[Contribution from the Laboratory of Organic Chemistry of the State University of Iowa]

ACTION OF BROMINE ON VANILLIN, ISOVANILLIN, AND SOME OF THEIR DERIVATIVES, AND MODIFICATION OF THE DIRECTIVE INFLUENCE OF HYDROXYL IN THESE COMPOUNDS

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The position taken by a radical that enters a benzene substitution product is determined largely by the character of the substituent already there. The rules formulated to cover this behavior (1) apply in general to those cases where but one substituent is present in the starting material, and they predict the structures of the chief products only. When two or more substituents are present, the position taken by a new one is less easily predicted; consequently it was desired to study compounds in which this behavior could be tested further.

In such studies another consideration is of interest, *viz.*, the extent to which the directive influence of hydroxyl may be modified or suppressed by changing its composition through acylation or alkylation[1]. The derivatives of vanillin[2] and isovanillin offered an opportunity to extend such studies.

Derivatives of vanillin. In previous work it has been found that treatment of vanillin, 3-methoxy-4-hydroxybenzaldehyde, with chlorine (2), bromine (3), iodine (4), and nitric acid (5), respectively, gives high yields of derivatives in which the entering substituent takes position 5 (CHO = 1). Since that position is ortho with respect to hydroxyl and meta with respect to the aldehyde group it might be assumed, on the basis of the above observations alone, that these radicals exercised equal influence in determining the position taken by the entering substituent. That this is probably not the case is indicated by the work of Martinsen (6), who found that ortho-para directing groups facilitate substitution in the benzene ring, while groups of the meta directing type have a retarding influence. Therefore, in the reactions cited above it would appear that the chief directive influence was probably exerted by hydroxyl. When acetylvanillin is used,

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[1] Data on the behavior of alkyl derivatives of vanillin, soon to be published, have been obtained by R. P. Perry formerly of this laboratory.

[2] In recent years all the chlorine and bromine substitution products of vanillin demanded by theory have been obtained in this laboratory [*J. Am. Chem. Soc.*, **57**, 2500 (1935)].

bromination gives 87% of the 6-bromo derivative (7), while nitration gives as much as 80% of the 2-nitro compound and about 5% of the 6-isomeride (8). Benzoylvanillin gives similar results (9), indicating that acylation of hydroxyl suppresses its activity to such an extent that the directive influence in the acyl derivatives is due to the methoxyl radical[3]. Apparently, the aldehyde radical, which occupies position 1, exercises no influence in these types.

In view of these observations, it was of particular interest to study the behavior of related compounds in which position 1 was occupied by some meta-directing radical other than the aldehyde group. For this purpose vanillonitrile, vanillic acid, methyl vanillate, and 1-nitro-3-methoxy-4-hydroxybenzene [4-nitroguaiacol (OH = 1)] were selected. Treatment of these with bromine gave, in each case, the 5-bromo derivative in high yield, indicating again that the position taken by halogen must be determined chiefly by the hydroxyl group. Next, each starting material was acetylated and the products were tested with bromine as before[4]. The aldehyde, the acid, and the ester gave the corresponding 6-bromo derivatives in yields shown below. From the nitrile and the nitro compound no reaction products could be isolated, but starting material was recovered as shown in Table I.

Derivatives of isovanillin. Bromination of isovanillin was carried through in accordance with the general directions of Henry and Sharp (10), with a much larger quantity of material than they used. The product consisted of 33% of 2-bromoisovanillin and 55% of the 6-isomeride. With the hope of securing the 5-bromo compound by use of the Sandmeyer reaction, acetylisovanillin was nitrated as directed by Pschorr and Stöhrer (11), and the 5-nitro compound, which melted at 119–120.5°[5], was subjected to the action of several reducing agents. With ferrous hydroxide in the presence of ammonia water (12), the required amino compound seemed to be produced, but it could not be isolated in pure form. In another experiment sodium amalgam was used and the mixture was kept faintly alkaline by addition of hydrobromic acid. When the change seemed to be complete, the liquid was decanted from the mercury, and rendered neutral by addition of acid. The precipitate obtained was dissolved in hydrobromic acid,

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[3] This difference in directive influence between acyloxyl and alkoxyl has been noted by Klemenc [*Monatsh.*, **33**, 701 (1912)] and by Cardwell and Robinson [*J. Chem. Soc.*, **107**, 256 (1915)] in the nitration of acetylguaiacol.

