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(Synthesis & Reactions of Model Compounds)  
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# PROJECT REPORT FORM

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Irwin A. Pearl

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Notebook 1294  
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## PREPARATION OF SEVERAL LIGNIN MODEL COMPOUNDS IN THE $C_6-C_3$ SERIES

In connection with our studies on the isolation of pure compounds from lignin oxidation mixtures and from wood extractives and from other reactions of wood it was desired to have on hand a number of compounds which might be found in such mixtures. The present report records the synthesis of a number of such compounds in the para-hydroxyphenyl, guaiacyl, and syringyl series having three carbon side chains. In some instances the syntheses are complete, and in other cases the syntheses are continuing and only some of the intermediates are reported herein.

The first synthesis was that of coniferyl alcohol, a compound which has been synthesized by lithium aluminum hydride reduction of ethyl acetyl ferulate (1). Ferulic acid was prepared by condensing vanillin with malonic acid in the presence of piperidine as described in Progress Report Fifteen in Project 809.

ETHYL FERULATE--A mixture of 200 grams of ferulic acid, 1000 ml. of absolute ethanol, and 40 ml. of concentrated sulfuric acid was heated to boiling under reflux for 7 hours and allowed to cool overnight. The reaction mixture was concentrated under reduced pressure to about 500 ml. and then stirred into 2 gallons of water. The mixture was neutralized with a slurry of sodium bicarbonate and extracted with ether. The ether was dried with sodium sulfate and distilled, finally under reduced pressure to yield 258

grams of crude ester. The crude product, which crystallized on standing, was distilled in vacuum as a very viscous light yellow oil boiling at 165° at 0.2 mm. and crystallized on cooling. The yield was 210 grams.

ETHYL ACETYLFERULATE--A mixture of 210 grams of ethyl ferulate, 600 ml. of pyridine, and 400 ml. of acetic anhydride was allowed to stand at room temperature for 48 hours. The colorless solution containing white needles in suspension was stirred into 7 liters of ice-water mixture. The white crystalline precipitate was filtered, washed with cold dilute hydrochloric acid, and then with water. The precipitate was dried to yield 232 grams of white crystals melting at 120-121° which upon recrystallization from ethanol melted at 122-123°. Kratzl and Billek (2) reported a melting point of 122-123° for ethyl acetylferulate.

CONIFERYL ALCOHOL--A mixture of 2.5 grams (0.0658 mole) of lithium aluminum hydride and 400 ml. of dry ether in a 2-liter 3-neck flask fitted with a reflux condenser, mechanical mercury-sealed stirrer, calcium chloride tube, dropping funnel, nitrogen inlet, and thermometer was subjected to nitrogen gas. The flask was placed in a dry ice-acetone bath and the contents were cooled to -15°. A solution of 9 grams (0.034 mole) of ethyl acetylferulate in 700 ml. of dry ether was added over a period of 2 hours with stirring under nitrogen, maintaining the temperature below -10°. The reaction mixture was stirred cold for another 2 hours, then allowed to warm to room temperature with stirring, and finally allowed to stand overnight without stirring. The mixture was filtered, and the white and yellow precipitate was washed with 200 ml. of dry ether. The precipitate was then added gradually

to a solution of 5 grams of ammonium carbonate monohydrate in 250 ml. of water covered with 100 ml. of ether. The ether was separated, and the aqueous layer was extracted with two 100 ml. portions of ether. The combined ether solutions were evaporated to 50 ml. and diluted with 750 ml. of petroleum ether (b.r. 30-75°) with vigorous shaking. The turbid solution deposited some oil and white crystals. The crystals were filtered and washed with petroleum ether to give white needles of pure coniferyl alcohol melting at 72-73°. The oil was dissolved in ether, added to the petroleum ether filtrate, and returned to the freezer to give another crop of oil and crystals. A total of 4.8 grams of pure coniferyl alcohol was obtained in this manner from 6 batches of crystals. The final oily precipitate was dissolved in 8% sodium hydroxide solution and treated with stirring with an excess of benzoyl chloride. The precipitate was filtered and recrystallized from ethanol to yield crystals of 4-benzoyloxy-3-methoxycinnamyl alcohol melting at 61-63°. Coniferyl alcohol has also been prepared by reduction of acetyl ferulic acid chloride with lithium aluminum hydride at room temperature (2).

The next synthesis was that of dihydroconiferyl alcohol, a compound which has been isolated recently from coniferous spent sulfite liquor (3). The procedure used was a modification of that recently employed by Granath and Schuerch (4).

ETHYL ACETYLDIHYDROFERULATE--A solution of 13.2 grams (0.05 mole) of ethyl acetylferulate in 150 ml. of warm glacial acetic acid was treated with 0.1 gram of platinum oxide and subjected to hydrogenation at an initial pressure of 49 p.s.i. A total of 0.28 mole of hydrogen was absorbed. The reaction mixture was filtered, and the filtrate was stirred into 800 ml. of

cracked ice. The white crystalline precipitate which separated was filtered in the presence of ice, washed with water and dried on porous plate to give 11.7 grams of ethyl dihydroferulate melting at 44-45°. Granath and Schuerch recorded 45-46.5° as the melting point for ethyl dihydroferulate.

DIHYDROCONIFERYL ALCOHOL--The apparatus employed in this experiment was that used above for the lithium aluminum hydride reduction of ethyl acetylferulate. A mixture of 5 grams of lithium aluminum hydride and 800 ml. of anhydrous ether was placed in the apparatus and treated under nitrogen with stirring with a solution of 6 grams of ethyl acetyldihydroferulate in 200 ml. of dry ether over a period of 90 minutes while maintaining the temperature below 10°. The mixture was stirred an additional 4 hours while warming to room temperature, and allowed to stand overnight without stirring. The mixture was filtered, and the precipitate was washed with anhydrous ether. The washed precipitate was added gradually to a solution of 10 grams of ammonium carbonate in 500 ml. of water overlaid with 200 ml. of ether. The ether was separated, and the aqueous solution was extracted twice with ether. The combined ether solutions were dried with anhydrous sodium sulfate and distilled to leave 5.5 grams of dihydroconiferyl alcohol as a cloudy colorless oil with index of refraction  $n_D^{27}$  1.5452. Granath and Schuerch (4) record an index of refraction  $n_D^{25}$  1.5543. The benzoate was prepared as before and recrystallized from ethanol and then from petroleum ether (b.r. 60-110°) to give white needles of 4-benzoxo-3-methoxydihydrocinnamyl alcohol melting at 58-59°.

An attempt was also made to prepare dihydroconiferyl alcohol from ethyl acetylferulate directly by reduction with sodium and ethanol. A mixture of 26.4 grams (0.1 mole) of ethyl acetylferulate and 1000 ml. of anhydrous methanol was placed in a 2-liter flask fitted with a reflux condenser. Over a period of two hours this mixture was treated with 23 grams (1.0 mole) of sodium metal in small pieces. As the sodium was added, the solution became yellow, and the suspended crystals gradually dissolved. A clear yellow solution resulted by the time all the sodium had been added. The clear solution was heated to boiling under reflux, and a yellow granular precipitate began to separate. Water (500 ml.) was added, and refluxing was continued for one hour, after which the mixture was allowed to stand overnight. The reaction mixture was concentrated under reduced pressure to remove the ethanol, and the volume was maintained with water. After all the ethanol was removed, the solution was cooled, saturated with carbon dioxide and extracted with ether. The ether was dried and distilled to yield crude dihydroconiferyl alcohol as a viscous colorless oil which was benzoylated to give 4-benzoxy-3-methoxydihydrocinnamyl alcohol melting at 58-59° and not depressing a mixed melting point with the product prepared above by the lithium aluminum hydride reduction of ethyl acetyldihydroferulate. The carbonated solution yielded 14 grams of ferulic acid on acidification.

DIHYDROFERULIC ACID--A few grams of ethyl acetyldihydroferulate were suspended in an excess of 4% sodium hydroxide solution, treated with a few ml. of methanol, and boiled at atmospheric pressure. A clear solution resulted after 15 minutes. After 30 minutes, the solution was cooled,

acidified with dilute hydrochloric and concentrated somewhat. An oil separated upon cooling, and after standing, the oil solidified. The solidified oil was recrystallized from water to give needles melting at 88-89° which corresponds with the melting point recorded by Tiemann and Nagai (5) for dihydroferulic acid which they prepared by reduction of ferulic acid with excess sodium amalgam.

It was next desired to prepare the p-hydroxyphenyl and syringyl analogs of the above compounds because of the possibility of finding such compounds in aspenwood reactions.

COUMARIC ACID--This compound was prepared by the procedure employed earlier for ferulic acid. A mixture of 244 grams (2.0 moles) p-hydroxybenzaldehyde, 460 grams (4.4 moles) malonic acid, 20 grams of piperidine, and 1000 ml. of pyridine was shaken and allowed to stand at room temperature for 3 weeks. The mixture was poured with stirring into 2000 grams of cracked ice and 1200 ml. of concentrated hydrochloric acid. The fine white precipitate was filtered, washed first with dilute hydrochloric acid and then with water, and air dried to yield 300 grams of crude coumaric acid melting at 179-182°. Recrystallization from water yielded white crystals melting sharply at 220-221° with gas evolution. A number of authors have prepared coumaric acid in the past (6), but all melting points recorded for the material are below 210°.

