STUDIES IN THE POLYOXYPHENOL SERIES

VII. THE OXIDATION OF VANILLIN WITH SODIUM CHLORITE AND CHLORINE DIOXIDE[1]

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ABSTRACT

Vanillin almost instantly reduced 1.2 to 1.5 moles of aqueous chlorine dioxide at 20°C. or 5°C. and any pH between 1.2 and 6.5, and a white crystalline substance with the composition of a dihydroxyvanillin, $C_7H_5O_4(OCH_3)$, was isolated in roughly 25% yield independently of the pH. When oxidized with aqueous sodium chlorite at 20°C. and pH 0.5, these crystals gave another crystalline substance with the composition of a dihydroxyvanillic acid, $C_7H_5O_5(OCH_3)$. Although both these substances decomposed readily to red oils and then to brown powders free of methoxyl groups, seven well characterized derivatives were prepared. The results showed that the substances were unsaturated, monohydroxy, diketone tautomers of a dihydroxyvanillin and the corresponding dihydroxyvanillic acid, but precise structures could not be assigned. Parallel oxidations of vanillin with aqueous sodium chlorite at 20°C. and pH 6 proceeded at a negligible rate, but near pH 5 a reaction that often seemed autocatalytic produced about 19% of 5-chlorovanillin. At pH 4 the aldehyde $C_7H_5O_4(OCH_3)$ was isolated in 19% yield; at pH 1 this aldehyde (15%) was mixed with 7.7% of the corresponding acid $C_7H_5O_5(OCH_3)$, but at pH 0.5 the latter alone was produced (28%). Chlorine dioxide and sodium chlorite therefore differed markedly in their oxidizing action and in the effect of pH upon it. When acting on vanillin, both oxidants also produced deep red, unstable oils with quinone-like properties and often containing chlorine.

INTRODUCTION

The earliest study of the action of chlorine dioxide on an organic substance was published in 1881 by Fürst (4), who noticed that the gas reacted rapidly with ethylene exposed to bright sunlight. Schmidt and his collaborators (17, 18, 19) used aqueous chlorine dioxide to remove lignin (a condensed phenolic ether) from wood, and extended Fürst's observation to many unsaturated aliphatic compounds and to phenols. Catalytic amounts of vanadium trichloride were sometimes used in these oxidations (19). The work of Fuchs and Honsig (3), later extended by Sarkar (15), showed that phenolic ethers and esters were oxidized by aqueous chlorine dioxide at a much slower rate than the phenols themselves, and that the oxidation products included carbon dioxide, oxalic acid, maleic acid, and small amounts of undefined, chlorinated compounds. With the exception of thio compounds and those containing reactive methylene groups, all saturated aliphatic substances examined, including polysaccharides and reducing sugars, were stable to aqueous chlorine dioxide. All of the above research was of a qualitative nature, and the hydrogen ion concentration was in no case controlled.

Since an acidified solution of sodium chlorite displayed the same selectivity as an oxidant, and spontaneously decomposed to chlorine dioxide, the assump-

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tion was often made that chlorine dioxide was the active agent in this case also. Jeanes and Isbell (7), however, observed that sodium chlorite oxidized aldose sugars quantitatively to the aldonic acids at a rate which increased as the pH decreased from 8, but that aqueous chlorine dioxide did so only with very great difficulty at any pH in the above range. Although chlorites and chlorine dioxide are now used to bleach cellulose pulps free from residual lignin, the above résumé shows that detailed knowledge concerning their oxidizing action on phenols and phenolic ethers is still exceedingly scanty. Information concerning vanillin, for example, is restricted to the remark that it is oxidized by chlorine dioxide (3, 15), and to the fact that a small yield of 2,4-furane dicarboxylic acid is formed in oxidations carried out with aqueous sodium chlorite near pH 3 (13). The present research had the object of extending these observations.

RESULTS AND DISCUSSION

The concentration of dilute aqueous solutions of sodium chlorite, buffered within 0.1 unit at various pH values and kept at 20°C., was determined from time to time by an iodometric method responsive to chlorite, chlorine dioxide, and hypochlorite, but not to chlorate. These solutions were stable for many hours except at pH 1, when loss by the volatilization of chlorine dioxide might sometimes have been appreciable. As the plots A in Fig. 1 show, aqueous solutions containing about 13.5 mM. of chlorine dioxide per liter were fairly stable on the acid side of pH 6, but at pH 7.3 decreased rapidly in strength owing to the formation of equimolecular amounts of chlorite and chlorate ion. The change was complete within 12 hr. More concentrated, 0.02 to 0.025 *M*, solutions of chlorine dioxide decomposed rather slowly when kept on the acid side of pH 4.5, but near pH 5 the decomposition assumed an autocatalytic form before becoming very rapid at pH 6.65 (plots B). This decomposition was among those reviewed by Taylor, White, Vincent, and Cunningham (22, 23) in their study of the inorganic chemistry of chlorine dioxide and chlorites. Taube and Dodgen (21) used radioactive chlorine to reveal the mechanisms involved when the oxidation state of the halogen changed.

