

3,4,5-Trimethoxybenzaldehyde.—5-Hydroxyvanillin was methylated with dimethyl sulfate and alkali following the procedure employed by Buck⁷ for the methylation of vanillin to veratraldehyde, and the product was recrystallized from water to give 77% of pure 3,4,5-trimethoxybenzaldehyde melting at 74–75° and not depressing a mixed melting point with authentic 3,4,5-trimethoxybenzaldehyde prepared by methylating gallaldehyde according to Rosenmund and Zetzsche.⁸

Syringaldehyde.—A mixture of 10 g. of recrystallized 3,4,5-trimethoxybenzaldehyde and 56 g. of concentrated sulfuric acid was maintained at 40° in a water-bath for 8 hours and then allowed to stand overnight at room temperature. The mixture was stirred into 100 cc. of cold water and cooled. The clear solution was decanted from the little tar that separated and was extracted with ether. The ether was dried and distilled to yield 8.9 g. (96%) of almost pure (as indicated by chromatography) syringaldehyde which, upon crystallization from petroleum ether (b.p. 65–110°), melted at 109° and did not depress the melting point of a mixture with authentic syringaldehyde.⁹

The use of crude 3,4,5-trimethoxybenzaldehyde or of longer reaction times resulted in poorer yields and in much cruder products.

Reaction of 5-Hydroxyvanillin with One Mole of Potassium Hydroxide and One Mole of Dimethyl Sulfate.—5-Hydroxyvanillin (16.8 g., 0.1 mole) was treated with 7.7 g. (0.1 mole) of potassium hydroxide in 60 cc. of water and with 12.6 g. (0.1 mole) of dimethyl sulfate in the same manner employed for the complete methylation noted above. The cooled reaction mixture was extracted with ether and the ether was washed with 5% sodium hydroxide solution and then with water. The alkaline solution and washings were acidified and extracted with ether to yield 16.0 g. of oily product. The original ether solution, when dried and distilled, yielded 3.3 g. of crude 3,4,5-trimethoxybenzaldehyde melting at 70°. Recrystallization from petroleum ether (b.p. 65–120°) yielded crystals melting at 74–75° which did not depress a mixed melting point with authentic 3,4,5-trimethoxybenzaldehyde.

The oily phenolic product was chromatographed on benzene on acid-washed Magnesol and developed with benzene-ethanol (100:1). The bands were located by streaking with 2,4-dinitrophenylhydrazine, potassium perman-

ganate and ferric chloride.¹⁰ The leading band was eluted with acetone to yield 40% of 5-hydroxyveratraldehyde melting at 63–64° and not depressing a mixed melting point with authentic 5-hydroxyveratraldehyde.¹¹ The next band, upon elution, yielded 13% syringaldehyde melting at 109–110°, and the upper band yielded 20% of unchanged 5-hydroxyvanillin melting at 132–133°.

Reaction of 5-Bromovanillin with Sodium Hydroxide Solution in the Presence of Active Copper.—Active copper powder was prepared according to Brewster and Groening.¹² A mixture of 155 g. of 5-bromovanillin, 50 g. of freshly prepared active copper powder and 3000 cc. of 8% sodium hydroxide solution was placed in a one-gallon stirring autoclave, heated to 200–210° with stirring for one hour and allowed to cool with stirring. The copper was filtered, and the alkaline solution was acidified with dilute sulfuric acid. Some tar was removed by filtration, and the filtrate was concentrated to a small volume in a vacuum circulating evaporator below 50°. The tar was boiled with water and filtered hot. Cooling of this filtrate yielded 4.4 g. of crude 5-bromovanillic acid which, recrystallized from water in the presence of charcoal, yielded white needles melting at 226° and not depressing a mixed melting point with authentic 5-bromovanillic acid.¹³

The concentrated original aqueous filtrate deposited a crystalline precipitate on cooling. The crystals were filtered and recrystallized from water to yield 5.1 g. of vanillic acid melting at 210–211°. The filtrate was extracted with ether, and the ether was extracted successively with 21% sodium bisulfite, 8% sodium bicarbonate and 5% sodium hydroxide solutions. Work up of the bisulfite extract and chromatographing the residue yielded 6.6 g. of vanillin and 1.8 g. of 5-hydroxyvanillin. The bicarbonate solution yielded 0.8 g. of vanillic acid. The sodium hydroxide extract, upon acidification and extraction with ether, yielded 13.6 g. of phenolic oil which was distilled at 0.4 mm. pressure to give pure guaiacol, whose benzoate melted at 58–59° and did not depress a mixed melting point with the benzoate prepared from authentic guaiacol. Guaiacol was also recovered from the condensate of the original vacuum concentration.

