Anal. Calcd. for $C_{10}H_{12}O_2N_4S$: N, 11.1 (2 N by Kjeldahl). Found: N, 10.7.

CONTRIBUTION NO. 285 FROM THE
RESEARCH LABORATORIES OF
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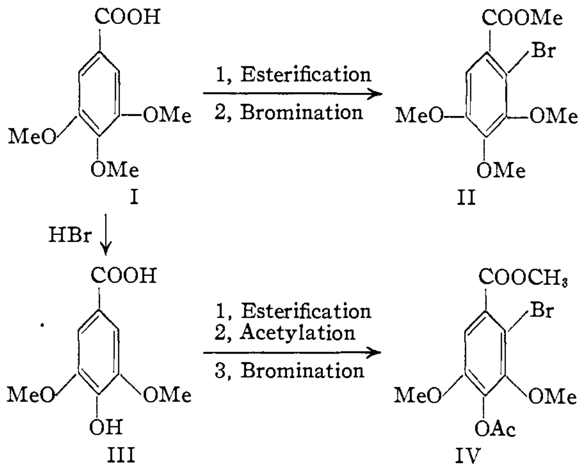
NUTLEY, N. J.

Polymethoxybromobenzenes[1]

BY E. C. HORNING[2] AND JOHN A. PARKER[3]

Investigations of the structure and physiological activity of compounds related to colchicine, which have been underway for some time, have made it necessary to develop a satisfactory means of obtaining monobromo derivatives of a variety of polymethoxybenzenes. The usual methods of direct bromination in inert solvents generally give small amounts of the desired products, but demethylation and polybromination occur as well, and as a result indirect or special methods have usually been employed to provide better yields of the compounds. A method which we have found satisfactory involves a ferric chloride-catalyzed bromination in acetic anhydride, with pyridinium bromide perbromide as the source of bromine. Although no new reagent or new solvent is employed, we have found no record of previous use of this method.



The bromination of methyl 3,4,5-trimethoxybenzoate by this procedure proceeds smoothly and gives good yields (85%) of product (II). This bromination has been reported several times, but with divergent results. The method reported here leads to a low-melting (34–36°) monobromo ester, correctly described by Feist and Dschu,[4] although if the reaction mixture is heated an unidentified product, m.p. 88–89°, perhaps identical with the material prepared in another way and also described as methyl 2-bromo-3,4,5-trimethoxybenzoate,[5] may also be obtained. A related ester, methyl 2-bromo-3,5-dimethoxy-4-acetoxybenzoate, was prepared by the same bromination method. The generality of the procedure was examined through the bromination of veratrole and 1,2,3-trimethoxybenzene, but has not been extended beyond these examples.

Experimental

Methyl 3,4,5-Trimethoxybenzoate.—A 100-g. quantity of 3,4,5-trimethoxybenzoic acid was suspended in 500 ml. of dry methanol, and hydrogen chloride was bubbled rapidly through the mixture without temperature control until the methanol was saturated and the acid dissolved. The mixture was chilled (24 hours) and the crystalline product was removed by filtration, washed with chilled methanol, and dried to yield 101.5 g. (94%) of the ester, m.p. 83–84° (reported[6] m.p. 83–84°).

Methyl 2-Bromo-3,4,5-trimethoxybenzoate (II).—A few crystals (approximately 200 mg.) of ferric chloride (hydrated) were dissolved in a solution of 22.6 g. (0.10 mole) of methyl 3,4,5-trimethoxybenzoate in 100 ml. of acetic anhydride. A total of 35.5 g. of pyridinium bromide perbromide was added in small portions, with stirring or shaking,[7] and the resulting solution was heated at 50–55° for five minutes to ensure completeness of reaction. The mixture was added slowly with good stirring to 500 ml. of hot (60–70°) water in order to hydrolyze the solvent and, after cooling, the mixture was extracted with 1:1 ether–ethyl acetate. The combined organic extracts were washed with 5% hydrochloric acid, 5% sodium hydroxide solution, water and 2% aqueous acetic acid. The organic material was dried (magnesium sulfate), the solvents were removed, and the crude yield of 32.5 g. of product was distilled under reduced pressure to provide 2.0 g. of fore-run (b.p. to 160° (2 mm.)) and 28.5 g. of product, b.p. 160–161° (2 mm.). The colorless ester was recrystallized from ether–pentane to give 25.8 g. (85%) of methyl 2-bromo-3,4,5-trimethoxybenzoate, m.p. 34–36°. The correct structure was assigned to this compound by Feist and Dschu,[4] who reported m.p. 33°.

