Willgerodt reaction is applied to compounds of the type RC(CH₃)=CH₂ there is obtained as a cleavage product a small amount of material of the empirical formula C₅H₈NOS. Degradative hydrolyses and an independent synthesis have shown that this material is dithiooxalodimorpholide.

(15) A fairly general method used by Kindler, *Ann.*, **431**, 187 (1923), for the conversion of amides to thioamides.

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Studies on Lignin and Related Compounds. LXXXIII. Synthesis of 3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone¹

By HERBERT E. FISHER AND HAROLD HIBBERT

In previous reviews on the structure of lignin^{2,3,4} the opinion has been expressed that native lignin is derived, essentially, from a very

(1) Based, in part, on a thesis submitted by H. E. Fisher to the Faculty of Graduate Studies and Research, McGill University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, October, 1943. The preliminary part of this investigation was carried out at the Pulp and Paper Research Institute, McGill University, Montreal. Numerous modifications and improvements resulted from a more extended research carried out by one of us (H. F.) in the Department of Chemistry, University of British Columbia, with funds generously supplied by the senior author (H. H.). The untimely death of the latter interrupted our collaboration before completion of the manuscript for publication.

(2) Hibbert, *Paper Trade J.*, **113**, No. 4, 35 (1941).

(3) Hibbert, *Ann. Rev. Biochem.*, **11**, 183 (1942).

(4) Eastham, Fisher, Kulka and Hibbert, *THIS JOURNAL*, **66**, 26 (1944).

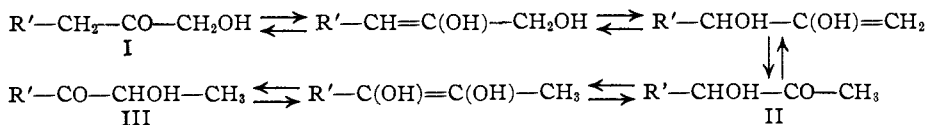
reactive progenitor, β -oxyconiferyl alcohol, R—CH=C(OH)—CH₂OH, this product being the enol form of a keto alcohol, R—CH₂—CO—CH₂OH (R = 4-hydroxy-3-methoxyphenyl).

The veratryl analog has been synthesized,⁵ and after ethanolysis was found to yield the two benzoin ethyl ethers, R'—CHOC₂H₅—CO—CH₃ and R'—CO—CHOC₂H₅—CH₃ (R' = 3,4-dimethoxyphenyl). Considerable evidence has been obtained recently^{6,7} that the parent benzoin II and III may be formed from the veratryl analog of oxyconiferyl alcohol, I, by the following series of reactions

(5) Fisher, Kulka and Hibbert, *ibid.*, **66**, 598 (1944).

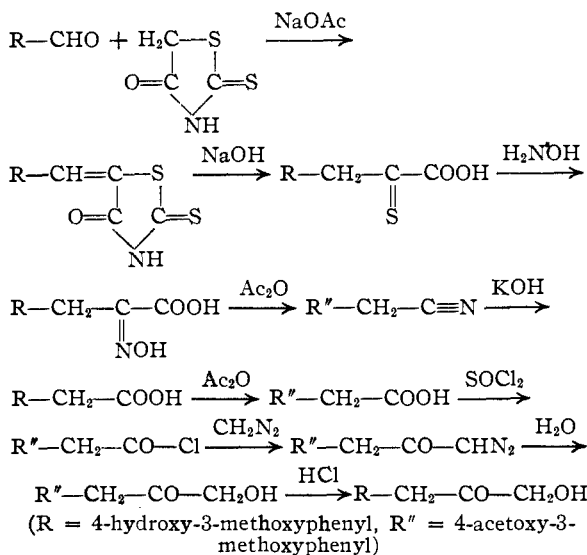
(6) Mitchell and Hibbert, *ibid.*, **66**, 602 (1944).

(7) Gardner and Hibbert, *ibid.*, **66**, 607 (1944).