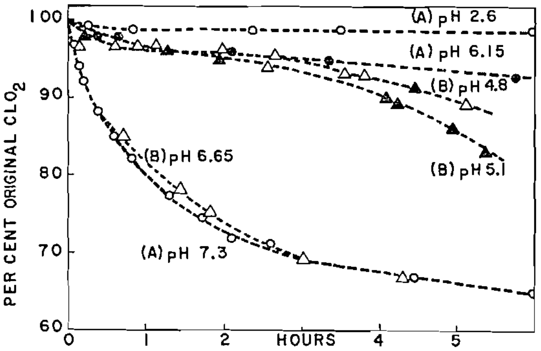
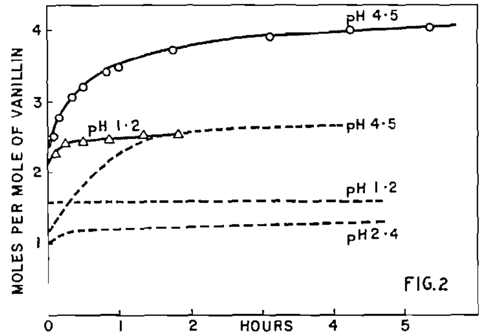


FIG. 1. Rate of decomposition of chlorine dioxide at 20°C. in aqueous 10% sodium acetate – acetic acid buffers. Plots A, 13.5 mM. of chlorine dioxide; plots B, 20 mM. to 25 mM., per liter.

A selection from more than thirty plots of the rate of reduction of the oxidant by vanillin is presented in Figs. 2 and 3, in which full lines refer to reductions of excess sodium chlorite, and broken lines to those of chlorine dioxide. Although the plots were corrected for the spontaneous decomposition of the oxidant, the rate of this decomposition might not be the same in the blank and in the presence of vanillin, since the residual concentrations at any time would be different. Moreover, most of the reductions were strongly exothermic, and it was difficult to keep the temperature at 20°C. during the initial period; the inorganic system was complex, and any quinone formed from the vanillin would interfere with the iodometric method used to determine the residual oxidant. Figs. 2 and 3, although reproducible, thus indicate merely the net change in the redox systems present, and details of the relevant estimations are omitted from this article.



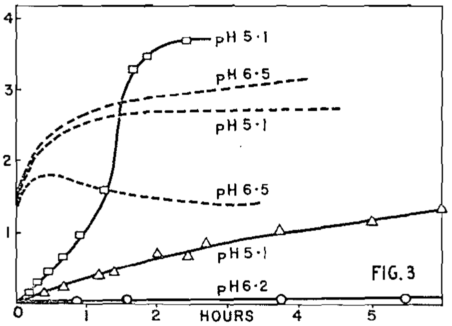


Fig. 2. Apparent rate of reduction of oxidant at 20°C. Solid lines: vanillin, 15 mM., and sodium chlorite, 60 mM. per liter. Broken lines: vanillin, 4 mM. and chlorine dioxide, 21 mM. to 29 mM. per liter.

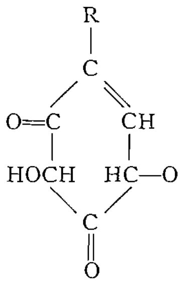
Fig. 3. See legend for Fig. 2. Upper broken line at pH 6.5 uncorrected for chlorine dioxide blank. Upper solid line at pH 5.1, 65 mM. of sodium chlorite per liter; lower solid line at pH 5.1. 60 mM. per liter.

At pH 1.2, 1 mole of vanillin apparently reduced about 2.5 moles of sodium chlorite within a few minutes, and the reaction then became extremely slow. Although the initial rapid reduction was preserved at pH 4.5, a secondary reaction was now marked. When this experiment was repeated at 4°C., the initial reduction was almost unaffected, but the secondary one took more than two hours, instead of less than 20 min., to increase the total consumption of chlorite to 3.0 mole (not shown). The lower plot at pH 5.1 in Fig. 3 was obtained with the same concentration (60 mM. per liter) of sodium chlorite, but a slight increase in concentration to 65 mM. per liter produced the upper plot, whose form suggested an autocatalytic reaction. A reaction at pH 4.6 and 3°C. became apparently autocatalytic within two minutes, but this behavior was never observed on the alkaline side of pH 5.4, even when the concentration of chlorite was increased (not shown). In experiments carried out at pH 5.1 and 6°C., the initial, nearly linear portion corresponding to the consumption of about 1 mole of chlorite required 2.5 hr., instead of 1 hr.; and 4 hr., instead of about 1.5 hr., elapsed before the total consumption was 3.0 mole per mole of vanillin. At 20°C. and on the alkaline side of pH 5.1, the linear portion of the plot decreased in slope very rapidly, until the consumption of 0.2 moles of chlorite required 14.25 hr. at pH 6.2. No odor of chlorine dioxide was ever noticed at any acidity in these oxidations until more than 2 moles of sodium chlorite per mole of vanillin had been utilized.

Figs. 2 and 3 (broken lines) also show that vanillin almost instantaneously reduced about 1.5 moles of chlorine dioxide at all pH values between 1.2 and 6.5. A slower secondary reduction was evident on the alkaline side of pH 4.5, but could not be even approximately assessed at pH 6.5 because the observed data (upper plot) gave an absurd result (lower plot) when corrected for the large and uncertain blank. The proper correction would probably have placed this plot close to that for the reduction at pH 5.1. This experiment differed from those carried out at pH values less than 6 in that a little by-product chlorate was formed, but aqueous potassium chlorate was found to have no action on vanillin at pH 6.9, 5.7, or even 2.6. When the plots in Figs. 2 and 3 were compared, it became evident that vanillin reduced approximately 1 mole more of sodium chlorite than of chlorine dioxide between pH 1 and pH 4.5 and at all times; between pH 5 and 6.5, however, the relationship was reversed. The course of the initial oxidation with sodium chlorite was highly sensitive to pH, whereas that with chlorine dioxide was apparently independent of this factor. The two oxidants were therefore by no means equivalent.