ETHYL COUMARATE--A mixture of 100 grams of coumaric acid, 500 ml. of absolute ethanol and 20 ml. of concentrated sulfuric acid was heated to

boiling under reflux for 7 hours and allowed to cool overnight. The mixture was concentrated under reduced pressure to about 200 ml. and stirred into 3 liters of ice and water. The acid solution was neutralized with excess slurry of sodium bicarbonate, and the solidified precipitate was filtered and washed with water. Air drying yielded 126 grams of crude ethyl coumarate which was recrystallized from petroleum ether to give crystals melting at 74-75°. Freudenberg and Gehrke (7) recorded a melting point of 83° for ethyl coumarate.

ETHYL ACETYLCOUMARATE--A mixture of 60 grams of ethyl coumarate, 200 ml. of pyridine and 150 ml. of acetic anhydride was allowed to stand 48 hours at room temperature and then stirred into 2 liters of mixed ice and water. The precipitate was filtered, washed first with cold dilute hydrochloric acid and then with water and air dried to give 65 grams of crude ethyl acetylcoumarate melting at 41-42°. Recrystallization from dilute methanol gave crystals of pure ethyl acetylcoumarate melting at 42-43°. Freudenberg and Gehrke (7) reported a melting point of 45° for the compound.

Reduction of this compound to coumaryl alcohol by the lithium aluminum hydride method will be reported later.

DIHYDROCOUMARIC ACID--A solution of 11.7 grams (0.05 mole) of ethyl acetylcoumarate in 150 ml. of warm acetic acid was treated with 0.1 gram of platinum oxide catalyst and hydrogenated at an initial pressure of 49.5 p.s.i. at 24.5°. After 15 minutes 0.05 mole of hydrogen was absorbed, and further hydrogenation gave no more absorption. The mixture was filtered and



stirred into 200 grams of cracked ice and 100 grams of water. An oil separated. The mixture was neutralized with sodium bicarbonate and extracted with ether. The ether was dried and distilled to give 10 grams of ethyl acetyldihydrocoumarate as a colorless sweet smelling oil. The oil was treated with an excess of 8% sodium hydroxide solution in which it was insoluble, and the resulting mixture was boiled under reflux for 3 hours. A clear solution resulted after short boiling. The alkaline solution was cooled and acidified with dilute sulfuric acid and extracted with ether. The ether was dried and evaporated to dryness. The white residue was recrystallized from benzene to yield white needles of dihydrocoumaric acid melting at 125-126°. Hlasiwetz (8) reported a melting point of 129° for dihydrocoumaric acid obtained by reduction of coumaric acid with sodium amalgam.

Reduction of the intermediate ethyl acetyldihydrocoumarate to dihydrocoumaryl alcohol by means of lithium aluminum hydride will be reported later.

SINAPIC ACID--A mixture of 182 grams (1.0 mole) of syringaldehyde, 230 grams (2.2 moles) of malonic acid, 10 grams (0.12 mole) of piperidine, and 500 ml. of pyridine was allowed to stand at room temperature for three weeks and then stirred into a mixture of 1000 grams of cracked ice and 600 ml. of concentrated hydrochloric acid. The yellow precipitate which formed was filtered and washed thoroughly with water. Upon air drying there was obtained 198 grams of crude sinapic acid melting at 192-193°. Recrystallization from methanol yielded very pale yellow crystals melting at 200-201°. Graebe and Martz (9) reported a melting point of 192° for the compound.

ETHYL SINAPATE--A mixture of 100 grams of sinapic acid, 500 ml. of absolute methanol and 20 ml. of concentrated sulfuric acid was heated to boiling under reflux for 7 hours, concentrated under reduced pressure to about 200 ml., and stirred into a mixture of ice and 3 liters of water. The mixture was neutralized with an excess of sodium bicarbonate slurry, and the precipitated solid was filtered, washed with cold water, and air dried to yield 116 grams of crude ethyl sinapate melting at 77-79°. Recrystallization from petroleum ether (b.p. 65-110°) gave pure ethyl sinapate melting at 83°. Freudenberg, Kraft and Heimberger (10) reported a melting point of 83° for ethyl sinapate.

ETHYL ACETYLSINAPATE--A mixture of 100 grams of crude ethyl sinapate, 200 ml. of acetic anhydride and 300 ml. of pyridine was allowed to stand two days at room temperature and then poured into 3.5 liters of mixed ice and water with vigorous stirring. The precipitate which separated was filtered and washed first with dilute hydrochloric acid and then with water. The crude product was air dried to yield 106 grams of crude ethyl acetyl sinapate melting at 110-112°. Recrystallization from ethanol raised the melting point to 117-118°. Freudenberg, Kraft and Heimberger (10) reported a melting point of 120-121° for the compound.

The reduction of ethyl acetylsinapate to sinapyl alcohol by means of lithium aluminum hydride will be reported later.

ETHYL DIHYDROSINAPATE--A solution of 19.7 grams (0.05 mole) of ethyl acetylsinapate in 150 ml. of warm acetic acid was treated with 0.1 gram

of platinum oxide and hydrogenated at an initial pressure of 49 p.s.i. at 24°. No absorption of hydrogen took place at all. The mixture was filtered, and the catalyst was washed with a little acetic acid. Attempts at hydrogenation were repeated with palladium oxide, platinum black, and 5% platinum on carbon as catalysts, but no hydrogen was absorbed under any of these conditions. Finally the filtered solution was diluted with a little water, transferred to a round bottom flask, treated with an excess of zinc dust, and heated on the steam bath a short while. The mixture was finally heated to boiling under reflux for one hour and allowed to stand overnight. The mixture was reheated to boiling and filtered. The precipitate was washed with acetic acid. The combined filtrate and washings were stirred into one liter of mixed cracked ice and water. The white precipitate which separated was filtered, washed thoroughly with water, and sucked as dry as possible. The still wet precipitate was dissolved in warm methanol, filtered and chilled to yield colorless crystals of ethyl dihydrosinapate melting at 48-49°. Brewer, Cook and Hibbert (11) reported ethyl dihydrosinapate boiling at 178-179° at 1 mm. pressure.

Calculated for ethyl dihydrosinapate,  $C_{13}H_{18}O_5$ : C, 61.40; H, 7.14.  
Found (File 169194): C, 61.25; H, 6.89.

DIHYDROSINAPIC ACID--Some of the above ethyl dihydrosinapate was boiled under reflux with excess 8% sodium hydroxide solution. The clear yellow solution was acidified with dilute sulfuric acid and extracted with ether. The ether was dried and distilled to leave white crystals of crude dihydrosinapic acid which were recrystallized from benzene-petroleum ether

mixture to give crystals of pure dihydrosinapic acid melting at 102-103° and not depressing a mixed melting point with authentic dihydrosinapic acid prepared by reduction of sinapic acid in the next experiment.

A solution of 10 grams of sinapic acid in 400 ml. of 4% sodium hydroxide solution was treated with stirring with 10 grams of Raney nickel alloy in one gram amounts over a period of 15 minutes. After stirring an additional 15 minutes, the mixture was filtered, and the filtrate was stirred into a mixture of ice and excess hydrochloric acid. The clear solution was extracted with ether, and the ether was dried and distilled, finally in a rotating evaporator at room temperature. The white residue was recrystallized from benzene to give crystals of pure dihydrosinapic acid melting at 102-103°.

Calculated for dihydrosinapic acid,  $C_{11}H_{14}O_5$ : C, 58.40; H, 6.24.  
Found (File 169195): C, 58.54; H, 6.34.

Brewer, Cook and Hibbert prepared dihydrosinapic acid by high pressure hydrogenation of sinapic acid over Raney nickel and reported a melting point of 102-103°.

4-HYDROXY-3-METHOXYPHENYLPROPANE (DIHYDROEUGENOL, CORULIGNOL)--A solution of 50 grams (0.3 mole) of eugenol in 200 ml. of absolute ethanol was treated with 0.5 gram of 10% palladium on carbon catalyst and hydrogenated at 24° with an initial hydrogen pressure of 48 p.s.i. After 15 minutes, 0.3 mole of hydrogen had been absorbed, and no further pressure drop was observed. The mixture was filtered, and the clear filtrate was concentrated to dryness

in a rotating evaporator at room temperature to yield 50 grams of crude 4-hydroxy-3-methoxyphenylpropane. The material was distilled under reduced pressure to give a colorless oil boiling at 110° at 3.5 mm. and having an index of refraction  $n_D^{24}$  1.5196.

The 4-hydroxy-3-methoxyphenylpropane was benzoylated by means of benzoyl chloride in sodium hydroxide solution, and the crude product was recrystallized from ethanol to yield 4-benzoxy-3-methoxyphenylpropane melting at 71-72°. Fournier (12) recorded a melting point of 72-73° for 4-benzoxy-3-methoxyphenylpropane.

The benzoate of the starting eugenol was prepared in the same manner and found to melt at 64-65°. Tiemann and Kraaz (13) reported 69-70° as the melting point of eugenol benzoate.

Hydrogenation of isoeugenol in the same manner yielded 4-hydroxy-3-methoxyphenylpropane in almost quantitative yield, and the benzoate had the same melting point and mixed melting point as that prepared from eugenol.

The benzoate of isoeugenol was prepared and found to melt at 99-100°. Tiemann (14) reported 103-104° as the melting point of isoeugenol benzoate.