When the reaction mixture was heated at 90–100° for periods of 30 minutes or longer, the reaction product was a colorless crystalline material, m.p. 89–90°, of unidentified structure, which was perhaps similar to the products usually obtained by bromination of the ester with bromine in acetic anhydride at room temperature.[5]

3,5-Dimethoxy-4-hydroxybenzoic Acid (Syringic Acid).—A mixture of 50.0 g. of 3,4,5-trimethoxybenzoic acid, 200 ml. of acetic acid and 40 ml. of concentrated hydrobromic acid was heated under reflux for three hours. After dilution with 800 ml. of water, followed by chilling (24 hours), a 38.6 g. (83%) yield of syringic acid, m.p. 202–203° (reported m.p. 204°), was obtained.

Methyl 3,5-Dimethoxy-4-acetoxybenzoate.—A solution of 30.0 g. (0.15 mole) of 3,5-dimethoxy-4-hydroxybenzoic acid in 100 ml. of dry methanol was saturated with hydrogen chloride. After standing for 24 hours, the solvent was evaporated, leaving a residue of 31.2 g. of crude ester. A 30.0 g. quantity of this material was dissolved in 120 ml. of acetic anhydride, and the mixture was heated under reflux for 30 minutes. The solution was added to 500 ml. of warm (50–60°) water, and the crystalline product was separated after chilling. The yield was 24.5 g. (64%) of colorless ester, m.p. 128–129°. This material has been prepared previously.[5]

Anal. Calcd. for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.62; H, 5.46.

Methyl 2-Bromo-3,5-dimethoxy-4-acetoxybenzoate (IV).—The bromination procedure described previously was carried out with 20.0 g. (0.074 mole) of methyl 3,5-dimethoxy-4-acetoxybenzoate and 28.0 g. of pyridinium bromide perbromide in 125 ml. of acetic anhydride. The crude product was crystallized from ether–pentane to yield 16.0 g. (62%) of colorless ester, m.p. 75–76°.

Anal. Calcd. for $C_{12}H_{13}O_6B$: C, 43.26; H, 3.93. Found: C, 43.53; H, 4.19.

1,2,3-Trimethoxy-4-bromobenzene.—To a stirred solution of 67.2 g. (0.40 mole) of 1,2,3-trimethoxybenzene in 400 ml. of acetic anhydride, containing a few crystals of ferric chloride, was added, in small portions, 144 g. of pyridinium bromide perbromide. The solution was heated for

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[2] National Heart Institute, Bethesda, Maryland.

[3] National Institutes of Health Predoctoral Fellow, 1950–1951.

[4] K. Feist and G. Dschu, "Festchrift A. Tschirch," Leipzig, 1926, p. 29; *Chem. Zentr.*, **98**, II, 58 (1927).

[5] M. T. Bogert and E. Plaut, THIS JOURNAL, **37**, 2723 (1915).

[6] F. W. Semmler, *Ber.*, **41**, 1774 (1908).

[7] It is advisable to follow the precautions mentioned by Bogert,[5] although we have noted no difficulties.

five minutes at 50–55°, and was then poured slowly into 2000 ml. of hot water. The crude product was isolated as described in previous experiments, and amounted to 98.4 g. of oil. Distillation through a Podbielniak column at 50 mm. pressure gave a small fore-run (4.8 g.) and the following fractions: (a) 5.0 g., b.p. 150–153°, of material which solidified and which was identified as starting 1,2,3-trimethoxybenzene; (b) 4.5 g., b.p. 153–179°, of intermediate material; (c) 77.2 g., b.p. 179°, of 1,2,3-trimethoxy-4-bromobenzene (78% yield); (d) 4.5 g. of residue. The product turned dark on standing, and carbon analyses were consistently low. Freshly prepared material was used in Ullmann reactions to yield the expected products.

4-Bromoveratrole.—Veratrole was brominated by this method to provide 4-bromoveratrole, b.p. 164–167° (50 mm.), in 84% yield. This compound has been prepared previously by a variety of methods, including direct bromination,[8] with bromine diluted with air,[9] cyanogen bromide,[10] N-bromosuccinimide,[11] and by methylation[8] of bromoguaiacol.

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(8) R. Y. Moir and C. B. Purves, *Can. J. Research*, **26B**, 694 (1948).

(9) M. Gaspari, *Gazz. chim. ital.*, **28**, **II**, 230 (1896).

(10) G. Bargellini and F. Madesani, *ibid.*, **61**, 684 (1931).

(11) Ph. Buu-Hoï, *Ann.*, **556**, 7 (1944).

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An Unusual Salting-out Effect of Hydrohalogen Acids on Water–Dioxane Mixtures

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In the course of some reaction studies in the solvent system water–dioxane, it was found that the addition of hydrogen chloride or hydrogen bromide caused the formation of two phases over a limited concentration range. This behavior has not been previously reported despite the extensive use of water–dioxane as a medium for reactions under acidic conditions. Infinite miscibility of water with dioxane is ordinarily presumed,[1] although the 1–1–2 ternary compound $H_2O–HClO_4–O(CH_2CH_2)_2O$ has been reported.[2]

The authors therefore undertook a phase study of the ternary system water–dioxane–HX at 25° and atmospheric pressure.