(10) I. A. Pearl and E. E. Dickey, *ibid.*, **73**, 863 (1951).

(11) E. Späth and H. Röder, *Monatsh.*, **43**, 106 (1922).

(12) R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 446.

(13) L. C. Raiford and D. J. Potter, *THIS JOURNAL*, **55**, 1682 (1933).

APPLETON, WISCONSIN

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Reactions of Vanillin and its Derived Compounds. XVIII.¹ Preparation and Reactions of Lignin Model Substances Related to 5-Carboxyvanillic Acid^{2,3}

BY IRWIN A. PEARL AND DONALD L. BEYER

RECEIVED MARCH 5, 1952

5-Allylvanillin was isomerized by low temperature caustic fusion to yield 5-propenylvanillin. Ethyl vanillate and ethyl orthovanillate were converted to ethyl 5-allylvanillate and ethyl 5-allylorthovanillate, respectively, and these were treated directly with fused caustic to yield 5-propenylvanillic acid and 5-propenylorthovanillic acid. Oxidation of the propenyl compounds with nitrobenzene and alkali at 160–165° gave the corresponding formyl derivatives as the major products of reaction along with other intermediates. All the formyl derivatives were oxidized by means of alkali and silver oxide to 5-carboxyvanillic acid.

The recent isolations of 5-carboxyvanillic acid and 5-carboxyvanillin from metallic oxide oxida-

tions of lignosulfonate materials^{4–6} led to a study of the preparation of these materials and of the reactions of the lignin model substances employed in their preparation. The present paper describes the preparation of the propenyl derivatives of vanillin, vanillic acid and orthovanillic acid and their oxidation with nitrobenzene and alkali to form 5-formylvanillin, 5-formylvanillic acid and 5-

(1) For Paper XVII of this series, see *THIS JOURNAL*, **74**, 4262 (1952).

(2) Presented before the Division of Cellulose Chemistry at the 121st Meeting of the American Chemical Society, Milwaukee, Wisconsin, March 30 to April 3, 1952.

(3) This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

(4) I. A. Pearl, *THIS JOURNAL*, **72**, 1427 (1950).

(5) I. A. Pearl, *ibid.*, **72**, 2309 (1950).

(6) I. A. Pearl and D. L. Beyer, *Tappi*, **33**, 508 (1950).

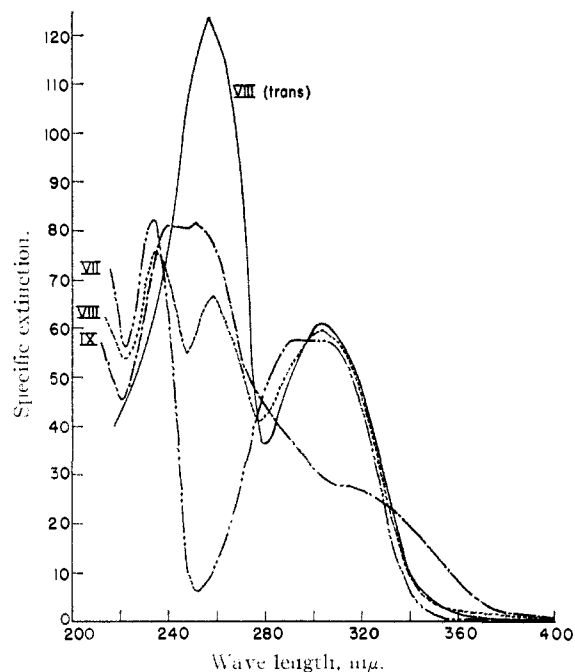


Fig. 1.—Ultraviolet absorption spectra in 95% ethanol: VII, 5-allylvanillin; VIII, 5-propenylvanillin (*cis* and *trans*); IX, 5-formylvanillin.

carboxyvanillin, respectively. The latter compounds are all oxidized by alkali and silver oxide to yield 5-carboxyvanillic acid.

Attempts to further isomerize 5-allylvanillin (VII)⁷ to 5-propenylvanillin (VIII) with potassium hydroxide in amyl alcohol by the general procedure of Tiemann⁸ or with potassium hydroxide in methanol by the general procedure of Klages⁹ gave only small yields of the desired compound. 5-Propenylvanillin was easily prepared in good yield by the fusion of 5-allylvanillin with potassium hydroxide at 160–180° and was obtained as white needles melting at 73°. Pew¹⁰ has very recently reported the preparation of 5-propenylvanillin melting at 98–99° by the treatment of 5-allylvanillin with potassium hydroxide in methanol. The 73° and the 98° compounds are apparently *cis-trans* isomers. The *cis*-73° compound is easily converted to the *trans*-98° compound by boiling with methanolic potassium hydroxide, but the *trans*-98° product is stable under conditions originally forming the *cis*-compound.

