SOME DERIVATIVES OF VANILLIN

by

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INTRODUCTION

Vanillin, 3-methoxy-4-hydroxy benzaldehyde, gets its name from the vanilla bean in which it occurs to the extent of 2 to 3%. The first chemist to isolate it was Gobley (1) who obtained it by the fractional crystallization of a strong alcoholic extract of vanilla beans.

Tiemann (1), famous nineteenth century chemist, who has contributed much original work to the chemistry of perfume materials is credited with the first synthesis of vanillin. His starting material was pine wood - a rather remarkable fact, since history has only recently completed the circle by the commercial lignin process. The last named process uses for its prime material the waste sulfite liquors resulting from the manufacture of paper from wood pulp, an industry which booms in the North woods of Wisconsin.

Tiemann did not have this convenient paper by-product to work with. He was investigating coniferin, a glucoside which occurs in pine wood. When this glucoside was split into its sugar component and its other component or aglucon, the latter was found to be coniferyl alcohol. Tiemann subjected the last named compound to a number of reactions to break it down into known compounds that would clarify its structure. Using a mixture of potassium dichromate and sulfuric acid Tiemann found that coniferyl alcohol gave vanillin and acetaldehyde.

From Gobley's extraction of the vanilla bean to the recent synthesis from sulfite waste liquors there have been many more syntheses of vanillin,

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(1) The Givaudanian, page 4, August 1938.

and the price has fallen from $800 a pound to $2 to $3 per pound along with an increase in supply that not only equals but exceeds the demand.

Due to the high cost of vanillin before the development of the sulfite liquor process there was only a limited amount of work done on it. However, in the past six years there has been an enormous amount of experimental work done on this compound.

Vanillin is an essential flavor and perfume material and serves as a possible starting point for certain drug syntheses.

REVIEW OF LITERATURE

Derivatives of Vanillin

Cerezo (1) and Blauksma (2) condensed vanillin and 2, 4-dinitrophenylhydrazone to produce the corresponding vanillin derivative. By using 2, 4-dinitrophenylmethylhydrazone Blauksma also prepared the vanillin (2,4-dinitrophenyl) methylhydrazone. Strain (3) used 3-nitrobenzohydrazone to prepare vanillin-3-nitrobenzohydrazone and to prepare vanillin nitroguanylhydrazone, Whitmore (4) condensed vanillin with nitroaminoguanidine. Maurenbrecker (5) used diphenylhydrazone and prepared vanillindiphenylhydrazone while Graziani (6) made use of p-chlorophenylhydrazone to prepare the corresponding vanillin hydrazone. To prepare vanillin-2-anthraquinonylhydrazone Mohlau (7) condensed vanillin with 2-anthraquinonylhydrazone and Padoa (8) condensed vanillin with p-anislyhydrazone to form the corresponding derivative. Padoa also condensed vanillin with 1,4,5-xylyhydrazone (9), 1,2,4-xylyhydrazone and 1,3,4-xylyhydrazone (10).

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(1) J. Cerezo and E. Olay, Anoles soc. espan. fis. quim 32, 1090-9 (1934).
(2) J. Blauksma and M. Wackers, Rec. trav. chim., 55,655-60 (1936).
(3) H. Strain, J. Am. Chem. Soc., 57,758-81 (1935).
(4) W. Whitmore and G. Smith, ibid., 57,706-7 (1935).
(5) A.Maurenbrecker, Ber. 39,3583-87.
(6) F. Graziani, Atti. acad. Lincei, 22, I, 623-9.
(7) R. Mohlau, Ber. 45, 2244-8.
(8) M. Padoa, Atti. acad. Lincei, 20, II, 196-200.
(9) ibid. 19, II, 193-6.
(10) ibid. 18, II, 559-64.

Continuing his work with vanillin Padoa prepared vanillinnaphthylhydrazone (1), vanillinmethylphenylhydrazone (2), and vanillin-p-tolyhydrazone (3). Working with vanillin and n-methyl-p-nitrophenylhydrazone Ciusa (4) prepared the corresponding vanillin derivative, and using benzyl-β-naphthlyhydrazine his product was vanillinbenzyl-β-naphthylhydrazine (5). Rothenfusser (6) changed to β-naphthylhydrazine hydrochloride and got the corresponding vanillin derivative. Using ethyl-p-nitrophenylhydrazine Barattini (7) prepared vanillin-N-ethyl-p-nitrophenylhydrazine. By condensing vanillin and p-bis-triazobenzene hydrochloride Schoutissen (8) prepared vanillin-p-hydrazinobenzene and Tierie (9) prepared 3-methoxy-4-hydroxybenzal by using oxanilhydrazide (5-phenylsemioxamazide).

Bulow (10) found that vanillin-2,4-dichlorophenylhydrazine gives a diazonium salt with chlorine in cold alcohol. By reacting acetylvanillin and p-nitrophenyl hydrazone Quilico (11) prepared acetylvanillin-p-nitro-

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(1) M. Padoa, Atti. acad. Lincei, 20, II, 712-7.
(2) ibid., 22, II, 32-41.
(3) ibid., 18, II, 269.
(4) V. Ciusa and G. Rastelli, Gazz. chim. ital., 54, 72-8 (1934).
(5) ibid., 58, 153-9 (1928).
(6) S. Rothenfusser, Arch. Pharm., 245, 360-76.
(7) Barattini, Grazz. chim. ital., 56, 821-5 (1926).
(8) H. Schoutissen, Rec. trav. chim., 53, 561-6 (1934).
(9) G. Tierie, ibid. 52, 533-7 (1933).
(10) C. Bulow, J. Chem. Soc., 114, I, 314-5.
(11) A. Quilico and E. Fleischner, Gazz. chim. ital, 59, 39-49 (1928).

phenylhydrazone. Hann (1) from chlorovanillin prepared the following derivatives: oxime, oxime hydrochloride, oxime hydrobromide, hydrazone, phenylhydrazone, semicarbazide, and thiosemicarbazide.

