That the substance was not an acetylated enolic or alkali-interconverted sugar was determined by the fact that it did not decolorize a solution of bromine in carbon tetrachloride and on deacetylation with sodium ethylate followed by reacetylation with warm acetic anhydride and sodium acetate, β-glucose pentaacetate (m. p. 131°; $[\alpha]_D$ +4°, $CHCl_3$) was produced.

The substance was also formed, although in lower yield, by the room temperature acetylation of *aldehydo*-glucose pentaacetate with acetic anhydride and zinc chloride. *Aldehydo*-glucose pentaacetate (2 g.) was added to a solution of 1 g. of freshly fused zinc chloride in 40 cc. of acetic anhydride and the solution allowed to stand overnight (fifteen hours). The solution was then poured on cracked ice and neutralized with sodium bicarbonate, extracted with chloroform and the extract washed with water and dried. The sirup obtained after solvent removal was crystallized from hot ethanol (carboraffin); yield, 0.2 g.; m. p. 117.5–118.5°; $[\alpha]_D$ +8° (*c*, 3; $CHCl_3$).

Aldehydo-*l*-arabinose Hexaacetate.[11]—*Aldehydo-l*-arabinose tetraacetate[13] (20 g.) was acetylated with a solution of 20 g. of zinc chloride (freshly fused) in one liter of acetic anhydride as described above for the preparation of glucose heptaacetate. The resultant sirup was crystallized from hot ethanol; yield, 9 g.; m. p. 85°. Pure material was obtained by solution in just sufficient hot ethanol so that no crystallization occurred on cooling and repeatedly adding water in small quantities to the above solution at ice box temperature; m. p. 89.5°; $[\alpha]^{27}_D$ −27° (*c*, 4; $CHCl_3$). The solubilities of this substance were similar to those of the corresponding glucose compound.

Anal. Calcd. for $C_5H_6O_6(CH_3CO)_6$: C, 48.57; H, 5.76; acetyl, 14.3 cc. 0.1 *N* NaOH per 100 mg. Found: C, 48.57; H, 5.68; acetyl, 14.3 cc.

The experimental work herein reported was carried on in this Laboratory rather incidentally over a considerable period of time and I wish to make due acknowledgment to the assistance rendered by Messrs. W. M. Morgan, J. L. Quinn, R. L. Whistler and M. Konigsberg.

Summary

1. The chloride, bromide and iodide forms of *aldehydo-d*-galactose hexaacetate 1-halide have been synthesized in crystalline form. It is pointed out that these substances are the open chain analogs of the cyclic acetohalogen sugars.

2. *Aldehydo-d*-glucose heptaacetate and *aldehydo-l*-arabinose hexaacetate have been synthesized in pure crystalline form. It is pointed out that these compounds may be expected to be formed in reactions involving the cyclic forms of the sugars, rather than the free carbonyl or *aldehydo*-structures.

COLUMBUS, OHIO RECEIVED OCTOBER 4, 1935

---

(13) M. L. Wolfrom and Mildred R. Newlin, THIS JOURNAL, **52**, 3619 (1930).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

Iodine Substitution Products of Vanillin and Some of their Derivatives

BY L. CHAS. RAIFORD AND EUGENE H. WELLS

In work published from this Laboratory[1] the chlorine and bromine substitution products of vanillin demanded by theory were prepared and characterized by a study of their interactions with typical amino compounds. Steric hindrance[2] was noted only when both ortho positions in the aldehyde were substituted, and was then less pronounced than expected. In the present work the iodine derivatives have been examined. The high yields of products indicated little, if any, hindrance.

The Action of Iodine on Vanillin.—Carles[3] treated vanillin with warm alcoholic solutions of iodine of different concentrations and obtained products that analyzed for mono- and diiodovanillin, respectively. He did not determine the structures of these compounds or study them further, and they are recorded as having the halogen in unknown positions.[4] The monoiodo derivative was reported to melt at 174° and was probably an impure sample of that, m. p. 180°, obtained by Hann[5] and reported as 5-iodovanillin, but without proof of structure. No melting point was given for the diiodo compound. Carles' work has been repeated and, while the monoiodo

---

(1) Raiford and Lichty, THIS JOURNAL, **52**, 4576 (1930). Other references to these studies are given there.