Ethyl vanillate (I) was converted to ethyl 5-allylvanillate (III) in the same manner, and the resulting ester was hydrolyzed to 5-allylvanillic acid (IV) melting at 147–148°. By essentially the same reactions Takahashi and Kawashima¹¹ obtained the same intermediates, but recorded 200–202° as the melting point for 5-allylvanillic acid. Low temperature caustic fusion of either 5-allylvanillic acid or its ethyl ester resulted in the formation of 5-propenylvanillic acid (V). Similarly,

(7) L. Claisen and O. Eisleb, *Ann.*, **401**, 112 (1913).

(8) F. Tiemann, *Ber.*, **24**, 2871 (1891).

(9) A. Klages, *ibid.*, **39**, 2591 (1906).

(10) J. C. Pew, *This Journal*, **73**, 1684 (1951).

(11) T. Takahashi and M. Kawashima, *J. Pharm. Soc. Japan*, **63**, 155 (1943); *C. A.*, **45**, 2907 (1951). Abstract only available.

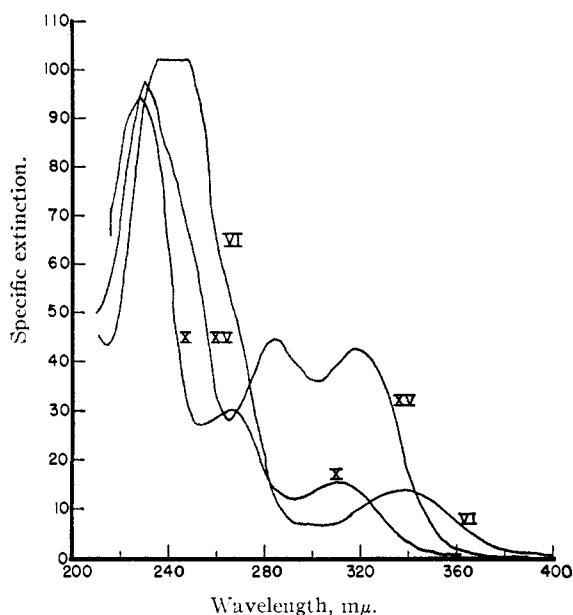


Fig. 2.—Ultraviolet absorption in 95% ethanol: II, ethyl vanillate allyl ether; IV, 5-allylvanillic acid; V, 5-propenylvanillic acid.

ethyl orthovanillate (XI) was transformed into ethyl 5-allylorthovanillate (XIII) which was isomerized directly by fusion with potassium hydroxide to 5-propenylorthovanillic acid (XIV), a compound previously prepared in an analogous manner from methyl orthovanillate by Freudenberg and Klink.¹²

Preliminary oxidation of the above propenyl compounds by boiling with nitrobenzene and alkali at atmospheric pressure under conditions employed for the conversion of isoeugenol to vanillin¹³ resulted in recovery of only the starting material in the case of 5-propenylvanillin and in the formation of only small yields of the desired formyl derivatives in the cases of the other two propenyl compounds. The propenyl compounds were then treated with alkali and nitrobenzene at superatmospheric pressure under conditions similar to those employed by Freudenberg, Lautsch and Engler¹⁴ in their original study on the oxidation of lignin materials with nitrobenzene and alkali. Such oxidation of *cis*-5-propenylvanillin gave a good yield of 5-formylvanillin (IX) and 5-carboxyvanillin (XV) and a small amount of 5-carboxyvanillic acid (X) as a by-product. 5-Formylvanillin was first prepared by Koetschet and Koetschet¹⁵ as a by-product in the preparation of vanillin by the Reimer-Tiemann reaction on guaiacol. The high yield of 5-carboxyvanillin in this experiment and the absence of 5-formylvanillic acid indicate that the formyl group ortho to the hydroxyl group in the guaiacyl nucleus is more susceptible to oxidation than the formyl group in the para position. This fact helps to explain the presence of only vanillin derivatives in lignin oxidation mixtures and the apparent ab-

(12) K. Freudenberg and F. Klink, *Ber.*, **73**, 1371 (1940).

(13) J. D. Riedel, British Patent 285,451 (Sept. 13, 1928).