Henderson (2) prepared vanillin semicarbazonedihydrochloride while Toschi (3) prepared vanillin diphenylsemicarbazone. Vanillin-4-(p-nitrophenyl) semicarbazide was prepared by Barre (4) and Tierie (5) using vanillin and semioxamazone prepared 3-methoxy-4-hydroxy benzal. De Vries (6) made vanillin-5-cyclohexylsemioxamazone and Brady (7) made vanillin-oxime. Raiford (8) prepared vanillin nitrooxime and vanillamide-2-nitroacetate while Bellavita (9) prepared n-p-tolyvanillaldoxime. Brady (10) converted 5-bromovanillin into the oxime in the presence of sodium acetate. Raiford (11) found that 6-bromovanillinoxime and acetic anhydride give the acetyl derivative.

In a reaction of vanillin and phenylisoazolone Meyer (12) prepared vanillin phenylisoazolone. Lapworth (13) reacted equal moles of vanillin and $NCCH_2CO_2CH_2CH_2$ to form the product ethylanillylidenecyanoacetate.

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(1) R. Hann and G. Spencer, J. Am. Chem., Soc., 49, 535-7 (1927).
(2) J. Henderson and I. Heilbron, J. Chem. Soc., 107, 1740-52 (1915).
(3) B. Toschi and A. Angiolani, Gazz. chim. ital., 45, I, 205-13 (1915).
(4) R. Barre and L. Piche, Can. J. Research, 20B, 17-20 (1942).
(5) G. Tierie, Rec. trav. chim., 52, 357-65 (1933).
(6) K. de Vries, ibid. 61 223-43 (1942).
(7) O. Brady and F. Dunn, J. Chem. Soc., 105, 2409-19 (1914).
(8) L. Raiford and O. Nitz, Proc. Iowa Acad. Sci., 45, 127-32 (1938).
(9) V. Bellavita, Gazz. Chim. ital., 70, 584-94 (1940).
(10) Brady and Dunn, J. Chem. Soc., 107, 1858-62 (1915).
(11) L. Raiford and W. Stoesser, J. Am. Chem. Soc., 2556-63 (1928).
(12) A. Meyer, Compt. rend., 156, 714-7.
(13) Lapworth, J. Chem. Soc., 111, 790-8 (1917).

Using p-aminobenzoic acid Wheeler (1) prepared 3-methoxy-4-hydroxybenzal-p-aminobenzoic acid, while Clarke (2) used benzidene to get 3-methoxy-4-hydroxybenzalbenzidene and Dugan (3) condensed vanillin and 4-aminomorpholine to prepare vanillin-4-aminomorpholine. Carre (4) condensed vanillin and aniline in the presence of ethyl alcohol to produce vanillinaniline, m.p. 155-6 degrees Centigrade, which he claims loses water at 115 degrees Centigrade to give vanillalaniline. Working with vanillin and 2,4-dinitrotoluene Pastak (5) prepared 2,4-dinitro-3-methoxy-4-hydroxystilbene while from 2,4,6-trinitrotoluene the product was 2,4,6-trinitro-3-methoxy-4-hydroxystilbene. Senier (6) prepared vanillidene-m-toluidine and by treating vanillin with $NH_2OH.HCl$ Nelson (7) made vanillylamine. From acetic anhydride and vanillylideneanthranilic acid Ekeley (8) prepared 3-methoxy-4-hydroxyphenylacetoketodihydrobenzeneozazine, while Raiford (9) condensed vanillalacetone with 4-dimethylaminobenzaldehyde to prepare Vanillal(4-dimethylaminobenzal) acetone. By treating vanillyamine with acid chlorides Ford (10) found

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(1) A. Wheeler, J.Am.Chem.Soc., 35, 976-8.
(2) E. Clarke and H. Torrey, ibid., 31, 583-5.
(3) L. Dugan and H. Haendler, ibid., 64, 2502 (1942).
(4) Carre, Bull. soc. chim., 43, 73-4 (1928).
(5) A. Pastak, ibid., 39, 72-7 (1926).
(6) A. Senier and Shephea, J. Am. Chem. Soc., 95, 1943-55.
(7) E. Nelson, U.S. Patent 1,329,272, Jan. 27, 1920.
(8) J. Ekeley and P. Dunn, J. Am. Chem. Soc., 34, 161-4.
(9) L. Raiford and M. Cooper, J. Org. Chem., 3,11 (1938).
(10) A. Ford and J. Phillips, Rec. trav. chim., 53, 847-59 (1934).

that the corresponding vanillyamides were formed. From vanillal and phenylethylamine Becker (1) prepared vanillalphenethylamine. Through vanillin cyanohydrin by reacting it with the imido ester hydrochloride and ethyl ester Schwartz (2) prepared 4-hydroxy-3-methoxymandelamide. Raiford (3) prepared 2-iodovanillin through the diazo reaction on 2-aminovanillin and the iodovanillin reacted with dimethyl sulfate gives iodo-3,4-dimethoxybenzaldehyde. Kornr (4) reports that "American pepper gas", a powerful irritant, is n-heptoylvanillylamide. Hann (5) prepared the following 5-iodovanillin derivatives; aniline, o- and p-chloroaniline, p-iodoaniline, p-bromoaniline, o- , p- , and m-toluidine, α-naphthylamine, psuedocumidine, and benzidene. Makarov (6) prepared vanillidene methyl amine from vanillin and methylamine and claims that vanillin and nitromethane condense to give vanillidenenitromethane while Raiford (7) claims that vanillin and nitromethane condense to give the related β-nitrostyrenes.

