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

Bromination of Benzoic Esters of Some Phenolic Compounds

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Bromination of vanillin (3-methoxy-4-hydroxybenzaldehyde) under different conditions[1] gives a high yield of the 5-bromo compound, showing the ortho directive influence of the hydroxyl radical. Nitration of acetylvanillin gives the 2-nitro compound as the chief product,[2] but bromination gives only the 6-bromo derivative. To explain this difference one might assume that the acyloxy radical directs to the meta position[3] or that acylation of hydroxyl suppresses its activity[4] to such an extent that the chief influence in this case was due to the methoxyl radical which has *o-p* directing effect. Support for the latter view is found in the fact (Experimental Part) that 4-benzoyloxybenzaldehyde, which represents benzoylvanillin without the methoxyl radical, is not brominated at all under conditions that give a good yield of bromine derivative of vanillin.

In the present work the behavior of the benzoyl derivatives of phenol, the cresols, vanillin and *p*-hydroxybenzaldehyde toward bromine under different conditions has been examined. It was found that bromine entered the para position of the phenyl or cresyl radical most easily, when this was available, the ortho position less readily. No meta derivatives were obtained. In many cases the hydrogen bromide formed hydrolyzed a portion of the ester,[5] and the resulting phenol was brominated. Thus, phenyl benzoate gave the 4-bromophenyl ester, *sym*-tribromophenol and benzoic acid by each method. The cresyl esters gave similar results, but hydrolysis was less extensive. Additional data for the para compound are given under Table I.

The behavior of benzoylvanillin was similar to that indicated above for the acetyl derivative, though the reaction was slower. Nitration gave 70% of the 2-nitro compound with 4% of the 6-derivative, while bromination gave the 6-compound only. Treatment with phosphorus pentabromide[6] gave the corresponding benzal bromide.

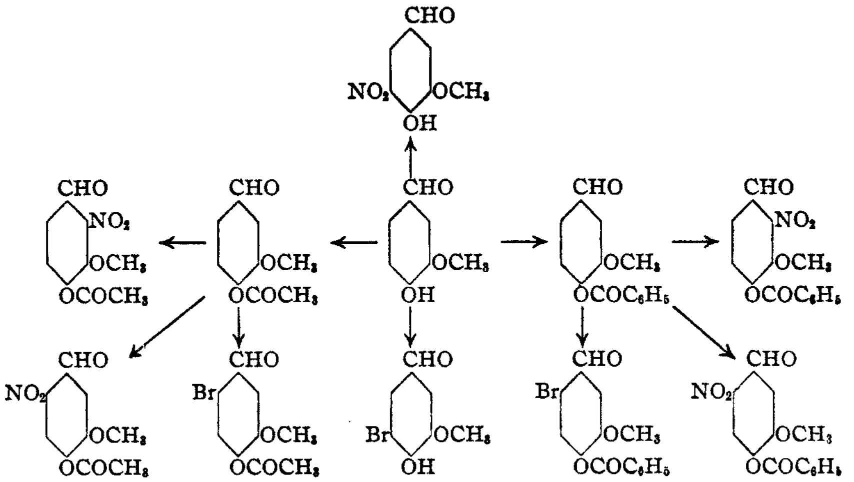

DIAGRAM I

When 4-benzoyloxybenzaldehyde was treated with bromine as indicated above, no bromine derivative was obtained, but 4-benzoyloxybenzoic acid was isolated. A number of substitution products behaved similarly, as indicated in Table II.

Experimental Part

Methods Used.—1. One of Kauschke's[7] methods was modified to the extent that iodine was used as a catalyst and the temperature was kept below 60° in an open vessel. 2. Bromine was added to an acetic acid solution of the starting material, sodium acetate and iodine, and the

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[1] Carles, *Bull. soc. chim.*, [2] **17**, 15 (1872); Tiemann and Haarmann, *Ber.*, **7**, 615 (1874); Torrey and Clarke, THIS JOURNAL, **31**, 584 (1909); Dakin, *Am. Chem. J.*, **42**, 493 (1909), and Brady and Dunn, *J. Chem. Soc.*, **107**, 1859 (1915).