(14) K. Freudenberg, W. Lautsch and K. Engler, *Ber.*, **73**, 171 (1940).

(15) J. Koetschet and P. Koetschet, *Helv. Chim. Acta*, **13**, 482 (1930).

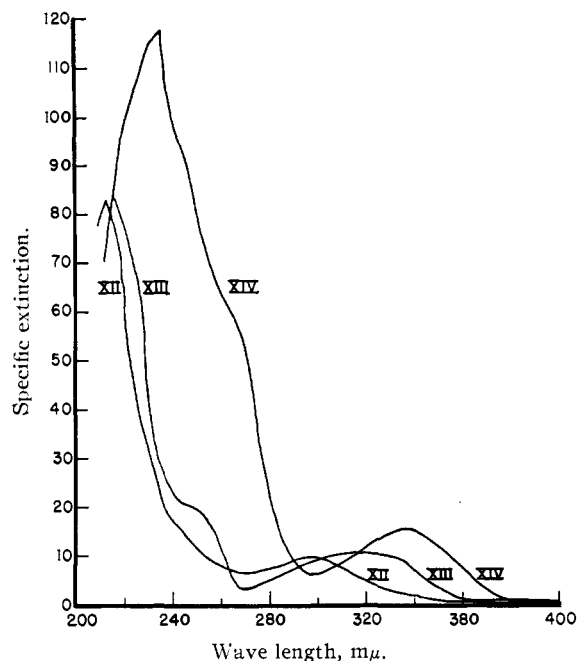


Fig. 3.—Ultraviolet absorption spectra in 95% ethanol: XII, ethyl orthovanillate allyl ether; XIII, ethyl 5-allyl-orthovanillate; XIV, 5-propenylorthovanillic acid.

sence of orthovanillin derivatives. Under the same conditions *trans*-5-propenylvanillin gave a small yield of the desired 5-formylvanillin and a high yield of unchanged starting material. Thus, the *cis*-compound appears to be much more susceptible to nitrobenzene oxidation.

Similar oxidation of 5-propenylvanillic acid gave 5-formylvanillic acid (VI) and 5-carboxyvanillic acid as the only oxidation products, both in fair yield. On the other hand, oxidation of 5-propenyl-orthovanillic acid yielded over 90% of 5-carboxyvanillin and only a trace of 5-carboxyvanillic acid. Again, these data appear to indicate that the formyl group ortho to the hydroxyl group in the guaiacyl nucleus is more susceptible to oxidation than the formyl group in the para position.

It is interesting to note that neither vanillin nor vanillic acid were produced in any of the above superatmospheric oxidations with nitrobenzene and alkali through decarboxylation. Leopold¹⁶ oxidized 5-allylvanillin (VII) with nitrobenzene and alkali and obtained a negligible amount of vanillin, 20% 5-formylvanillin and 6% 5-carboxyvanillin.

Oxidation of either 5-formylvanillic acid or 5-carboxyvanillin with one mole of silver oxide and excess alkali by a previously described procedure¹⁷ gave substantially quantitative yields of 5-carboxyvanillic acid. Analogous oxidation of 5-formylvanillin with two moles of silver oxide and excess alkali yielded 5-carboxyvanillic acid, along with 5-carboxyvanillin and some resinous products. Perkins and Stoye¹⁸ noted that 5-carboxyvanillin reduced ammoniacal silver nitrate but they did not record the fate of the 5-carboxyvanillin.

(16) B. Leopold, *Acta Chem. Scand.*, **4**, 1523 (1950).

(17) I. A. Pearl and D. L. Beyer, *THIS JOURNAL*, **74**, 3188 (1952).

(18) W. H. Perkins and F. W. Stoye, *J. Chem. Soc.*, **123**, 3171 (1923).

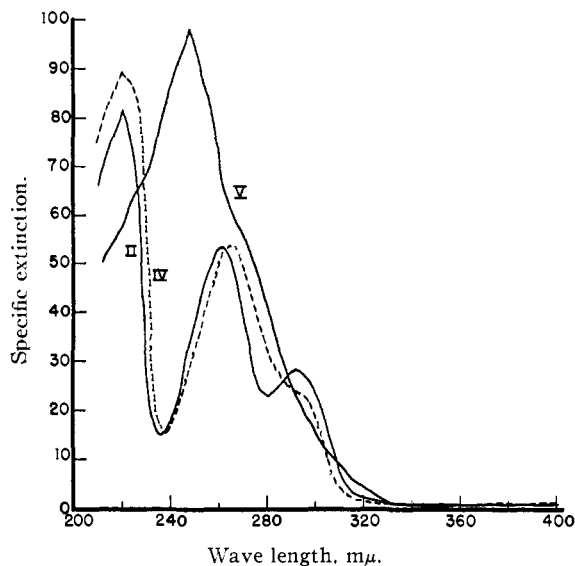


Fig. 4.—Ultraviolet absorption spectra in 95% ethanol: VI, 5-formylvanillic acid; X, 5-carboxyvanillic acid; XV, 5-carboxyvanillin.