Working with vanillin and p-thio-p-tolyaniline Heiduschka (8) prepared vanillidene-p-thio-p-tolyaniline and Hann (9) changed to 2-phenylimino-3-phenyl-4-thiozolidone and chlorine to produce the chlorovanillin

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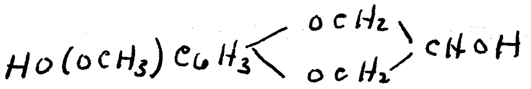
(1) H. and P. Becker, Ann., 395, 362-77.
(2) H. Schwartz and J. McCarthy, Can. J. Research, 19B, 150-2 (1942).
(3) L. Raiford and E. Wells, J. Am. Chem. Soc., 57, 2500-3 (1935).
(4) N. Kornr, Gasschutz u. Luftschutz, 7, 45-6 (1937).
(5) R. Hann, J. Wash. Acad. Sci., 14, 79-86 (1924).
(6) S. Makarov, J. Prakt. chim., 141, 77-90 (1934).
(7) L. Raiford and Perry, J. Org. Chem., 7, 354 (1942).
(8) A. Heiduschka and H. Longkammerer, J. Prakt. chim., 88, 425-42.
(9) Hann, J. Wash. Acad. Sci., 16, 169-75 (1926).

derivative. Vanillin-p-thiocyanophenylhydrazine acetate was prepared by Horii (1) and mesylvanillin was prepared by Helfrich (2) from chloromethylsulfonate and vanillin.

Finkelstein (3) produced a dark red amorphorous powder, $C_{14}H_{12}O_5$, by reacting vanillin and phloroglycinol, while vanillin condensed with p-methylcyclohexanol gives vanillin-p-methylcyclohexanol according to Bethune (4). Dodge (5) condensed vanillin with glycerol to form vanillin glyceride to which he gives the following structure:



$$HO(OCH_3)C_6H_3\left<\begin{matrix}OCH_2\\ OCH_2\end{matrix}\right>CHOH$$

Helferich (6) prepared the hepta-acetate derivative of vanillin- -d-lactoside by reacting vanillin and acetobromolactose with potassium hydroxide while Reichel (7) claims that vanillin and acetobromoglucose in acetone condense to form vanillin-β-d-glucoside tetraacetate, and Claser (8) prepared pentaacetyl-β-vanillin-α-glucoheptoside by reacting vanillin and β-acetobromo-α-glucoheptose. Hoesch (9) found that vanillonitrite, phloroglucinol and anhydrous zinc chloride treated in ethyl alcohol with hydrogen chloride gas yields a mass of the ketone-

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(1) Z. Horii, J. Pharm. Soc. Japan, 56, 53-7 (1936).
(2) B. Helfrich and P. Papalambrau, Ann., 551, 242-8 (1942).
(3) L. Finkelstein, Montash., 34, 1913-55.
(4) C. de Bethune, Fr. Petent No. 42,143, May 31, 1933.
(5) F. Dodge, J. Am. Chem. Soc., 44, 1405-7 (1922).
(6) B. Helferich and R. Griebel, Ann., 544, 191-205 (1940).
(7) L. Reichel and R. Schickle, Ber., 76B, 1134-7 (1943).
(8) E. Claser and N. Zuckermann, Z. Physiol. Chem., 166, 103-24 (1927).
(9) K. Hoesch and T. Zarzecki, J. Chem. Soc., 112, I, 342-3.

imidehydrochloride which is hydrolyzed by boiling water to vanillophloroglucinol and by substituting resorcinol for phloroglucinol vanilloresorcinol is formed.

By condensing vanillin and sulfanilic acid in the presence of potassium hydroxide Haussler (1) formed potassium-1-hydroxy-2-methoxy-4-benzylidine-1-aniline-4-sulfonate while Holmberg (3) prepared a derivative of vanillin using thiohydracrylic acid. Raiford (4) made use of α-acetylaminocinnamic acid in anhydrous sodium acetate to prepare vanillin-α-acetylaminocinnamic acid and Madsen (5) reacted vanillin with salicylic acid to form vanillin salicylate. Adams (6) prepared vanillin oxalate by using oxalic acid, Dalal (7) used malonic acid to prepare a vanillin derivative. Akabori (8) prepared a vanillin derivative of 1,3-dimethylbarbituric acid while Weil (9) condensed vanillin with pyruvic acid to get the product $C_{29}H_{28}O_7N_2$. Pauley (10) reacted methoxymethyl-p-vanillin with acetic acid to form methoxymethyl-p-coniferaldehyde which upon hydrolysis gives p-coniferaldehyde and Hann (11) found that the halogen vanillal tolylrhodanic acids are formed by the condensation of rhodanic

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(1) E. Haussler, Z. anal. chem., 53, 691-5 (1914).
(3) B. Holmberg, Arkivemi, Mineral Geol., 15A, No. 8, 1-15 (1942).
(4) L. Raiford and C. Buurman, J. Org. Chem., 8, 466-72 (1943).
(5) E. Madsen, Arch. Pharm., 247, 65-77.
(6) R. Adams and H. Gilmer, J. Am. Chem. Soc., 37, 2716-20 (1915).
(7) M. Dalal and S. Dutt, J. Indian Chem. Soc., 9309-14 (1932).
(8) S. Akabori, Proc. Imp. Acad. (Japan)3, 342-4 (1927).
(9) St. Weil, Bull. trav. inst. etat. No. 6, 1-6 (1927).
(10) H. Pauley and K. Wascher, Ber., 56B, 603-10 (1923).
(11) R. Hann, J. Am. Chem. Soc., 47, 1998-2002 (1925).

acid and halogenated vanillin in acetic acid.

Raiford (1) prepared vanillamide-2-nitroacetate and vanillinnitrooxime while Csaros (2) condensed vanillin and urea. By reacting vanillin and p-nitrobenzylchloride Nair (3) prepared ortho- and paranitrobenzylvanillin and Raiford (4) nitrated and brominated vanillin benzoate, while Lyons (5) by condensing p-nitrobenzyl and vanillic acid prepared the p-nitrobenzyl ester of vanillic acid. Borsche (6) treated acetyl vanillonitrite with cold fuming nitric acid to get nitro-4-cyano-6-methoxyphenylacetate, and Raiford (7) reports that chlorine and bromine substituted vanillinoxime causes no appreciable hindrance in the formation of acetoxynitriles.

