

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

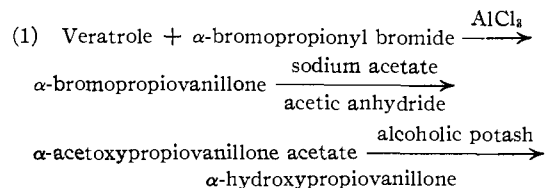
Studies on Lignin and Related Compounds. XLV. Synthesis and Properties of α -Hydroxypropiovanillone

BY A. B. CRAMER¹ AND HAROLD HIBBERT

In a previous communication the isolation of α -ethoxypropiovanillone from the ethanolysis products of spruce² and of maple woods³ was described. The relation of these to the corresponding hydroxy derivatives in connection with the role of the latter as the possible precursors of lignin has been discussed in a comprehensive manner by Hibbert⁴ in a recent paper.

The present communication deals with the synthesis and properties of α -hydroxypropiovanillone.

This synthesis was carried out by the following series of reactions



Reaction (1), which is based on the synthesis of α -bromoacetovanillone,⁵ is of interest in that condensation and demethylation occur simultaneously.

α -Bromopropiovanillone is a colorless, crystalline product (m. p. 105–106°), which on prolonged heating with organic solvents (such as petroleum ether), in which it is only slightly soluble, undergoes conversion to tarry materials. This did not occur with solvents such as ethanol in which it is readily soluble, so that its purification entailed considerable experimentation; yield 35%. Its conversion into the crystalline diacetate (m. p. 122–123°) in yield of 84% takes place quite smoothly. This acetate, on treatment with alcoholic potassium hydroxide, gives almost the theoretical yield (92%) of crystalline α -hydroxypropiovanillone, m. p. 109–110°.

Properties of α -Hydroxypropiovanillone.—The secondary hydroxyl group present in the side chain has certain rather remarkable properties.

(1) Postgraduate Student and holder of a Hibbert-Cole Scholarship.

(2) (a) Cramer, Hunter and Hibbert, *THIS JOURNAL*, **61**, 509 (1939); (b) Brickman, Pyle, McCarthy and Hibbert, *ibid.*, **61**, 868 (1939).

(3) Hunter, Cramer and Hibbert, *ibid.*, **61**, 516 (1939).

(4) Hibbert, *ibid.*, **61**, 725 (1939).

(5) Doig and Robertson, *J. Chem. Soc.*, **123**, 750 (1923).

Thus it is etherified, as in the case of benzoin,⁶ by ethanol-hydrogen chloride, but does not react with diazomethane. The carbonyl group, due to its location *para* to the phenol group, shows similar abnormal properties to those possessed by related substances,⁷ such as *p*-oxybenzaldehyde, vanillin and certain syringyl derivatives. Thus in the Grignard machine⁸ the amounts of active hydrogen and carbonyl addition, 1.75 and 0.75 moles, respectively (based on a molecular weight of 196), are much smaller than the theoretical values 2.0 and 1.0, respectively.

Action of Acids.— α -Hydroxypropiovanillone exhibits a similar, reactive behavior, on treatment with acids, to that shown by various benzoin.⁹ When it is refluxed with dilute sulfuric acid (5%), methanol-hydrochloric acid or formic acid, amorphous lignin-like products are formed. The carbon content of these derivatives is high, namely, 70–70.3% as compared with values of 63.6–67% found for "extracted lignins."¹⁰ Whether this is due to the presence of carbohydrate condensation products in the customarily "extracted" lignins or to a different type of polymerization-condensation reaction taking place in the plant, as compared with that brought about by acids,¹⁰ can only be decided after considerable further experimentation.

It is of interest, however, that the analytical values for a condensation, furan trimer (A) of α -hydroxypropiovanillone, of the type shown below, are in agreement with the theoretical figures for the formic acid polymer. No great significance can, however, be attached to this until a more complete investigation (now in progress) has been completed.

The similarity, however, between (A) and the furan trimer (B) obtained by Japp and Meldrum¹¹

(6) E. Fischer, *Ber.*, **26**, 2413 (1893).

(7) (a) Lock, *ibid.*, **61**, 2234 (1928); **62**, 1177 (1929); (b) Lief, Wright and Hibbert, *THIS JOURNAL*, **61**, 865 (1939); (c) Hunter and Hibbert, *ibid.*, **61**, 2190 (1939).