3,5-DIMETHOXY-4-HYDROXYPHENYLPROPANE--A solution of 19.4 grams (0.1 mole) of 2,6-dimethoxy-4-allylphenol (see Project Report 29 of D. L. Beyer on Project 809-7) in 150 ml. of absolute ethanol was treated with 0.5 gram of 10% palladium on charcoal and hydrogenated at 23° with an initial hydrogen

pressure of 47.5 p.s.i. After 15 minutes the required 0.1 mole of hydrogen was taken up. The mixture was filtered and the clear filtrate was evaporated to dryness in the rotating evaporator to yield 19 grams of crude 3,5-dimethoxy-4-hydroxyphenylpropane as a dark oil which was distilled under reduced pressure to yield the pure product as a viscous light colored oil boiling at 160° at 6 mm. and having an index of refraction  $n_D^{25}$  1.5259. The benzoate was prepared and recrystallized from ethanol to give 3,5-dimethoxy-4-benzoxypheylpropane melting at 85-86°. Hoffman (15) reported a melting point of 91° for 3,5-dimethoxy-4-benzoxypheylpropane.

The benzoate of the starting 2,6-dimethoxy-4-allylphenol was prepared and found to melt at 68-69°.

The acetate of 3,5-dimethoxy-4-hydroxyphenylpropane was prepared by treating with acetic anhydride and pyridine at room temperature overnight. The reaction mixture was poured into ice water, and the precipitate was filtered, washed with water and recrystallized from ethanol to yield 4-acetoxy-3,5-dimethoxyphenylpropane melting at 84-85°. Brewer, Cook and Hibbert (11) recorded a melting point of 87-88° for this acetate.

p-HYDROXYPHENYLPROPANE--This compound was prepared by hydrogenation of readily available anethole and demethylation of the intermediate p-methoxyphenylpropane. A solution of 14.8 grams (0.1 mole) of anethole in 150 ml. of absolute ethanol was treated with 0.5 gram of 10% palladium on charcoal catalyst and hydrogenated at 24° with an initial pressure of 48 p.s.i. The required 0.1 mole of hydrogen was absorbed after 15 minutes. The experiment was repeated until 1.0 mole of anethole had been hydrogenated. The mixed

reaction products were filtered, and the filtrate was evaporated to dryness in a rotating evaporator. The residual liquid was distilled under reduced pressure to give 140 grams of p-methoxyphenylpropane boiling at 67° at 2.0 mm. and having an index of refraction  $n_D^{23}$  1.5024. Klages (16) reported a boiling point of 215-216° at atmospheric pressure and an index of refraction  $n_D^{20}$  1.5045 for p-methoxyphenylpropane which he prepared by treatment of anethole with sodium and ethanol.

A solution of 60 grams of p-methoxyphenylpropane in 600 ml. of acetic acid was heated to boiling under reflux and treated over a period of one hour with 120 ml. of 48% hydrobromic acid through the condenser. After all hydrobromic acid had been added, the solution was boiled 4 hours and then concentrated under reduced pressure and magnetic stirring to about 200 ml. volume. The solution was stirred into excess water, neutralized with a slurry of sodium bicarbonate, and extracted with ether. The ether was dried and distilled to leave an oil which was redistilled under reduced pressure to give pure p-hydroxyphenylpropane boiling at 90° at 3.0 mm. and having an index of refraction  $n_D^{23}$  1.5231. The benzoate was prepared in the usual manner and recrystallized from ethanol to give white crystals of p-benzoxypheylpropane melting at 35-36°. Coulthard, Marshall and Pyman (17) reported a melting point of 37-38° for p-benzoxypheylpropane prepared by benzoylating the Clemmenson reduction product of p-hydroxypropiophenone.

The synthesis of more compounds in these series is continuing and will be reported in the future. In addition, data on  $R_f$  values, ultraviolet absorption, and infrared curves will be given.

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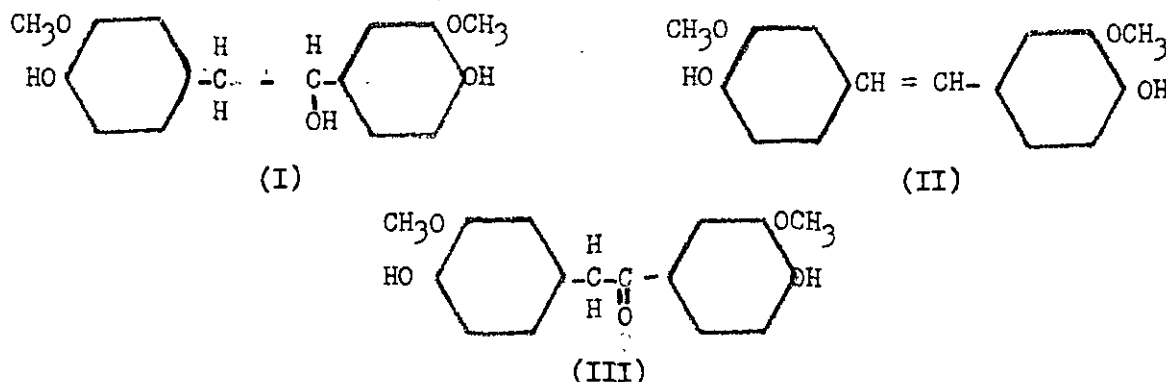
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102-103, 117-118,  
147-155

Notebook 1142: 11.

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SIGNED *Irwin A. Pearl*  
Irwin A. Pearl

## THE REACTION OF DESOXYVANILLOIN WITH REDUCING AGENTS.

In Project Report 107 of Project 809-7 the reduction of vanillil by means of a number of reducing agents was reported. In that report the preparation of three new reduction products of vanillil, namely bivanillyl, vanilloin, and desoxyvanilloin, were reported for the first time. Attempts to prepare 4,4'-dihydroxy-3,3'-dimethoxyphenylbenzylcarbinol (I) and its dehydration product, 4,4'-dihydroxy-3,3'-dimethoxystilbene (II), resulted in failure. The present report describes a number of experiments on the reduction of desoxyvanilloin (III) in an attempt to prepare the desired compounds.



It was first desired to prepare some derivative of desoxyvanilloin such as its oxime or semicarbazone so that the original material could be identified in its reaction mixtures. A solution of 2.38 grams (0.01 mole) of desoxyvanilloin in 30 ml. of hot ethanol was shaken with a solution containing 1.4 grams (0.02 mole) of hydroxylamine hydrochloride and 2.0 grams (0.02 mole) of potassium acetate until cool. The white crystals which

precipitated were filtered, washed with water and recrystallized from ethanol to give pure recovered desoxyvanilloin melting at 156-157°.

In another experiment 2.88 grams of desoxyvanilloin were dissolved in a solution of 1.0 grams (0.024 mole) of sodium hydroxide in 35 ml. of water and treated with stirring with 1.70 grams (0.024 mole) of hydroxylamine hydrochloride. The reaction mixture containing crystals was allowed to stand until cool. The crystals were filtered, washed, air dried, and recrystallized from ethanol to give unchanged desoxyvanilloin melting at 155-156°.

A solution of 10 grams of desoxyvanilloin in ethanol was treated with a water solution of 15 grams (0.135 mole) of semicarbazide hydrochloride and 22.5 grams (0.16 mole) of sodium acetate. The resulting clear solution was warmed on the steam bath for one hour, allowed to cool, and placed in the refrigerator. No crystals separated from the clear solution. The solution was evaporated to a small volume at atmospheric pressure and allowed to cool. The crystals that separated were filtered and recrystallized from ethanol to yield desoxyvanilloin semicarbazone melting at 208-209°.

Calculated for desoxyvanilloin semicarbazone,  $C_{17}H_{19}O_5N_3$ : C, 59.12; H, 5.55. Found (File 150331): C, 58.43; H, 5.69.

Failure to obtain an oxime from desoxyvanilloin led to an attempt to prepare the oxime of vanilloin. A solution of 3.04 grams (0.01 mole) of vanilloin and 1.0 grams (0.024 mole) of sodium hydroxide in 30 ml. of water

was heated to boiling, removed from the source of heat, and treated with 1.10 grams (0.024 mole) of hydroxylamine hydrochloride. An oil separated in the hot solution, but it solidified on cooling. The solid was removed by filtration. After washing with water it was recrystallized from water to give unchanged vanilloin melting at 159-160°.

No further experiments were performed on the preparation of oximes of desoxyvanilloin and the related vanilloin.

Desoxyvanilloin was subjected to hydrogenation under several conditions. Reaction of desoxyvanilloin in alkaline solution in the presence of Baker's Colloid with hydrogen at 50 psi. and room temperature for 3 hours gave no hydrogen absorption and a quantitative recovery of desoxyvanilloin.

Two grams of desoxyvanilloin were dissolved in 75 ml. of hot ethanol, treated with 0.5 grams of platinum oxide, and hydrogenated with an initial pressure of 50 psi. Some reduction of hydrogen pressure was indicated, but only desoxyvanilloin melting at 155-156° could be isolated from the hydrogenation mixture. Hydrogenation in the presence of twice as much catalyst or in the presence of platinum on charcoal did not alter the results.