(2) Hantzsch [*Ber.*, **23**, 2776 (1890)] could not condense *sym*-tribromo- and trinitroaniline with benzaldehyde, but Lowy and coworkers [THIS JOURNAL, **43**, 1961 (1921)] found that when the nitro radical was in the aldehyde, condensation with aniline did take place, though they studied no aldehyde containing a substituent other than the nitro radical. Their results may not be typical for Meyer [*Z. physik. Chem.*, **24**, 219 (1897)] found that while hindrance in esterification of *o*-substituted benzoic acids was often proportional to the weight of the *o*-substituent, that produced by the nitro group was much greater than expected. On the other hand, Fischer and Giebe [*Ber.*, **31**, 546 (1898)] found that the *o*-nitro radical in benzaldehyde favors acetal formation.

(3) Carles, *Bull. soc. chim.*, [2] **17**, 14 (1872).

(4) Beilstein, "Handbuch org. Chem.," Vierte Auflage, 1925, VIII, p. 251.

(5) Hann, THIS JOURNAL, **47**, 2000 (1925).

compound only was obtained by his method, both were prepared in other ways and their structures established.

To determine the position of iodine in the first product here studied the start was made with the nitrovanillin, m. p. 137°, first obtained by Pschorr and Sumuleanu.[6] In later work, the hydroxyl group of this compound was methylated, and the resulting product was oxidized into a nitroveratric acid. The latter was reduced, the resulting amine diazotized and converted by the Sandmeyer method into a cyanide that on hydrolysis gave hemipinic acid.[7] The starting material must therefore have been 2-nitrovanillin (CHO = 1). In the present work this nitro compound was reduced and the resulting amino radical replaced by iodine in the usual way.

The position of iodine in the monoiodo compound reported by Carles was oriented as follows. That nitro compound, m. p. 175–176°, obtained by direct nitration of vanillin[8] and proved by Vogl[9] to have the nitro radical in position 5, was in our work reduced by stannous chloride and hydrochloric acid. Though the free amine was not obtained, the hydrochloride and the stannic chloride double salt were isolated, and from the former several derivatives were prepared. The salt was diazotized and separate portions were subjected to the Sandmeyer reaction with cuprous chloride, cuprous bromide and potassium iodide, respectively. In the first two cases 5-chloro- and 5-bromovanillin, in which the position of halogen had previously been determined by a different method, were obtained. In the third case Carles' monoiodovanillin was isolated, which proves that it is 5-iodovanillin.

By methods described below, 5-iodovanillin was converted into acetyl-5-iodovanillin, and into 3-methoxy-4-acetoxy-5-iodobenzal diacetate. Nitration of these products gave the same compound, acetyl-2-nitro-5-iodovanillin. The acetyl group was removed by hydrolysis, the nitro compound was reduced, the resulting amine was diazotized and the diazonium salt treated with potassium iodide. The diiodovanillin formed melted at 199–200°,[10] and was identical with that obtained by direct iodination of 2-iodovanillin.

With the hope of obtaining 6-iodovanillin, acetylvanillin was treated with iodine[11] and with iodine monochloride,[12] respectively. Only 5-iodovanillin and starting material were obtained. Similarly, treatment of 3-methoxy-4-acetoxybenzal diacetate[13] failed to give the desired product.

Experimental Part

2-Iodovanillin.—Twenty grams of 2-aminovanillin[14] was dissolved in 350 cc. of 15% hydrochloric acid, cooled to 0° and diazotized. A cold solution of 30 g. of potassium iodide was added, and the mixture kept at about 0° for two hours, and some tar that had separated was removed and examined. The remainder was heated on the steam-bath for an hour, then boiled over a free flame to remove free iodine; yield 54%. After boiling the alcoholic solution with norite and filtering, addition of hot water to the filtrate and cooling gave nearly colorless needles; m. p. 155–156°.

Anal. Calcd. for $C_8H_7O_3I$: I, 45.68. Found: I, 45.53.

