[Contribution from the Northern Regional Research Laboratory][1]

Synthesis and Proof of Structure of 5-Acetylvanillin

By Herbert E. Smith, Charles R. Russell and L. E. Schniepp

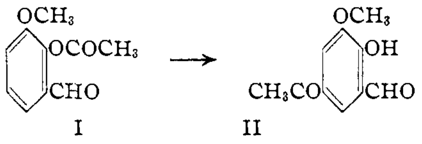
In his preparation of a synthetic lignin-like material by subjecting vanillin acetate to Fries rearrangement conditions, Alfred Russell[2] postulated the intermediate formation of 2-hydroxy-3-methoxy-5-formylacetophenone (5-acetylvanillin) and the spontaneous polycondensation of this product to an equilibrium mixture of a polychalcone and poly-8-methoxydihydrobenzopyrone. The same route to polymer formation was indicated in the preparation of amorphous polymers from *o*- and *p*-acetoxybenzaldehydes,[3] but in none of these cases was the methylketo-aldehyde, or monomeric unit, isolated.

The formation of amorphous lignin-like polymers by polycondensation of hydroxyaryl-methylketo-aldehydes was established by synthesis of three chelation-stabilized monomers and their separate polymerization.[4] Although the results are strongly indicative of the mode of polymerization, they do not in themselves constitute unequivocal evidence of the structure of the resulting products.

The many similarities in physical, chemical and analytical properties of the polymer from vanillin acetate and of those reported for various spruce lignins makes it of interest to establish additional evidence of the structure of this synthetic product.

Oxidative degradation studies on the synthetic polymer showed this material to be fully as resistant to breakdown as natural lignins. In fact, the yields of veratric and isohemipinic acids from permanganate oxidation of the methylated polymer, and of vanillin, and vanillin-5-carboxylic acid by treatment of the polymer with alkali and nitrobenzene were lower than those reported by Freudenberg[5,6] from his spruce lignins. These data further emphasized the desirability of synthesizing the monomeric unit, 5-acetylvanillin, and studying its polymerization under controlled conditions.

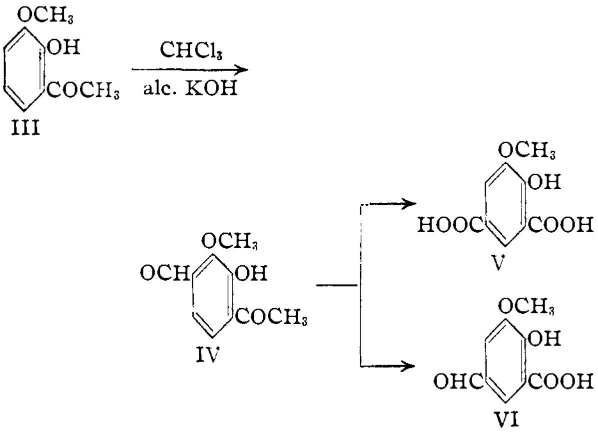
Attempts to isolate this monomer from the products of Fries rearrangement of vanillin acetate over a range of time and temperature conditions were totally unsuccessful. The isolation of a small amount of the isomeric 5-formyl-acetovanillone (II) from the reaction products of a Fries rearrangement of *o*-vanillin acetate (I) indicates that the acyl group rearranges in the expected manner.



I II

Attempts to prepare the monomer by Fries rearrangement of the anil and thioacetal of vanillin acetate were also unsuccessful.

The synthesis of the desired monomer (IV) was accomplished by formylation of 2-hydroxy-3-methoxyacetophenone (III), the latter having been prepared by known methods from *o*-vanillin.[7-10]



In most instances, the literature methods involved unduly laborious procedures. Several significant modifications and improvements are indicated in the experimental section.

The new step of the synthesis, formylation of III by the Reimer–Tiemann reaction[11] is of particular interest since it was accomplished under conditions normally assumed to be conducive to self-condensation of IV. The success of this reaction is a point in favor of the Armstrong and Richardson[12] theory that an intermediate formation of an acetal is involved in the preparation of hydroxyarylaldehydes by this method.