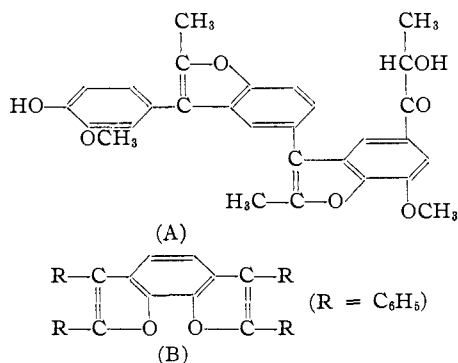
(8) Kohler, Fuson and Stone, *ibid.*, **49**, 3181 (1927); Kohler and Richtmyer, *ibid.*, **52**, 3736 (1930).

(9) Irvine and McNicol, *J. Chem. Soc.*, **93**, 950, 1609 (1908).

(10) Freudenberg, "Tannin, Cellulose, Lignin," Verlag von Julius Springer, Berlin, 1933, p. 118; Freudenberg, Zocher and Dürr, *Ber.*, **62**, 1816 (1929).

(11) Japp and Meldrum, *J. Chem. Soc.*, **75**, 1037 (1890).

by heating a mixture of benzoin and pyrocatechol with sulfuric acid (73%) is noteworthy.



Experimental Part

I. Synthesis of α -Hydroxypropiovanillone

Step 1. Preparation of α -Bromopropiovanillone.—Aluminum chloride (Merck) (40 g.) was added to carbon disulfide (150 cc.) in a 3-necked flask fitted with stirrer, dropping funnel and condenser. Veratrole (40 g.) was added rapidly at room temperature through the dropping funnel over a period of twenty-five minutes, the solution being stirred vigorously. When the reaction had subsided, α -bromopropionyl bromide (66 g.) was added slowly (during sixty minutes) to the mixture, and a further 40 g. of aluminum chloride then added in small portions (during sixty minutes). After stirring vigorously for a further thirty minutes the mixture was allowed to stand overnight. The carbon disulfide was decanted, and the product decomposed with ice and concentrated hydrochloric acid. The crude, oily bromo compound was washed by stirring repeatedly with dilute hydrochloric acid followed by water, dilute sodium bicarbonate, and finally water. This crude moist product was dissolved in ether, and the solvent removed slowly from the solution, in an open dish, by drawing a stream of air over the surface. Crystals formed around the edges of the dish and were stirred into the main body of the product. The thick sirup on standing for a short time changed to a sticky granular mass. This was filtered and washed with a small amount of petroleum ether, leaving a comparatively pure bromo derivative. The filtrate was concentrated similarly by slow evaporation and again filtered, giving a second crop of crude α -bromopropiovanillone; yield of relatively pure α -bromopropiovanillone obtained from three crops of crystals was 35%.

A small amount was purified for analysis by recrystallization from a chloroform-petroleum ether mixture (1:3); m. p. 105–106°.

Anal. Calcd. for C₉H₉O₂Br(OCH₃): C, 46.4; H, 4.24; Br, 30.9; OCH₃, 11.9. Found: C, 46.3; H, 4.40; Br, 31.2; OCH₃, 12.1.

Step 2. Preparation of α -Acetoxypropiovanillone Acetate.—Crude α -bromopropiovanillone (70 g.), anhydrous sodium acetate (140 g.) and acetic anhydride (490 cc.) were mixed in a one-liter flask and heated on the steam-bath for four hours. The mixture was then poured into five liters of water and stirred vigorously for four hours.

The resulting oil crystallized rapidly and was filtered off, washed thoroughly with water, pressed dry on the Büchner funnel, and recrystallized from alcohol; yield 60 g. (84%); m. p. 122–123°.

Anal. Calcd. for C₁₂H₁₃O₅(OCH₃): C, 60.0; H, 5.72; OCH₃, 11.05. Found: C, 59.8; H, 5.90; OCH₃, 11.08.