Ultraviolet absorption spectra of the above compounds were determined in 95% ethanol with a Beckman spectrophotometer at minimum slit width. These spectra are pictured in the figures. The effect of isomerization of allyl ethers to carbon-allyl linkages is very apparent in all cases as are the isomerizations from allyl side chains to propenyl side chains. Ultraviolet absorption spectra serve admirably for distinguishing these isomers and proved very useful in following the progress of some of the experiments in this work. The ultraviolet absorption curves determined on these synthetic compounds have proven invaluable in the identification work we have carried on with the products isolated from lignin oxidation reactions.

Experimental

All melting points are uncorrected.

5-Propenylvanillin (VIII).—A mixture of 500 g. of potassium hydroxide and 150 cc. of water was heated by means of an electric hot-plate in a stainless steel beaker to 140° and treated with vigorous stirring with 200 g. of 5-allylvanillin.⁷ The mixture became thick and orange colored. The temperature was raised to 160°, at which point the hot plate was turned off. The temperature continued to rise to 180°, and the mixture became quite fluid. Stirring was continued, and the temperature remained above 160° for about 15 minutes. When the temperature reached 120°, the mixture was diluted with 4 liters of water to effect solution of the fused mass and was stirred until cool. The cold alkaline solution was acidified with dilute sulfuric acid, and the oil which separated solidified upon stirring and cooling. The yield of crude 5-propenylvanillin was 200 g. or 100%. Recrystallization from either water or petroleum ether gave white needles melting at 73°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; CH_3O , 16.14. Found: C, 68.88; H, 6.40; CH_3O , 16.14.

Ethyl Vanillate Allyl Ether (II).—This compound was prepared by alkylation of ethyl vanillate and was obtained as a colorless oil boiling at 144–145° at 1.4–1.5 mm., n_D^{20} 1.5370. Takahashi and Kawashima¹¹ prepared this ester and reported a pale yellow oil boiling at 160° at 10 mm.

Vanillic Acid Allyl Ether.—The allyl ether of ethyl vanillate was boiled with a dilute alcoholic solution of sodium hydroxide, and the clear solution obtained was cooled, filtered, diluted with water and acidified with dilute hydrochloric acid. The heavy precipitate was filtered, washed

with water, and recrystallized from dilute ethanol in the presence of carbon to yield white crystals melting at 175–176°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.46; H, 5.93.

Ethyl 5-Allylvanillate (III).—This compound was prepared by rearrangement of ethyl vanillate allyl ether according to Takahashi and Kawashima¹¹ and was obtained as iridescent plates from petroleum ether (b.p. 30–60°) melting at 49–50°.

5-Allylvanillic Acid (IV).—Ethyl 5-allylvanillate was warmed on the steam-bath with dilute aqueous sodium hydroxide. After 30 minutes the clear solution was acidified with sulfur dioxide. The white precipitate was filtered and recrystallized from water to give fine white needles melting at 147–148°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.60; H, 5.90.

Takahashi and Kawashima¹¹ reported a melting point of 200–202° for 5-allylvanillic acid.

5-Propenylvanillic Acid (V).—A mixture of 100 g. of potassium hydroxide and 50 g. of water was heated with stirring to 120° and treated with 45 g. of 5-allylvanillic acid. The reaction mixture became semi-solid. The temperature was raised to 160° and maintained at 160–180° for 10 minutes. After cooling, the caustic mixture was diluted with water and acidified with sulfur dioxide. The crude 5-propenylvanillic acid weighed 42 g. (93%). Recrystallization from dilute ethanol, dilute methanol, or benzene-petroleum ether yielded white crystals melting at 125–126°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.41; H, 5.88.

