Summary

The chloromethyl ethers of three nitro alcohols have been prepared.

Evidence suggests that the formation of these chloromethyl ethers takes place through the formal as an intermediate.

Several mixed acetals have been prepared from chloromethyl ethers of nitro alcohols and the nitro groups in these compounds have been reduced to amino groups.

TERRE HAUTE, INDIANA RECEIVED JANUARY 2, 1948

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Reactions of Vanillin and its Derived Compounds. VI.[1] The Reaction of Vanillin with Mercuric Oxide[2,3]

BY IRWIN A. PEARL

The high yields of vanillic acid obtained when vanillin is treated with alkali and 0.5 mole of silver oxide in aqueous solution[4,5] and the interesting reactions of vanillin with alkali in the presence of silver oxide and silver metal[6] led to a study of the reaction of vanillin with alkali and other metallic oxides. This paper reports the study with mercuric oxide.

Vanillin gradually reacts with an excess of mercuric oxide in a boiling aqueous solution containing at least two moles of alkali to give a clear alkaline solution which may be treated by various procedures to give several different reaction products. All forms of mercuric oxide are operative, but the more reactive, freshly precipitated forms require less time. The reaction time is also dependent, to a considerable extent, upon the temperature of boiling which, in turn, is dependent upon dilution. The reaction of vanillin with mercuric oxide is much slower than that with silver oxide.

Acidification of the alkaline reaction mixture with a non-reducing acid (such as sulfuric acid) gives a high yield of 5-hydroxymercurivanillin and minor amounts of oxidized mercurated compounds. Acidification with hydrochloric acid yields 5-hydroxymercurivanillin as the chief product, together with minor quantities of 5-chloromercurivanillin and other mercurated compounds, including oxidized and bis derivatives.

Treatment of the alkaline solution with sulfur dioxide, followed by short boiling, decomposes the organic mercury compounds and gives a 60–70% yield of vanillic acid and a 25–35% yield of recovered vanillin. No mercurated products are obtained after the sulfur dioxide treatment, and most of the mercury is recovered as the free metal.

When only one mole of vanillin is employed in the above reaction, the vanillic acid yield is very low, and almost all the initial vanillin is recovered after the sulfur dioxide treatment.

Long boiling of vanillin with technical dry mercuric oxide and excess alkaline solution resulted in considerable decarboxylation of the originally formed vanillic acid to yield 11% of guaiacol. This was an unexpected result, because earlier work[7,8] on the caustic fusion of vanillin to yield protocatechuic acid indicated that the carboxyl group was much more resistant to removal by drastic alkaline treatment than was the methoxyl group. All attempts to oxidize vanillin by means of mercuric oxide without alkali in a non-aqueous solvent were unsuccessful.

5-Hydroxymercurivanillin was identified by converting it successively to 5-acetoxymercurivanillin, 5-chloromercurivanillin, and 5-iodovanillin, which compounds were compared with the corresponding compounds prepared according to Paolini,[9] who obtained acetoxymercurivanillin by treating vanillin with mercuric oxide in boiling glacial acetic acid. Paolini's compound was proved to be 5-acetoxymercurivanillin by Henry and Sharp.[10] 5-Iodovanillin was also compared with the iodovanillin prepared according to Carles[11] which Raiford and Wells[12] proved to be 5-iodovanillin.

Paolini's[9] 5-acetoxymercurivanillin, upon boiling with *N* potassium hydroxide solution and acidifying with hydrochloric acid, yielded 5-chloromercurivanillin, but all attempts to isolate 5-hydroxymercurivanillin from 5-acetoxymercurivanillin failed.

5-Hydroxymercurivanillin possesses remarkable toxicity toward representative microörganisms, such as sporeforming and non-sporeforming aerobic bacteria and molds and compares favorably with such outstanding antiseptics as ethylmercury and phenylmercury derivatives. On the other

---

(1) For paper V of this series, see Pearl and McCoy, THIS JOURNAL, **69**, 3071 (1947).

(2) Presented before the Division of Organic Chemistry at the 112th meeting of The American Chemical Society, New York, N. Y., September 15–19, 1947.

(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) Pearl, THIS JOURNAL, **68**, 429 (1946).

(5) Pearl, *ibid.*, **68**, 1100 (1946).

(6) Pearl, *J. Org. Chem.*, **12**, 79 (1947).

(7) Tiemann, *Ber.*, **8**, 512 (1875).