Currie (8) shook vanillin, dimethyl ketone, and vertroyl chloride for two hours to prepare 3,3,4-trimethoxy-p-dibenzaldehyde while Claser (9) condensed vanillin and dimethyl ketone in the presence of hydrochloric acid to produce divanillin acetone and Ichikawa (10) condensed vanillin with methylethyl ketone to prepare 4-hydroxy-3-methoxystyrylethylketone. Horning (11) used menthone to prepare the corresponding

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(1) L. Raiford and O. Nitz, Proc. Iowa Acad. Sci., 45, 127-32 (1938).
(2) Z. Csaros and F. Vass, Magyar Chem. Folyoirat, 45, 30-54 (1939).
(3) P. Nair and R. Robinson, J. Chem. Soc., 1932, 1236-9.
(4) L. Raiford and J. Milbery, J. Am. Chem. Soc., 2727-9 (1934).
(5) E. Lyons and E. Reid, ibid, 39, 1727-50 (1917).
(6) W. Borsche, J. Chem. Soc., 114, I, 11-4.
(7) L. Raiford and D. Porter, J. Am. Chem. Soc., 55, 1682-5 (1933).
(8) T. Currie and A. Russell, J. Chem. Soc., 1932, 2263-5.
(9) E. Claser and E. Tramer, J. Prakt. Chem., 116, 331-46 (1927).
(10) J. Ichikawa, Sci. Rept. Tohoku Imp. Univ., 14, 127-9 (1925).
(11) E. and M. Horning, J. Org. Chem., 11, 9509 (1946).

vanillin derivative. By refluxing 6-bromovanillin and anhydrous acetone in potassium carbonate Helferich (1) prepared the allyl ether while Raiford (2) found that the chlorine and bromine derivatives of vanillin condense in the presence of sodium hydroxide with acetophenone to give mono- and diacetophenone. Using palladiumized animal charcoal Merz (3) prepared vanillylacetone from vanillidene acetone, and from acetylvanillin and dimethylcyclohexanedione Bernardi (4) produced a compound $C_{26}H_{32}O_7$.

Using mercuric oxide as an oxidizing agent Pearl (5) converted vanillin to vanillic acid while Richtzenhain (6) used hydrogen peroxide and got the following acids: formic, acetic, glycolic, lactic, malonic and tartonic.

Raiford (7) and Pschorr (8) brominated vanillin with bromine in carbon tetrachloride to prepare 5-bromovanillin, and Raiford (9) also prepared the 5,6-dibromo derivative by bromination in glacial acetic acid. Cartwright (10) refluxed 5-bromovanillin and ethylmagnesiumiodide, 5-bromovanillin and acetic anhydride, 5-bromovanillin and malonic acid to prepare 1-(5-bromo-4-hydroxy-3-methoxy phenyl) propyl alcohol, 5-bromo-4-hydroxy-3-methoxy benzaldehyde and 5-bromo-4-hydroxy-3-methoxy cinnamic

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(1) B. Helferich and R. Griebel, Ann., 544, 191-205 (1940).
(2) L. Raiford, Proc. Iowa Acad. Sci., 39, 175 (1932).
(3) K. Merz and C. Mannich, Arch. Pharm., 265, 104-6 (1927).
(4) A. Bernardi, Ann. chim. applicata, 17, 163-6 (1927).
(5) I. A. Pearl to C. G. Parker, U.S. Patent No. 2, 414,119, Jan. 14, 1947.
(6) H. Richtzenhain, Ber., 75B, 269 (1942).
(7) L. Raiford and M. Ravely, J. Org. Chem., 5, 204 (1940).
(8) R. Pschorr, Ann., 391, 23-39.
(9) L. Raiford and H. Gilman, J. Am. Chem. Soc., 49, 1571-7 (1927).
(10) N. Cartwright and R. Haworth, J. Chem. Soc., 1944, 535-7.

acid respectively, while Ittyerah (1) claims 5-bromovanillin and malonic acid condense to give 5-bromo-4-hydroxy-3-methoxy cinnamanilide.

Vanillin hydrobromide was prepared by Gomberg (2) and Raiford (3) prepared 5-iodovanillin and 2,5-diiodovanillin, and Howells (4) prepared α-(4-benzoyl-3-methoxyphenyl) butylcarbinol from vanillin benzoate and butylmagnesiumiodide.

Adams (5) hydrogenated vanillin using platinum oxide as a catalyst while Pearl (6) reduced vanillin to unpolymerized vanillyl alcohol by the crossed Cannizzaro reaction with excess formaldehyde and sodium hydroxide using silver as a catalyst. King (7) prepared vanillin ethers and esters by treating acyl or aralkyl derivatives of vanilloyl chloride in solution in toluene at boiling temperature with hydrogen in the presence of a catalyst such as nickel. The esters and ethers of vanilloyl chloride may be prepared by treating vanillic acid with acyl or aralkyl chlorides and converting with thionyl chloride. Pearl (8) also reacted vanillin with sodium hydroxide using silver oxide as a catalyst to prepare 4,4'-dihydroxy-3,3'-dimethoxydiphenylmethane and by caustic fusion of vanillin

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(1) P. Ittyerah and K. Pandya, Proc. Indian Acad. Sci., 20A, 169-74 (1944).
(2) M. Gomberg and L. Cone, Ann., 376, 183-283.
(3) L. Raiford and E. Wells, Proc. Iowa Acad. Sci., 43, 207 (1936).
(4) H. Howells and H. Andersen, J. Am. Chem. Soc., 4076-82 (1930).
(5) Adams, J. Am. Chem. Soc., 46, 1675-83 (1924).
(6) Pearl, I. A. to C. G. Parker, U.S. Patent No. 2,414,120, Jan. 1, 1947.
(7) A. King and T. Kane, Brit. Patent No. 131,161, Aug. 20, 1918.
(8) I. Pearl, J. Am. Chem. Soc., 67, 1628-9 (1945).

below 250 degrees Centigrade. He (1) prepared vanillic acid quantitatively whereas above 250 degrees Centigrade the product is protocatechuic acid.