Similar interconversions were postulated earlier to explain the formation, presumably from oxyconiferyl alcohol, of the corresponding non-methylated benzoin ethyl ethers, isolated from the ethanolysis products of spruce wood.^{8,9} Other products isolated were the diketone R-CO-CO-CH_3 , and the desoxybenzoin $\text{R-CH}_2\text{-CO-CH}_3$. All four of these types of compound were obtained by the ethanolysis of the acetyl derivative, $\text{R}''\text{-CH(OAc)-CO-CH}_3$ ($\text{R}'' = 4\text{-acetoxy-3-methoxyphenyl}$).⁶ This result, together with the above theoretical scheme, would seem to indicate the ready formation of the desoxybenzoin, $\text{R-CH}_2\text{-CO-CH}_3$ and the diketone, R-CO-CO-CH_3 from the keto form of β -oxyconiferyl alcohol, I, which is regarded by Hibbert as the prime progenitor of native lignin. The synthesis of β -oxyconiferyl alcohol described in the present paper renders the substance available for future studies of its behavior on ethanolysis and toward mild acidic and basic reagents.

After much unsuccessful prior experimentation, the synthesis was finally effected by the following series of reactions



The synthesis of homovanillic acid from vanillin was accomplished by adapting the method of Julian and Sturgis.¹⁰ The homoacid was then acetylated to protect the phenolic hydroxyl group in subsequent reactions, and treated with thionyl chloride, followed by diazomethane as in the previous synthesis of the veratryl analog, 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone⁵ (β -oxyconiferyl alcohol, methylated keto form). Treat-

ment of the diazoketone with hot water followed by 0.1 *N* hydrochloric acid yielded the desired product, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone (β -oxyconiferyl alcohol, keto form).

Identification of the new compound was afforded by acetylation with acetyl chloride and pyridine, according to the procedure of Smith and Bryant¹¹ and comparison of melting point and mixed melting point of the semicarbazone of the product with an authentic sample of 3-acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone semicarbazone previously synthesized in these laboratories¹²

Additional proof of structure was afforded by the properties of the semicarbazone of the new ketoI, which differed considerably from those of the semicarbazones of other known isomers of β -oxyconiferyl alcohol.

The keto form of β -oxyconiferyl alcohol is a white, crystalline solid, m. p. 81–82°, with a faint vanillin-like odor. Its semicarbazone, obtained from water in white microcrystals, melts at 147–148°.

Experimental

(I) Synthesis of Homovanillic Acid

A. Vanillal Rhodanine.—Vanillin (100 g.), rhodanine (87.5 g.) and freshly fused sodium acetate (150 g.) were heated at reflux temperature with glacial acetic acid (400 cc.) for forty minutes. The reaction mixture was decanted into distilled water (3000 cc.), stirred for three hours, the product filtered with suction, washed well with water, and dried *in vacuo*; yield was 169.5 g. (97%), m. p. 227–228°; yellow microcrystals from acetone, m. p. 227–228°.

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{O}_3\text{NS}_2$: OCH_3 , 11.7. Found: OCH_3 , 11.7.

B. α -Thioketo- β -4-hydroxy-3-methoxyphenyl Pyruvic Acid.—Vanillal rhodanine (40 g.) was heated at 100° for forty-five minutes with 15% aqueous sodium hydroxide (260 cc.). The dark red solution was cooled to –15° and acidified rapidly by the addition of 10% hydrochloric acid (278 cc.). Crystallization of the product at –15° was complete in thirty minutes, after which time it was filtered with suction, washed well with water, and dried *in vacuo*; Yield of pale yellow product was 34.0 g. (100%), m. p. 153–155°. Recrystallization from methanol gave yellow crystals, m. p. 157–158°.

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_4\text{S}$: OCH_3 , 13.7. Found: OCH_3 , 13.7.