The product obtained by formylation of III gave positive tests for the phenolic hydroxyl-, aldehyde- and methylketo groups and yielded the bis-semicarbazone and bis-phenylhydrazone derivatives. Analytical values for the compound itself and for its derivatives were in good agreement with calculated values. The position of the formyl group was definitely established by conversion of IV to 4-hydroxy-5-methoxy-isophthalic acid (V) and to vanillin-5-carboxylic acid (VI). Identity of these products was established by mixed melting points with authentic samples prepared by other routes.

Direct conversion of IV to VI by the haloform reaction was not successful, but treatment of the benzenesulfonyl derivative (VII) with sodium hypochlorite gave VI in poor yield. More conclusive structure proof was obtained by permanganate oxidation of VII to VIII, followed by hypochlorite oxi-

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(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) A. Russell, This Journal, **70**, 1060 (1948).

(3) A. Russell, *ibid.*, **70**, 2864 (1948).

(4) A. Russell, J. H. Baity and H. E. Smith, *ibid.*, **71**, 956 (1949).

(5) Freudenberg, Engler, Flickinger, Sobek and Klink, *Ber.*, **71**, 1810 (1938).

(6) Freundenberg, Lautsch and Engler, *ibid.*, **73**, 167 (1940).

(7) Pauly, Schübel and Lockemann, *Ann.*, **383**, 288 (1911).

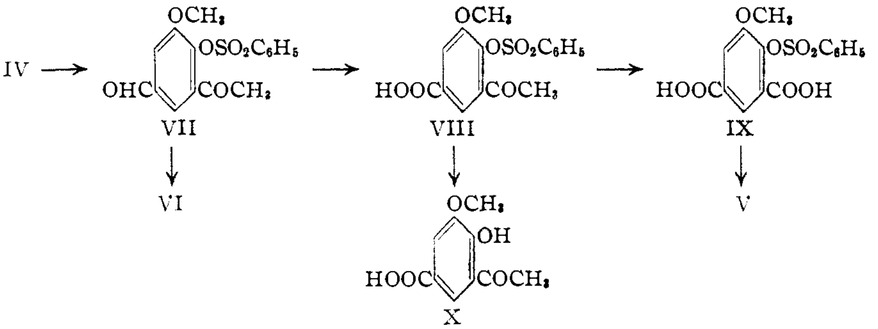
(8) Pauly and Buttlar, *ibid.*, **383**, 230 (1911).

(9) Krannichfeldt, *Ber.*, **46**, 4016 (1913).

(10) Reichstein, *Helv. Chim. Acta*, **10**, 392 (1927).

(11) Numerous attempts to prepare IV by various modifications of the Gattermann aldehyde synthesis on III resulted only in small yields of polymer and recovery of starting material.

(12) Armstrong and Richardson, *J. Chem. Soc.*, 496 (1933).



dation of VIII and subsequent hydrolysis of IX to give V in significant yield.

Hydrolysis of VIII gave 5-acetylvanillic acid (X), a new compound. Attempts to prepare X by the Fries rearrangement of vanillic acid acetate, the Hoesch synthesis using acetonitrile on vanillic acid, and the Reimer–Tiemann reaction using carbon tetrachloride on 2-hydroxy-3-methoxyacetophenone were unsuccessful.

The reference sample of V was obtained by partial demethylation of isohemipinic acid prepared by the method of Tiemann and Mendelsohn.[13]

The authentic sample of VI was prepared by formylation of *o*-vanillic acid by a modification of the procedure of Perkin and Stoyle.[14]

Experimental

2,3-Dimethoxybenzaldehyde.—Methylation of *o*-vanillin, by Buck's[15] procedure for veratraldehyde, and recrystallization from a decolorized solution in 66% ethanol gave a 78% yield of product melting at 50–52°. This was used in the subsequent step. A second recrystallization was necessary to attain the literature m.p. of 53–54°.[7]

2,3-Dimethoxyphenylmethylcarbinol.—Pauly and Buttlar's[8] method was modified by reducing the ratio of Grignard reagent to aldehyde to 2:1 and allowing the complex to stand overnight in the cold before decomposing. The crude product, obtained in 94% yield, slowly crystallized on prolonged standing in the cold (m.p. 34–37°), and was sufficiently pure for use in the subsequent oxidation step. Vacuum distillation of the crude carbinol gave a colorless product, b.p. 121° at 1.5 mm., n^{25}D 1.5295. Distillation of large quantities always resulted in considerable formation of the corresponding ether. This ether distilled at 195–196° at 3 mm. and melted at 58–60°. *Anal.*[16] Calcd. for $C_{20}H_{26}O_5$: C, 69.5; H, 7.57; OCH_3, 35.9. Found: C, 69.2; H, 7.4; OCH_3, 36.1