Christi (2) prepared a vanillin derivative by reacting vanillin with thallous salts and Nakatsuka (3) prepared copper vanillin-o-phenylenediimine by reacting vanillin and copper acetate, and from vanillin and o-amino aniline and copper acetate he prepared vanillin-o-amino phenylimine dicopper. Vanino (4) prepared bismuth vanillate from vanillin and bismuth salts.

By the action of mercuric acetate on methyl lignin Freudenberg (5) prepared vanillinacetoxymercuric while Henry (6) and Rossi (7) prepared a mercury derivative of vanillin using mercuric acetate and Paolini (8) prepared acetomerivanillin from vanillin and mercuric acetate in acetic acid. Takaki (9) reacted vanillin and NH_4-Hg to get vanillic acid. Using vanillin and ferric acetate in sodium hydroxide Weinland (10) prepared sodium tetravanillin-ferrate.

Methylating vanillin in the presence of potassium hydroxide Decker (11)

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(1) I. Pearl, J. Am. Chem. Soc., 68, 1100-1 (1946).
(2) Christi, J. Chem. Soc., 2369-73 (1925).
(3) Y. Nakatsuka and H. Iimuma, Bull. Chem. Soc. Japan, 11, 358-62 (1936).
(4) L. Vanino and F. Mussgung, Arch. Pharm., 251, 261-9 (1919).
(5) K. Freundenberg and H. Muller, Ber., 71B, 2500-4 (1938).
(6) T. Henry and T. Sharp, J.Chem. Soc., 1930, 2279-89.
(7) G. Rossi and M. Ragno, Ann. chim. applicata, 29, 146-7 (1939).
(8) V. Paolini, Gazz. chim. ital., 51, II, 188-94 (1921).
(9) S. Takaki and T. Ueda, J. Pharm. Soc. Japan, 58, 44-59 (1938).
(10) R. Weinland and H. Neff, Arch. Pharm., 252, 600-8 (1910).
(11) H. Decker and O. Koch, Ber., 40, 4795.

prepared potassium vanillate.

Russell (1) prepared a substance very much like lignin by acetylating vanillin and then treating the product with aluminum chloride.

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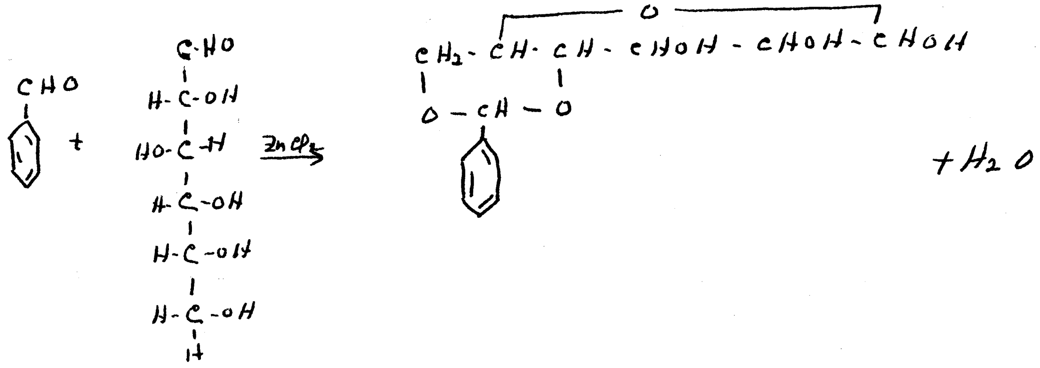
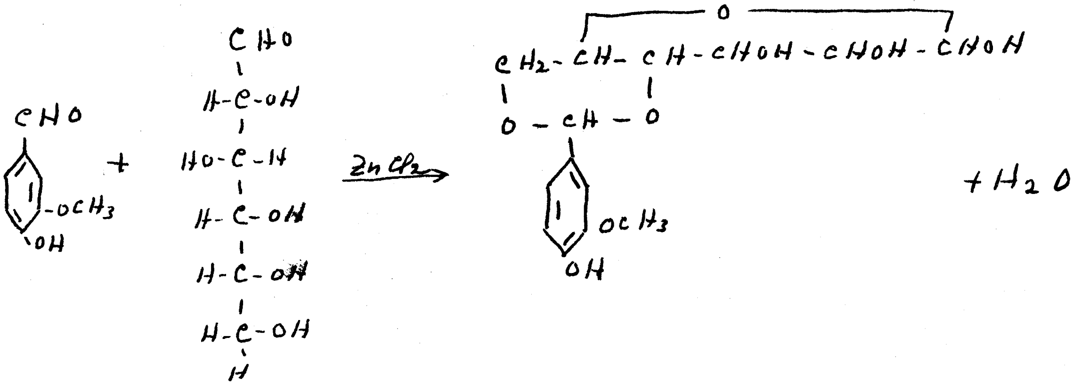
(1) A. Russell, Chem. and Eng. News, 2894, Oct. 6, 1947.

DISCUSSION OF RESULTS

In the reaction of vanillin and glucose in 1,4-dioxane with anhydrous zinc chloride as the condensing agent it was hoped to get a reaction analogous to that of glucose and benzaldehyde as follows (1):



The corresponding vanillin and glucose reaction hoped for is as follows:



There was a resinous material formed that decomposed at 118 degrees Centigrade giving off a gas. However, all attempts to purify and crystallize this material failed which greatly complicates this reaction.