C. α -Oximino- β -4-hydroxy-3-methoxyphenyl Pyruvic Acid.—Hydroxylamine hydrochloride (48 g.) in water (43 cc.) was treated with sodium (17.5 g.) in anhydrous ethanol (450 cc.). After filtration of inorganic material, the free base was added to the thioketo acid (50 g.) and the mixture refluxed sixty minutes on a steam-bath. After removal of solvent under reduced pressure (carbon dioxide) below 50° the residue was dissolved in 5% aqueous sodium hydroxide (380 cc.), filtered through sintered glass, cooled to –15° and acidified with 10% hydrochloric acid (360 cc.). On scratching the vessel, the oximino acid crystallized in colorless plates. The product was washed

(8) Cramer, Hunter and Hibbert, *THIS JOURNAL*, **61**, 509 (1939).

(9) West, MacInnes and Hibbert, *ibid.*, **65**, 1187 (1943).

(10) Julian and Sturgis, *ibid.*, **87**, 1126 (1935).

(11) Smith and Bryant, *ibid.*, **57**, 61 (1935).

(12) Kulka and Hibbert, unpublished results.

with water and dried *in vacuo*; yield was 49.5 g. (100%); recrystallized from water, m. p. 138–139°.

Anal. Calcd. for $C_{10}H_{11}O_5N$: OCH_3 , 13.8. Found: OCH_3 , 13.8.

D. Acetylhomovanillonitrile.— α -Oximino- β -4-hydroxy-3-methoxy-phenylpyruvic acid (51.5 g.) was warmed gently with acetic anhydride (220 cc.) until solution was complete and evolution of carbon dioxide had ceased, then refluxed in an all-glass apparatus fitted with a calcium chloride drying tube for an additional two hours. Excess acetic anhydride was removed by distillation under reduced pressure, and the residue dissolved in benzene (800 cc.), the benzene solution washed with water, 1% aqueous sodium bicarbonate, again with water, and dried over anhydrous sodium sulfate. After removal of solvent under reduced pressure, the residue was distilled at 200–220° bath temperature and 15 mm. pressure. The product (39.7 g., 84.5%) solidified quickly to a white crystalline material, m. p. 51–52°. Hahn and Schales¹³ give 52° as the melting point of acetylhomovanillonitrile.

E. Homovanillic Acid.—Acetylhomovanillonitrile (18 g.) was refluxed twelve hours with potassium hydroxide (27 g.), water (161 cc.) and ethanol (180 cc.). The reaction product was concentrated to remove ethanol, cooled and acidified with dilute (1:1) hydrochloric acid (115 cc.). Crystallization was completed at 0°, yielding the white crystalline product which was washed with a small amount of ethanol and dried *in vacuo*; yield was 14.1 g. (88%), m. p. 142–143° (homovanillic acid melts at 143° according to Hahn and Schales.¹³)

(II) Synthesis of β -Oxyconiferyl Alcohol

A. Acetylhomovanillic Acid.—Homovanillic acid (25 g.) was refluxed with acetic anhydride (150 cc.) in an all-glass apparatus for six hours. The solution was decanted into distilled water (1600 cc.), and stirred for two hours, following which the solution was filtered, and the filtrate concentrated to dryness under reduced pressure. The residue crystallized from hot water (400 cc.), in white plates, m. p. 139–140°. Yield was 25.5 g. (83%) (Tiemann and Nagai¹⁴ report 140° to be the melting point of acetylhomovanillic acid).

B. Acetylhomovanilloyl Chloride.—Acetylhomovanillic acid (25.0 g.) was refluxed gently in an all-glass apparatus with freshly purified thionyl chloride¹⁵ (50 cc.) for sixty minutes. Four 25-cc. portions of benzene were then added successively and distilled off to remove the last traces of thionyl chloride, leaving a reddish oil weighing 27 g. (100%).

C. Acetylhomovanilloyl Diazomethane.—Acetylhomovanilloyl chloride (27 g.) was dissolved in benzene (50 cc.) and added slowly, with stirring at 0°, to a solution of diazomethane (from 55 g. nitrosomethyl urea) in dry ether (550 cc.). The solution was allowed to warm slowly to room temperature and to react overnight. Removal of the solvents under reduced pressure (carbon dioxide) below 50° left a reddish oil weighing 27.5 g. (100%).

