

in good yield and oxidation followed by alkaline fusion produced the hydroxy acid in 33% yield. The 4-methoxy ester was obtained as above, but saponification with 15% aqueous sodium hydroxide for as long as twelve hours failed to yield the pure 4-methoxy tricarboxylic acid, perhaps because of steric hindrance. To obtain this acid it was necessary to convert the 4-sulfonic acid into the 4-phenol (yield 30%). The methyl ether of the latter gave what was probably 2-methyl-4-methoxybenzene-1,3-dicarboxylic acid by heating with aqueous potassium permanganate for five hours since the acid did not form an anhydride at 220°, but by heating for a longer period 4-methoxybenzene-1,2,3-tricarboxylic acid (crude form) was obtained in 30% yield.

An examination of the two series of derivatives indicates that the methoxy esters are to be preferred as reference compounds.

Experimental

All melting points and boiling points are uncorrected.

Pseudocumene (I).—4-Amino-1,3-dimethylbenzene, 393.8 g., was converted by the method of Smith and Lund⁴ into 70.2 g. of the hydrocarbon, b. p. 68.5–69° (22–22.5 mm.) and n_D^{20} 1.5031 (Smith and Lund give b. p. 68–68.5 (22 mm.) and n_D^{20} 1.5032).

Pseudocumene-5-sulfonic Acid (II).—Pseudocumene, 8 cc., was sulfonated by the method of Smith and Cass⁵ to give 11.8 g. of purified acid, m. p. 111–112° after softening at 108° (Smith and Cass give 110–111°).

5-Hydroxybenzene-1,2,4-tricarboxylic Acid (III).—This acid was synthesized by a procedure essentially that of the French and German Patents.⁶ Pseudocumene-5-sulfonic acid, 10 g., and 4 g. of sodium hydroxide were dissolved in 250 cc. of water and the solution was heated to 90–100°, after which 47.1 g. of pulverized potassium permanganate was added, with stirring, at such a rate as to prevent boiling. The oxidation was continued for twenty-four hours more at this temperature, after which the solution was decolorized by the cautious addition of alcohol. The precipitated manganese dioxide was filtered off by suction and extracted twice with 150-cc. portions of boiling water.

The combined filtrates were evaporated to dryness with occasional stirring to prevent caking and the pulverized residue, after being mixed with 40 g. of potassium hydroxide and about 5 cc. of water, was fused with occasional stirring at 200–220° for from four to five hours in a nickel crucible. The melt was then mixed with 60 cc. of water and the mixture in a beaker was acidified cautiously with concentrated hydrochloric acid. Water, 150 cc. more, was added and the solution was heated to boiling (if all the salts did not dissolve, sufficient concentrated hydrochloric acid was added to effect solution). To aid in the filtration for the removal of silica shredded filter paper was added. The filtrate was then evaporated to dryness to remove hydrochloric acid since 5-hydroxybenzene-1,2,4-tricarboxylic acid, in contrast to the inorganic salts, is more soluble in acid than in neutral solution. Treatment of the residue with 270 cc. of boiling water gave a mixture which, when cooled in the refrigerator, produced more solids. Purification by solution in 60 cc. of hot 5% hydrochloric acid solution followed by treatment with 1 g. of Norite and cooling yielded 7.2 g., m. p. 238° with effervescence. Two more crystallizations from 5% hydrochloric acid solution and drying *in vacuo* over calcium chloride gave the hydrated acid, m. p. 239.5–240° with effervescence (French and German patents⁶ give 240° with effervescence), which gives a red color with ferric chloride.

(4) Smith and Lund, *THIS JOURNAL*, **52**, 4144 (1930).

(5) Smith and Cass, *ibid.*, **54**, 1603 (1932).

(6) French Patent 816,718; German Patent 636,908.

Anal. Calcd. for $C_9H_6O_7 \cdot 2H_2O$: C, 41.23; H, 3.84; neut. equiv., 87.4; loss of weight on drying, 13.74. Found: C, 41.36, 41.28; H, 4.12, 4.05; neut. equiv., 87.1; loss of weight on drying, 13.79, 13.79.

Heating at around 102° for three hours gave the anhydrous acid, m. p. 240° with effervescence.

Anal. Calcd. for $C_9H_6O_7$: C, 47.80; H, 2.67; neut. equiv., 75.4. Found: C, 48.10, 48.03; H, 2.77, 2.86; neut. equiv., 75.2, 75.1.

Trimethyl-5-methoxybenzene-1,2,4-tricarboxylate (IV).—5-Hydroxytrimellitic acid in ethanol at 0° was methylated with diazomethane in ether in the usual manner. The product crystallized from ligroin melted at 62.5–63.0°.

Anal. Calcd. for $C_{12}H_{14}O_7$: C, 55.32; H, 5.00. Found: C, 55.75, 56.03; H, 5.09, 5.08.