Chemical reducing agents were then tried on desoxyvanilloin. Five grams of desoxyvanilloin were dissolved in 200 ml. of 10% sodium hydroxide solution and the solution was heated on the steam bath and treated portionwise with 20 grams of sodium hydrosulfite. The color changed from

yellow to yellow-green. The mixture was filtered, and the filtrate was acidified with carbon dioxide. A quantitative recovery of desoxyvanilloin melting at 152-153° was obtained. A mixed melting point with authentic desoxyvanilloin was not depressed.

Five grams of desoxyvanilloin was covered with 200 ml. of ethanol and 30 ml. of acetic acid. Twenty grams of zinc dust were added, and the mixture heated on the steam bath for one hour. The hot mixture was filtered, and the clear filtrate was concentrated under reduced pressure. The last traces of ethanol were removed by codistillation with water. The residue was diluted with water, and the precipitate was filtered, washed, air dried, and recrystallized from ethanol to give unchanged desoxyvanilloin melting at 153-154° and not depressing a mixed melting point with the starting material.

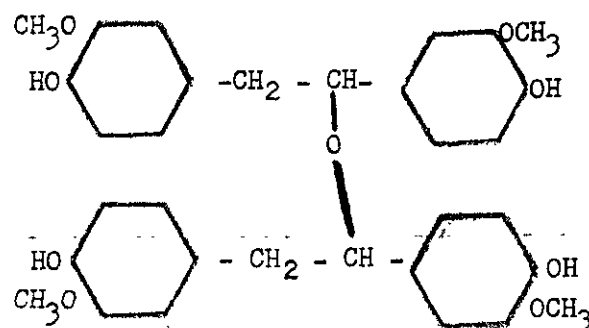
A solution of 10 grams of desoxyvanilloin in 300 ml. of 10% sodium hydroxide solution was treated with 10 grams of Raney Nickel Alloy in small portions. After reaction ceased, the mixture was filtered, and the nickel precipitate was washed with water. The combined filtrate and washings were acidified with sulfur dioxide to yield first an oil and then a granular precipitate. After cooling, the solidified oil and the granular precipitate were filtered and washed with water. The mixture appeared to be a mixture of a low melting material (105° with gas evolution) and high melting material (198-209°) which was very fluorescent in ultraviolet light. Recrystallization of the total product first from benzene and then

from either ethanol or acetic acid gave crystals of 4,4'-dihydroxy-3,3'-dimethoxystilbene melting at 210-211° and not depressing a mixed melting point with authentic 4,4'-dihydroxy-3,3'-dimethoxystilbene. The acetate was prepared by the pyridine and acetic anhydride procedure and found to melt at 225-227° and did not depress the melting point of a mixture with authentic 4,4'-dihydroxy-3,3'-dimethoxystilbene diacetate.

It appeared that the 105° melting material was the desired intermediate 4,4'-dihydroxy-3,3'-dimethoxyphenylbenzylcarbinol (I) which dehydrated spontaneously during the recrystallization procedure. An attempt was made to repeat this experiment and isolate pure (I).

The experiment was repeated through the acidification with sulfur dioxide stage. The crude mixture of solidified oil and granular precipitate was dried and boiled with petroleum ether. The boiling solution was filtered hot, and the filtrate was cooled, but nothing was obtained. The residue was covered with benzene and allowed to stand at room temperature for 24 hours. The benzene mixture was filtered, and the filtrate was diluted with petroleum ether. A white precipitate separated. This was filtered and air dried and found to melt at 93°. A purification by solution in cold benzene and precipitation by dilution with petroleum ether did not change the melting point. Analysis (File 150312) indicated 68.52% carbon and 6.08% hydrogen. The ultraviolet absorption spectrum had a maximum at 282 mμ and was very similar in appearance to that of bivanillyl. Analysis

did not correspond with the desired 4,4-dihydroxy-3,3'-dimethoxyphenyl-benzylcarbinol (Calculated for  $C_{16}H_{18}O_5$ : C, 66.19; H, 6.25) but rather for a hemihydrate of 4,4'-dihydroxy-3,3'-dimethoxystilbene (II) (Calculated for  $C_{16}H_{17}O_{4.5}$ : C, 68.31; H, 6.09) or its dimer 1,1', 2,2'-tetrakis (4-hydroxy-3-methoxyphenyl) diethylether (IV).



(IV)

The residue from the benzene treatment was boiled with benzene (all soluble) and cooled to give a crude mixture of II which upon recrystallization from acetic acid melted at 222-223°.

An attempted reduction of desoxyvanilloin with aluminum isopropoxide in isopropyl alcohol resulted in the recovery of only the starting material.

Desoxyvanilloin was then subjected to the reducing reaction of the new reducing agent, sodium borohydride, in accordance with the reducing procedure reported by Zelinski and coworkers [J. Am. Chem. Soc. 73, 5532 (1951)]. A solution of 6.5 grams (0.0225 mole) of desoxyvanilloin and 2.0 grams (0.05 mole) of sodium hydroxide in 50 ml. of water was gradually added to

a mixture of 0.35 grams (0.009 mole) of sodium borohydride in 5 ml. of water. The mixture was heated on the steam bath to 60-75° for 40 minutes and then boiled 30 minutes with 3 grams of sodium hydroxide. The resulting solution was cooled and acidified with dilute sulfuric acid. The precipitate was filtered and recrystallized from ethanol to give still crude crystals melting at 172-180°. Recrystallization from benzene gave crystals melting at 185° whose analysis agreed fairly well with that of the stilbene (II) and whose ultraviolet absorption spectrum had maxima at 288 and 333 mμ and a break in the curve at 230 mμ.

Calculated for 4,4'-dihydroxy-3,3'-dimethoxystilbene,  $C_{16}H_{16}O_4$ .  
C, 70.57; H, 5.92. Found (File 149867): C, 70.22; H, 6.31.

Inasmuch as the stilbene (II) was already known with a melting point of 225-226° it is possible that the instant compound melting at 185° is the cis form of the compound.

The experiment was repeated, but this time the filtered precipitate after acidification was boiled with ethanol, and the ethanol was evaporated to a small volume at atmospheric pressure. Cooling gave white crystals melting at 279-282° which were insoluble in boiling methanol and in boiling acetic acid, but which were washed with these two boiling solvents to give a crystalline powder melting at 282-283°. As yet this product is unidentified. Analysis (File 150214) was as follows: C, 66.98, 67.13; H, 5.36, 5.39. The ultraviolet absorption spectrum indicated maxima at 250, 290, and 355 mμ.

These high melting crystals were methylated with dimethyl sulfate and alkali and the product was recrystallized from ethanol to give white powdery crystals melting sharply at 119°. Analysis (File 150344) indicated C, 66.65, 66.73 and H, 5.99, 6.00. Ultraviolet absorption curve indicated maxima at 232, 282, and 310 mμ. More work will be done on these compounds in the future.

The success of the reduction of desoxyvanilloin with Raney Nickel alloy led to an experiment on the treatment of the intermediate hydrovanilloin with Raney Nickel alloy in alkaline solution to determine whether the stilbene (II) might be made from the more readily available compound.

A solution of 10 grams of hydrovanilloin in 200 ml. of 10% sodium hydroxide solution was treated portionwise with 15 grams of Raney Nickel alloy. After all reaction was complete, the mixture was filtered, and the nickel precipitate was washed thoroughly with water. The combined filtrate and washings were acidified with sulfur dioxide to give a quantitative recovery of hydrovanilloin melting at 195-207° which upon recrystallization from acetic acid, melted at 222-223° and did not depress a mixed melting point with authentic hydrovanilloin.

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## THE OXIDATION OF VANILLIL REDUCTION PRODUCTS WITH FEHLING SOLUTION

Mr. Beyer in his Project Report 12 in Project 1027 described experiments on the oxidation of vanillil reduction products with cupric hydroxide and alkali under pressure. The present report describes a few more experiments on the oxidation of these compounds with the more mild Fehling Solution at atmospheric pressure.

Five grams of vanilloin were added to 600 ml. of mixed Fehling Solution. The mixture first turned green in color and then brown. The brown mixture was heated to boiling under reflux for four hours and allowed to cool. The heavy deposit of cuprous oxide was filtered and washed with water. The combined filtrate and washings were saturated with sulfur dioxide and filtered. The precipitate was recrystallized from acetic acid to give 4.0 grams of pure vanillil melting at 230-231° and not depressing a mixed melting point with authentic vanillil. Only vanillil could be recovered from the filtrate from the recrystallization.

Six hundred ml. of mixed Fehling Solution was treated with 2.5 grams of bivanillyl. No change in color was noted. The mixture was heated to

boiling under reflux for 5 hours and cooled. The little cuprous oxide was filtered, and the filtrate was acidified with dilute sulfuric acid. The precipitate was recrystallized from ethanol to give 2.4 grams of unchanged bivanillyl melting at 164-165° and not depressing a mixed melting point with authentic bivanillyl.

Five grams of desoxyvanilloin was added to 600 ml. of mixed Fehling Solution. The solution turned dark green at room temperature. The green solution gradually turned to light green and finally to brown with a heavy deposit of cuprous oxide. The brown mixture was boiled under reflux for 4 hours and allowed to cool. The cool mixture was filtered, and the light green filtrate was acidified with dilute sulfuric acid. The precipitate was filtered, washed with water and recrystallized from acetic acid to yield 5 grams of vanillil as fine almost white needles melting at 229-230° and not depressing a mixed melting point with authentic vanillil.