[4] In these experiments sodium acetate was added to the reaction-mixture to interact with the hydrogen bromide liberated and thus prevent the hydrolysis of the acetyl derivative. This precaution was found necessary by Raiford and coworkers [*J. Am. Chem. Soc.*, **49**, 1078 (1927); **53**, 1057 (1931)] in the study of closely related cases.

[5] Pschorr and Stöhrer, *loc. cit.*, reported 113°.

cooled to 0°, and diazotized with sodium nitrite. Treatment of the resulting product with a hydrobromic acid solution of cuprous bromide gave a black, resinous material from which nothing could be identified.

To obtain isovanillonitrile, isovanillin was converted to the oxime and this was changed to the acetoxynitrile by boiling with purified acetic anhydride (13),[6] as directed by Marcus and elaborated by Raiford and Potter (14). The nitrile was obtained by hydrolysis of the acetoxy derivative with normal potassium hydroxide solution at room temperature for a few hours. Treatment of the nitrile with bromine gave 32% of the 2-bromo and 15% of the 6-bromo derivative, both in purified form. Next the nitrile was hydrolyzed to the acid by boiling with potassium hydroxide solution, though it was subsequently found that oxidation of an acetic acid solution of acetylisovanillin with potassium permanganate was more satisfactory for the preparation of the acid. Bromination of isovanillic acid gave but one of the expected products, the 6-isomeride in a yield of 13%, while 27% of purified starting material was recovered.

TABLE I

BROMINATION OF VANILLIN AND RELATED COMPOUNDS

STARTING MATERIAL	SUBSTITUENT IN POSITION 1	POSITION TAKEN BY HALOGEN	YIELD %
Vanillin	CHO	5	88
Acetylvanillin		6	87
Vanillonitrile	CN	5	85
Acetovanillonitrile		No reaction product obtained	[a]
Vanillic acid	COOH	5	82
Acetylvanillic acid		6	80
Methyl vanillate	$COOCH_3$	5	97
Methyl ester of acetylvanillic acid		6	30[b]
1-Nitro-3-methoxy-4-hydroxybenzene (4-nitroguaiacol)	NO_2	5	87
1-Nitro-3-methoxy-4-acetoxybenzene		No reaction product isolated	[c]

[a] 99% of starting material was recovered.

[b] This represents purified compound. The crude product contained considerable resin and starting material.

[c] Starting material was recovered to the extent of 88%.