Much time was spent in attempts to isolate a crystalline product from the clear, bright red solutions that resulted when vanillin was oxidized with aqueous chlorine dioxide at pH 1 or pH 2.3. Such solutions, and also the unstable red oils isolated from them by evaporation or by extraction with ether, assumed a pale yellow color when reduced by sulphurous acid or by hydrogenation under mild conditions, and the red color was regenerated by the addition of benzoquinone or by the access of air. Condensations with aniline, *p*-anisidine, hydroxylamine, *o*-phenylenediamine, and diazotized anilines provided small yields of brown or black powders. The whole mass of observations suggested that the initial product of the oxidations was an unstable, methoxylated quinone that readily changed to brown, amorphous substances of lower methoxyl content. Eventually small yields of a white substance, melting at 101°C. and crystallizing as tufts of very fine needles or as prisms, were isolated. Success in isolating these crystals depended upon extracting the solution of the oxidized vanillin at the proper time with ether, upon maintaining a low temperature, and upon speed in freeing the extract from water and any traces of acid. Buffers employing sulphuric, phosphoric, or citric acid had to be used, because acetic acid was readily extracted from the aqueous solution by the ether and accelerated the decomposition of the product. The final procedure made it possible to isolate the purified crystals from oxidations at pH 1, pH 4, and pH 5.8 in a uniform yield of 25% to 30% by weight. In addition to these crystals, the ether extract contained considerable amounts of an unstable, chlorinated oil whose orange color quickly darkened on standing. Neither this oil nor the aqueous residue, which turned black when warmed to expel the ether, were examined further.

The crystalline product possessed the formula $C_7H_5O_4(OCH_3)$ and was extracted less readily by ether from solution in aqueous sodium bisulphite than from a more concentrated solution in water. Ammoniacal silver nitrate (Tollen's solution) was quickly reduced by the crystals, which also yielded a crystalline mono-2,4-dinitrophenyl hydrazone and a crystalline monosemicarbazone. This evidence for the presence of an aldehyde group was confirmed by oxidizing the substance at pH 0.5 with chlorous acid to a crystalline acidic substance, $C_7H_5O_5(OCH_3)$, decomposing at 143° to 144°C., and giving a nearly quantitative yield of a crystalline monoester when boiled with methanol containing a trace of sulphuric acid. Although two acidic groups were revealed in the acid by a potentiometric titration against standard sodium hydroxide, a marked buffering effect between pH 9 and pH 11 suggested that one of these groups was phenolic or enolic. When added to saturated sodium bicarbonate solution, the aldehyde displayed a slight acidity that was also attributed to a phenolic unit. Since both substances were derived from vanillin, $C_7H_5O_2(OCH_3)$, the aldehyde was at first regarded as a dihydroxy vanillin, and the acid as the corresponding dihydroxyvanillic acid.



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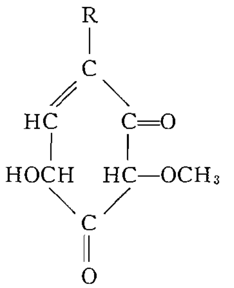

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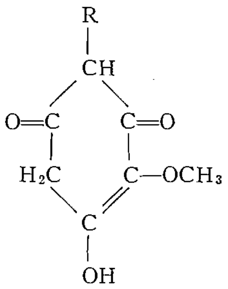

III

R = CHO or COOH

Both the aldehyde and acid, however, failed to give a distinctive color in the ferric chloride test for phenol. When examined by the Zerewitinoff method with methyl magnesium iodide, the aldehyde was found to contain only one atom, instead of the expected three atoms, of active hydrogen, and to add 3 moles, instead of the expected 1 mole, of the Grignard reagent. In similar fashion, the acid contained only 2 moles of active hydrogen and added 3 moles of the reagent. These observations suggested that the aldehyde and acid existed as ketonic tautomers analogous to the keto forms in which metapolyhydric phenols like resorcinol and phloroglucinol tended to react. Structures I, II, and III, which were metadiketones derived from 5,6-, 2,5-, and 2,6-dihydroxyvanillin, thus came into consideration.

Although the acid (R = COOH) slowly added two atoms of bromine per mole, an attempt to hydrogenate it over a palladium catalyst and with two atmospheres pressure of hydrogen ended with no absorption of the gas. Since double bonds conjugated with ketone or carboxyl groups tended to be hydrogenated less readily than isolated double bonds (5), the observation gave support to Structures I and II rather than to Structure III. Hydrogenation of the aldehyde (R = CHO) under the same conditions required 2 moles per mole and yielded a distillable oil with the formula $C_7H_9O_4(OCH_3)$ which might have been a mixture of *cis–trans* isomers. Since this oil failed to form a phenylhydrazone and contained two atoms of active hydrogen, it appeared that the aldehyde had been reduced to a benzyl alcohol group, and that the double bond was then reactive enough to absorb the second mole of hydrogen. The replacement of the palladium by a platinum catalyst caused the consumption of a third mole of hydrogen, possibly by the reduction of the aldehyde to a methyl unit, as was shown to occur when vanillin was hydrogenated under the same conditions. An attempt to demonstrate the presence of ketone groups in the acid (R = COOH) by preparing a 2,4-dinitrophenyl hydrazone failed.