2-Iodo-3,4-dimethoxybenzaldehyde.—To a potassium hydroxide solution of 2-iodovanillin held between 50 and 60°, excess of dimethyl sulfate was slowly added with shaking; yield 84%. Crystallization from dilute alcohol gave pale yellow needles; m. p. 82°.

Anal. Calcd. for $C_9H_9O_3I$: I, 43.49. Found: I, 43.65.

Analytical data for other derivatives are given in Table I.

Stannic Chloride Double Salt of 5-Aminovanillin.—To a boiling suspension of 160 g. of 5-nitrovanillin[15] in 750 cc. of alcohol there was added in small portions a solution of 800 g. of stannous chloride in 800 cc. of concentrated hydrochloric acid. After addition of a few portions the heat of reaction kept the mixture boiling. When all the reducing agent was in, 1500 cc. of concentrated acid was added and the mixture allowed to cool. When the resulting solid was dissolved in hot 2.5 *N* hydrochloric acid, and one volume of concentrated acid was added, orange crystals were obtained; yield 88%.

Anal. Calcd. for $C_{16}H_{20}O_6N_2SnCl_6$: N, 4.19; Cl, 31.88. Found: N, 4.24; Cl, 31.61.

5-Aminovanillin Hydrochloride.—A hot dilute hydrochloric acid solution of the tin salt indicated above was treated with hydrogen sulfide as long as change took place, the mixture filtered, the filtrate mixed with two volumes of concentrated hydrochloric acid, and cooled in ice; yield 70%. Recrystallization as indicated above gave yellowish-brown prisms.

---

(6) Pschorr and Sumuleanu, *Ber.*, **32**, 3408 (1899).

(7) Sumuleanu, *Ann. Sci. Univ. Jassy*, **2**, 131 (1902–1903).

(8) Bentley, *Am. Chem. J.*, **24**, 171 (1900); Hayduck, *Ber.*, **36**, 2933 (1903).

(9) Vogl, *Monatsh.*, **20**, 385 (1899).

(10) Carles (Ref. 3) recorded no melting point for his diiodo compound.

(11) Raiford and Stoesser [This Journal, **49**, 1078 (1927)] found that treatment of acetylvanillin with bromine in the presence of sodium acetate gave a high yield of 6-bromovanillin, and no other derivative could be isolated.

(12) Prepared as directed by Cornog and Karges, *ibid.*, **54**, 1882 (1932).

(13) Raiford and Lichty (Ref. 1) showed that treatment of this compound with chlorine gave a 90% yield of 6-chlorovanillin.

(14) Prepared as directed by Pschorr and Sumuleanu [*Ber.*, **32**, 3408 (1899)].

(15) This was obtained in 70% yield by Bentley's method [*Am. Chem. J.*, **24**, 171 (1900)], modified to the extent of cooling the vanillin solution and adding the nitric acid slowly.

TABLE I

DERIVATIVES OF 2-IODOVANILLIN

Compound	Yield, %	Solvent	Crystal form	M. p., °C.	Formula	Halogen, % Calcd.	Halogen, % Found
Acetyl	85	Dil. alcohol	Plates	70–72	$C_{10}H_9O_4I$	39.68	39.73
Oxime	98	Dil. alcohol	Diamond plates	Softened[a] about 122	$C_8H_8O_3NI\cdot{}^1/_2H_2O$	42.05	42.01
Semicarbazone	93	Dil. alcohol	Plates	199–200	$C_9H_{10}O_3N_3I$	37.91	38.01
p-Nitrophenylhydrazone	98	Dil. alcohol[b]	Red needles	211–212	$C_{14}H_{12}O_4N_3I$	30.75	30.60
Bis-benzidine	Nearly quant.	Dil. pyridine	Brown plates	228–230 (dec.)	$C_{28}H_{22}O_4N_2I_2\cdot$[c] $2C_5H_5N$	29.46	29.54

[a] Heating for 24 hours at 107° gave a product that melted at 142.5–143.5°. *Anal.* Calcd. for $C_8H_8O_3NI$: I, 44.34. Found: I, 43.42. [b] Hot water was added to the hot alcoholic solution until turbid. [c] Extraction of the crude material with alcohol to remove foreign matter gave a product that decomposed at about 232–233°. *Anal.* Calcd. for $C_{28}H_{22}O_4N_2I_2$: I, 36.07. Found: I, 36.20.