In another similar experiment the filtered alkaline solution was acidified with sulfur dioxide. The resulting precipitate was then treated with dilute sulfuric acid and filtered. The remaining precipitate was recrystallized from acetic acid to yield crystals melting at 267-268°. The structure of these crystals is still unknown.

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## FURTHER STUDIES ON THE OXIDATION OF HYDROVANILLOIN

In Project Report 100 of Project 809-7 a number of experiments were reported on the attempted oxidation of hydrovanilloin to vanillil and the successful oxidation by means of cupric hydroxide in acetic acid medium. The present report describes a few more experiments along such lines with different reagents.

The method of Weiss and Appel [J. Am. Chem. Soc. 70, 3666 (1948)] was tried. A mixture of 46 grams (0.15 mole) of hydrovanilloin, 30 grams (0.375 mole) of ammonium nitrate, 0.3 gram (0.003 mole) of cupric hydroxide and 210 ml. of 80% acetic acid was placed in a 500 ml. flask and heated to boiling under reflux with magnetic stirring. Complete solution resulted after about 15 minutes and the resulting solution was purple in color. After 1.5 hours of boiling, the mixture was cooled and diluted with water. A dark tar resulted, and resisted all efforts to obtain a crystalline product.

The next experiment was the reaction of hydrovanilloin with one mole of silver oxide in sodium hydroxide solution. Silver oxide was prepared by mixing aqueous solutions of 34 grams (0.2 mole) of silver nitrate and 8 grams (0.2 mole) of sodium hydroxide. The precipitate was washed thoroughly with water. A solution of 30.6 grams (0.1 mole) of

hydrovanilloin in a solution of 24 grams of sodium hydroxide in 300 ml. of water was heated to 50° and treated at one time with the freshly prepared silver oxide and 200 ml. of water. The temperature rose to 60° and decolorization of the silver oxide took place immediately. The mixture was warmed to 75°, allowed to cool, and filtered. The silver residue was washed thoroughly with water, and the combined filtrate and washings were acidified with sulfur dioxide and cooled. The precipitate was filtered, washed with water and dried to give 15 grams of unchanged product melting at 191-195°. Boiling of this product with methanol raised the melting point to 223-224° and the resulting crystals did not depress a mixed melting point with authentic hydrovanilloin. The sulfur dioxide saturated filtrate was acidified with sulfuric acid and boiled to remove all sulfur dioxide. Cooling gave crystals of vanillin melting at 80-81° and not depressing a mixed melting point with authentic vanillin. The stability of vanillin in the presence of silver in alkaline solution is unexplained. It is possible that the short reaction time is responsible for this phenomenon.

In the next experiment two moles of silver oxide was employed. Silver oxide was prepared in the same manner from 68 grams (0.4 mole) of silver nitrate and washed thoroughly with water. A solution of 30.6 grams (0.1 mole) of hydrovanilloin and 24 grams (0.6 mole) of sodium hydroxide in 300 ml. water was heated to 50° and treated at one time with a slurry of the above silver oxide in 200 ml. of water at 50°. An immediate decolorizing of the silver oxide took place, but no temperature rise was noted. The mixture was stirred for 30 minutes and filtered. The silver

metal was washed with water, and the combined filtrate and washings were acidified with sulfur dioxide. The white precipitate was filtered, washed, and dried to give a quantitative yield (31 grams) of vanillic acid melting at 209-210° and not depressing the melting point of a mixture with authentic vanillic acid.

One experiment was tried on the oxidation of the bis benzyl ether of hydrovanilloin with potassium permanganate in acetone solution. A solution of 24.3 grams (0.05 mole) of hydrovanilloin bis benzyl ether (see Project Report 3) in 500 ml. of dry acetone was placed in a flask attached to a Soxhlet apparatus. The Soxhlet thimble was filled with 5.3 grams (0.033 mole) of powdered potassium permanganate, and the acetone solution was boiled. Each addition of permanganate by extraction resulted in immediate decolorization. Boiling was continued until the acetone extract from the thimble was colorless (about 5 hours). The acetone was removed by boiling, and the volume was maintained with water. The mixture was cooled and filtered. The precipitate was stirred with a solution of sodium bisulfite, and all precipitated manganese dioxide dissolved leaving a bright yellow crystalline product. The yield was 24 grams of material melting at 100-106°. Recrystallization from methanol gave an almost colorless crystalline material melting at 138-139° which proved to be unchanged bis benzyl ether of hydrovanilloin by mixed melting point. Unfortunately the mother liquors from recrystallization were not saved, because they must have contained the transformed material.

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## THE PREPARATION OF HOMOSYRINGIC ACID

The preparation of homosyringic acid involves a five step synthesis. This procedure is the same as that used several years ago to prepare homovanillic acid. (Project 809-7 Report Number 39.) The five steps in this synthesis are as follows: the preparation of syringal rhodanine, the preparation of  $\alpha$ -thioketo- $\beta$ -4-hydroxy-3,5-dimethoxyphenyl pyruvic acid, the preparation of  $\alpha$ -oximino- $\beta$ -4-hydroxy-3,5-dimethoxyphenyl pyruvic acid, the preparation of acetylhomosyringonitrile, and finally the preparation of homosyringic acid.

### The Preparation of Syringal Rhodanine

A mixture of 120 grams of syringaldehyde, 88 grams of rhodanine, 150 grams of anhydrous sodium acetate, and 400 ml. of glacial acetic acid is heated to boiling under reflux for 40 minutes. A heavy precipitate was present as the entire mixture was stirred into 3 liters of water. The mixture was stirred for 3 hours. The precipitate was filtered and washed well with water. The solid was air dried. The yield was 205 grams 105%, the crude m.p. was 249-251°. A sample of the product was recrystallized from chloroform yielding reddish brown needles, m.p. 250-251°. A sample was sent in for analysis under our number 1516-118-A. As yet no results have been received.

### The Preparation of $\alpha$ -Thioketo- $\beta$ -4-Hydroxy-3,5-Dimethoxyphenyl Pyruvic Acid.

A solution of 134 grams of syringal rhodanine in 780 ml. of 15% sodium hydroxide was boiled under reflux for 45 minutes. As the solution

cooled, a precipitate separated. The mixture was cooled to  $-15^{\circ}$  using dry ice in an ethanol bath. While the mixture was kept at  $-15^{\circ}$ , it was rapidly acidified with a 10% hydrochloric acid solution (834 ml. were used). The acidified mixture was kept at  $-15^{\circ}$  for 30 minutes by which time crystallization should be complete. The solid was filtered and washed with water. The product was air dried and amounted to 95 grams, 83%, m.p.  $130-144^{\circ}$ . A sample of the product was recrystallized from chloroform yielding light yellow crystals m.p.  $155-158^{\circ}$ . A second recrystallization raised the melting point to  $158-159^{\circ}$ . A sample of the product was sent in for analysis under our number 1516-119-A. The results have not as yet been received.

#### The Preparation of $\alpha$ -Oximino- $\beta$ -4-Hydroxy-3,5-Dimethoxyphenol Pyruvic Acid.

A solution of 17.5 grams of sodium metal dissolved in 450 ml. of ethanol was prepared. This solution was added to a mixture of 48 grams of hydroxylamine hydrochloride in 43 ml. of water. The inorganic material that separated was filtered and discarded. The free base was added to 57 grams of recrystallized  $\alpha$ -thioketo- $\beta$ -4-hydroxy-3,5-dimethoxyphenyl pyruvic acid. The mixture was boiled under reflux for one hour on the steam bath. A heavy precipitate separated during this period. The precipitate was filtered and the filtrate was distilled below  $50^{\circ}$  under reduced pressure to remove all the solvent. Both the solid and the residue were dissolved in 380 ml. of 5% aqueous sodium hydroxide. A little insoluble material was filtered and discarded. The aqueous filtrate was cooled to  $-15^{\circ}$  and acidified with 360 ml. of 10% hydrochloric acid. The mixture was kept at  $-15^{\circ}$  for 30 minutes by which time crystallization should be complete. The solid was filtered and washed with water, then left to air dry. The crude yield was 42 grams, 80% m.p.  $85-95^{\circ}$  solidified and melted again at  $150^{\circ}$  very sharply. A sample was sent in for analysis under our number 1516-121-A. No results have been received.

### The Preparation of Acetylhomosyringonitrile

A sample of 40 grams of  $\alpha$ -oximino- $\beta$ -4-hydroxy-3,5-dimethoxyphenyl pyruvic acid was warmed in 150 ml. of acetic anhydride until completely dissolved and the evolution of carbon dioxide had ceased. The solution was then boiled under reflux for 2 hours under a calcium chloride tube. The excess acetic anhydride was distilled under reduced pressure. The residue was dissolved in 550 ml. of benzene. The benzene solution was washed with water using a separatory funnel. The benzene solution was next washed with a 1% solution of sodium bicarbonate and finally given another water wash. The benzene solution was dried with anhydrous sodium sulfate and distilled to dryness under reduced pressure. The viscous residue was left to stand overnight. A crystalline product had separated upon standing. The solid was filtered and washed with ethanol. The yield was 24 grams, 65%. A sample was recrystallized from high boiling petroleum ether yielding white crystals, m.p. 79-82°. A sample was sent in for analysis under our number 1516-123-A. No results have been received.

The viscous residue plus the ethanol washings were evaporated to dryness using the rotating evaporator. A viscous oil remained, yield 13 grams, 35%.