Methylation of the acid with silver oxide and methyl iodide gave a practically quantitative yield of a colorless, distillable oil with the composition, $C_7H_3O_3(OCH_3)_3$, expected for the monomethyl ether-monomethyl ester. An attempt to saponify this ester with hot 5% aqueous sodium hydroxide, however, produced a crystalline substance which contained no methoxyl groups and had the composition of a tetrahydroxybenzoic acid, $C_7H_2O_2(OH)_4$. When titrated potentiometrically with alkali, this substance gave a plot similar to that obtained in the titration of the original acid (R = COOH) and the presence of one carboxyl and one acidic hydroxyl group was inferred. The substance probably existed in a ketone form analogous to one or other of the Structures I, II, or III, because it contained only three atoms of active hydrogen per mole, instead of the five expected for a tetrahydroxybenzoic acid. This substance was also obtained in good yield when an attempt was made to methylate the original acid (R = COOH) with sodium hydroxide and dimethyl sulphate. Such easy demethylations of the acid and its monoether-monoester seemed consistent with the alternative structures advanced, since both the methyl ether and the phenolic hydroxyl positions would probably be highly activated by neighboring functional groups. The methylation of the acid (R = COOH) with diazomethane in ether yielded, not the expected monomethyl methyl ester, but unstable colorless needles melting with decomposition at 116° to 118°C. and having the formula $C_7H_3O_3(OCH_3)_3(CH_2N_2)_2$. Since treatment of the monomethyl methyl ester with diazomethane gave the same substance, it was thought probable that two molecules of diazomethane had added to the two ketone groups. The usual result of such addition is ring expansion with loss of nitrogen; but in this case the adduct was stable enough to be isolated. One mole of the diazomethane, of course, might have added to the double bond. An attempt to methylate the aldehyde (R = CHO) with diazomethane yielded 46% by weight of an unstable orange glass with the methoxyl content required for the adduct $C_7H_4O_3(OCH_3)_2(CH_2N_2)_2$, but the substance decomposed before further data could be secured.

Dr. D. A. Ramsay, of the National Research Council of Canada, kindly determined the infrared absorption of the acid (R = COOH) in the form of a mull in Nujol. He attributed a broad band from wavelength 3400 cm.$^{-1}$ to 3000 cm.$^{-1}$ to hydroxyl groups in a state of hydrogen bonding; the absence of a sharp band in the region 3600 cm.$^{-1}$ to 3700 cm.$^{-1}$ indicated that no unbonded hydroxyl groups were present. Three bands at 1724 cm.$^{-1}$, 1704 cm.$^{-1}$, and 1689 cm.$^{-1}$ were consistent with a structure containing one carboxyl group and one unconjugated and one conjugated ketone group. Two bands at 1651 cm.$^{-1}$ and 1612 cm.$^{-1}$ suggested the presence of two, rather than only one, ethylenic linkages, and the bands at 1450 cm.$^{-1}$ and 1379 cm.$^{-1}$ might be correlated with the methoxy group. Although the remaining bands in the spectrum were difficult to interpret, the absorption at 835 cm.$^{-1}$ was consistent with triple substitution around a double bond ($R_1R_2C{=}CHR_3$) because such substitution was usually accompanied by absorption in the region 810 cm.$^{-1}$ to 840 cm.$^{-1}$. Thus the absorption in the infrared supported structures I, II, and III, but failed to discriminate sharply between them; the authors' preference for Structure I therefore rested on nothing more than the observation that vanillin was substituted as a rule in the fifth or sixth, rather than in the second, position. Baker and Brown (2), for example, obtained 5-hydroxyvanillin (3,4-dihydroxy-5-methoxy-benzaldehyde) in 3.6% yield by an Elbs oxidation of vanillin by potassium persulphate in alkaline solution.

Attempts to elucidate the nature of the aldehyde (R = CHO) were greatly hampered by its instability. Although the pure white crystals could be preserved for some time in a desiccator containing a dehydrating agent, a cold aqueous solution assumed a deep red color within a few hours. The same change occurred very quickly in cold, aqueous sodium bicarbonate. When a trace of pyridine or piperidine was added to a solution of the crystals in ether, a red oil quickly separated. This oil initially had a methoxyl content approaching that of the original aldehyde (16.9%), but when kept either *in vacuo* or in aqueous solution quickly changed to a brown, amorphous substance almost free of methoxyl groups and insoluble in ether, although still soluble in water. Attempts to acetylate the aldehyde with acetic anhydride and pyridine under various conditions gave red solutions from which no well-defined acetate could be recovered. A freshly prepared aqueous solution of the aldehyde had a marked tanning action on the skin, and much of the solute was absorbed by hide powder in the standard test for tannins. Aqueous solutions of the acid (R = COOH) were considerably more stable than those of the aldehyde, but nevertheless soon decomposed to red substances.

As already mentioned, the initial oxidation of vanillin by aqueous sodium chlorite, unlike that by chlorine dioxide, was greatly dependent upon the pH of the system (Figs. 2 and 3). At pH 0.5, the sodium chlorite oxidation yielded 40% by weight (28% of theory) of the acid (R = COOH), at pH 1.0 a mixture of the aldehyde (R = CHO) and acid resulted, and at pH 4.0 25% (19% of theory) of the aldehyde was the only product identified. Sodium chlorite therefore differed from chlorine dioxide in oxidizing the aldehyde group of vanillin when the pH was sufficiently low, as Jeanes and Isbell (7) had previously observed in their oxidations of glucose. The other product isolated when vanillin was oxidized with sodium chlorite was 5-chlorovanillin, which was carefully differentiated from the 6-chloro isomer. Experiments carried out at pH 4.7 and pH 5.05 near 5°C., and at pH 6.0 and higher at room temperature, produced 4%, 17% to 19%, a trace, and 0%, respectively, of 5-chlorovanillin. A sharp maximum in yield therefore occurred near pH 5, or in the region where the rate of oxidation plot (Fig. 3) often suggested an autocatalytic reaction. The yield was negligible at pH 6 or more because the whole reaction was negligible, and trial showed that 5-chlorovanillin itself was rapidly oxidized to a dark colored oil in media more acidic than pH 5. The production of the 5-chloro derivative was attributed to a side-reaction peculiar to sodium chlorite; none was observed in the experiments with chlorine dioxide, but this oxidant was too active, even at pH 5, to permit any 5-chlorovanillin formed to survive unchanged.