[2] Pschorr and Sumuleanu [*Ber.*, **32**, 3408 (1899)] obtained a 75% yield, which was confirmed by Raiford and Stoesser [THIS JOURNAL, **50**, 2558 (1928)] who found that about 5% of the 6-nitro isomeride was also formed in this experiment.

[3] Claus and Hirsch [*J. prakt. Chem.*, [2] **39**, 63 (1889)] claim to have obtained *m*-bromo derivatives by direct bromination of acetic acid solutions of phenyl and *m*-cresyl acetates, respectively, but their results were not confirmed by Seelig [*ibid.*, [2] **39**, 176 (1889)] nor by McCormack and Dougherty [unpublished reports] working in this Laboratory.

[4] This view was recorded in connection with the nitration of *p*-cresyl carbonate [German Patent 206,638; *Frdl.*, **9**, 151 (1908)] and may have been noted earlier.

[5] Raiford and Stoesser [THIS JOURNAL, **49**, 1078 (1927)] used sodium acetate to prevent the hydrolysis of acetylvanillin. In this work hydrolysis sometimes occurred in the presence of the salt.

[6] Autenrieth and Mühlinghaus, *Ber.*, **40**, 747 (1907).

[7] Kauschke [*J. prakt. Chem.*, [2] **51**, 210 (1895)] did not indicate temperature ranges except in sealed tube experiments.

mixture allowed to stand at about 40° for forty-eight hours.[5] 3. The catalyst described by Fierz-David[8] was added to the mixture indicated in 2, and the whole heated under reflux until the color of bromine was discharged. 4. A mixture of the ester and phosphorus pentabromide in an open vessel protected from moisture was heated at about 100° as long as change was evident. The new products obtained from the phenyl and cresyl esters are indicated in Table I.

Table I

Bromine Substitution Products of Benzoic Esters[a]

	Products (substituted phenyl)	Solvent	Crystal form	Yield, %	M. p., °C.	Formula	Halogen Analyses, % Calcd.	Found
1	2-Methyl-4-bromo-	Alcohol	Colorless leaflets	80	67–68[b]	$C_{14}H_{11}O_2Br$	27.49	27.28
2	2-Bromo-4-nitro-	Alcohol	Silky needles	[c]	131–132	$C_{13}H_8O_4NBr$	24.84	24.74
3	4-Bromomethyl-[d]	Ligroin	Colorless flakes	14	109–110	$C_{14}H_{11}O_2Br$	27.49	27.15
4	2-Bromo-4-methyl-	Alcohol (synth. method)	Colorless needles (asbestos-like)	91	71–72	$C_{14}H_{11}O_2Br$	27.49	27.51
5	3-Bromo-4-methyl-	Ligroin	Fine needles	Nearly quant.	75–76	$C_{14}H_{11}O_2Br$	27.49	27.23

[a] Each product was compared with that obtained from benzoyl chloride and the required phenol.

[b] Kauschke [*J. prakt. Chem.*, [2] **51**, 213 (1895)] reported 59°. He recorded no analyses and did not orient the bromine in his products.

[c] After repeated crystallization, the product obtained by bromination of 4-nitrophenyl benzoate had the same melting range, 113 to 117°, as an equimolecular mixture of starting material and the 2-bromo derivative, and halogen content agreed with this. *Anal.* Calcd. for $C_{13}H_8O_4NBr + C_{13}H_9O_4N$: Br, 14.15. Found: Br, 14.36. The remainder of the data refers to the synthetic sample.

[d] This product, obtained in 14% yield by method 3, was identified further by conversion into 4-benzoyloxybenzylpyridinium bromide, in 96% yield, as directed by Auwers [*Ber.*, **36**, 1884 (1903)], which crystallized with one molecular proportion of water; m. p. (anhydrous) 174–175°. *Anal.* Calcd. for $C_{19}H_{16}O_2NBr \cdot H_2O$: H_2O, 4.63; Br, 20.61. Found: H_2O, 4.66; Br, 20.58. In addition, when a portion of it was boiled for five minutes with potassium hydroxide solution bromine was lost and there was isolated a product that melted at 122–123°, and which dissolved in concentrated sulfuric acid to give a deep red color, as noted by Biedermann [*Ber.*, **19**, 2375 (1886)] for *p*-hydroxybenzyl alcohol. Auwers and Daecke [*ibid.*, **32**, 3375 (1899)] found 124.5–125.5° for the melting point of this alcohol.