2,3-Dimethoxyacetophenone.—The dichromate oxidation of the carbinol by the procedure of Krannichfeldt[9] was difficult to control and gave low yields. By adding the acidic dichromate solution to the carbinol in 67% aqueous acetone below 10° the product after extraction, washing, drying and distillation was obtained in 65% yield. Material of b.p. 121–124° (3 mm.); n^{25}D 1.5300 was satisfactory for use in the next step. Redistillation gave a colorless product of b.p. 105–107° (1.5 mm.); n^{25}D 1.5305.[17]

2-Hydroxy-3-methoxyacetophenone (III).—Reichstein's[10] procedure of demethylation with aluminum chloride in nitrobenzene gave good results, but isolation of the product was laborious. Much better results were obtained with 30% hydrobromic acid in glacial acetic acid at 30° for 25 minutes. The crude product, from the bicarbonate washed ether extract, was obtained in 92% yield and was used in the subsequent step. Steam distillation gave a product of literature m.p. 53–54°.[10]

5-Acetylvanillin (IV).—To 192 g. (3.42 moles) of potassium hydroxide dissolved in 580 ml. of water was added 80 g. (0.48 mole) of 2-hydroxy-3-methoxyacetophenone (III) with stirring. The resulting suspension was dissolved by adding 400 ml. of ethanol and 800 ml. of water. Stirring was continued while 192 g. (1.6 moles) of chloroform was added over 10 minutes, the mixture heated to reflux, and an additional 192 g. of chloroform added over a thirty-minute period. Excess chloroform was removed under reduced pressure and the reaction mixture cooled in an ice-bath and made slightly acid by addition of 5 *N* HCl. Five successive ether extracts (300 ml. each) were combined, washed twice with 200-ml. portions of water and then extracted four times (100 ml. each) with freshly prepared 40% sodium bisulfite solution. Two (100 ml. each) water washes of the ether layer were added to the bisulfite extract. Removal of the ether on a steam-bath and steam distillation of the residue gave a 32 g. (40%) recovery of starting material (III).

The bisulfite solution was carefully acidified by portionwise addition of 25% sulfuric acid while air was bubbled through the solution to remove sulfur dioxide. When precipitation was complete (about 18 hours), the crude product was removed by filtration, washed with water, and dried. A suspension of this material in 800 ml. of methylcyclohexane was heated to boiling and filtered. The gummy residue was extracted twice more with 200-ml. portions of boiling solvent. The product, which crystallized from the cooled filtrate, was redissolved in 750 ml. of hot methylcyclohexane, the solution decolorized with activated carbon, and filtered. Cooling the filtrate gave 10.5 g. (18.7% of theory) of pale yellow needles, m.p. 120–121°. Qualitative tests for phenolic hydroxyl-, aldehyde- and methylketo groups were positive. *Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.84; H, 5.19; OCH_3, 15.98. Found: C, 61.8; H, 5.14; OCH_3, 16.09. The bis-semicarbazone, recrystallized from dilute ethanol, melted at 335–338° with decomposition. *Anal.* Calcd. for $C_{12}H_{16}O_4N_6$: C, 46.76; H, 5.19; N, 27.27. Found: C, 47.2; H, 5.2; N, 27.3. The bis-phenylhydrazone recrystallized from dilute ethanol melted at 186–188°. *Anal.* Calcd. for $C_{22}H_{22}O_2N_4$: C, 70.56; H, 5.92; N, 14.96. Found: C, 70.2; H, 5.5; N, 14.4.

5-Acetylvanillin Benzenesulfonate (VII).—5-Acetylvanillin (IV) was treated with benzenesulfonyl chloride in dry pyridine and the reaction mixture poured into cold water. The oily product solidified when stirred. The crude product was dried and recrystallized from isoöctane to give an 84.5% yield of white crystals m.p. 123–125°. *Anal.* Calcd. for $C_{15}H_{14}O_6S$: C, 57.8; H, 4.22; S, 9.58. Found: C, 57.8; H, 4.10; S, 9.52.