EXPERIMENTAL

The vanillin used was recrystallized from aqueous alcohol until it melted correctly at 82° to 83°C. Sodium chlorite, of analytical grade, was kindly presented by the Mathieson Alkali Company of New York. The Coleman pH Electrometer was frequently standardized against 0.05 M potassium acid phthalate, whose pH at 25°C. was accepted as 4.0 (6, 11).

Reduction of Sodium Chlorite by Vanillin (*Figs. 2 and 3*)

The buffers used consisted of dilute sulphuric acid for pH 1, 10% acetic acid for pH 2.2, and 5.2% sodium acetate plus the appropriate amount of acetic acid for the higher pH range. Frequent tests during each experiment showed that these buffers maintained the original pH to within one-tenth of a unit. Vanillin, 0.913 gm. (6 mM.), was dissolved in 200 cc. of the buffer contained in a glass-stoppered, amber bottle maintained at $20° \pm 0.1°$C. in a thermostat. An equal volume of 0.12 M sodium chlorite, also at 20°C., was added at zero time with thorough mixing. A blank containing no vanillin was simultaneously prepared. At intervals a 10 cc. aliquot was removed and was mixed with about 90 cc. of water containing 10 cc. of aqueous 10% potassium iodide and 20 cc. of 20% sulphuric acid. The liberated iodine was titrated with 0.025 N sodium thiosulphate with a starch solution as indicator, and the result when corrected for the corresponding blank was expressed as moles of sodium chlorite reduced. One mole was considered equivalent to 4 liters of N iodine (22, 23). Concordant results were obtained by treating the 10 cc. aliquot with 15 cc. of the potassium iodide solution and 15 cc. of 30% acetic acid according to Jeanes and Isbell (7), but acidification with only 10 cc. of 20% sulphuric acid was insufficient.

5-Chlorovanillin

Three grams (19.7 mM.) of vanillin, dissolved in 200 cc. of an adequate sodium acetate buffer at pH 5.05, was mixed near 5°C. with 77.5 cc. of 1.04 M aqueous sodium chlorite (80.5 mM.). The separation of a buff-colored solid from the cold solution was essentially complete after 42 hr. and the clear, dark red color of the filtrate could be discharged to orange-yellow by sulphur dioxide. A 1.03 gm. sample of the solid was extracted with ether in a Soxhlet apparatus and, when concentrated, the red ether extract slowly deposited cubical crystals. The remainder of the product consisted of dark red, viscous oils which were soluble in benzene, and of amorphous, insoluble solids.

After several recrystallizations from benzene, the above crystals, now shining white leaflets, had the elementary analysis and the Rast molecular weight of a chlorovanillin. Their melting point, 164° to 165.4°C., was correct for 5-chlorovanillin, and was not depressed by admixture with an authentic sample: admixture with authentic 6-chlorovanillin (m.p. 170°C.) depressed the value below 143°C. Acetylation of 0.14 gm. of the crystals with 2 cc. of acetic anhydride and one drop of concentrated sulphuric acid gave a 90% yield of pure 3-methoxy-4-acetoxy-5-chlorobenzal diacetate melting correctly at 118°C. (corrected). Authentic samples of the above diacetate, and also of the 6-chloro isomer (m.p. 144°C.) were prepared according to the method of Raiford and Lichty (14) for comparison. The yield of pure 5- chlorovanillin was 0.62 gm. or 17% of theory, and was 19% in a duplicate experiment.

Preparation and Analysis of Aqueous Chlorine Dioxide

To avoid the risk of explosions, chlorine dioxide gas was always prepared in dilution with an equimolecular amount of carbon dioxide by Schacherl's method (16), as described in detail by Sarkar (15). This method involved heating a mixture of potassium chlorate, 25 gm., oxalic acid dihydrate, 20 gm., and 80 cc. of cold 33% (by volume) sulphuric acid to 30° to 60°C. The evolution of gases from larger-scale preparations occasionally became too violent to be easily controlled. An all-glass apparatus coated with black paint was used, and the effluent mixture of gases was scrubbed with a saturated solution of sodium chlorite to replace any chlorine with chlorine dioxide. The effluent chlorine dioxide was absorbed in ice-cold, distilled water contained in a glass-stoppered, amber bottle until a concentration of 0.2 M to 0.3 M was attained.

These solutions were tested for their content of chlorine or hypochlorous acid by titrating aliquots iodometrically in a phosphate buffer at pH 7, and then by continuing the titration to the end point in dilute sulphuric acid. The first titration measured only one of the five oxidizing equivalents of the chlorine dioxide, *plus* those of any chlorine or hypochlorous acid, while the second or "acid" titration determined only the remaining four oxidizing equivalents of the chlorine dioxide. Five-fourths of the "acid" titration therefore gave the molar equivalent of the chlorine dioxide, and the difference between one-fourth and the first titration corresponded to the content of chlorine and hypochlorous acid. In practice, this content never exceeded 2 mM. per liter, or was almost within the experimental error. Since the solutions were usually diluted to 0.03 M to 0.07 M in chlorine dioxide before use, they were considered to be free of chlorine. Routine estimations could then be performed in acid solution as described for sodium chlorite solutions, 1 mole of chlorine dioxide being assumed to liberate five atoms of iodine.