5-Propenylvanillic acid was also prepared directly from ethyl 5-allylvanillate (III). A fusion mixture of 400 g. of potassium hydroxide and 200 cc. of water at 110° was treated with 200 g. of ethyl 5-allylvanillate. A viscous sludge of the potassium salt of the ester resulted. The temperature was raised with continued stirring, and at 120–130° a vigorous reaction took place, resulting in a more viscous slurry. The temperature was gradually raised to 200°, and then the mixture was allowed to cool. Slight reaction took place all the time until 200° was reached. When the mixture had cooled to 120°, it was diluted with 2.5 liters of water and stirred to effect solution. The clear solution was acidified with sulfur dioxide, and the precipitate was filtered and dried to yield 145 g. (82%) of crude 5-propenylvanillic acid which was recrystallized from dilute methanol to give white crystals melting at 125–126°.

Ethyl 5-Allylorthovanillate (XIII).—Ethyl orthovanillate (XI) was allylated in a manner identical with that employed for the preparation of the allyl ether of ethyl vanillate. The allyl ether of ethyl orthovanillate (XII) was rearranged directly by boiling under reflux for one hour at 60 mm. pressure and then distilling under vacuum to yield XIII as a colorless viscous oil boiling at 128–132° at 0.5 mm., n_D^{20} 1.5221. The over-all yield was 88%.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.06; H, 6.83.

5-Propenylorthovanillic Acid (XIV).—Treatment of ethyl 5-allylorthovanillate with fused caustic by the same procedure employed for the preparation of 5-propenylvanillic acid from ethyl 5-allylvanillate gave an 89% yield of 5-propenylorthovanillic acid which, upon recrystallization from water, yielded colorless crystals melting at 155°. Frenenberg and Klink¹² reported 157° as the melting point of XIV prepared by caustic fusion of methyl 5-allylorthovanillate at 235°.

Oxidations with Nitrobenzene and Alkali at Atmospheric Pressure.—A mixture of 35 g. of 5-propenylvanillic acid, 140 g. of nitrobenzene, 50 g. of sodium hydroxide and 150 cc. of water was boiled under reflux for 6 hours, cooled, diluted with water, and extracted with ether. The alkaline aqueous solution was acidified with dilute sulfuric acid. A heavy precipitate was obtained. Upon crystallization from dilute ethanol or water, the precipitate yielded colorless crystals of the starting 5-propenylvanillic acid. The filtrate from this precipitate was extracted with ether, and the ether was extracted with 21% sodium bisulfite solution. The bisulfite extract was acidified with sulfuric acid, boiled, cooled and extracted with ether. The ether was dried and distilled, and the residue was recrystallized twice from water to give

colorless crystals of 5-formylvanillic acid melting at 222–223° and giving a deep violet color with ferric chloride solution. The yield was 5.5 g.

Anal. Calcd. for $C_9H_8O_5$: C, 55.11; H, 4.11; CH_3O , 15.82. Found: C, 55.22; H, 4.19; CH_3O , 15.83.

Tiemann and Mendelsohn¹⁹ prepared 5-formylvanillic acid by the Reimer-Tiemann reaction on vanillic acid and reported a melting point of 221–222°.

Similar treatment of 5-propenylorthovanillic acid with nitrobenzene and alkali at atmospheric pressure resulted in the recovery of most of the starting material. In addition, 4.2 g. of 5-carboxyvanillin melting at 256–257° (from 70 g. of 5-propenylorthovanillic acid) was obtained from the sodium bisulfite-soluble fraction.

Analogous treatment of 5-propenylvanillin yielded only the starting material.

5-Carboxyvanillin (XV).—A mixture of 65 g. of 5-propenylorthovanillic acid, 217 g. of nitrobenzene, 87 g. of sodium hydroxide and 870 g. of water was heated in a one-gallon stirring autoclave during the course of 0.5 hr. to 160°, maintained at $160 \pm 5^\circ$ for one hour, and allowed to cool. The mixture was diluted with water and extracted completely with ether to remove all nitrobenzene and its reduction products. The aqueous solution was acidified with sulfur dioxide and extracted with ether. The ether was dried and distilled to yield 4.5 g. of crystalline residue. Leaching with 21% sodium bisulfite solution left a little insoluble material which, upon recrystallization from water, gave a few mg. of 5-carboxyvanillic acid melting at 271–272°. Acidification of the bisulfite solution and extraction with ether yielded 4.2 g. of 5-carboxyvanillin melting at 256–258°.

The original sulfur dioxide-saturated aqueous solution was acidified with sulfuric acid and boiled to remove dissolved sulfur dioxide. A heavy crystalline precipitate separated in the boiling solution. The mixture was allowed to cool and was then filtered. The precipitate was washed with water and dried to give 45 g. of crude 5-carboxyvanillin which, upon recrystallization from water, melted at 257–258°. The filtrate from this precipitate was extracted with ether, and the ether was dried and distilled to yield 5.5 g. of crude 5-carboxyvanillin which also yielded crystals melting at 256–257° upon recrystallization from water. The total yield of crude 5-carboxyvanillin was 90%.