TABLE II

DERIVATIVES OF 5-IODOVANILLIN

Compound	Yield, %	Solvent	Crystal form	M. p., °C.	Formula	Halogen, % Calcd.	Halogen, % Found
Acetyl	66	50% alcohol	Colorless plates	105–106	$C_{10}H_9O_4I$	39.68	39.78
Benzoyl	82[a]	Dil. alcohol	Fibrous masses	135.5–136.5	$C_{15}H_{11}O_4I$	33.24	33.26
Acetyl diacetate	95	Ligroin	Colorless cubes	132–133	$C_{14}H_{15}O_7I$	30.09	30.16
Oxime	88	Dil. alcohol	Nearly colorless needles	178–179[b]	$C_8H_8O_3NI$	43.34	43.18
Semicarbazone	98	Dil. alcohol	Yellow needles	205–205.5	$C_9H_{10}O_3N_3I$	37.91	37.92
p-Nitrophenylhydrazone	85	80% Alcohol	Red needles	242–243 (dec.)	$C_{14}H_{12}O_4N_3I$	30.75	30.55
Bis-benzidine	88	Pyridine and water	Brown plates	232 (dec.)	$C_{28}H_{22}O_4N_2I_2$	36.08	36.08
Methyl	70	Dil. alcohol	Fibrous masses	69–70	$C_9H_9O_3I$	43.49	43.39

[a] Obtained in presence of pyridine as directed by Einhorn and Hollandt. The Schotten–Baumann method gave only 7%. [b] A mixture of this and 5-iodovanillin, m. p. 179–180°, melted at 150–160°.

TABLE III

DERIVATIVES OF 2-NITRO-5-IODOVANILLIN

Compound	Yield, %	Solvent	Crystal form	M. p., °C.	Formula	Halogen, % Calcd.	Halogen, % Found
Oxime	97	Benzene	Yellow rods	128–129	$C_8H_7O_5N_2I$	37.57	37.76
Semicarbazone	51	Alcohol	Yellow needles	187–188 (dec.)	$C_9H_9O_5N_4I$	33.33	33.31
p-Nitrophenylhydrazone	70	Alcohol	Red plates	228–230 (dec.)	$C_{14}H_{11}O_6N_4I\cdot{}^1/_2C_2H_5OH$	26.40	26.42
Bis-benzidine	82	[a]	Yellow powder	[b]	$C_{28}H_{20}O_8N_4I_2$	31.98	31.43

[a] Purification was accomplished by extraction of foreign material by alcohol. [b] It was heated to about 335° but gave no melting point.

Anal. Calcd. for $C_8H_{10}O_3NCl$: N, 6.87; Cl, 17.44. Found: N, 6.68; Cl, 16.55.

3 - Methoxy - 4 - acetoxy - 5 - acetylaminobenzaldehyde.—A portion of the amino hydrochloride was dissolved in 10% solution of potassium hydroxide by gentle warming, cooled to room temperature and shaken with an ether solution of acetic anhydride; yield 66%. Crystallization from water gave colorless needles; m. p. 174–176°.

Anal. Calcd. for $C_{12}H_{13}O_5N$: N, 5.57. Found: N, 5.36.

3 - Methoxy - 4 - benzoxy - 5 - benzoylaminobenzaldehyde.—This was obtained in 75% yield by treatment of an alkaline solution of the base with benzoyl chloride. Crystallization from alcohol gave colorless needles; m. p. 161–162°.

Anal. Calcd. for $C_{22}H_{17}O_5N$: N, 3.73. Found: N, 3.83.

5-Iodovanillin.—Five grams of the amino hydrochloride was suspended in 20 cc. of dilute hydrochloric acid, cooled below 0° and diazotized. To the clear liquid a cold solution of potassium iodide was added, the mixture warmed slowly and finally boiled to remove free iodine; yield 79% of brown solid. Repeated crystallization from dilute alcohol gave light brown needles, m. p. 179–180°, and identical with Carles' product.[16] Data for derivatives are given in Table II.