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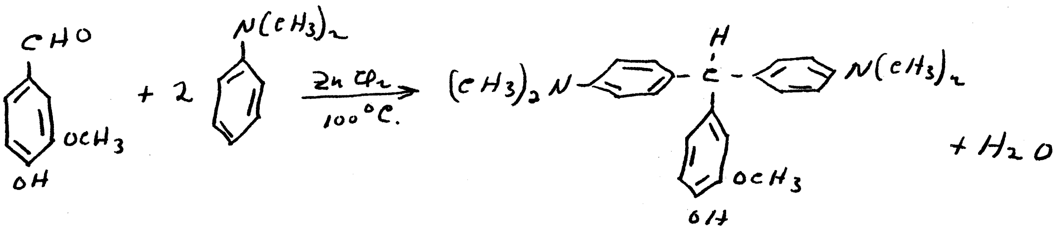
(1) L. Zervas, Ber., 64, 2293 (1931)

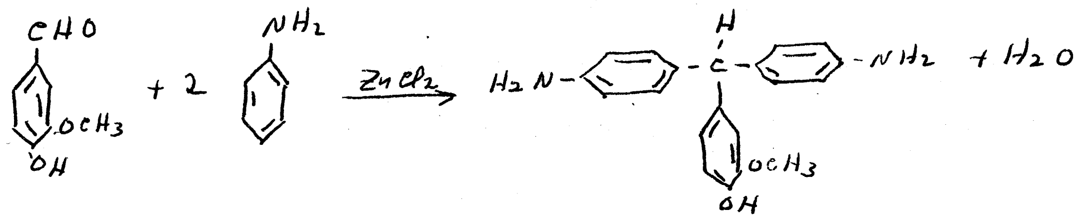
In the reaction of vanillin and dimethylaniline using anhydrous zinc chloride as the condensing agent, two moles of dimethyl aniline condense with one mole of vanillin to form a triphenyl methane derivative, tetramethyl-diamino-p-hydroxy-m-methoxytriphenylmethane, m.p. 128.5-29.5 degrees Centigrade. The reaction is as follows:



Three runs were made and the first was only heated on the water bath for three hours and gave a yield of 11.1%. In the second by only changing the reaction time by increasing the time on the water bath to ten hours the yield was increased to 15.6% and in the third run the mixture was constantly stirred throughout the whole ten hours on the water bath and the yield was increased to 22.5%.

The reaction proceeds without any particular difficulty and the product prepared is of well-defined crystalline form, easily purified by recrystallizing from benzene. The molecular weight determinations, methoxy determinations and acetylations agree with the structure given above.

In the reaction of vanillin and aniline using anhydrous zinc chloride as the condensing agent, two moles of aniline condense with one mole of vanillin to form a triphenyl methane derivative, diamino-p-hydroxy-m-methoxytriphenyl methane, m.p. 153-4 degrees Centigrade. The reaction is as follows:



Carre (1) prepared a derivative of vanillin by condensing it with aniline in the presence of ethyl alcohol. His product lost water at 115 degrees Centigrade and melted with decomposition at 155-6 degrees Centigrade. This is as far as he went with his work on this compound.

The yield in this reaction given above is 24.1% and it proceeds without any difficulty. The product crystallizes in well-defined rhombohederal crystalls and is easily purified by recrystallizing from benzene. The molecular weight determinations, methoxy determinations and the acetylations agree with the structure as given above.

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(1) Carre, Bull. soc. chim., 43, 73-4 (1928).

EXPERIMENTAL

Description of Apparatus Used

For the vanillin-glucose reaction a 500-ml. three neck round bottom flask was used for the reaction mixture. A thermometer was placed in one small neck and a reflux condenser attached to the large neck. The reaction mixture was heated on an oil bath, the heat being supplied from an electric hot plate.

For the vanillin-dimethyl aniline reaction a 500-ml. flask was used with an electric stirrer attached through the neck.

There is not any apparatus needed for the vanillinaniline reaction other than an ordinary beaker because the reaction is exothermic and proceeds almost instantaneously.

Melting points were determined in the ordinary way using a bath of 85% phosphoric acid.

For molecular weights which were all obtained by the freezing point method, an ice bath and Beckman thermometer were used. The solvents used were benzene and nitrobenzene.

For the methoxy determinations a 125-ml. distilling flask with a side arm was used. Carbon dioxide, generated from a Kipp generator and then passed through a flask containing a dilute solution of lead acetate, was passed into the side arm of the distilling flask. The distilling flask was then attached to a reflux condenser, cooled by water. To the condenser was attached a u-tube used as a wash bath, and containing red phosphorus suspended in water. To this wash bath was connected two receivers containing 15 mls. of 10% sodium acetate in glacial acetic acid and 15 drops of bromine.

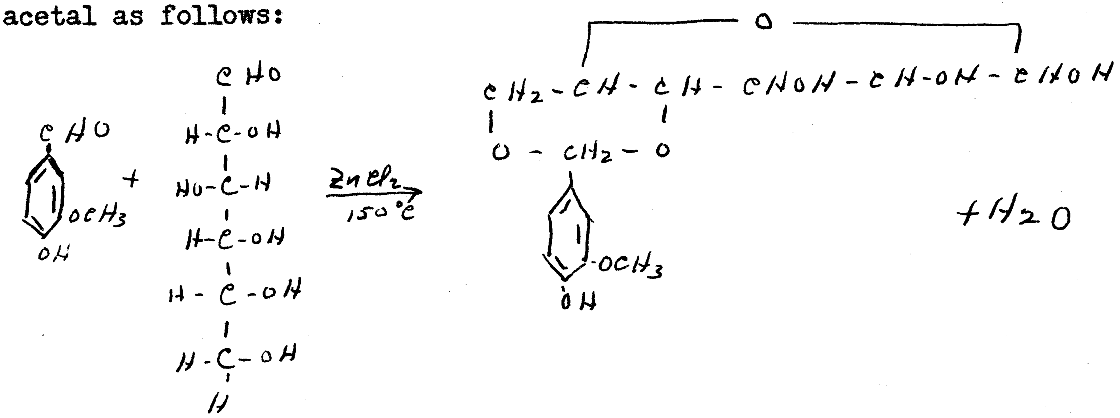
The acetylation reactions were all carried out in an ordinary beaker using acetyl bromide.