A mixed melting point of this 5-carboxyvanillin with that isolated from a cupric oxide-alkali oxidation of spent sulfite liquor¹³ gave no depression.

5-Formylvanillic Acid (VI).—5-Propenylvanillic acid was treated with nitrobenzene and alkali in the identical manner, except that the reaction mixture was maintained at 160° for 2 hours. Treatment of the ether-extracted alkaline reaction mixture with sulfur dioxide precipitated some unreacted 5-propenylvanillic acid. Ether extraction of the filtered sulfur dioxide-saturated solution yielded 16 g. of 5-carboxyvanillic acid (X), melting at 271–272°. Repeated recrystallization from water yielded crystals melting at 281–282°. The sulfur dioxide-saturated aqueous solution was acidified with sulfuric acid, boiled to expel sulfur dioxide, and cooled. A light tan crystalline solid separated. This was filtered, washed with water, and dried to give 39 g. of 5-formylvanillic acid which, upon recrystallization from dilute ethanol, water, or dioxane-petroleum ether, yielded colorless crystals melting at 223–224°. A mixed melting point with authentic 5-formylvanillic acid was not depressed.

5-Formylvanillin (IX).—Similar treatment of 75 g. of *cis*-5-propenylvanillin with 250 g. of nitrobenzene, 100 g. of sodium hydroxide and 1000 g. of water at 165° for one hour gave a reaction mixture which was diluted, cooled, and extracted with ether. The aqueous alkaline solution was acidified with sulfur dioxide, cooled, and extracted with ether; the ether was dried and distilled to yield 5.2 g. of crude 5-carboxyvanillic acid which was recrystallized from water to give colorless crystals melting at 280–281°. The sulfur dioxide-saturated solution was acidified with sulfuric acid and boiled. The solution was cooled and extracted with ether. The ether was dried and distilled to yield 44.0 g. of 5-formylvanillin which, upon recrystallization from petroleum ether (b.p. 65–110°), gave colorless spherical crystals melting at 125–126°. Koetschet and Koetschet¹⁶ recorded 119–121° as the melting point of 5-formylvanillin prepared as a by-product in the preparation of vanillin and orthovanillin by the Reimer-Tiemann process.

(19) F. Tiemann and B. Mendelsohn, *Ber.*, **9**, 1280 (1876).

Anal. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.74; CH_3O , 17.22. Found: C, 59.99; H, 4.70; CH_3O , 17.25.

5-Carboxyvanillic Acid (X). From 5-Carboxyvanillin.—Silver oxide (0.017 mole, freshly prepd. from 5.8 g. of silver nitrate) was covered with 50 cc. of water and treated with 5.1 g. (0.128 mole) of C.P. sodium hydroxide. This mixture at 47° was treated with 3.3 g. (0.017 mole) of 5-carboxyvanillin and heated to 65°, at which point a reaction took place. The source of heat was removed and the temperature rose to 73°. The reaction mixture was cooled and filtered, and the silver precipitate was washed with water. The filtrate was acidified with dilute sulfuric acid and cooled. The white fluffy precipitate was filtered, washed with water, and dried to yield 3.3 g. (94.3%) of 5-carboxyvanillic acid melting at 282°; this did not depress the melting points with a sample of 5-carboxyvanillic acid isolated in the nitrobenzene oxidations described above or with that isolated from metallic oxide oxidations of lignin materials.⁴⁻⁶

Anal. Calcd. for $C_9H_8O_6$: C, 50.93; H, 3.80; CH_3O , 14.63. Found: C, 50.88; H, 3.80; CH_3O , 14.60.

Under certain conditions of crystallization from water a dihydrate of 5-carboxyvanillic acid is obtained. This product is obtained as fluffy white needles with the same melting point and ultraviolet absorption spectrum as the anhydrous product. However, during the melting point deter-

mination, dehydration is observed at temperatures above 110°.

Anal. Calcd. for $C_9H_8O_6 \cdot 2H_2O$: C, 43.56; H, 4.87; CH_3O , 12.50. Found: C, 43.75; H, 4.77; CH_3O , 12.54.

Drying of this compound at 105° yielded the theoretical amount of moisture.