### The Preparation of Homosyringic Acid.

A sample of 21 grams of acetylhomosyringonitrile was dissolved in a solution of 27 grams of potassium hydroxide in 160 ml. of water and 180 ml. of ethanol. The solution was boiled under reflux for 12 hours. The ethanol was removed under reduced pressure on the steam bath. The aqueous solution was cooled and acidified with 120 ml. of 1:1 hydrochloric acid. The acidified solution was left to stand in the refrigerator for several days. A



crystalline product separated upon standing. The solid was filtered and air dried. Yield was 15 grams. The filtrate was extracted with ether, the ether was evaporated to dryness leaving a solid product amounting to 5 grams. The total yield was 20 grams, 105%. The product was recrystallized from low boiling petroleum ether yielding a crystalline solid, m.p. 125-127°. The product was recrystallized a second time, this time from low boiling petroleum ether - ether yielding needles, m.p. 126-127°. The ether - petroleum ether filtrate was evaporated to dryness leaving a small amount of a white crystalline solid, m.p. 182-183°.

The two products were chromatographed with the following results:

Homosyringic acid, m.p. 126-127° BuOH 2% aqueous ammonia - Rf 0.10  
BuOH, pyridine, water (10:3:3) - Rf 0.20

Unknown material, m.p. 182-183° - contains a little homosyringic acid.

BuOH 2% aqueous ammonia - Rf 0.23

10:3:3 - BuOH, Py, H<sub>2</sub>O - Rf 0.44

This unknown does not give a positive Maule test. The amount of material was insufficient to attempt an identification.

The 13 grams of a viscous oil obtained as a crude acetylhomosyringonitrile was hydrolyzed in an identical manner as the first sample. The product obtained was crude homosyringic acid containing some of this unknown material as an impurity.

We ran an analysis for methoxyl on the five prepared compounds. The results cannot be accepted as accurate since we have had a great deal of difficulty in obtaining checks on authentic syringal compounds. We shall check these results when we finally overcome the present difficulties.

	Calc. MeO, %	Found MeO, % av.
Syringal Rhodanine	20.88	15.16
$\alpha$ -Thioketo-etc-pyruvic acid	24.22	23.30
$\alpha$ -Oximino-etc-pyruvic acid	24.32	22.45
Acetylhomosyringonitrile	25.45	25.94
Homosyringic acid	29.20	29.00

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## FURTHER EXPERIMENTS ON THE DEHYDRATION OF HYDROVANILLOIN

In Project Report 108 in Project 809-7 several preliminary experiments were reported on the reaction of hydrovanilloin with sulfuric acid and the isolation of an acetate of the rearrangement product obtained. At that time, there were several possible structures for the product of reaction. Since Report 108 in Project 809-7 from time to time a few experiments have been made on the dehydration of hydrovanilloin under various conditions. As yet, the answer is still unknown, but this report assembles in one place the data obtained in the various experiments.

Several attempts were made to dehydrate hydrovanilloin with agents other than sulfuric acid.

A mixture of 28.5 grams of hydrovanilloin and 100 grams of oxalic acid crystals was heated to 170° at which point a black liquid mixture was obtained. The temperature was allowed to drop to 156° and maintained there for 2 hours. After cooling overnight, the black mass was diluted with water and extracted with ether. The ether solution was distilled to dryness to leave a tarry residue which could not be crystallized. The experiment

was abandoned.

Ten grams of hydrovanilloin was covered with 50 ml. of acetic anhydride, and the suspension was treated with one drop of concentrated sulfuric acid. An immediate darkening took place, and the hydrovanilloin dissolved to a clear tan solution. The solution, which became very warm, was heated on the steam bath for 15 minutes and allowed to stand overnight. The solution was poured with stirring into excess water to yield a taffy-like precipitate. The precipitate was washed several times with water by decantation and finally boiled with methanol to yield a white powder melting at 195-196° and not depressing a mixed melting point with authentic hydrovanilloin tetraacetate. Hydrolysis with potassium hydroxide yielded only hydrovanilloin.

A clear pink solution obtained by stirring 10 grams of hydrovanilloin into 75 cc. of 85% phosphoric acid at room temperature was allowed to stand at room temperature. After a short while, a crystalline solid separated in the syrupy mixture. After 15 minutes, the liquid was decanted from the solid into an excess of water to give a yellow precipitate. The precipitate was filtered and washed with water. The airdry precipitate was boiled with benzene under a water-separatory head and then filtered hot. Upon cooling, the benzene solution remained clear. It was stirred into an excess of petroleum ether to give an almost white precipitate melting at 103-110°. Recrystallization from petroleum ether (b.p. 65-110°) gave a crystalline product melting at 111-126°, apparently similar to the product

obtained by boiling hydrovanilloin with dilute sulfuric acid. Nothing could be isolated from the original crystalline product which separated in the phosphoric acid.

Reaction of hydrovanilloin with chromic acid in boiling acetic acid yielded only the starting material as a product.

An attempt was made to dehydrate hydrovanilloin by boiling with xylene under a water separatory head. Twenty-five grams of hydrovanilloin was covered with 500 ml. of xylene and boiled under reflux five hours under a water-separatory head. A total of 4 ml. of water was collected. The hot mixture was filtered, and the powdery precipitate was washed with benzene and air dried to give a crystalline product melting at 185-186° with vigorous gas evolution. Analysis and ultraviolet absorption spectrum agreed exactly with the starting hydrovanilloin even though the melting point was very much lower. The product was acetylated with acetic anhydride in pyridine and gave the tetraacetate of hydrovanilloin melting at 196-197° which did not depress the melting point of authentic hydrovanilloin tetraacetate. Apparently the 185-186° melting material is another form of hydrovanilloin. Recrystallization of these crystals from acetic acid yielded the higher melting form of hydrovanilloin melting at 223°.

Hydrovanilloin was fused at 275-290° and allowed to cool. The product was covered with cold ethanol to give a powdery precipitate melting at 228-229° which melting point did not change on boiling with ethanol,

acetic acid or dioxane. The product did not depress the melting point of a mixture with hydrovanilloin. Acetylation with acetic anhydride and pyridine gave hydrovanilloin tetraacetate. The explanation for the variation in melting point of these hydrovanilloin products is still unknown.

Hydrovanilloin was treated with a recently available condensing agent, trifluoroacetic anhydride. A mixture of 20 grams of hydrovanilloin, 500 ml. of absolute ethanol and 25 ml. of trifluoroacetic anhydride was heated to boiling under reflux with magnetic stirring. The turbid white mixture became clear after about 3 hours of boiling. Boiling was continued another three hours and the mixture was allowed to cool. The solution was filtered to remove a trace of precipitate and placed in the freezer, but nothing separated under these conditions. The solution was concentrated to a small volume and frozen again. Again, no crystals separated. The product was stirred into a large excess of water to give a resinous precipitate, but no crystalline product could be obtained from the resin.

The last experiment was repeated through the boiling stage. Water was added and then 10 grams of sodium hydroxide. The boiling was continued another hour during which time the mixture became deep purple in color. The mixture was cooled and acidified with sulfur dioxide which caused the color to change to dark red. The solution was evaporated to dryness, and the residue was dissolved in methanol and filtered. The filtered solution was poured into excess ether, and the precipitate was filtered and washed with ether. The precipitate was obtained as a red powder melting

with decomposition at about 70°. The product was very soluble in water and was red in acid and blue in base.

Twenty-five grams of hydrovanilloin was covered with 400 ml. of anhydrous ethanol and heated to boiling under reflux. The hydrovanilloin remained insoluble. Hydrogen chloride gas was introduced below the surface of the boiling solution. After about 15 minutes a clear yellow solution resulted. Boiling and hydrogen chloride introduction were continued another 15 minutes, and then the reaction mixture was poured into one liter of cold water. A turbid solution resulted. This turbid acid solution was neutralized with a slurry of sodium bicarbonate, and the oily precipitate was extracted with ether. The ether was dried and concentrated to a small volume. The clear solution was placed in the freezer, but no crystalline material could be obtained. An attempt to reduce this material with sodium and boiling butanol produced no crystalline product.

A similar attempt to rearrange hydrovanilloin with sulfuric acid in absolute ethanolic solution gave a deep violet colored solution which yielded no crystalline material.

Several repeat experiments were performed on the aqueous sulfuric acid rearrangement of hydrovanilloin reported earlier. Attempts to purify the crude precipitate failed to give a more definite crystalline material.

A mixture of 20 grams of hydrovanilloin and 600 ml. of 6N sulfuric acid was heated under reflux to boiling with occasional shaking. After short boiling (one to two minutes) the white powdery solid had changed to a light yellow oil. Boiling was continued for one hour, and the mixture was cooled. The aqueous solution was decanted from the solidified oil, and the solid was washed several times with water by decantation. The solid was then dissolved in excess 8% sodium hydroxide solution and treated with dimethyl sulfate with stirring until no more precipitate formed. The precipitate was filtered, washed thoroughly with water, dissolved in methanol, and stirred into excess water. The yellow precipitate was air dried to give 20 grams of methylated product. Ten grams of this methylated product was dissolved in 50 ml. of acetic acid and treated with a solution of 5 grams of chromic acid in a mixture of 5 ml. of water and 60 ml. of acetic acid. The mixture was stirred for three hours and then concentrated almost to dryness under reduced pressure. The residue was stirred with a mixture of water and chloroform. The chloroform layer was removed, and the aqueous layer was extracted with chloroform. The combined chloroform solutions were evaporated to dryness at room temperature. The residue was recrystallized twice from methanol to give light yellow crystals melting at 144-145°. Analysis (File 162070) indicated 67.07% carbon, 6.15% hydrogen, and 27.4% methoxyl and the ultraviolet absorption spectrum contained absorption maxima at 233, 284, and 310 mμ. To date no configuration has been found to fit these data.