(8) Pearl, THIS JOURNAL, **68**, 2180 (1946).

(9) Paolini, *Gazz. chim. ital.*, **51**, II, 188 (1921).

(10) Henry and Sharp, *J. Chem. Soc.*, 8288 (1930).

(11) Carles, *Bull. soc. chim.*, **17**, 14 (1872).

(12) Raiford and Wells, THIS JOURNAL, **57**, 2500 (1935).

hand, 5-hydroxymercurivanillin is much less toxic toward fish than the ethylmercury and phenylmercury compounds and, therefore, its use as a mill disinfectant or slime control agent is indicated. 5-Hydroxymercurivanillin also appears to have medicinal uses.

Experimental

All melting points given are uncorrected.

Reaction of Vanillin with Alkali and Mercuric Oxide.—To a solution of 136 g. of mercuric chloride in 400 cc. of hot water was added a hot solution of 100 g. of sodium hydroxide in 100 cc. of water. The mixture was vigorously stirred and treated with 25 g. of vanillin. The reaction mixture was heated to boiling under a reflux with mercury-sealed stirring for ten hours and allowed to cool.

Acidification with Sulfuric Acid. Preparation of 5-Hydroxymercurivanillin.—The above reaction mixture was filtered and the inorganic precipitate was washed with water. The combined filtrate and washings were acidified with 1:3 sulfuric acid. The thick white precipitate which separated was filtered, washed with water, and dried in a vacuum desiccator. The yield was 40 g. Recrystallization from water, ethanol, methanol, acetone, or dioxane gave colorless needles of 5-hydroxymercurivanillin melting at 235°. 5-Hydroxymercurivanillin is very slightly soluble in the above solvents, but is soluble in dilute alkali, glacial acetic acid, and concentrated sulfuric acid.

Anal. Calcd. for $C_8H_8O_4Hg$: CH_3O, 8.4. Found: CH_3O, 8.4.

A sample was dissolved in the minimum amount of boiling acetic acid. On cooling a fine crystalline powder of 5-acetoxymercurivanillin separated, which melted at 196–198°.

Anal. Calcd. for $C_{10}H_{10}O_5Hg$: CH_3O, 7.56. Found: CH_3O, 7.61.

A suspension of 5-acetoxymercurivanillin in a solution of excess sodium chloride was boiled several hours and cooled. The glistening precipitate was filtered and recrystallized from methanol to yield 5-chloromercurivanillin melting at 242–243° and not depressing a mixed melting point with Paolini's compound.[9]

Anal. Calcd. for $C_8H_7O_3HgCl$: C, 24.8; H, 1.83; Cl, 9.17. Found: C, 24.2; H, 1.89; Cl, 9.2.

5-Chloromercurivanillin was warmed with a solution of iodine in ethanol and cooled. The light yellow crystals were recrystallized twice from water and twice from 50% ethanol to give colorless crystals of 5-iodovanillin which melted at 176° and did not depress a mixed melting point with Carles'[11] authentic 5-iodovanillin.

Acidification with Sulfur Dioxide. Preparation of Vanillic Acid.—A hot solution of 80 g. of sodium hydroxide in 500 cc. of water was treated with stirring with 108 g. of C. P. dry yellow mercuric oxide and then with 25 g. of vanillin. The mixture was boiled under a reflux with mercury-sealed stirring for seven hours and allowed to cool. The precipitate was filtered and washed with water. The filtrate and washings were acidified with sulfur dioxide, which caused the separation of a granular white precipitate. This precipitate was filtered, washed with water, dried, and washed with ether. The filtrate was thoroughly extracted with ether and the combined ether extracts were extracted with 8% sodium bicarbonate solution; the extract yielded 17.9 g. (65%) of vanillic acid melting at 207–208°. Recrystallization from water or ethanol yielded colorless crystals which melted at 209–210° and did not depress a mixed melting point with authentic vanillic acid.[4]

The sulfur dioxide-saturated aqueous solution was acidified with sulfuric acid, aspirated with air, and extracted with ether. The ether was extracted successively with 21% sodium bisulfite, 8% sodium bicarbonate, and 5% sodium hydroxide solutions. No bisulfite extract was obtained. A little more vanillic acid was obtained from the bicarbonate extract. Approximately 30% vanillin was recovered by acidification of the sodium hydroxide extract. The occurrence of vanillin in the sodium hydroxide extract, rather than in the bisulfite extract in this experiment, has not been satisfactorily explained, although it is apparent that the aldehyde group must be protected in some manner until treated with strong alkali.