5-Methoxybenzene-1,2,4-tricarboxylic Acid (V).—The trimethyl ester was saponified with 5% aqueous sodium hydroxide solution to give a product, m. p. 224–225° with effervescence.

Anal. Calcd. for $C_{10}H_8O_7$: C, 50.01; H, 3.36; neut. equiv., 80.7. Found: C, 49.67, 49.75; H, 3.72, 3.54; neut. equiv., 79.8, 79.9.

Hemimellitene.—This hydrocarbon was prepared by two methods: (1) Benzyl chloride, b. p. 172–175°, 1416 g., was converted by the method of Smith and Spillane⁷ into 77.4 g. of the hydrocarbon, b. p. 171.5–172.2° (741 mm.) and n_D^{20} 1.5130 (Smith and Spillane give b. p. 172.2–172.5° (741.4 mm.) and n_D^{20} 1.5130).

(2) *o*-Xylene was chloromethylated to give a mixture of 2,3-dimethylbenzyl chloride and 3,4-dimethylbenzyl chloride, which mixture was converted into pseudocumene and hemimellitene by forming the Grignard reagents and hydrolyzing. The hydrocarbons were separated by fractional distillation to give a product, b. p. 175–176° (740.5 mm.).⁸

Hemimellitene-4-sulfonic Acid.—Hemimellitene, 8 cc., was shaken with 16 cc. of concentrated sulfuric acid in a glass-stoppered flask until solution was complete (ten to fifteen minutes). This solution was added in 5-cc. portions, with stirring, to 32 cc. of cold concentrated hydrochloric acid, with cooling after each addition. Precipitation resulted, and after final cooling the solid was filtered dry by suction and crystallized twice from 100-cc. portions of cold 20% hydrochloric acid solution to give 11.5 g. of white plates, m. p. 115° (von Auwers and Wieners⁹ give 111–114°).

4-Hydroxybenzene-1,2,3-tricarboxylic Acid.—This acid was prepared by a method similar to that used for 5-hydroxybenzene-1,2,4-tricarboxylic acid.⁶ Hemimellitene-4-sulfonic acid, 10 g., was subjected to like treatment up to the point at which the filtrate was evaporated to dryness to remove hydrochloric acid. Then, upon the addition of 270 cc. of boiling water to the residue followed by heating for a short time, not all of the mono-potassium salt dissolved, but this amount of water was sufficient to dissolve the inorganic salts. Cooling in the refrigerator gave an additional amount of solid, the total of which, when crystallized five times from 40-cc. portions of 10% hydrochloric acid and dried in a vacuum desiccator, amounted to 4 g. and melted at 205–206° with effervescence.

Anal. Calcd. for $C_9H_6O_7 \cdot 1H_2O$: loss of weight on heating, 6.55. Found: 6.76, 6.89.

Heating at 102° for three hours gave the anhydrous acid.

Anal. Calcd. for $C_9H_6O_7$: C, 47.80; H, 2.67; neut. equiv., 76. Found: C, 48.28, 48.18; H, 2.89, 2.89; neut. equiv., 75.3, 75.0.

(7) Smith and Spillane, *THIS JOURNAL*, **62**, 2639 (1940).

(8) We are indebted to Mr. Comer Shacklett of this Laboratory for the hemimellitene prepared by this preferred procedure. Details of the method will be published by him later. This product is the purer, the Bureau of Standards value, A.P.I. Res. Project 44 at NBS; "Selected Values of Properties of Hydrocarbons" Table 5a, dated June 30, 1945, for pure hemimellitene being 176.15° (760 mm.).

(9) von Auwers and Wieners, *Ber.*, **58**, 2815 (1925).

Trimethyl 4-Hydroxybenzene-1,2,3-tricarboxylate.—The mother liquor from which the 4-hydroxy acid precipitated and the filtrates from the crystallization of the final product were combined and evaporated to dryness with occasional stirring. The pulverized residue in 500 cc. of dry methanol was saturated with hydrogen chloride and the mixture was refluxed for twenty-two hours while hydrogen chloride was introduced. Recovery in the usual manner and crystallization from 50% methanol gave 1.0 g. of white needles, m. p. 85.5–86°, which produce a red color with aqueous ferric chloride.

Anal. Calcd. for $C_{12}H_{12}O_7$: C, 53.73; H, 4.51. Found: C, 53.92, 53.99; H, 4.64, 4.84.

Trimethyl 4-Methoxybenzene-1,2,3-tricarboxylate.—The 4-hydroxy acid, 5 g., was methylated with diazomethane in the usual manner. The recovered product crystallized from methanol, 4.2 g., melted at 91.0–92.0°.

Anal. Calcd. for $C_{13}H_{14}O_7$: C, 55.32, H, 5.00. Found: C, 55.22, 55.45; H, 5.15, 5.21.