Step 3. Hydrolysis of α -Hydroxypropiovanillone Acetate.—The diacetate (54 g.) was dissolved in hot methanol (500 cc.) and a solution of potassium hydroxide (54 g.) in hot methanol (540 cc.) added. The mixture was warmed on the steam-bath for fifteen minutes and then cooled. On allowing to stand several hours the crystalline potassium salt of α -hydroxypropiovanillone settled out and was filtered off. Concentration of the filtrate gave a further crop of crystals.

The combined potassium salts were dissolved in 125 cc. of warm water and a slight excess of sulfuric acid (30–40%) added. The heavy oil which separated from the warm solution crystallized completely on scratching the sides of the flask. The reaction mixture was cooled to about 0° and filtered. The crystalline mass was washed several times with ice water, filtered, and dried in a vacuum desiccator; yield 34 g. (92%); m. p. 101°; recrystallized from benzene, m. p. 109–110°.

Anal. Calcd. for C₉H₉O₃(OCH₃): C, 61.2; H, 6.12; OCH₃, 15.8. Found: C, 61.0; H, 6.21; OCH₃, 15.7.

II. Properties of α -Hydroxypropiovanillone

(1) **Etherification.**— α -Hydroxypropiovanillone (2 g.) was dissolved in absolute ethanol (50 cc.) containing 0.5% dry hydrogen chloride. The solution was allowed to stand at room temperature for seventy-two hours during which time it became dark brown in color. It was then refluxed for six hours and the solvent removed, leaving a black tarry residue. An attempt to isolate a pure ethoxy derivative from this by solvent extraction with boiling petroleum ether (60–70°) was unsuccessful. The product was therefore freed from the last traces of solvent at 100° (30 mm.) and distilled at 125–140° (0.005 mm.). There were obtained a clear, yellow, non-crystallizable sirup (0.6 g.) and a black tarry undistillable residue. Analysis indicated the former product to be α -ethoxypropiovanillone. The slightly lower alkoxy, carbon and hydrogen values are due presumably to the presence of a small amount of unetherified product which it was not found possible to remove by a subsequent distillation or crystallization.

Anal. Calcd. for C₁₂H₁₅O₄: C, 69.3; H, 7.79; alkoxy calculated as methoxy, 29.8. Found: C, 68.5; H, 7.20; alkoxy calculated as methoxy, 28.9.

(2) **Methylation with Diazomethane.**— α -Hydroxypropiovanillone (1 g.) was dissolved in ether (100 cc.) and to this an ethereal solution containing two equivalents of diazomethane was then added. The mixture was allowed to stand overnight, filtered from the diazomethane polymer and the ether removed. The product on distillation (130–150° (0.010 mm.)) yielded a clear yellowish-colored, highly viscous sirup which could not be caused to crystallize. Calcd. for C₉H₉O₂(OCH₃)₂: OCH₃, 28.5. Found: OCH₃, 28.1.

(3) **Grignard Analysis.**—Calcd. for α -hydroxypropiovanillone: active hydrogen 2.0 moles; carbonyl addition

1.0 moles, per molecular weight of 196. Found: 1.75 and 0.75, respectively.

(4) **Action of Acids on α -Hydroxypropiovanillone**

(a) **Sulfuric Acid (5%).**— α -Hydroxypropiovanillone (1 g.) was refluxed with 50 cc. of sulfuric acid (5%) for twenty-four hours. The resulting dark brown insoluble material was filtered, washed with water, dissolved in acetone (10 cc.) and precipitated into water (200 cc.). The flocculent precipitate was centrifuged, the liquors discarded and the product dried in the vacuum desiccator. It was redissolved in chloroform (10 cc.) and reprecipitated into petroleum ether (b. p. 60–70°) (200 cc.). The centrifuged material was stirred with petroleum ether (b. p. 30–50°), centrifuged and dried in the vacuum desiccator; yield 0.25 g. (25%). The light brown amorphous product was soluble in alkali. *Anal.* Found: C, 70.0; H, 4.94; OCH₃, 17.1.

(b) **Methanolic Hydrogen Chloride.**— α -Hydroxypropiovanillone (1 g.) treated similarly with a 5% solution of anhydrous hydrogen chloride in methanol (20 cc.) gave a similar dark colored, alkali-soluble, amorphous product; yield, 31%. *Anal.* Found: C, 70.3; H, 4.96; OCH₃, 20.6.