Acetyl-2-nitro-5-iodovanillin.—Eighty grams of acetyl-5-iodovanillin was dissolved in 175 cc. of fuming nitric acid at 6° or below with stirring, the solution held at this temperature for half an hour, and the dark red liquid poured into a liter of ice and water. The oil that separated solidified on standing, was washed free from acid and boiled with water to remove a little free iodine; yield 83%. Crystallization from acetic acid, using norite, gave nearly colorless plates, m. p. 124–125°. The same product was obtained by nitration of 3-methoxy-4-acetoxy-5-iodobenzal diacetate.

Anal. Calcd. for $C_{10}H_8O_6NI$: I, 34.79. Found: I, 34.97.

---

(16) This compound was also obtained by the action of iodine monochloride an vanillin.

TABLE IV

DERIVATIVES OF 2,5-IODOVANILLIN

Compound	Yield, %	Solvent	Crystal form	M. p., °C.	Formula	Halogen, % Calcd.	Halogen, % Found
Acetyl	97	Dil. alcohol	Square prisms	127–128	$C_{10}H_8O_4I_2$	56.95	57.22
Oxime	95	Dil. alcohol	Needles	174.5–175.5	$C_8H_7O_3NI_2$	60.62	60.47
Semicarbazone	96	Alcohol	Needles	235 (dec.)	$C_9H_9O_3N_3I_2$	55.09	55.36
p-Nitrophenylhydrazone	95	Acetic acid	Orange	252–253 (dec.)	$C_{14}H_{11}O_4N_3I_2$	47.12	46.97
Bis-benzidine	83	[a]	Powder	[b]	$C_{28}H_{20}O_4N_2I_4$	53.13	52.17

[a] Could not be crystallized. [b] Gave no melting point.

Hydrolysis of this product with caustic potash solution gave 2-nitro-5-iodovanillin. Crystallization from 30% acetic acid gave colorless rods; m. p. 146–147°.

Anal. Calcd. for $C_8H_6O_5NI$: I, 39.30. Found: I, 39.57.

Data for derivatives are given in Table III.

2-Amino-5-iodovanillin.—Thirty-four grams of the nitro compound was reduced by ferrous hydroxide in the presence of ammonia water; yield 69%. Repeated crystallization from dilute alcohol, using norite, gave light brown needles, m. p. 155°.

Anal. Calcd. for $C_8H_8O_3NI$: I, 43.34. Found: I, 43.56.

Treatment of the diazonium salt from the above amine with potassium iodide gave 2,5-diiodovanillin, which was also obtained in another way and characterized as indicated below.

2,5-Diiodovanillin.—A mixture of 15 g. of 2-iodovanillin, 8 g. of anhydrous sodium acetate, 80 g. of acetic acid and 14 g. of iodine was kept at about 60° with continual stirring for twenty-four hours, one liter of water was then added and the mixture boiled to remove free iodine; yield 69%. Repeated crystallization from alcohol gave colorless rods; m. p. 200°.

Anal. Calcd. for $C_8H_6O_3I_2$: I, 62.87. Found: I, 62.87.

Treatment of this product with dimethyl sulfate under the conditions described for the monoiodo compound gave a 33% yield of 2,5-diiodo-3,4-dimethoxybenzaldehyde, while 60% of starting material was recovered. The new product was obtained as colorless needles by addition of hot water to the hot alcoholic solution, and cooling; m. p. 94°. Data for derivatives are given in Table IV.

Anal. Calcd. for $C_9H_8O_3I_2$: I, 60.76. Found: I, 60.56.

Summary

Several iodine substitution products of vanillin, including Carles' compounds, have been prepared and their structures determined. The behavior of these products toward typical amino compounds has been tested. No pronounced steric hindrance was noted in the latter reactions.

The relation between the numerical values of the melting points and the positions of the halogen atoms in the iodine derivatives, so far as they have been obtained, is in good agreement with that observed in the cases of the chlorine and bromine compounds, *viz.*, that the lowest value is found for position 2, the next higher for 5 and the highest for 6. Likewise, for a given position the lowest is found for the chloride, the next higher for the bromide and the highest for the iodide.

Further work is in progress.

IOWA CITY, IOWA RECEIVED OCTOBER 2, 1935