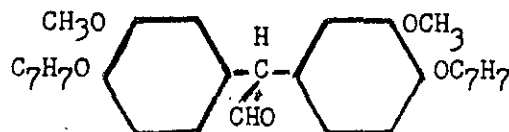
A mixture of 40 grams of hydrovanilloin, 1000 ml. of water and 200 ml. of concentrated sulfuric acid was boiled with stirring under reflux for 4 hours and allowed to cool. The solidified oil was washed by decantation several times with water and finally covered with 1000 ml. of normal butanol. This mixture was boiled under a water-separatory head until all water was removed. The water-separatory head was removed and the mixture was boiled under reflux. Twenty grams of sodium metal in small pieces were added through the condenser over a period of 4 hours, and then the mixture containing a heavy yellow precipitate was boiled another 3 hours. The precipitate was filtered after cooling, washed with butanol, and dissolved in water. The solution, which still contained a little butanol, was distilled under reduced pressure to remove all butanol, cooled, and acidified with sulfur dioxide. The solution was decanted from the separated oil which solidified, and the solid was washed several times with water by decantation. The residue was covered with benzene and boiled under water-separatory reflux. The water-free benzene mixture was filtered, and the clear filtrate was stirred into excess petroleum ether to give a light yellow precipitate which was filtered and washed with petroleum ether. The yield 17 grams of yellow powder melting at 138-147°. Attempts to improve the melting point by recrystallization failed. The crude product was acetylated and recrystallized from methanol to give a dark yellow powdery material melting at 124-136°. The melting point of this product could also not be improved by recrystallization.

Hydrovanilloin was then benzylated to determine whether the dibenzyl ether of hydrovanilloin could be rearranged by acid to a determinable compound. A stirred mixture of 43 grams (0.625 mole) of 85% potassium hydroxide and 600 ml. of 95% ethanol was treated with 96 grams (0.31 mole) of hydrovanilloin and then with 87 grams (0.665 mole) of benzyl chloride. The resulting thick white mixture was boiled under reflux with stirring for 7 hours and allowed to cool overnight. The almost solid mixture was added to a large excess of dilute potassium hydroxide solution with stirring, and the mixture was filtered. The precipitate was washed with dilute potassium hydroxide solution, then with water, and finally with methanol and air dried to yield 125 grams of crude bisbenzyl ether of hydrovanilloin melting at 135-137°. Recrystallization from methanol raised the melting point to 137-138°.

Calculated for the bis benzyl ether of hydrovanilloin,  $C_{30}H_{30}O_6$ :  
C, 74.05; H, 6.22. Found: (File 156421) C, 74.13; H, 6.26.

A mixture of 20 grams of hydrovanilloin bis benzyl ether, 400 ml. of water and 100 ml. of concentrated sulfuric acid was heated to boiling under reflux with magnetic stirring for 2 hours. The solid material became semisolid in nature. The mixture was cooled, and the precipitate was filtered and washed with water. The product was air dried and recrystallized from benzene-petroleum ether to give a crystalline product melting at 124-126°.

The product was dissolved in boiling benzene and diluted with petroleum ether (b.p. 65-110°) to incipient precipitation. The solution was filtered hot at this point and allowed to cool to room temperature. A heavy oil had separated. The clear solution was removed by decantation and placed in the freezer to yield crystals. These were filtered and washed with petroleum ether and melted at 126-127°. The analysis of this product (File 157408: C, 77.17, 77.29; H, 6.13, 6.18) agrees fairly well with that of the desired bis benzyl ether of desoxyvanilloin of the bis benzyl ether of diguaiacylacetaldehyde. Inasmuch as the bisbenzyl ether of desoxyvanilloin melts at 144-145° the compound might be the bis benzyl ether of diguaiacylacetaldehyde.



Calculated for the bisbenzyl ether of diguaiacylacetaldehyde,  
 $C_{30}H_{28}O_5$ : C, 76.90; H, 6.02.

Work in this field has been stopped for the present. It is hoped that the opportunity will come to re-examine this interesting reaction of hydrovanilloin and to determine the nature of the rearrangement product and of some of the other soluble materials obtainable from the refractory hydrovanilloin.

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## THE PREPARATION OF SYRINGALDEHYDE

For the preparation of syringaldehyde, an intermediate compound, 5-iodovanillin, is required. The procedure for the preparation of 5-iodovanillin has previously been reported in project report five for Project 809-13. In all, ten identical experiments were performed preparing approximately 5000 grams of 5-iodovanillin.

The procedure used in the preparation of syringaldehyde has been reported in Project 809-13 Progress Report 23; also small scale experimental runs were described in Project 809-13, project report five.

The procedure briefly is as follows. One pound of sodium metal is dissolved in 12500 cc. of methanol. The sodium methalate plus 650 grams of 5-iodovanillin and 125 grams of copper are reacted in the large five-gallon autoclave for five hours at 130°. The copper used in each of the ten runs was from the British Drug House and classified as precipitated copper.

The work-up of the reaction mixture was as follows. The mixture was filtered. If any solid was present, besides the copper, it was dissolved in water and acidified with dilute hydrochloric acid. Should a precipitate separate it would be filtered, washed and air dried, This product is A-1. The aqueous solution was extracted with chloroform. The chloroform is dried and distilled to dryness leaving fraction A-2.

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The methanol filtrate was distilled under a reduced pressure until the precipitate which separates out causes bumping. The mixture is filtered. The solid is dissolved in water and acidified. As before any solid is filtered and this fraction is B-1. The aqueous solution is again extracted with chloroform. The chloroform is distilled and fraction B-2 is obtained. The methanol filtrate is then distilled further, until more precipitate separates. Fractions C-1 and C-2, the second methanol precipitates are obtained in the same manner as before.

The remaining methanol solution is diluted with water and acidified. The solution is extracted with chloroform and fraction D is obtained.

A chart follows showing the results of each of the ten runs. The data for each fraction includes the yield and the estimated percent breakdown of the fraction. This breakdown is estimated from chromatograms of each fraction. The chromatogram is developed in butyl ether saturated with water and sprayed with bis-diaotized benzidine.

No.	Temp. °C.	Max. Temp hr.	A-1	A-2	B-1	B-2	C-1	C-2	D	
1	130	3.5	32 S-80% 5-I-20%	70 S-100%	19 S-20% 5-I-80%	38 S-95% V-5%	--	147 S-80% V-20%	188 S-40% V-30% U-30%	
2	140	3.5	--	--	40 5-I-100%	10 S-65% V-35%	162 S-10% 5-I-90%	97 S-50% V-50%	86 S-50% V-40% U-10%	5-Iodovanillin impure=contained inorganic- salts
3	131	5.5	--	--	127 S-80% 5-I-20%	56 S-100%	82 5-I-100%	141 S-70 % V-30%	72 S-60% V-40%	
4	130	5.0	34 S-90% 5-I-10%	65 S-90% V-10%	--	98 S-80% V-20%	--	196 S-60% V-25% U-15%	77 S-60% V-25% U-15%	
5	130	5.0	--	--	16 5-I-100%	40 S-100%	20 S-10% 5-I-90%	318 S-65% V-35%	102 S-60% V-35% U-5%	
6	134	5.0	--	--	29 S-20% 5-I-80%	96 S-95% V-5%	14 S-10% 5-I-90%	183 S-80% V-15% U-5%	214 S-70% V-25% U-5%	
7	132	5.0	15 5-I-100%	194 S-80% V-20%	13 S-5% 5-I-95%	83 S-80% V-20%	5 5-I-100%	8 S-70% V-30%	168 S-70% V-20% U-10%	
8	131	5.0	100 S-80% 5-I-20%	27 S-100%	--	171 S-90% V-10%	--	20 S-80% V-20%	181 S-80% V-20%	
9	131	5.0	119 S-90% 5-I-10%	50 S-95% V-5%	--	194 S-85% V-15%	--	128 S-80% V-20%	17 S-80% V-20%	
10	131	3.5	170 S-95% 5-I-5%	21 S-95% V-5%		56 S-85% V-15%		176 S-85% V-15%	75 S-80% V-20%	MeOH leaked through packing gland.

# PROJECT REPORT FORM

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Notebook 1294  
Pages 73-76  
Notebook 1482  
Pages 22-26  
and 29-31

PROJECT NO. 1929 ✓ X  
COOPERATOR I.P.C.  
REPORT NO. 1  
DATE August 3, 1956  
NOTE BOOK 1294 and 1482  
PAGE \_\_\_\_\_ TO \_\_\_\_\_  
SIGNED *Irwin A. Pearl*  
Irwin A. Pearl

## OXIDATION OF LIGNIN MODEL COMPOUNDS AND SYNTHESIS OF SEVERAL INTERMEDIATES

A few years ago the possibility of the presence in at least a part of the complex lignin structure of a linkage between the  $\alpha$ -carbon atoms of two  $C_6-C_3$  units was suggested (1), 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  $\alpha$ -carbon atoms (2). 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  $\alpha$ -carbon atoms and containing 5-carbon side chains and with two  $C_6-C_3$  units linked through their  $\alpha$ -carbon atoms. The first group of model compounds comprises 5-allylvanillil, 5,5'-diallylvanillil, 5-propenylvanillil, and 5,5'-dipropenylvanillil (3). The second group comprises 3,3'-dimethoxydiethylstilbestrol (4), 3,3'-dimethoxyhexestrol, and 3,3'-dimethoxydienestrol. These oxidations are compared with similar oxidations of coniferous lignosulfonate materials.