4-Hydroxy-1,2,3-trimethylbenzene.—This phenol was prepared by a modification of the method of von Auwers and Wieners⁹ as follows: In a nickel crucible 120 g. of potassium hydroxide was heated to 250° at which time 65 g. of hemimellitene-4-sulfonic acid was added slowly with stirring while the temperature was allowed to rise to 325°. At this point a dark oil separated on top of the fused mixture. Upon cooling, the mixture was dissolved in 400 cc. of water and the solution was acidified with sulfuric acid, after which the phenol was removed by steam distillation. Extraction with ether and evaporation gave 13.5 g. of product. One crystallization from petroleum ether gave long white needles, m. p. 76–77° (von Auwers and Wieners obtained two crystalline forms: one on cooling the liquid, m. p. 69°; a second on crystallizing from solvents, m. p. 81°).

4-Methoxyhemimellitene.—4-Hydroxyhemimellitene, 14.7 g., was methylated with dimethyl sulfate and sodium hydroxide to give 13.1 g. of a colorless oil, b. p. 216–218° (728 mm.). Fractionation using an Anschütz thermometer produced a sample for analysis, b. p. 215.5–216.5° (740 mm.), n_D^{20} 1.5200.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.76, 79.72; H, 9.22, 9.39.

2(?) -Methyl-4-methoxybenzene-1,3-dicarboxylic Acid.—This procedure was a modification of that given by Grewe¹⁰ as follows: In a 3-liter, three-necked flask, equipped with an agitator, a separatory funnel and a reflux condenser, 13.1 g. of 4-methoxyhemimellitene was suspended in 50 cc. of 10% aqueous sodium hydroxide solution. While the suspension was agitated vigorously on a steam-bath, a solution of 114 g. of potassium permanganate dissolved in 1760 cc. of water was added over a three-hour period and the mixture was allowed to react for two hours longer. Methanol was then added to reduce the excess of permanganate and after filtering the filtrate was concentrated to 300 cc. Acidification, evaporation to dryness and extraction with 350 cc. of acetone followed by evaporation gave 4.1 g. of a slightly yellow product. Several

crystallizations from water produced small white crystals, m. p. 216.0–216.5°. No anhydride was formed when this acid was heated to 220° for fifteen minutes.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80; neut. equiv., 105.1. Found: C, 57.05, 56.90; H, 4.60, 4.70; neut. equiv., 105.9.

4-Methoxybenzene-1,2,3-tricarboxylic Acid.—For a more strenuous oxidation procedure that given by Wilds and Djerassi¹¹ was modified as follows: In the apparatus described above, 4 g. of 4-methoxyhemimellitene was suspended in 324 cc. of 5% aqueous potassium hydroxide solution. While the suspension was heated on a steam-bath and agitated vigorously, 600 cc. of 0.35 *M* aqueous potassium permanganate solution was allowed to drop into the flask over a five-hour period. The mixture was allowed to react at this temperature until the purple color had disappeared, after which 25 cc. more of the permanganate solution was added over an hour period. When the color of permanganate had disappeared, another 25 cc. of the permanganate solution was added, and this process was repeated until a total of 725 cc. of the oxidizing solution had been added. At the end the excess permanganate was removed by the addition of sodium bisulfite and the mixture was filtered.

The most satisfactory method to remove the acid from the filtrate, concentrated to 500 cc., was that of Schultze.¹² After acidification with concentrated sulfuric acid, this concentrate was extracted twice with 200-cc. portions of ether (since the desired acid is insoluble in ether, only ether-soluble impurities are removed). The water layer was then saturated with sodium sulfate and extracted seven times with 250-cc. portions of ethyl acetate. Upon evaporating the combined portions of ethyl acetate to dryness, 2 g. of crude acid was obtained. Several crystallizations from small amounts of water gave 0.5 g. of white crystals, m. p. 215.0–216.0° with previous softening.

Crystallization from glacial acetic acid gave a product whose melting point was practically identical, but its analysis and neutral equivalent indicated that some anhydride formation had occurred.

Anal. Calcd. for $C_{10}H_8O_7$: C, 50.00; H, 3.36; neut. equiv., 80.0. Found: C, 49.96, 49.98; H, 3.27, 3.30; neut. equiv., 79.8.

Summary

4-Hydroxybenzene-1,2,3-tricarboxylic acid and 5-hydroxybenzene-1,2,4-tricarboxylic acid have been synthesized from hemimellitene and pseudocumene, respectively. In addition, the methoxy-trimethyl esters, the methoxytricarboxylic acids and several miscellaneous derivatives have been prepared. The methoxytrimethyl esters are to be preferred as reference compounds.

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RECEIVED JUNE 30, 1948

(11) Wilds and Djerassi, *This Journal*, **68**, 1862 (1946).

(12) Schultze, *Ann.*, **359**, 141 (1908).

(10) Grewe, *Ber.*, **71**, 910 (1938).