Benzoyl-6-bromovanillin.—To a solution containing 10 g. of benzoylvanillin,[9] 6.5 g. of sodium acetate and 0.1 g. of iodine in 50 cc. of acetic acid, slightly more than one molecular proportion of bromine was added, the liquid allowed to stand for six days at 35–40°, and then poured into about 750 cc. of a mixture of ice and water. This was stirred for several hours and the solid, which was a mixture of fluffy crystals and hard amorphous-appearing lumps, was filtered off, dried and separated mechanically as well as possible. Repeated crystallization of the former from alcohol gave colorless prisms, m. p. 117–118°, which did not depress the melting point of the product obtained by benzoylation of 6-bromovanillin. Hydrolysis with a solution of potassium hydroxide gave 6-bromovanillin. *Anal.* Calcd. for $C_{15}H_{11}O_4Br$: Br, 23.86. Found: Br, 23.70.

The hard lumps were dissolved in ether, the solution extracted with caustic alkali, dried and the ether distilled. Crystallization of the residue from alcohol gave large plates that melted over a range of 84 to 96°. Analysis indicated a mixture of about equimolecular proportions of benzoyl-6-bromovanillin and starting material. An equimolecular mixture of the pure products showed the same melting range.

3-Methoxy-4-benzoyloxybenzal Bromide.—A mixture of 19 g. of benzoylvanillin and somewhat more than one molecular proportion of phosphorus pentabromide was heated on a water-bath as indicated under method 4. The mass melted rapidly to a black liquid that evolved neither bromine nor hydrogen bromide and which, after about ten minutes, was poured into water. The resulting solid was removed, triturated with more water and filtered out; yield, 95%. Repeated crystallization from alcohol gave small white satin-like plates, m. p. 108.5–109.5°. Treatment of its alcoholic solution with alcoholic solution of silver nitrate removed all bromine as silver bromide, and served as a method of analysis.

Anal. Calcd. for $C_{15}H_{12}O_3Br_2$: Br, 40.00. Found: Br, 39.99.

4-Benzoyloxybenzaldehyde.—This was obtained in 94% yield from the required aldehyde by the Schotten–Baumann method. Repeated crystallization from alcohol and finally from ligroin gave very small colorless needles; m. p. 90°. Since a product prepared as indicated was previously reported with a much lower melting point[10] the material here obtained was characterized further.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.42; mol. wt., 226. Found: C, 74.40; H, 4.52; mol. wt. (Rast), 224.

4-Bromophenylhydrazone of 4-Benzoyloxybenzaldehyde.—To a solution of 2.2 g. of *p*-bromophenylhydrazine hydrochloride in 10 cc. of alcohol 1 g. of sodium bicarbonate was gradually added, the precipitated sodium chloride filtered off and 2 g. of the aldehyde added to the filtrate. Slight warming completed the reaction and caused the hydrazone to settle out, yield, 95%. Crystallization from acetic acid gave tan-colored needles that became pink in diffused daylight but remained unchanged in the dark; m. p. 179–180°, with evolution of gas.

Anal. Calcd. for $C_{20}H_{15}O_2N_2Br$: Br, 20.25. Found: Br, 20.35.

Behavior of 4-Benzoyloxybenzaldehyde toward Bromine.—Four grams of the aldehyde, 3 g. of sodium acetate and a crystal of iodine were dissolved in 30 cc. of acetic

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(8) Fierz-David, *Naturwiss.*, **19**, 13 (1929).

(9) Prepared by a slight modification of the method of Howells, Little and Andersen [This Journal, **52**, 4078 (1930)].

(10) Kopp [*Ann.*, **277**, 350 (1893)] reported 72°; Rosenmund [*Ber.*, **46**, 1039 (1913)] prepared it but recorded no physical constants, and no further reference to it was found.

acid, 5 cc. of bromine was added and the mixture allowed to stand for forty-eight hours. The solid deposited contained no bromine. Crystallization from dilute alcohol gave colorless scales; m. p. 219°. The filtrate contained a mixture of this product and unchanged aldehyde. The new compound did not depress the melting point of that (m. p. 220°)[11] obtained from *p*-hydroxybenzoic acid and benzoyl chloride.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.13; mol. wt., 242. Found: C, 69.39; H, 4.20; mol. wt. (Rast), 236.

