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The Preparation of 2,3,5-Trihydroxybenzoic Acid

A. Kreuchunas

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A new method for preparing 2,3,5-trihydroxybenzoic acid (I) has been developed. The method consists of treating 2,3,5-trimethoxybromobenzene[1] with ethyllithium, followed by carbonation and subsequent demethylation with anhydrous aluminum chloride.

The earlier methods[2–5] for the preparation of I are based on the persulfate oxidation of either salicylic acid or *alpha*-resorcylic acid. These methods gave uniformly poor yields and products of uncertain purity.

For example, Schock, Jr. and Tabern,[3] who have worked out the persulfate oxidation of salicylic acid under a range of conditions point out that mixtures of acids are obtained which are very difficult to separate by normal recrystallization procedures. They report that using a 300% excess of ammonium persulfate with salicylic acid a sharp melting mixture was obtained consisting of 80% I and 20% gentisic acid (m.p. 227° dec.). The mixture could not be purified by recrystallization. Another experiment yielded a mixture of 15% I and 85% gentisic acid which melted sharply at 209–210°.

Three melting points for I are listed in the literature: 216° dec.,[4] 223° dec.,[2] and 233° dec.[3] In view of this wide variation of melting point values and the results of the work of Schock, Jr., and Tabern[3] it seemed advisable to develop a new synthesis which would be less likely to yield a mixture of products. Our value for the melting point of I was 234.5–235.5° with decomposition.

EXPERIMENTAL[6]

2,3,5-Trimethoxybenzoic acid. To a stirred mixture of 7.5 g. (1.08 g.-atom) of lithium metal pieces in 300 ml. of anhydrous ether at −20° to −30° was added a mixture of 58.9 g. (0.54 mole) of ethyl bromide in 200 ml. of anhydrous ether over a period of 30 minutes. The reaction mixture was stirred for an additional 40 minutes.

A solution of 80 g. (0.32 mole) of 2,3,5-trimethoxybromobenzene[1] in 200 ml. of anhydrous ether was added to the above mixture over a period of 20 minutes. The reaction mixture was poured over two pounds of crushed Dry Ice. Water (600 ml.) was added as soon as the mixture had warmed to near room temperature. The aqueous portion was filtered and treated with 50 ml. of concentrated hydrochloric acid. The solid which separated was collected by filtration, washed with 300 ml. of water, dried open to the air, and then at 70° to constant weight.

The crude product was recrystallized by six extractions with the same portion of cyclohexane (1100 ml.), yielding 43.5 g., 64.1%, m.p. 99–101.5°. A small sample was recrystallized from a 2:1 mixture of benzene and cyclohexane, m.p. 99.5–100.5°; reported m.p. 101–102°,[7] 105°.[8]

The ether layer yielded 6 g. of an oil which was presumably a mixture of 2,3,5-trimethoxybromobenzene and 1,2,4-trimethoxybenzene. The latter compound was formed by the partial hydrolysis of the lithium derivative.

2,3,5-Trihydroxybenzoic acid. (I) A mixture of 34.5 g. (0.16 mole) of 2,3,5-trimethoxybenzoic acid, 300 ml. of chlorobenzene, and 86.4 g. (0.64 mole) of sublimed, anhydrous aluminum chloride was stirred under reflux for 45 minutes, cooled under argon, and poured over 300 g. of ice. The flask was washed with 200 ml. of water. The mixture was filtered. The clear, brown aqueous portion was separated, extracted with 2 × 100 ml. of ether and acidified with 80 ml. of concentrated hydrochloric acid. A voluminous solid separated which was collected by filtration, washed with 2 × 100 ml. of water, and dried at 70° to constant weight. A small portion of product was obtained by an ether extraction of the aqueous filtrate. The total crude yield was 26 g.

The crude product was recrystallized by three successive extractions with the same portion of glacial acetic acid (175 ml.), yielding 20.3 g., pale yellow powder, 73.8%, m.p. 233–235° with decomposition. The material gives a reddish-brown color with alcoholic ferric chloride. A small sample was recrystallized from glacial acetic acid and was dried *in vacuo* over refluxing ethylene dichloride, m.p. 234.5–235.5° with decomposition.

Anal. Calc'd for $C_6H_5O_3COOH$: Neut. Equiv., 170.1. Found: 168.8.

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Lark Research Laboratory
P.O. Box 3922
Detroit 27, Michigan

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[1] Prepared by the method of Dorn, Warren, and Bullock, *J. Am. Chem. Soc.*, **61**, 144 (1939). They refer to this material as the trimethyl ether of 6-bromohydroxyhydroquinone.

[2] Corbett, Hassall, Johnson, and Todd, *J. Chem. Soc.*, 1 (1950).

[3] Schock, Jr., and Tabern, *J. Org. Chem.*, **16**, 1772 (1951).

[4] Horii, Komiyama, Otsuki, and Yamamura, *J. Pharm. Soc. Japan*, **72**, 1520 (1952).

[5] Schock, Jr., and Tabern, U. S. Patent 2,641,609 [*Chem. Abstr.*, **48**, 6468^a (1954)].

[6] Melting points are uncorrected.

[7] Faltis and Kloiber, *Monatsh.*, **53/54**, 620 (1929).

[8] Smith and LaForge, *J. Am. Chem. Soc.*, **53**, 3072 (1931).