The rapid deterioration of 0.0134 M chlorine dioxide in a buffer at pH 7.3 (Fig. 1, plot A) was followed by titrating 10 cc. aliquots iodometrically in acid solution. After 12 hr. at 20°C., 16.57 cc. of 0.0246 N sodium thiosulphate was required, corresponding to 0.0082 M chlorine dioxide. Another 10 cc. aliquot was analyzed by the method of Kolthoff and Furman (9) to include chlorate by being boiled for one minute with 1.3 gm. of ferrous sulphate. Excess potassium iodide was then added to reduce the ferric iron formed, and the liberated iodine was titrated with 35.5 cc. of the standard sodium thiosulphate. After correction for the ferrous sulphate blank (1.55 cc.) and for the chlorine dioxide (16.57 cc.), the chlorate corresponded to 17.4 cc. or was 0.0071 *M*. This value was in fair agreement with the figure of 0.0067 *M* calculated for the complete decomposition of chlorine dioxide into equimolecular amounts of chlorite and chlorate.

Reduction of Chlorine Dioxide by Vanillin (Figs. 2 and 3)

The buffers were those used in the parallel reductions of sodium chlorite. In a typical experiment, 100 cc. of 0.008 *M* vanillin in the desired buffer, contained in a glass-stoppered, amber bottle, was brought to 20°±0.05°C. in a constant temperature bath. A blank containing no vanillin was prepared. At zero time, cold, approximately 0.03 *M* aqueous chlorine dioxide, 100 cc., was added to the solution and the blank, and the stoppered bottles were quickly shaken. The heat of the initial reaction raised the temperature of the vanillin solution close to that of the bath almost immediately. From time to time, the residual oxidant in 10 cc. aliquots was determined iodometrically as chlorine dioxide. The apparent chlorine dioxide content of the blanks was plotted against time (cf. Fig. 1), and the difference between these plots and the corresponding values for the solution was accepted as the chlorine dioxide reduced by the vanillin.

Preparation of Aldehyde $C_7H_5O_4(OCH_3)$

(*a*) With chlorine dioxide. Thirty grams (0.2 mole) of vanillin was dissolved in 1400 cc. of a 0.4 *M* citric acid – 0.8 *M* disodium hydrogen phosphate buffer for pH 4.0 made up according to McIlvaine's proportions (10) but with four times the recommended concentrations. After this solution had been chilled, 820 cc. of 0.41 *M* aqueous chlorine dioxide (0.4 mole) was added near 0°C., and the flask was cooled efficiently to dissipate the considerable heat of the reaction. The solution immediately became dark red but this color changed in about two hours to a golden yellow. At this stage the excess chlorine dioxide was removed by passing nitrogen gas through the solution, which was then extracted with 2 liters of ether. Toward the end of the extraction the solution gradually became opaque and dark red-brown in color. The yellow ether extract was dried over anhydrous sodium sulphate and was concentrated to about 150 cc. on a steam bath. When this concentrate was further evaporated *in vacuo* without warming or access of moisture, it became very cold and deposited white crystals, which were recovered on a filter and were freed from traces of an orange-brown oil by washing with a small amount of cold, anhydrous ether. Concentration and "freezing out" were repeated three or four times to give a total yield of 9.0 gm. (25%) of the crystals, and the final mother liquor contained 7.1 gm. of a chlorine-containing, orange oil which darkened on standing. Benzene was the best solvent found for recrystallization, and the pure prisms melted at 104° to 105°C. Found: C, 52.1, 52.4; H, 4.4, 4.4; OCH_3, 16.7, 16.7%; mol. wt. (Rast) 182. Calc. for $C_7H_5O_4(OCH_3)$: C, 52.1; H, 4.4; OCH_3, 16.9%; mol. wt. 184.

The substance evolved 1.06, 1.01 atoms of active hydrogen in the Zerewitinoff (12) estimation, and 3.83, 3.90 moles of the Grignard reagent was consumed per gram mol. wt. Pyridine was the solvent for the sample and butyl ether for the methyl magnesium iodide.

(*b*) With sodium chlorite at pH 4. Two grams of vanillin was dissolved in 100 cc. of the McIlvaine standard buffer, pH 4.0, but used in four times the usual strength. When 5 gm. of sodium chlorite in 25 cc. of distilled water was added, the solution turned orange, green, and then yellow, and the presence of chlorine dioxide became apparent for the first time at the yellow stage. The aldehyde was isolated as already described in a yield of 0.5 gm. or 19%, m.p. 104° to 105°C., not depressed by admixture with a sample prepared with chlorine dioxide. None of the acid $C_7H_5O_5(OCH_3)$ (see below) could be isolated.

2,4-Dinitrophenylhydrazone of Aldehyde $C_7H_5O_4(OCH_3)$

A 0.20 gm. sample, dissolved in a few cc. of alcohol, was stirred with 60 cc. of filtered Brady's solution containing 4 gm. of the dinitrophenylhydrazine per liter. After about 20 sec. the solution became opalescent, and after one hour the bright yellow deposit was collected and thoroughly washed with water. Yield 0.37 gm. or 97% of theory, and m.p., 192° to 193° (uncorrected). Found: N, 15.7, 15.8%. Calc. for $C_{14}H_{12}N_4O_8$: N, 15.4%.