Distillation was carried out in the customary apparatus.

The apparatus for preparing hydriodic acid consists of a hydrogen sulfide generator, a 500 ml. round bottom flask with a stirrer inserted through the neck and a delivery tube running from the reaction flask to a beaker containing sodium hydroxide. This beaker is to destroy any excess hydrogen sulfide not used in the reaction.

Vanillin-Glucose Reaction

The reaction hoped for in this case was the formation of a hemiacetal as follows:



But due to the inability to prepare a compound free of resinous material this was not accomplished.

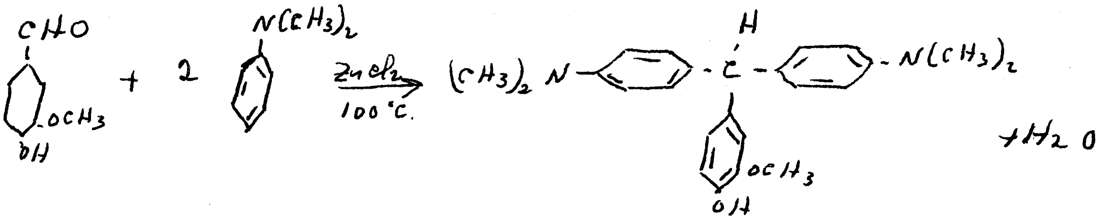
90.8 grams of anhydrous d-glucose (Merck & Co.) were added to 15.5 grams of vanillin (General Drug Co.) and to this mixture was added 400 ml. of 1,4-dioxane (Eastman Kodak Co.). To this mixture was added slowly 60.0 grams of anhydrous zinc chloride (General Chemical Co.). This mixture was heated under a reflux condenser for an hour on a water bath, after which an oil bath was used and the temperature raised to 150 degrees Centigrade and refluxed for a total of eight hours. After about two hours of refluxing the mixture turned a deep amber in color and at the end was almost black.

The dioxane was distilled off under pressure leaving a heavy viscous mass in the flask. The mass was dissolved in methyl alcohol and transferred to a beaker. Upon addition of ether or an excess of methyl alcohol a dark brown precipitate forms which is filtered off. This precipitate dries to a hard resinous compound which is soluble in alcohol, acetone, dioxane, and sodium hydroxide. It is insoluble in water, ether, carbon tetrachloride and benzene. And after many repeated attempts the resinous material could not be crystallized from any of the above solvents or mixtures of the solvents.

This resinous material would not melt but decomposed giving off a gas at 118 degrees Centigrade.

Vanillin-Dimethylaniline

The object of this reaction was to prepare a triphenyl methane derivative of vanillin by condensing vanillin and dimethylaniline in the presence of anhydrous zinc chloride as follows:



20 grams of vanillin (General Drug Co.), 40 grams of dimethylaniline (General Chemical Co.) were mixed together and heated on a water bath until all the vanillin had gone into solution. Then 30 grams of anhydrous zinc chloride (General Chemical Co.) were added slowly and the mixture heated at 100 degrees Centigrade on a water bath for three hours.

The solution after heating was a green viscous mass and was repeatedly washed with boiling water and then dissolved in hot benzene. The benzene solution was a dark red in color and from this solution pink crystals were obtained upon evaporation of the benzene. These crystals then turned blue upon complete evaporation of the benzene. After being recrystallized three times from benzene these crystals melted at 128.5-29,5 degrees Centigrade. The crude yield was five grams or 11.1% yield.

The same reaction was then run again exactly as before, only the time of heating on the water bath was increased to ten hours and the yield increased to 15.6%.

The same reaction was then run a third time and this time 40 grams of vanillin, 70 grams of dimethylaniline and 60 grams of anhydrous zinc chloride were used. The mixture was constantly stirred with an electric stirrer during the ten hours of heating on the water bath and the yield was increased to 22 grams or 22.5%.

A Hinsberg qualitative test was run on this compound, and it was found to contain a Tertiary amine group.

Molecular weight determinations.

Three samples weighing 0.1268 grams, 0.1132 grams and 0.0848 grams were dissolved in nitrobenzene and the freezing point lowering observed and from that the molecular weight of the compound was calculated. The three calculated weights were 377.31, 378.42, and 372.49, the average of which was 376.076 which is the theoretical molecular weight of the compound.

Methoxy Determinations.

Two samples of the compound 0.0354 grams and 0.1424 grams were weighed out and the methoxy content determined by refluxing with hydroiodic acid (freshly prepared), thus converting the methoxy group to the halide, then replacing the iodine with bromine and forming iodobromine, which is converted to hydrogen iodate by water and bromine. Then an excess of potassium iodide is added and the liberated iodine is titrated with 0.0940 N sodium thiosulfate which has been standardized against potassium iodate. The corresponding methoxy percentages were 8.73% and 8.41% or an average of 8.57% as compared to a theoretical methoxy content of 8.24%.

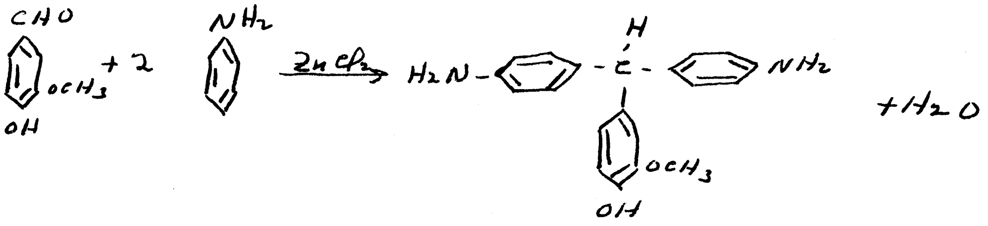
Acetylation of the Compound.