From 5-Formylvanillic Acid.—Silver oxide was prepared, covered with water, and treated with sodium hydroxide exactly as above. This mixture at 40° was treated with 5-formylvanillic acid in the same manner; a reaction took place raising the temperature to 52°. The reaction mixture was treated as above to yield 100% of 5-carboxyvanillic acid melting at 283–284° and not depressing a mixed melting point with authentic 5-carboxyvanillic acid.

From 5-Formylvanillin.—Similar oxidation of 5-formylvanillin with twice as much silver oxide but with the same amount of alkali resulted in the formation of 5-carboxyvanillic acid as the main product, together with some bisulfite-soluble 5-carboxyvanillin and a little resinous material which was not characterized.

Acknowledgment.—The authors wish to thank Mr. Donald McDonnell for the analyses and spectra reported in this paper.

APPLETON, WISCONSIN

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Synthesis of 5-Carbethoxyuracils

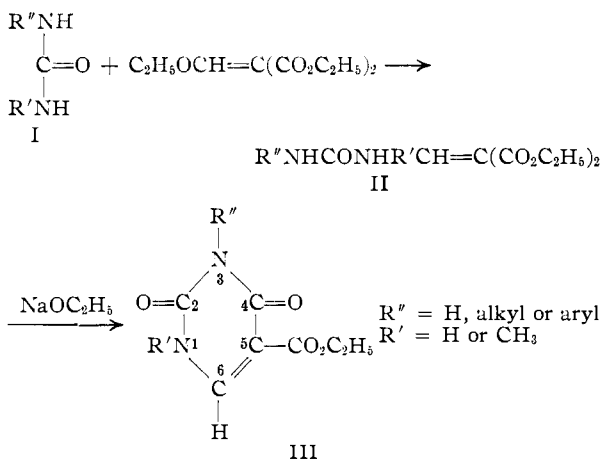
BY CALVERT W. WHITEHEAD

RECEIVED FEBRUARY 15, 1952

Diethyl ethoxymethylenemalonate undergoes condensation with urea and N-substituted ureas. The condensation has been carried out by heating the ethoxymethylenemalonate with N,N'-dimethylurea to obtain directly 1,3-dimethyl-5-carbethoxyuracil; with N-methylurea to obtain 3-methyl-5-carbethoxyuracil and with higher N-alkylureas to obtain alkylureidomethylenemalonates which were converted to the 3-alkyl-5-carbethoxyuracil in the presence of a basic catalyst. The condensation was also carried out with urea and a number of N-alkyl- and N-arylureas with diethyl ethoxymethylenemalonate in alcoholic solution in the presence of a base catalyst to obtain directly the 5-carbethoxyuracil in good yield. These uracils containing a functional ester group made possible the convenient preparation of a number of new heterocyclic acids and amides some of which have shown diuretic activity in animals.

The facility with which diethyl ethoxymethylenemalonate, $C_2H_5OCH=C(CO_2C_2H_5)_2$ condenses with basic nitrogen compounds has been demonstrated in reactions with ammonia,¹ amines,² acetamidine³ and ethylisothiourea.⁴ The product from the latter reaction was 2-ethylmercapto-5-carbethoxy-6-oxypyrimidine. Wheeler⁴ reported that urea showed no sign of reacting with diethyl ethoxymethylenemalonate at 140° and a condensation was not effected on standing in alkaline solutions. Other attempts to condense diethyl ethoxymethylenemalonate with urea or substituted ureas are not found in the literature. An investigation has been made into the condensation of diethyl ethoxymethylenemalonate with urea and N-substituted ureas as a method of synthesizing N-substituted-5-carbethoxyuracils and also as a study of the reactions of diethyl ethoxymethylenemalonate with weakly basic nitrogen compounds.

The condensations proceeded according to the general equation



When diethyl ethoxymethylenemalonate was heated with an equimolar quantity of an N-mono-alkylurea at 120°, ethanol was eliminated and the corresponding diethyl alkylureidomethylenemalonate (II) was formed. In the case of the methylureidomethylenemalonate (II, $R' = H$, $R'' = CH_3$), further heating at 150° gave the uracil (III). The higher alkyl homologs did not cyclize when they were heated at 150° and diethyl n-propylureido-

(1) L. Claisen, *Ann.*, **297**, 77 (1897).

(2) C. C. Price and R. M. Roberts, *THIS JOURNAL*, **68**, 1204 (1946).

(3) T. A. Geissman, M. J. Schlatter, I. D. Webb and J. D. Roberts, *J. Org. Chem.*, **11**, 741 (1946).

(4) H. J. Wheeler, T. B. Johnson and C. O. Johns, *Am. Chem. J.*, **37**, 392 (1907).