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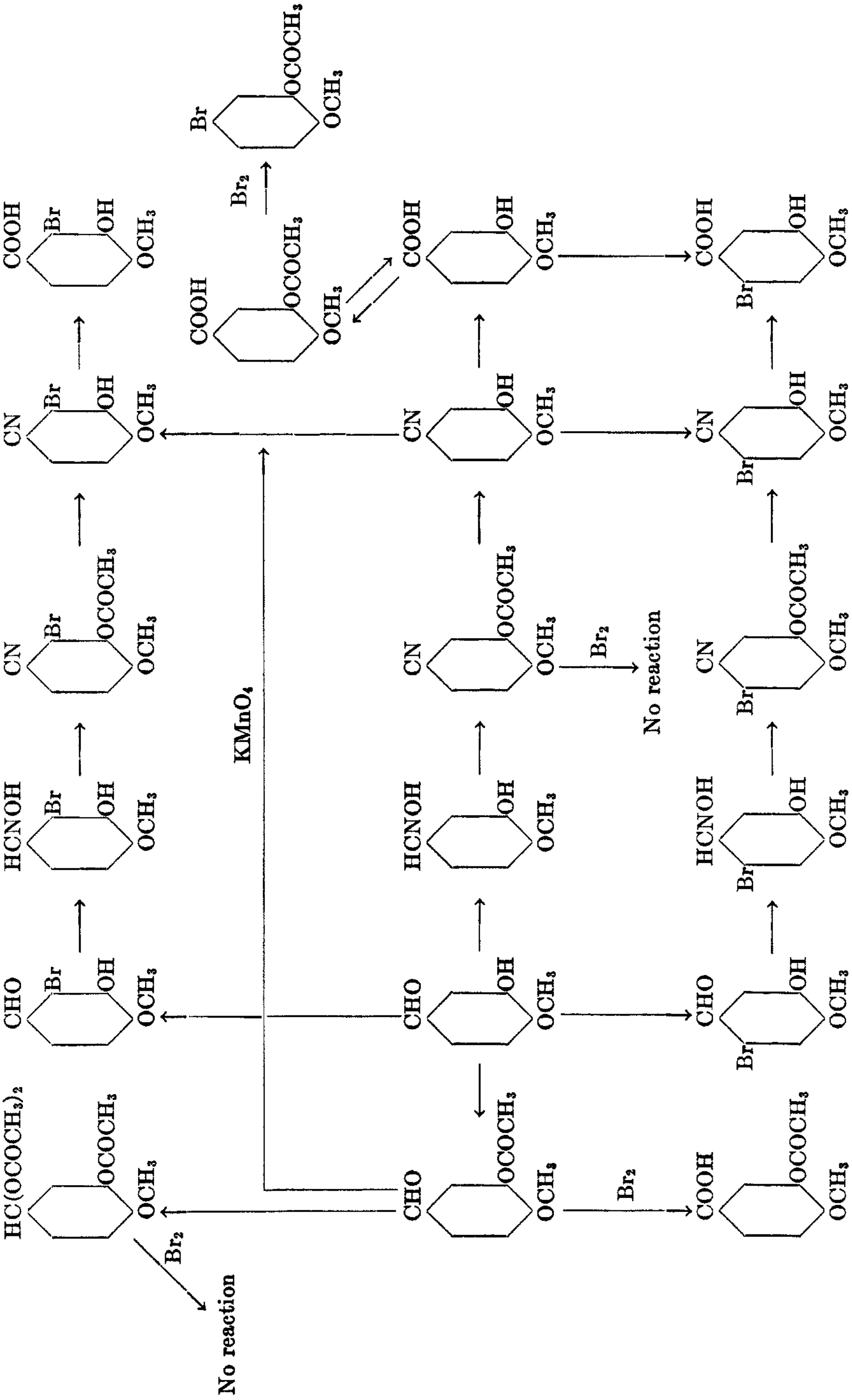
[6] When the available C. P. grade was used, the acetoxynitrile obtained was contaminated with resin and was difficult to purify. In subsequent work the anhydride was purified by fractionation in an apparatus with ground glass joints, and the portion that distilled at 137.5-139° was collected for use. With some lots of C. P. grade, more than one-fourth was rejected in this way.

FIGURE I



Attempts to brominate acetylisovanillin were unsuccessful. With acetic acid solution at 50–60°, and iodine as a catalyst, starting material was recovered to the extent of 95%. When sodium acetate was present in the above mixture and bromine was added at the temperature of the steam bath, the aldehyde was oxidized[7] and acetylisovanillic acid m.p. 216–218°,[8] was obtained. In subsequent experiments attempts were made to protect the aldehyde group. Isovanillin was converted into 3-acetoxy-4-methoxybenzal diacetate (see below), and this was subjected to the action of bromine. Starting material only could be recovered.

Bromination of acetylisovanillic acid proved to be impossible under any conditions here tried. When an acetic acid solution of the acetyl acid in the presence of sodium acetate was treated with 50% excess of bromine for eight to ten hours on a steam-bath, the product turned out to be a mixture with a wide melting range. By fractional crystallization the portion containing halogen was obtained in nearly pure form in a yield of about 12%. It melted at 62–64° and was identified as 2-methoxy-5-bromophenyl acetate, previously obtained by Jona (15) by acetylation of 5-bromoguaiacol (OH = 1) and by Hindmarsh, Knight and Robinson (16) by the bromination of acetylguaiacol. In the present work the carboxyl group was replaced by halogen.

Treatment of an acetic acid solution of acetylisovanillonitrile, to which sodium acetate and iodine had been added, with 50% excess of bromine, in the cold and at the temperature of the steam-bath failed to give a bromine substitution product. About 75% of starting material was recovered. These relations are shown in Figure I.