Exactly 1.0 grams of the compound was dissolved in one ml. of 10% sodium hydroxide and 0.5 ml. of acetyl bromide added. Solidification took place immediately and the substance was washed with water and recrystallized from alcohol. This compound melts at 125-6 degrees Centigrade, and does not give any phenolic test with ferric chloride, as did the compound from which it was prepared, thus indicating that the reaction was complete. Two samples 0.0975 and 0.1062 grams were dissolved in nitrobenzene and the freezing point lowering observed. From this the molecular weight was calculated and found to be 420.6 and 419.2 or an average of 419.9 as compared to the theoretical molecular weight of 418. A Hinsberg qualitative test was run on this compound and it was positive for tertiary amine.

Two more samples weighing 0.6300 grams and 0.4058 grams were placed in a 250 ml. flask and 25 ml. of 12% acetic anhydride solution in pyridine were added to each and then the mixtures were heated on a water bath for one-half an hour. After cooling 25 ml. of cold water were added and the solutions were titrated with 1.0892 N sodium hydroxide. 25 ml. of the original acetic anhydride solution were measured out, 25 ml. of cold water added and titrated as the other and the difference represents the amount of acetic acid equivalents which have gone to acetylate the compound. Theoretically it should have taken 0.1008 grams and 0.0649 grams of acetic acid equivalents to acetylate these compounds if one hydroxyl group is present. By experiment the amounts used were 0.1038 grams and 0.0658 grams which is in close agreement.

Vanillin-Aniline

The object of this reaction was to prepare a triphenyl methane derivative of vanillin by condensing vanillin and aniline as follows:



30 grams of vanillin (General Drug Co.) were dissolved in 100 grams of aniline (Eastman Kodak Co.) and 40 grams of anhydrous zinc chloride (General Chemical Co.) added. The orange solution solidified at once turning yellow and the temperature rose to 105 degrees Centigrade. In approximately one-half hour there was a yellow powder formed that was almost completely dry. This powder was washed several times with hot water and then dissolved in hot benzene. The benzene solution was light amber in color and from this solution there crystallized rhombohedral crystals. These crystals were clear, light amber in color, but turned light green upon being ground up and dried.

The melting point of this compound was 153-4 degrees Centigrade as against 155-6 degrees of the compound prepared by Carre (1) from aniline and vanillin condensed in ethyl alcohol. Carre's compound also decomposed upon melting while this one does not. This compound was purified by recrystallizing three times from benzene. The crude yield was 20 grams or

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(1) Carre, Bull. soc. chim. 43, 73-4 (1928).

24.1%.

A Hinsberg qualitative test was run on this compound and it indicated the presence of a primary amine group.

Molecular weight Determinations.

Three samples of the material, 0.1020 grams, 0.1222 grams and 0.0712 grams were dissolved in nitrobenzene and from the observed lowering of the freezing point the molecular weight was calculated. It was found to be 316.92, 322.54, and 318.26 or an average of 319.24 as compared to the theoretical of 320.

Methoxy Determinations.

Two samples of the compound weighing 0.0727 grams and 0.0980 grams were weighed out and the methoxy content determined by refluxing with hydriodic acid (freshly prepared) thus converting the methoxy group of the halide, then replacing the iodine with bromine and forming iodobromine, which is then converted to hydrogen iodate by water and bromine. Then an excess of potassium iodide is added and the liberated iodine is titrated with 0.0940 N sodium thiosulfate. The corresponding methoxy percentages were 11.45% and 10.02% or an average of 10.73% as against a theoretical methoxy content of 9.69%.

Acetylation of the Compound.

Exactly 1.0 gram of the compound was dissolved in 1 ml. of 10% sodium hydroxide and 0.5 ml. of acetyl bromide added. Solidification took place immediately and the substance was washed several times with water and recrystallized from alcohol. This compound melts at 116-17 degrees Centigrade and does not give any phenolic tests with ferric chloride, resorcinol, or phloroglucinol as did the compound from which it was prepared, thus indicating that the reaction was complete.

Two samples of this acetylated product weighing 0.1482 grams and 0.0876 grams were dissolved in nitrobenzene and from the lowering of the freezing point the molecular weight was calculated to be 358.62 and 361.03 or an average of 359.82 as against the theoretical molecular weight of 362.

Two more samples weighing 0.2508 and 0.1203 grams were placed in a 250 ml. flask and 25 ml. of a 12% acetic anhydride solution in pyridine were added to each and then the mixtures were heated on a water bath for one-half an hour. After cooling, 25 ml. of cold water were added and the solutions were titrated with 1.0892 N sodium hydroxide. 25 ml. of the original acetic anhydride solution were measured out, 25 ml. of cold water added and titrated as the other and the difference represents the amount of acetic acid equivalents which have gone to acetylate the compound. Theoretically it should have taken 0.0476 grams and 0.0228 grams of acetic acid equivalents to acetylate these compounds if one hydroxyl group is present and 0.1428 grams and 0.0684 grams if there are one hydroxyl and two primary amine groups present. By experiment the amounts used were 0.1503 grams and 0.0696 grams which indicates that there is present one hydroxyl and two primary amine groups and that all have been acetylated.

SUGGESTIONS FOR FUTURE WORK

For the vanillin and glucose reaction the conditions of reaction should be changed. It may be that the reaction was carried out at too high a temperature, thus causing the mixture to resinify more readily. Also by changing the dehydrating agent, zinc chloride, may lead to less complications.

For the two reactions of vanillin with dimethylaniline and with aniline the yield may be increased by using hydrochloric or sulfuric acid rather than zinc chloride as the dehydrating agent. These two compounds prepared should also be oxidized probably with lead dioxide to see if they have possibilities in the dye field. The compounds could possibly be leuco bases of dyes.

The yield may also be increased by merely lengthening the time of heating in the case of vanillin and dimethylaniline.