5-Acetylvanillic Acid Benzenesulfonate (VIII).—A solution of VII in acetone was heated to reflux and treated with an aqueous solution of potassium permanganate. The reaction mixture was cooled to 20°, made slightly alkaline and filtered. The filtrate was acidified and extracted with ether. Extraction of the ether layer with sodium bicarbonate solution and acidification of the extract precipitated a viscous, sticky product which solidified on standing several days in a vacuum desiccator; yield 93.5% of theory. Two recrystallizations, first from a benzene–heptane mixture and then from carbon tetrachloride gave a product melting at 145–148°. *Anal.* Calcd. for $C_{16}H_{14}O_7S$: C, 54.8; H, 4.03; S, 9.14. Found: C, 54.5; H, 3.94; S, 9.14.

5-Acetylvanillic Acid (X).—Hydrolysis of 0.75 g. of crude VIII with 20 ml. of 10% sodium hydroxide, followed by acidification, gave a white flocculent precipitate which was recrystallized from 450 ml. of water to give 0.43 g. (95.6%) of a white crystalline product melting at 213° with sublimation. *Anal.* Calcd. for $C_{10}H_{10}O_5$: C, 57.2; H, 4.78; neut. equiv., 210. Found: C, 57.2; H, 4.76; neut. equiv., (potentiometric) 213.

4-Hydroxy-5-methoxyisophthalic Acid (V).—To a solution of 1.2 g. of crude VIII in 20 ml. of 10% sodium hydroxide at room temperature was added in one minute with stirring 25

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[13] Tiemann and Mendelsohn, *Ber.*, **10**, 393 (1877).

[14] Perkin and Stoyle, *J. Chem. Soc.*, **123**, 3171 (1923).

[15] Buck, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., p. 619.

[16] All analyses were micro-determinations by C. H. Van Etten and Mary Wiele of this Laboratory.

[17] Amstutz, THIS JOURNAL, **71**, 2836 (1949), reports $n^{25.5}$D 1.5368.

ml. of freshly prepared sodium hypochlorite solution.[18] Stirring was continued for 15 minutes at room temperature and then at reflux temperature for 30 minutes. Acetone was added to destroy excess hypochlorite and the cooled solution acidified with dilute sulfuric acid. The crude product was isolated by ether extraction followed by sodium bicarbonate extraction and acidification. One recrystallization from 7 ml. of dioxane, trituration with two 7-ml. portions of chloroform, and a final recrystallization from 15 ml. of water gave 150 mg. of white crystals melting at 274–276°. By reworking the filtrates and washings, an additional 30 mg. of product (total yield 180 mg. (24.8%)) and 130 mg. of an impure chloro-compound, m.p. 190–230°, were obtained. A sublimed sample melted at 274–276°, corresponding to the literature value,[19] and showed no depression when mixed with an authentic sample prepared by partial demethylation of isohemipinic acid.[13] *Anal.* Calcd. for $C_9H_8O_6$: C, 50.95; H, 3.80; OCH_3, 14.61. Found: C, 51.0; H, 4.15; OCH_3, 14.9.

Vanillin-5-carboxylic Acid (VI).—To a stirred solution of 2.4 g. of VII in 40 ml. of dioxane and 40 ml. of 10% sodium hydroxide was added, over one minute, 50 ml. of sodium hypochlorite solution.[18] After 20 minutes at room temperature and 30 minutes at reflux temperature, acetone was added to destroy excess hypochlorite and the reaction mixture cooled and acidified. The product was removed from an ether extract with 10% sodium bicarbonate solution. The bicarbonate layer, freed of dioxane and acetone by ether extraction, was acidified with dilute sulfuric acid and extracted with ether. A sodium bisulfite extract of this ether layer was filtered, acidified, aerated and then extracted with ether. After drying the extract, the ether was removed. The crude product was vacuum-sublimed twice and then recrystallized from water. The pure product, 30 mg. (2.1%), melted at 253–255°. A mixed melting point with an authentic sample of vanillin-5-carboxylic acid showed no depression.

Summary

5-Acetylvanillin (2-hydroxy-3-methoxy-5-formylacetophenone), which has been proposed to be the monomeric unit in the formation of a lignin-like polymer, has been prepared by a five-step synthesis from *o*-vanillin.