Cupric oxide and oxidation of 5-allylvanillin under conditions reported earlier (2) and isolation of reaction products by means of chromatography yielded products with and without the 5-carbon side chain. Much of the original 5-allylvanillin was recovered as its isomer, 5-propenylvanillin, under the conditions of the experiment. Other compounds isolated and identified were vanillin, 5-propenylvanillovanillone, 5-allylvanillin, 5-propenylvanillic acid, 5-carboxymethylvanillin, 5-carboxyvanillin, 5-carboxyvanillic acid, and vanillic acid. Almost identical results were obtained with 5-propenylvanillin, and similar results were obtained with 5,5'-diallylvanillin and 5,5'-dipropenylvanillin except that in the case of the bis-substituted compounds, the yields of unsubstituted guaiacyl compounds was 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  $\alpha$ -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-formylvanillin, 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  $\beta$  and  $\gamma$  carbon atoms of similar guaiacyl compounds with  $C_6-C_3$  units linked through their  $\alpha$ -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 (5). 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  $\alpha$ - $\alpha$  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'-dimethoxyhexesterol were oxidized with nitrobenzene, although in the latter case all yields were a little lower. Vanderlinde and co-workers (6) recently reported the alkaline oxidation of diethylstilbestrol to yield 4,4'-dihydroxybenzil and p-hydroxybenzoic acid, and postulated the formation of dienestrol as an intermediate in this oxidation. These authors proved that the  $\theta$  and  $\gamma$  atoms of two  $C_6-C_3$  units linked through their  $\alpha$ -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  $\alpha$ - $\alpha$  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 (3,4).

3,3'-Dimethoxyhexesterol ( $\alpha$ - $\alpha'$ -diethylbivanillyl). 3,3'-Dimethoxydiethylstilbesterol 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'-dimethoxyhexesterol 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:  $\lambda$ -max. 230 m $\mu$ ,  $\epsilon$  16470;  $\lambda$  max. 282 m $\mu$ ,  $\epsilon$  7130.

Anal. Calcd. for C<sub>20</sub>H<sub>26</sub>O<sub>4</sub>: C, 72.70; H, 7.93. Found: (File 169608)  
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'-dimethoxyhexesterol diacetate melting at 178-179° and giving the following ultraviolet absorption maximum:  $\lambda$  max. 280 m $\mu$ ,  $\epsilon$  5050.

Anal. Calcd. for  $C_{24}H_{30}O_6$ : C, 69.54; H, 7.30. Found: (File 169609)  
C, 69.57; H, 7.31.

3,3'-Dimethoxyhexesterol 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.  $\alpha,\alpha'$ -diethylhydrovanilloin (6), 5 g. acetyl chloride, and 50 ml. of acetic anhydride was boiled under reflux 4 hours, and the excess solvents removed under reduced pressure below  $40^\circ$ . 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  $147-148^\circ$  and giving the following maxima in its ultraviolet absorption spectrum:  $\lambda_{max}$ . 213  $m\mu$ ,  $\epsilon$  23000;  $\lambda_{max}$ . 240  $m\mu$ ,  $\epsilon$  14680;  $\lambda_{max}$ . 312  $m\mu$ ,  $\epsilon$  18860.

Anal. Calcd. for  $C_{24}H_{26}O_6$ : C, 70.23; H, 6.39. Found: (File 169673)  
C, 70.22; H, 6.40.

The mother liquor from the first recrystallization above was evaporated to dryness under reduced pressure at  $20^\circ$ , 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 (4).

General Cupric Oxide Oxidation Procedure. The Oxidation of 5-Allylvanillin. A mixture of 26 g. of 5-allylvanillin, 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 (7). 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-propenylvanillin (3). The acetate was prepared, and its melting point and mixed melting point with authentic 5-propenylvanillin 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-propenyl-vanillil. 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:  $\lambda_{\text{shoulder}}$  260 m $\mu$ ,  $\epsilon$  17620;  $\lambda_{\text{max}}$  320 m $\mu$ ,  $\epsilon$  16200.

Anal. Calcd. for  $C_{18}H_{18}O_5$ : C, 68.78; H, 5.77. Found (File 157763) 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 vanillin melting at 228-230° and not depressing the melting point of a mixture with authentic vanillin (8).

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  $\lambda_{max}$  245 m $\mu$ ,  $\epsilon$  21630. The analysis agrees with 5-propenylvanillic acid and the ultraviolet absorption spectrum is identical with that of 5-propenylvanillic acid (9) although the melting point is higher than that recorded earlier.

It is possible that the instant 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: (File 158358)  
C, 63.10; H, 5.82.

The benzene solution was chromatographed on acid-washed Magnesol and developed with 10:1 petroleum ether (b.p. 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-propenylvanillin containing 2.5 molecules of water, and had ultraviolet absorption spectrum identical with that of 5-propenylvanillin (3).

Anal. Calcd. for  $C_{19}H_{23}O_{8.5}$ : C, 58.91; H, 5.98. Found (File 158693) 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 maxima at 242 m $\mu$  and 332 m $\mu$ .

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:  $\lambda_{max}$ . 235 m $\mu$ ,  $\epsilon$  26420;  $\lambda_{max}$ . 323 m $\mu$ ,  $\epsilon$  18500. Analyses and properties correspond with 5-carboxymethylvanillin.



Anal. Calcd. for  $C_{18}H_{16}O_8$ : C, 60.00; H, 4.48. Found: (File 158593)  
C, 60.01; H, 4.64.

Fraction C contained two compounds having  $R_f$ s 0.11 (5-carboxy-methylvanillil) and 0.6. 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 (3) 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:  $\lambda_{max}$ . 230 m $\mu$ ,  $\epsilon$  26720;  $\lambda$  shoulder 292 m $\mu$ ,  $\epsilon$  14770;  $\lambda_{max}$ . 330 m $\mu$ ,  $\epsilon$  18710.

Anal. Calcd. for  $C_{17}H_{16}O_9$ : C, 56.04; H, 4.43. Found: (File 158832)  
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.

TABLE I

PRODUCTS FROM THE ALKALINE CUPRIC OXIDE OXIDATION OF 5-ALLYVANILLIL

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	<u>0.7</u>
	95.5

Other Oxidations of Allyl and Propenyl-vanillil 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.

5-Propenylvanillil was oxidized with nitrobenzene and alkali under conditions reported earlier (9), 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 (1). 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 propenyl-vanillil compounds were oxidized by the micro method of Stone and Blundell (10), 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 (4), 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-allylvanillin. The reaction mixture was analyzed in the same manner employed for similar oxidations of vanillin and its reduction products (2). The main products of oxidation were vanillin, 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'-dimethoxyhexesterol 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'-dimethoxyhexesterol diacetate.

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PROJECT NO. 1929 X  
COOPERATOR Institute  
REPORT NO. 1 (Beyer)  
DATE September 20, 1956  
NOTE BOOK 1516  
PAGE 11 TO 74  
SIGNED Donald L. Beyer  
Donald L. Beyer

## THE PREPARATION OF HYDROVANILLOIN, VANILLIL, GUAIACOL PROPIONATE, AND PROPIOVANILLONE

All of these compounds have been prepared and reported before. In the past these compounds were prepared under either project 809-7 or 1027. Since 809-7 has been withdrawn, the preparation of these synthetic materials were put on Institute projects, namely 1929- "Synthesis and Reactions of Model Compounds Related to Lignin."

The work here reported was done by Miss Sally Wilkinson during this past summer.

### Hydrovanilloin:

The preparation of hydrovanilloin has been reported in project 809-7 report number 68. In all, 33 preparations were made reacting 120 grams of vanillin each time. In all, approximately 3200 grams of hydrovanilloin were prepared.

### Vanillil:

The preparation of vanillil has been reported in several reports, the procedure followed, however, was from Project 809-7 report number 77. In all, a total of twelve experiments were performed, preparing approximately 1200 grams of vanillil.

### Guaiacol Propionate:

A single experiment was run reacting 1240 grams of guaiacol

with 950 grams of propionyl chloride at 50°. The mixture was then heated for four hours until most of the hydrogen chloride was evolved. The solution was washed with an 8% solution of sodium bicarbonate followed with a water wash. The crude product was then dried and distilled to dryness. The crude guaiacol propionate was distilled under vacuum. At 97°/0.15 mm. the product distilled as a light yellow oil. About 1575 grams were prepared. The preparation of guaiacol propionate involving a somewhat different method was reported in project 1027 report number 17.

Propiovanillone:

The preparation of propiovanillone has also been reported in Project 1027 report number 17. Two experiments were performed preparing the desired compound. The one experiment was successful and the other failed for some unknown reason. More is expected to be prepared at a later date and will be reported then.