EXPERIMENTAL

Methyl 5-bromovanillate. The methyl ester of vanillic acid, previously prepared by Matsmoto (17), who recorded no yield, was here obtained in 53% yield of purified material as follows: Gaseous hydrogen chloride was bubbled for about five hours through a boiling solution of 40 g. of vanillic acid in 200 cc. of absolute methyl alcohol under a reflux condenser, the upper end of which was protected by a drying-tube containing calcium chloride. The solution became dark brown. About two-thirds of the solvent was distilled off, the residue poured into four volumes of water, the oil that separated was extracted with ether, the solution was dried with calcium chloride, and the ether distilled. The greater portion of the oil distilled at 140–141° at 4 mm., and after several days at about −5° gave colorless needles that melted at 63–64°. Matsmoto recorded 62–63°.

A mixture of equal quantities of this ester and anhydrous sodium acetate was dissolved in about three times its weight of acetic acid, a crystal of iodine was added,

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[7] Raiford and Milbery [*J. Am. Chem. Soc.*, **56**, 2729 (1934)] found that attempts to brominate acetic acid solutions of 4-benzoyloxybenzaldehyde and a number of its substitution products, in contact with air, gave the corresponding acids.

[8] Matsmoto [*Ber.*, **11**, 130 (1878)] reported 206–207°.

and slightly more than one molecular proportion of bromine was run in slowly. The mixture was allowed to stand overnight and was then diluted with 200 cc. of water, which precipitated the product. A yield of 97% was obtained. Crystallization from alcohol gave tan leaflets that melted at 152–152.5°.

Anal. Calc'd for $C_9H_9BrO_4$: Br, 30.65. Found: Br, 30.76.

Hydrolysis of the above product with caustic potash solution gave 5-bromovanillic acid that melted at 231–232°, as previously recorded by Raiford and Potter (14).

Bromination of the acetyl derivative. Ten grams of methyl vanillate was dissolved in 40 cc. of freshly distilled acetic anhydride, a drop of concentrated sulfuric acid was added, the whole was allowed to stand overnight, and the solution poured into water, which precipitated an oil. Gentle warming and stirring caused the oil to solidify. A yield of 93% was obtained. Crystallization from 50% alcohol gave colorless fibrous masses, resembling cotton, that showed a melting point of 75.5–76°. Attempts were made to analyze the compound by determination of acetyl by the method used by Freudenberg and Harder (18). Non-uniform results varying from 18.78% to 21.39% of acetyl were obtained, while the theory requires 19.20%. Analysis for carbon and hydrogen showed that the product was nearly pure.

Anal. Calc'd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.35.
Found: C, 58.74; H, 5.40.

When 10 g. of the acetyl derivative was brominated as described above for the ester, and the product was poured into water, 11 g. of a solid precipitated; it contained resin and was difficult to purify. Crystallization from butyl alcohol gave 6.5 g. of colorless material that showed a melting range of 60–65°. This material was shaken with slightly warm alcohol, which removed starting material and left a residue that, after further crystallization from alcohol, separated in nearly colorless needles that melted at 95–95.5°.

Anal. Calc'd for $C_{11}H_{11}BrO_5$: Br, 26.40. Found: Br, 26.43.

Hydrolysis of this derivative with potassium hydroxide solution gave 6-bromovanillic acid that melted at 190–191° (19).

Acetylisovanillin. To a solution containing 152 g. of isovanillin and 56 g. of potassium hydroxide in 500 cc. of water, which was cooled to about 0°, a solution of 100 cc. of specially purified acetic anhydride in 100 cc. of ether was added dropwise, with constant shaking and continued cooling. The product separated as a liquid which soon solidified in colorless pellets. Crystallization from 50% alcohol gave thick colorless needles that melted at 88–89°[9]. By working up the mother liquor, a yield of 85% was obtained. Analysis indicated that our product was nearly pure.

Anal. Calc'd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.15.
Found: C, 61.80; H, 5.18.

3-Acetoxy-4-methoxybenzal diacetate. Five grams of isovanillin was dissolved in 25 cc. of acetic anhydride and a drop or two of concentrated sulfuric acid was added. The liquid, which developed a dark purple color and became warm, was allowed to stand about an hour and was then poured into a solution of sodium carbonate, which precipitated a yellowish solid. Repeated crystallization from alcohol gave large, nearly colorless plates that melted at 118–119°. The yield of purified material was 62%.

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[9] Pschorr and Stöhrer [*Ber.*, **35**, 4397 (1902)] obtained, by boiling isovanillin with acetic anhydride, a product which they recorded as melting at 64° but which they reported as having the composition of the one here under consideration. Later, Pacsu and Vargha [*Ber.*, **59**, 2822 (1926)] prepared this product in two different ways but did not analyze it. They found 88° as the melting point.