(c) **Formic Acid (95%).**— α -Hydroxypropiovanillone (1 g.) was treated in the same manner with 95% formic acid (20 cc.). The dark colored, alkali-soluble reaction product was purified similarly. *Anal.* Found: C, 70.0; H, 5.86; OCH₃, 17.3. A condensation trimer of type (A), C₂₇H₂₁O₅(OCH₃)₃ (mol. wt. 518) requires C, 69.5; H, 5.8; OCH₃, 17.9.

Acknowledgment.—The authors wish to thank the Carnegie Corporation of New York for kind financial assistance.

Summary

1. A description is given of the synthesis of α -hydroxypropiovanillone, a possible precursor of lignin, and of its behavior toward diazomethane and the Grignard reagent.

2. Hot dilute sulfuric acid, methanol-hydrochloric acid and formic acid (95%) convert it into alkali-soluble, lignin-like products.

MONTREAL, CANADA

RECEIVED JUNE 20, 1939

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY, HARVARD UNIVERSITY]

Synthesis of Quinones Related to Vitamins K₁ and K₂

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In a recent Communication⁴ we advanced structural formulas for the antihemorrhagic vitamins which Doisy and co-workers⁵ isolated in a condition of demonstrated purity, and there are now further indications that our conception of the structures is essentially correct. Of particular importance is the degradative work on vitamin K₁ by the Doisy group,⁶ reported in a Communication submitted about the same time as ours.

Since the evidence from the degradations is still incomplete and in some points uncertain, we shall include in the present paper a fuller account of the previous deductions and report certain observations of significance made in a study of synthetic model substances.

Following Doisy's report of the quinonoid character of vitamins K₁ and K₂, Dr. R. N. Jones

(1) Squibb Research Fellow.

(2) Du Pont Research Fellow.

(3) We are indebted to Mary Fieser and Marshall D. Gates, Jr., for the participation in the synthetic work indicated in the Experimental Part and to Dr. R. Norman Jones and Douglas M. Bowen for the determination of the absorption spectra.

(4) Fieser, Bowen, Campbell, M. Fieser, Fry, Jones, Riegel, Schweitzer and Smith, *THIS JOURNAL*, **61**, 1925 (1939).

(5) (a) McKee, Binkley, MacCorquodale, Thayer and Doisy, *ibid.*, **61**, 1295 (1939); (b) Binkley, MacCorquodale, Cheney, Thayer, McKee and Doisy, *ibid.*, **61**, 1613 (1939).

(6) MacCorquodale, Binkley, Thayer and Doisy, *ibid.*, **61**, 1928 (1939).

pointed out to us that in absorption spectra^{5,7} the substances resemble 1,4-naphthoquinones more closely than quinones of other series. Such a structure would account for the known lability to light,^{8,9} heat,^{5a} and alkali,⁷ for the yellow color and for the sensitivity of the hydroquinones to air oxidation.^{5b} Anthraquinones possess the last-named property but are far more stable substances. The next clue was the resistance of the dihydro vitamin diacetates to alkaline hydrolysis,^{5b} which suggested the presence of hindering substituents in the 2 and 3 positions adjacent to the acetoxy¹ groups, and an entirely analogous behavior has been encountered in 2,3-diallyl-1,4-naphthohydroquinone diacetate. Hindering substituents are also indicated by the failure of vitamin K₁ concentrates to react with carbonyl reagents.^{10,11} From these considerations it seemed

(7) Dam, Geiger, Glavind, P. Karrer, W. Karrer, Rothschild and Solomon, *Helv. Chim. Acta*, **22**, 310 (1939).

(8) Almquist, *J. Biol. Chem.*, **117**, 517 (1937); **120**, 635 (1937).

(9) MacCorquodale, Binkley, McKee, Thayer and Doisy, *Proc. Soc. Exptl. Biol. Med.*, **40**, 482 (1939).

(10) Klose, Almquist and Mecchi, *J. Biol. Chem.*, **125**, 681 (1938). These investigators observed that the antihemorrhagic activity is not destroyed by reduction and concluded that the vitamin is inert to reducing agents, but it is now evident that reoxidation could have occurred before the test was made.

(11) Riegel, Schweitzer and Smith, in press (personal communication from Dr. Riegel).