In an alternate procedure, the original sulfur dioxide-saturated reaction mixture containing the granular white precipitate was boiled for a short while and filtered. The clear solution deposited needles of vanillic acid upon cooling and the rest was secured by ether extraction.

The granular white precipitate appears to be a hydrated mercuric bisulfite or bisulfate. The ether-extracted white crystals, when boiled with water, yielded metallic mercury and sulfur dioxide.

Anal. Calcd. for $Hg(HSO_4)_2 \cdot 2H_2O$: Hg, 46.8; S, 14.8. Calcd. for $Hg(HSO_3)_2 \cdot 4H_2O$: Hg, 46.0; S, 14.8. Found: Hg, 46.20, 46.73; S, 14.83, 14.64.

In a similar experiment employing technical dry mercuric oxide, the sulfited reaction mixture was boiled, cooled, and extracted with ether. The ether was extracted with 8% sodium bicarbonate solution, which was acidified to yield 35.4% vanillic acid. The ether was dried and distilled. The oily residue, on distillation, yielded 11.0% of guaiacol boiling at 203–207°. The benzoate melted at 57° and did not depress a mixed melting point with authentic guaiacol benzoate. The original sulfited aqueous solution yielded 53.3% of recovered vanillin.

Reaction of Vanillin with Mercuric Oxide in Anhydrous Solvent.—A mixture of 15.2 g. of vanillin, 21.6 g. of C. P. dry mercuric oxide, and 250 cc. of dry benzene was boiled under reflux with occasional shaking for seven hours. No reduction of the oxide took place and all the vanillin was recovered.

Reaction of 5-Acetoxymercurivanillin with Alkali.—A mixture of 20 g. of 5-acetoxymercurivanillin and 400 cc. of *N* potassium hydroxide solution was boiled for two hours. The clear solution was filtered from a trace of metallic mercury, cooled, and acidified with sulfur dioxide. The acidified solution was heated to boiling with continued sulfur dioxide introduction for ten minutes. The sulfur dioxide introduction was discontinued, and boiling was continued for ten minutes. The mercury which separated was filtered, and the cooled filtrate was extracted with ether. The ether solution, when dried and distilled, gave 7 g. of vanillin melting at 78–79° and not depressing a mixed melting point with authentic vanillin.

In a similar experiment, the original filtered alkaline reaction mixture was acidified with dilute hydrochloric acid. The white flocculent precipitate was filtered, washed with water, dried, and recrystallized from methanol to yield white crystals of 5-chloromercurivanillin melting at 241°.

Anal. Calcd. for $C_8H_7O_3HgCl$: Cl, 9.2; CH_3O, 8.1. Found: Cl, 9.2; CH_3O, 8.4.

Solution of the 5-chloromercurivanillin in dilute potassium hydroxide and acidification with sulfur dioxide yielded vanillin.

Similar acidification of the 5-acetoxymercurivanillin-potassium hydroxide reaction mixture with dilute sulfuric acid yielded only a yellow brittle solid which contained 8.3% methoxyl and which would not melt. All attempts to isolate 5-hydroxymercurivanillin failed.

Toxicity Studies.—The toxicity of 5-hydroxymercurivanillin was determined for the representative micro-organisms, *Aerobacter aerogenes* (non-sporeforming bacteria), *Bacillus mycoides* (sporeforming bacteria), and *Aspergillus niger* (molds), by the method of Appling and McCoy[13] and compared with commercial samples of Merfenel (phenylmercuric acetate), Lignasan (ethylmercuric phosphate), and Santobrite (sodium

---

(13) Appling and McCoy, *Paper Trade J.*, **119**, No. 11, 116 (1944).

pentachlorophenate). The results are given in Table I.

TABLE I

INHIBITING CONCENTRATIONS FOR THREE TEST ORGANISMS (IN PER CENT. BY WEIGHT)

	A. aerogenes (increment 0.0001%)	*B. mycoides* (increment 0.0004%)	*A. niger* (increment 0.0004%)
5-Hydroxymercurivanillin	0.0004	0.0002	0.0010
Merfenel[a]	.0001	.00001	.0001
Lignasan[b]	.0010	.00016	.0006
Santobrite[c]	.0225	.0004	.0016

[a] Technical phenylmercuric acetate. [b] Contains 6.25 ethylmercury phosphate. [c] Technical sodium pentachlorophenate.