Data for the behavior of a number of substituted 4-benzoyloxybenzaldehydes are given in Table II.

The acids obtained from the above aldehydes were identified by comparison with reference compounds synthesized by standard methods. The new ones are indicated in Table III

TABLE II

SUBSTITUTED 4-BENZOYLOXYBENZALDEHYDES

	Substituent	Yield, %	Solvent	Crystal form	M. p., °C.	Formula	Halogen analyses, % Calcd.	Found
1	2-Chloro-	87	Alcohol[a]	Colorless needles	103–104	$C_{14}H_9O_3Cl$	13.62	13.70
2	3-Chloro-	97	Ligroin[b]	Small colorless needles	95–96	$C_{14}H_9O_3Cl$	13.62	13.85
3	4-Chloro-	Nearly quant.	Ligroin	Colorless needles	117–118	$C_{14}H_9O_3Cl$	13.62	13.72
4	3-Bromo-	Nearly quant.	Ligroin[c]	Silky needles	114–115	$C_{14}H_9O_3Br$	26.22	26.32
5	4-Nitro-	Nearly quant.	Acetic[d] acid	Clusters of tan needles	199–200	$C_{14}H_9O_5N$	N, 5.16	5.29

[a] Crystallization from acetic acid converted a portion into the corresponding acid.

[b] The mother liquor from crystallization with every solvent tried deposited acid upon standing.

[c] A solution of 5 g. of aldehyde in 60 cc. of acetic acid began to deposit solid on the twelfth day; on the twenty-first day this was removed and identified as 4-(3-bromobenzoyl)-oxybenzoic acid. At the end of one year the deposit was nearly quantitative.

[d] The deposit in the mother liquor after ten months of standing was identified as aldehyde.

TABLE III

SUBSTITUTED 4-BENZOYLOXYBENZOIC ACIDS

	Substituent	Yield, %	Solvent	Crystal form	M. p., °C.	Formula	Halogen analyses, % Calcd.	Found
1	2-Chloro-	82[a]	Alcohol	Small colorless needles	215–216[b]	$C_{14}H_9O_4Cl$	12.83	12.80
2	3-Chloro-	Poor	Alcohol	Colorless powder	217–218[b]	$C_{14}H_9O_4Cl$	12.83	12.67
3	4-Chloro-	Nearly[a] quant.	Alcohol	Matted colorless needles	239–240	$C_{14}H_9O_4Cl$	12.83	12.86
4	3-Bromo-	Poor	Alcohol	Colorless powder	211–212	$C_{14}H_9O_4Br$	24.92	24.79

[a] Purification required many crystallizations which caused much loss.

[b] A mixture of these products melted at 205 to 210°.

Summary

1. The benzoic esters of phenol and the cresols have been brominated under different conditions, and the position of bromine determined in each product. Halogen entered the para position in the phenyl radical, if available. The ortho position was substituted less readily. In no case was Claus and Hirsch's suggestion of meta substitution realized. In many instances the hydrogen bromide formed hydrolyzed a portion of the ester, and the resulting phenol was brominated.

2. Nitration and bromination of benzoylvanillin gave mainly the 2-nitro, and exclusively the 6-bromo compound, which agrees with the behavior of acetylvanillin previously reported. The active directing group in both cases appeared to be the methoxyl radical. The differences seem to depend, in part, on the chemical characters of the entering substituents.

3. Attempts to brominate acetic acid solutions of 4-benzoyloxybenzaldehyde and a number of its substitution products were unsuccessful. When the experiments were conducted in contact with air, the corresponding acids were obtained.

4. Further work is in progress.

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[11] Vorländer and Gahren [*Ber.*, **40**, 1968 (1907)] gave 220–222° but no method of preparation or identification; Francis and Nierenstein [*Ann.*, **382**, 197 and 201 (1911)] and Albright [THIS JOURNAL, **39**, 822 and 824 (1917)] mentioned the acid but gave no data.