D. 3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone.—Acetylhomovanilloyl diazomethane (27.5 g.) was dissolved in chloroform (40 cc.) and added to hot water (850 cc.) in a 3-necked flask fitted with a stirrer and thermometer. The mixture was heated on a steam-bath at 94° with vigorous mechanical stirring for four hours, after which period concentrated hydrochloric acid (7.5 cc.) was added to bring the solution to pH 1, and stirring and heating continued for an additional two hours. One-half hour before the conclusion of the second reaction period charcoal was added to decolorize the solution. At the end of the final period the hot solution was filtered, cooled to room temperature, and extracted with ten 75-cc. portions of chloroform. The extract was filtered through dry paper, then dried overnight over anhydrous sodium sulfate.

(13) Hahn and Schales, *Ber.*, **67**, 1486 (1934).

(14) Tiemann and Nagai, *ibid.*, **10**, 201 (1877).

(15) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 331.

The solution was filtered, the solvent removed under reduced pressure on a water-bath below 50°, and two small portions of dry chloroform added and distilled off under reduced pressure to dry the product completely. On removal of the final portion of chloroform, the product crystallized spontaneously, after which it was recrystallized from benzene, filtered with suction on a glass nail filter, dried first by suction, then in an Abderhalden drier for two hours at 61°; weight of first product, 10.35 g., m. p. 81–82°.

Concentration of the aqueous 0.1 *N* solution, which had been chloroform extracted, to 200 cc. under reduced pressure below 50°, followed by an additional ten chloroform extractions and working up the product as before yielded an additional 4.80 g. pure product, m. p. 81–82°. Total crystalline product obtained from 25 g. acetylhomovanillic acid was 15.15 g. (69% over four steps, average 90.6% per step), m. p. 81–82°.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.1; OCH_3 , 15.8. Found: C, 61.1; H, 6.2; OCH_3 , 15.8.

Semicarbazone of β -oxyconiferyl alcohol gave white needles from water, m. p. 147–148°.

Anal. Calcd. for $C_{11}H_{15}O_4N_3$: C, 52.2; H, 5.9; OCH_3 , 12.3. Found: C, 52.4; H, 5.9; OCH_3 , 12.2.

(III) Characterization of β -Oxyconiferyl Alcohol

Acetylation.—Pyridine (12 cc.) was added slowly, with shaking and cooling, to a solution of acetyl chloride (7.7 g.) in toluene (60 cc.). Crystalline β -oxyconiferyl alcohol (0.450 g.) was heated with this mixture, in a sealed flask, at 60° for forty-five minutes. After cooling, the reaction mixture was decomposed by the addition of distilled water (80 cc.), the toluene layer separated, washed twice with water, dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. Distillation of the residual oil at 180–185° bath temperature and 0.15 mm. pressure yielded a yellow viscous oil weighing 0.580 g. (91%), n_D^{25} 1.5150. The refractive index of a previously prepared sample¹² of 3-acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone, synthesized by the method used for its veratryl analog¹ was n_D^{25} 1.5150. The oil (0.20 g.) was dissolved in ethanol (3 cc.) and semicarbazide hydrochloride (0.2 g.) and potassium acetate (0.2 g.) in water (7 cc.) added. The resulting solution was heated at 60° for sixty minutes, cooled, the ethanol removed under reduced pressure and the solution allowed to crystallize at room temperature. After three hours the product was filtered, washed with water, dried by suction, then in an Abderhalden overnight at 61°. Weight of derivative was 0.20 g. (83%), m. p. 143–144°. Recrystallization from ethanol-petroleum ether raised the melting point to 144–145°. A mixed melting point determination with a previously prepared authentic sample¹² of 3-acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone semicarbazone (m. p. 144–145°) showed no depression.

In view of the high yields obtained in this experiment, it was considered to offer conclusive proof of the identity of the new compound as β -oxyconiferyl alcohol.

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Summary

The synthesis of a new compound, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone, (keto form of β -oxyconiferyl alcohol), thought to be the prime lignin progenitor, has been described and some of its derivatives investigated.