TABLE II
DERIVATIVES OF ISOVANILLIN

COMPOUND	YIELD %	SOLVENT	CRYSTAL FORM	M.P. °C.	COMPOSITION	ANALYSES Bromine Calc'd	ANALYSES Bromine Found	ANALYSES Nitrogen Calc'd	ANALYSES Nitrogen Found
Oxime	88	Alcohol	Colorless needles	143 -144	$C_8H_9NO_3$	—	—	8.38	8.61
Nitrile	85	Water	Colorless needles	130 -132[a]	$C_8H_7NO_2$	—	—	9.40	9.41
Acetonitrile	75	Water	Colorless needles	116 -117	$C_{10}H_9NO_3$	—	—	7.33	7.40
Acetyl-2-bromo-	72[b]	Alcohol	Colorless cubes	82 -84	$C_{10}H_9BrO_4$	29.30	29.24	—	—
2-Bromo-oxime	70[b]	Alcohol (25%)	Pale tan needles	174 -176	$C_8H_8BrNO_3$	32.52	32.49	5.69	5.68
2-Bromonitrile	74[b]	Alcohol (50%)	Colorless needles	171 -172.5	$C_8H_6BrNO_2$	35.09	34.93	6.14	6.16
Acetyl-2-bromonitrile	77[b]	Alcohol (50%)	Colorless needles	108 -109.5	$C_{10}H_8BrNO_3$	29.63	29.64	5.18	5.21
2-Bromoacid	43[b]	Water	Colorless fibrous masses	216.5-218	$C_8H_7BrO_4$	32.38	32.53	—	—
Acetyl-6-bromo-	84	Carbon tetrachloride	Colorless plates	106 -107	$C_{10}H_9BrO_4$	29.30	29.23	—	—
6-Bromo-oxime	92[c]	Alcohol	Thick colorless needles	224 -226	$C_8H_8BrNO_3$	32.52	32.46	5.69	5.68
6-Bromonitrile	86[c]	Alcohol (75%)	Small colorless needles	162 -163.5[d]	$C_8H_6BrNO_2$	35.09	35.12	6.14	6.17
Acetyl-6-bromonitrile	60[c]	Alcohol	Colorless needles	165 -167[d]	$C_{10}H_8BrNO_3$	29.63	29.54	5.18	5.20
6-Bromoacid	57	Water[e]	Tan needles	166.5-168.5	$C_8H_7BrO_4$[f]	32.38	32.62	—	—

[a] Mameli [*Gazz.*, (2) **37**, 377 (1907)] recorded 124° for a product that should have the composition and structure of the one here in question. His compound was obtained by conversion of 5-aminoguaiacol into a diazonium salt and subjection of the latter to the Sandmeyer reaction. The nitrile was obtained as brick-red needles.

[b] This represents purified material.

[c] Purification required many crystallizations and much loss of material occurred.

[d] A mixture of these products showed a melting range of 120-140°.

[e] When crystallized from water it combined with one-half molecular proportion of solvent. *Anal.* Calc'd for $C_8H_7BrO_4 + 0.5\ H_2O$: Br, 31.25; H_2O, 3.51. Found: Br, 31.75; H_2O, 3.55.

[f] Refers to anhydrous material obtained by drying to constant weight at about 110°.

Anal. Calc'd for $C_{14}H_{16}O_7$: C, 56.75; H, 5.40.
Found: C, 56.70; H, 5.50[10].

Analytical data and additional properties for other derivatives of isovanillin which were obtained by standard methods are given in Table II.

SUMMARY

1. A number of new derivatives of vanillin and isovanillin have been prepared and some of their reactions studied.

2. All attempts to prepare 5-bromoisovanillin, in which the halogen atom would be adjacent to the methoxyl group, have been unsuccessful. This failure, considered in the light of other reactions carried through in this work, shows that the alkoxyl radical tends to direct more strongly toward the para than toward the ortho position.

3. Additional data have been obtained to support the view that acylation of hydroxyl in a benzene derivative suppresses its directive influence.

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[10] After standing for one year in a glass-stoppered bottle some decomposition had taken place. This was shown by the pronounced odor of acetic acid, and by low values for the melting point and for carbon and hydrogen determinations.