The structure of this compound was established by converting it to 4-hydroxy-5-methoxyisophthalic acid and to vanillin-5-carboxylic acid. Mixed melting points of these products with authentic samples showed no depression.

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[18] Chlorine was passed into 20 ml. of 20% sodium hydroxide to neutrality. The solution was stabilized with an additional 5 ml. of base.

[19] Freudenberg and Klinck, *Ber.*, **73B**, 1369 (1940).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Acid-catalyzed Rearrangement of Some Aromatic Ketones[1]

BY WILLIAM A. MOSHER AND MELVIN L. HUBER[2]

In the course of a study of the reactions of Grignard reagents with β-benzopinacolone, we had occasion to reinvestigate the results in this connection reported by Schmidlin and Wohl.[3] These workers studied the forced reaction of phenylmagnesium iodide with β-benzopinacolone and reported "dehydropentaphenylethanol" as one of the products and described its isomerization with sulfuric acid to "isodehydropentaphenylethanol." However, the structures of these two compounds were not established.

When "dehydropentaphenylethanol" was oxidized with chromic anhydride in aqueous acetic acid, triphenylcarbinol and *o*-phenylbenzoic acid were obtained.[4] When heated with potassium hydroxide in alcohol, triphenylmethane and *o*-phenylbenzoic acid were formed. This latter method of cleavage has been used extensively in the determination of the structures of pinacolones in the aromatic series.[5] A new pinacolone which was identical with the product of the forced Grignard addition was synthesized by coupling triphenylmethylsodium with *o*-phenylbenzoyl chloride. "Dehydropentaphenylethanol" is, therefore, *o*-biphenyl triphenylmethyl ketone (I) which is formed by 1,4-addition of the Grignard reagent into the phenyl ring.

The infrared absorption spectra of "dehydropentaphenylethanol" (I) showed strong carbonyl absorption but was negative for the hydroxyl band; "isodehydropentaphenylethanol," on the other hand, was positive for hydroxyl but showed no carbonyl absorption band. Its structure was established by cleavage with potassium hydroxide to yield *o*-(α,α-diphenyl-*o*-tolyl)-benzophenone (III) and by oxidation with chromic acid to give the "keto-carbinol" (IV) described by Sergeev,[6a,b] The structure of the new ketone (III) was established by its cleavage into *o*-(α,α-diphenyl-*o*-tolyl)-benzoic acid on fusion with potassium hydroxide and by its synthesis from the methyl ester of *o*-(α,α-diphenyl-*o*-tolyl)-benzoic acid with one mole of phenylmagnesium bromide and also by its conversion with phenyl Grignard to the tertiary alcohol, *o*-(*o*-benzohydrylphenyl)-triphenylcarbinol, previously prepared.[6b] "Isodehydropentaphenylethanol" is therefore 9,10,10-triphenyl-9,10-dihydro-9-phenanthrol (II). This structure was confirmed by synthesis involving the reaction of phenyllithium on 10,10-diphenyl-9-phenanthrone (V). These facts are summarized in Fig. 1.

The rearrangement of *o*-biphenyl triphenylmethyl ketone was so unusual that the same reaction was employed using the related α-naphthyl triphenylmethyl ketone. In this case rearrangement was somewhat slower but the principal prod-

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[1] Presented before the Division of Organic Chemistry, American Chemical Society, Philadelphia, April, 1950. This manuscript taken from the Ph.D. dissertation of M. L. Huber, School of Graduate Studies, University of Delaware, 1950.

[2] F. G. Cottrell Research Fellow. Eastern Laboratory, E. I. du Pont de Nemours and Co., Gibbstown, N. J.

[3] Schmidlin and Wohl, *Ber.*, **43**, 1145 (1910).

[4] Schmidlin and Wohl[3] reported the formation of β-benzopinacolone when "dehydropentaphenylethanol" was oxidized with chromic anhydride in acetic acid solution. We have not been able to duplicate this observation although our "dehydropentaphenylethanol" has properties identical with those reported by them and it is converted to "isodehydropentaphenylethanol" identical in properties with theirs.

[5] *Cf.* W. E. Bachmann and J. W. Ferguson, THIS JOURNAL, **56**, 2081 (1934).

[6] (a) Chichibabin and Sergeev, *Ber.*, **59**, 657 (1926); (b) Sergeev, *J. Russ. Phys.-Chem. Soc.*, **61**, 1421 (1929).