Experimental

1,4-Dioxane.—Fisher Scientific Co. "Purified" 1,4-dioxane was further purified according to the general method which has been described by Kraus and Vingee.[3] However, during the final distillation a stream of dry nitrogen was passed through the condenser and over the collected dioxane to protect the material from atmospheric oxygen.[4] The dioxane was stored in a dark-colored bottle under dry nitrogen. The dioxane prepared in this manner was essentially free of peroxides, as indicated by a test with potassium iodide and acetic acid in the presence of Dry Ice; m.p. 11.78 ± 0.02° (previous value, 11.80[5]), n^{21}D 1.4218 (previous value, n^{21}D 1.4219[4]).

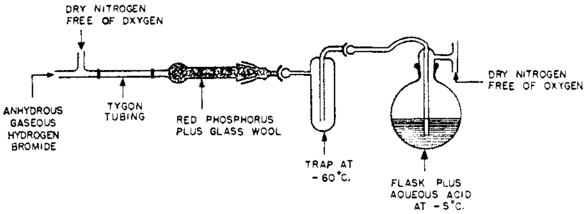

Fig. 1.—Apparatus for production of bromine-free aqueous hydrobromic acid.

Hydrogen Chloride.—du Pont analytical reagent grade hydrochloric acid was used without further purification. In some cases where higher concentrations were required Matheson anhydrous hydrogen chloride was added to the system.

Hydrogen Bromide.—Because reagent grade hydrobromic acid is available in only 42% concentration and may be contaminated by free bromine from atmospheric oxidation, the hydrogen bromide solution for these experiments was prepared by passing gaseous hydrogen bromide into distilled water employing the apparatus indicated in Fig. 1. The red phosphorus was used to remove bromine from the hydrogen bromide and the trap ensured the removal of phosphorus(III) bromide and any other high-boiling substances. At the start of the run dry nitrogen was allowed to pass through the system for 24 hours in order to sweep all oxygen from the lines and from the sample of distilled water. Then the hydrogen bromide was allowed to flow until a saturated solution was obtained (65% by wt.[6] was attained in approximately 5 hours). The colorless solution was stored under nitrogen until used.

Preliminary experiments showed that if a fairly concentrated aqueous acid solution was added with stirring into a sample of pure dioxane, the mixture remained clear up to a certain volume of acid, passed through a region of incom-

TABLE I

COMPOSITIONS OF THE SYSTEM H_2O–HCl–DIOXANE AT THE MISCIBILITY LIMITS

Aqueous acid added Volume,[a] ml.	Normality	Wt. % H_2O	Wt. % HCl	Wt. % Dioxane
0.65	12.00	1.87	1.04	98.08
.42	9.69	1.29	0.57	98.15
.53	7.08	1.73	.52	97.75
.90	4.87	3.06	.60	96.35
.96	2.42	3.44	.32	96.27
.90	3.13	3.18	.39	96.45
.86	4.09	2.98	.48	96.54
3.18	2.57	10.43	1.03	88.54
1.30	1.87	4.61	0.33	95.06
1.53	1.92	5.38	.39	94.30
2.05	2.12	7.05	.56	92.39
4.33	2.97	13.49	1.56	84.95
9.52	4.60	24.05	4.46	71.49
5.58	3.61	16.43	2.34	81.27
0.62	13.35	1.68	1.15	97.18
9.70	12.00	19.49	11.45	69.06
10.86	9.69	22.74	10.08	67.18
11.51	7.08	25.60	7.75	66.64
10.17	4.87	25.08	4.94	70.00
2.72	2.42	9.10	0.84	90.04
4.74	3.13	14.52	1.76	83.70
8.40	4.09	22.30	3.63	74.07
11.03	8.26	23.94	8.74	67.48
11.48	7.17	24.03	4.46	71.51
8.61	13.35	17.09	11.67	71.23
		5.10	7.26[b]	87.63
		7.32	8.81[b]	83.86
		13.22	10.96[b]	75.78
		11.38	10.37[b]	78.21
		14.72	12.98[b]	72.30

[a] Volume of acid added to 25.0 ml. of dioxane in each case. [b] Gaseous hydrogen chloride added to attain these concentrations (Method I).

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(1) F. Hovorka, R. A. Schaefer and D. Dreisbach, THIS JOURNAL, **58**, 2264 (1936).

(2) C. Smeets, *Naturw. Tijdschr.*, **19**, 12 (1937).

(3) C. A. Kraus and R. A. Vingee, THIS JOURNAL, **56**, 511 (1934).

(4) K. Hess and H. Frahm, *Ber.*, **71**, 2627 (1938).

(5) P. C. Teague and W. A. Felsing, THIS JOURNAL, **65**, 484 (1943).

(6) H. S. Booth, "Inorganic Synthesis," Vol. I, McGraw-Hill Book Co., Inc., New York, N. Y., 1939, p. 156.