Semicarbazone of Aldehyde $C_7H_5O_4(OCH_3)$

The sample (0.05 gm.) was mixed in a small centrifuge tube with 0.05 gm. of semicarbazide hydrochloride and 0.75 gm. of anhydrous sodium acetate. A few cubic centimeters of water was added with stirring, and the semicarbazone separated as the original substance dissolved. The white precipitate, after being washed in water and dried at 50°C. *in vacuo*, was recovered in quantitative yield. Found: N, 16.9; 17.1%. Calc. for $C_9H_{11}N_3O_5$: N, 17.4%. The semicarbazone melted at 163° (uncorrected) with decomposition.

Hydrogenation of Aldehyde $C_7H_5O_4(OCH_3)$

(*a*) The sample, 1.84 gm. (0.01 mole) was dissolved in 30 cc. of anhydrous dioxane, and 20 mgm. of a palladium catalyst (20) was added. The mixture when shaken in an Adkins hydrogenator at room temperature and about 35 p.s.i. hydrogen pressure absorbed 2 moles per mole in two hours, and no more was consumed in an additional hour.

After filtration, the colorless solution was evaporated in a vacuum to a slightly discolored, viscous oil weighing 1.85 gm. This oil when distilled at 120°C. and 125μ pressure yielded a colorless product with refractive index η_D^{20} 1.4670. Found: C, 51.5, 51.4; H, 6.4, 6.3; OCH_3, 16.6, 16.7%. Calc. for $C_7H_9O_4(OCH_3)$: C, 51.1; H, 6.4; OCH_3, 16.5%. A Zerewitinoff estimation (12) showed the presence of 2.03, 1.97 atoms of active hydrogen per mole.

(*b*) A microscale hydrogenation was carried out in apparatus described by Johns and Seiferle (8). When the apparatus was tested with pure vanillin and a platinum oxide catalyst, 1.98 moles of hydrogen per mole was used. The aldehyde group in vanillin had therefore been reduced to a methyl group.

Samples of the aldehyde, $C_7H_5O_4(OCH_3)$, 6.04 mgm. and 6.13 mgm., required 2.23 cc. and 2.27 cc. of hydrogen at S.T.P., corresponding to consumptions of 3.03, 3.04 moles, respectively, per calculated mol. wt. of 184. A repetition of the hydrogenation on a larger scale gave a colorless glass unaffected by aqueous sodium bicarbonate and by 2,4-dinitrophenylhydrazine, and giving no distinct color with ferric chloride solution.

Methylation of Aldehyde $C_7H_5O_4(OCH_3)$ with Diazomethane

A solution of 1 gm. of the aldehyde in anhydrous ether was mixed with excess of an ether solution of diazomethane prepared from 10 gm. of nitrosomethylurea (1). A pale yellow precipitate, 0.46 gm., settled, which after recovery became dark orange in color. The substance decomposed when heated to 80°C., was insoluble in petroleum ether and benzene, but dissolved in methanol, ethanol, and acetone. All attempts at recrystallization yielded an orange glass. Found: OCH_3, 22.1, 22.2%. Calc. for $C_7H_4O_3(OCH_3)_2(CH_2N_2)_2$: OCH_3, 22.0%. The residue from the ether was also a yellow glass that became dark on exposure to air.

Preparation of the Acid $C_7H_5O_5(OCH_3)$

(*a*) At pH 0.5. Thirty grams (0.2 mole) of vanillin, dissolved in 1500 cc. of aqueous sulphuric acid (pH 0.5), was mixed with 72 gm. (0.8 mole) of sodium chlorite dissolved in 150 cc. of water. The solution became dark red, but this color gradually faded to orange and then to golden yellow. After 45 min. the chlorine dioxide formed in the reaction was removed by bubbling nitrogen through the solution, which was then saturated with sodium chloride and extracted with ether. The ether extract was dried over anhydrous sodium sulphate and concentrated to about 150 cc. When the remaining ether was evaporated *in vacuo* at room temperature, a total of 12 gm. (28% of theory) of white crystals was recovered from 17 gm. of a residual yellow oil. Qualitative tests revealed a high chlorine content in this oil, but when exposed to the air it quickly changed to a dark, viscous tar.

The crystals were washed with cold, anhydrous ether, and when recrystallized from a mixture of ether and low-boiling petroleum ether formed large, colorless, glistening plates melting with decomposition at 143° to 144°C. (uncorrected). Found: C, 48.0, 48.1; H, 4.1, 4.1; OCH_3, 15.6, 15.5%. Calc. for $C_7H_5O_5(OCH_3)$: C, 48.0; H, 4.0; OCH_3, 15.5%. The total Grignard reagent consumed in a Zerewitinoff (12) estimation was 4.80, 4.87 moles, and 2.01, 1.97 atoms of hydrogen were evolved, per calculated mol. wt. of 200. A 50 mgm. sample was neutralized to a potentiometric end point near pH 8 by 5.60 cc. of 0.0914 *N* caustic soda, corresponding to a neutralization equivalent of 98.

The acid was insoluble in petroleum ether and benzene, but dissolved in alcohol, water, chloroform, and ether.