TABLE II

TOXICITY TOWARD LAKE EMERALD SHINER (*Notropis atherinoides*)

	Critical concn., p. p. m.	Survival period, min.
5-Hydroxymercurivanillin	5–7	600 (7.5 p. p. m.)
Merfenel[a]	0.02	15 (5.0 p. p. m.)
Lignasan[b]	0.8	128 (5.0 p. p. m.)
Santobrite[c]	0.4	16 (5.0 p. p. m.)

[a] Technical phenylmercuric acetate. [b] Contains 6.25 ethylmercury phosphate. [c] Technical sodium pentachlorophenate.

Fish toxicity tests were run according to the method of Van Horn[14] employing the lake emerald shiner (*Notropis atherinoides*) as the test fish. Van Horn has shown this fish to be one of the most sensitive for toxicity studies. The data are given in Table II.

Acknowledgment.—The author is indebted to the Analytical, Biology, and Microbiology Departments of The Institute of Paper Chemistry for the analyses and toxicity tests reported in this paper.

Summary

Reaction of vanillin with excess mercuric oxide and alkali in aqueous solution and acidification of the filtered reaction mixture with sulfur dioxide yields 60–70% vanillic acid. Similar reaction of vanillin with one or more moles of mercuric oxide and acidification with a non-reducing acid yields 5-hydroxymercurivanillin as the chief reaction product. 5-Hydroxymercurivanillin has demonstrated remarkable toxicity toward representative microorganisms, but was found to be much less toxic to fish than other well-known comparable antiseptics. Its use as a mill disinfectant or slime control agent is indicated.

[14] Van Horn, *Paper Trade J.*, **117**, No. 24, 33 (1943).

APPLETON, WISCONSIN RECEIVED JANUARY 23, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Bromination of Zein

BY W. W. BINKLEY[1]

Investigations of the chemical nature of zein have been largely indirect. Extensive studies have been made of the hydrolytic products of this corn protein.[2] Few reagents are selective enough to reveal any part of the intimate structure of this molecule. Neuberger,[3] using iodine and ammoniacal methanol, prepared an undegraded iodozein which indicated the combination of 0.064 g. atom of iodine with 100 g. of zein. The iodine was shown to be combined with the tyrosine residues in the protein. The halogenation of zein has been extended using chlorine and bromine.

The direct titration of zein with chlorine in acetic acid did not show the formation of a definite compound (Fig. 1). Bromine reacted with zein to form an undegraded or slightly degraded bromozein (Fig. 1). Iodine did not react with zein in the presence of acetic acid.

Dry ethyl ether and 0.25% aqueous sodium chloride were used as the precipitation media for the brominated zein. The product of the ether precipitation was acidic, reacted with sodium hydroxide, silver nitrate, and liberated iodine from potassium iodide; this compound was called bromozein hydrobromide. The other product was neutral, and did not react with sodium hydroxide, silver nitrate or potassium iodide; it was named bromozein.

A total of 0.24 g. atom of bromine was required to brominate 100 g. of zein (Fig. 1). Bromozein hydrobromide possessed 0.20 g. atom of this bromine (Table I).[4] Sodium hydroxide or silver nitrate reacted readily with 0.13 g. atom of the bromine in bromozein hydrobromide, while 0.07 g. atom of the bromine was firmly bound. The amino acids which occur in zein were titrated with bromine in acetic acid. Two of these amino acids reacted under these conditions, *viz.*, tyrosine and histidine (Table II). Folin and Ciocalteu[5] established the presence of 0.033 mole of tyrosine residues in 100 g. of zein. The bromination of these tyrosine residues would produce 0.066 g. atom of the alkali labile bromines and an equal number of the firmly bound bromines in bromozein hydrobromide. Osborne and Liddle[6] found

---

[1] Research Associate of The Ohio State University Research Foundation.

[2] E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publishing Corp., New York, N. Y., 1943, p. 358.

[3] A. Neuberger, *Biochem. J.*, **28**, 1892 (1934).

[4] Gram atoms of bromine are expressed per 100 g. of zein.

[5] O. Folin and V. Ciocalteu, *J. Biol. Chem.*, **73**, 627 (1927).

[6] T. B. Osborne and L. M. Liddle, *Am. J. Physiol.*, **26**, 295 (1910).