(*b*) At pH 1.0. A solution of 10 gm. of vanillin in 500 cc. of distilled water adjusted to pH 1 with sulphuric acid was mixed with another made from 19 gm. of sodium chlorite and 50 cc. of water. After 2.5 hr., during which time the color changes already described occurred, the mixture was saturated with salt and extracted with ether. The crystalline product, 2.8 gm., recovered from the ether was separated by extraction with benzene into the benzene-soluble aldehyde $C_7H_5O_4(OCH_3)$ (1.8 gm. or 15% of theory) melting at 104° to 105°C.

and the benzene-insoluble acid $C_7H_5O_5(OCH_3)$ (1.0 gm. or 7.7%), melting at 143° to 144°C. Neither melting point was depressed when samples of each product were mixed with the appropriate authentic specimen.

(*c*) From the aldehyde $C_7H_5O_4(OCH_3)$. The oxidation (*a*) was repeated at pH 0.5 with 2 gm. (0.013 mole) of the aldehyde dissolved in 100 cc. of aqueous sulphuric acid, 4.5 gm. (0.05 mole) of sodium chlorite being used. After removing the by product chlorine dioxide, the colorless aqueous solution was extracted with ether. A quantitative yield of the acid remained, and the melting point of this product was not depressed by admixture with an authentic sample. Found: OCH_3, 15.4, 15.5%. Calc. for $C_7H_5O_5(OCH_3)$: OCH_3, 15.5%.

Methylation of the Acid $C_7H_5O_5(OCH_3)$

(*a*) With diazomethane. An excess of an ethereal solution of diazomethane was added to a solution of 1 gm. of the acid dissolved in ether. Large, colorless needles, melting at 116° to 118°C. with decomposition, separated from the solution after a short time. No solvent was found from which the product could be recrystallized without decomposition. Found: C, 46.5, 46.2; H, 5.0, 5.1; OCH_3, 29.9, 29.9; N, 17.8, 17.8%. Calc. for $C_7H_3O_3(OCH_3)_3 \cdot 2CH_2N_2$: C, 46.5; H, 5.2; OCH_3, 30.0; N, 18.1%.

(*b*) With methanol. One gram of the acid was heated under reflux for 10 hr. with 10 cc. of dry methanol containing two drops of concentrated sulphuric acid. Concentration of the solution under vacuum brought about the separation of a crystalline mass melting at 115° to 118°C. with previous softening. Recrystallization from a low-boiling petroleum ether – ether mixture yielded a product which melted at 125° to 126°C. after being washed with water and dried. Found: OCH_3, 29.2, 29.1%. Calc. for $C_7H_4O_4(OCH_3)_2$: OCH_3, 29.0%.

This ester, when re-methylated with diazomethane, yielded the substance $C_7H_3O_3(OCH_3)_3 \cdot 2CH_2N_2$ with the proper melting point of 115° to 117°C., undepressed by admixture with the specimen prepared directly from the acid $C_7H_5O_5(OCH_3)$.

(*c*) With dimethyl sulphate. A solution of the acid, 1.4 gm., and sodium hydrosulphite, 0.2 gm., in a small amount of water was methylated by the alternate addition, with continuous stirring, of 2 cc. volumes of dimethyl sulphate and 5 cc. volumes of 30% sodium hydroxide. The total volumes added were 10 cc. and 20 cc., respectively. After the mixture had been kept near 100°C. for an additional two hours, acidification and continuous extraction with ether yielded 1.2 gm. of a red oil. This oil partly crystallized one day later, and after recovery the crystals were recrystallized from a very small volume of ethyl acetate. The product, still slightly pink in color, decomposed at 172° to 175°C. with discoloration and the evolution of gas. Found: C, 45.4, 45.0; H, 3.27, 3.23; OCH_3, 0.0%. Calc. for $C_7H_6O_6$: C, 45.2; H, 3.2%. The substance evolved 2.95 atoms of hydrogen per mol. wt. 186 in a Zerewitinoff estimation (12). A 15.15 mgm. sample, when titrated to a potentiometric end point near pH 8, consumed 6.80 cc. of 0.0239 *N* sodium hydroxide. The neutralization equivalent was therefore 93.

(*d*) With silver oxide and methyl iodide. A mixture of the following substances was heated under reflux for four hours on a steam bath: 4.0 gm. of the acid $C_7H_5O_5(OCH_3)$, 50 cc. of anhydrous acetone, 50 cc. of methyl iodide freshly distilled over phosphorous pentoxide, 12 gm. of dry silver oxide, and 8 gm. of regenerated Drierite. The acetone was included because the acid was insoluble in methyl iodide. The product, recovered by filtration of the reaction mixture and evaporation of the filtrate, consisted of a viscous, slightly yellow oil weighing 4.40 gm. One gram of this oil when distilled boiled at 92°C. and 120μ pressure, and the colorless product had the refractive index, n_D^{20}, 1.4940. Found: C, 52.4, 52.5; H, 5.3, 5.2; OCH_3, 40.7, 40.7%. Calc. for $C_7H_3O_3(OCH_3)_3$: C, 52.6; H, 5.3; OCH_3, 40.8%.

This oil, when re-methylated with diazomethane, yielded the crystals $C_7H_3O_3(OCH_3)_3 \cdot 2CH_2N_2$. Although the substance melted with decomposition at 110° to 112°C. instead of 116° to 118°C., and could not be recrystallized, a mixed melting point with a sample prepared directly from the acid $C_7H_5O_5(OCH_3)$ was not depressed.

Another portion of the above oil was heated on a steam bath with 5% aqueous sodium hydroxide; the solution was acidified and extracted with ether. The extract yielded a crystalline product whose melting point of 172° to 174°C. was not depressed by admixture with the crystals, $C_7H_6O_6$, obtained in the attempt to methylate the acid $C_7H_5O_5(OCH_3)$ with dimethyl sulphate and sodium hydroxide.

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