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The Preparation of *o*-Hydroxyphenylacetic Acid

BY JOSEPH LEVINE, T. E. EBLE AND HENRY FISCHBACH

A number of methods have been described for the preparation of *o*-hydroxyphenylacetic acid.[1] In general, the procedures require expensive reagents and usually produce low yields.

The procedure of Czaplicki, *et al.*,[2] entails simultaneous hydrolysis, reduction, and demethylation of *o*-methoxybenzaldehyde cyanohydrin with hydriodic acid. Modification of this procedure for the preparation of the cyanohydrin has now increased the yield from 44 to 95%. Conversion of the cyanohydrin to *o*-methoxyphenylacetic acid was effected in 90% yield with stannous chloride–hydrochloric acid[3] in the presence of a small amount of hydriodic acid. A 75% yield of the pure hydroxy acid was obtained by demethylation with acetic acid–hydrobromic acid mixture containing a small amount of hydriodic acid. In each of the two final steps the use of hydriodic acid resulted in a significant decrease in tar formation.

Methyl *o*-hydroxyphenylacetate, prepared by esterification of the acid with methanol and sulfuric acid, melted at 71°–72°. This compound was reported by Nozu, *et al.*,[4] as melting at 122–124°. From their method of preparation it is evident that their compound is actually the methyl ether, rather than the ester.

Experimental

***o*-Methoxybenzaldehyde** was prepared in 92% yield from salicylaldehyde according to the procedure given in "Organic Syntheses" for the preparation of veratraldehyde.[5] Recrystallized from petroleum ether, it melted sharply at 37°,[6a] as reported by Voswinckel.[6]

***o*-Methoxybenzaldehyde Cyanohydrin.**—To 99 g. of melted *o*-methoxybenzaldehyde was added a saturated solution of 104 g. (1.5 equivalents) of sodium metabisulfite. Upon stirring heat was evolved and the entire mixture solidified. Water was added to obtain a thick suspension, which was covered with ether and cooled. An ice-cold saturated solution of 99 g. of sodium cyanide was added with stirring, and a further 10 g. of sodium bisulfite added, stirring until most of the product was dissolved in the ether. The aqueous layer was diluted with water, extracted with ether, and the combined ether solutions washed with bisulfite solution and then with water. The ether was distilled off and the residue dissolved in benzene and dried azeotropically by refluxing with a water trap. Upon cooling, crystals of the cyanohydrin separated. Petroleum ether was added to effect complete separation. A yield of 113 g. (95%) of granular crystals, m. p. 71–72°, was obtained. Recrystallization from benzene gave a m. p. of 73–74° (Buck[7] reported 73°).

***o*-Methoxyphenylacetic Acid.**—A hot solution of 50 g. of crystalline stannous chloride in 50 ml. of acetic acid, 50 ml. of concentrated hydrochloric acid, and 5 ml. of hydriodic acid (sp. gr. 1.7) was added to 25 g. of *o*-methoxybenzaldehyde cyanohydrin, and the resultant solution heated three hours on a steam-bath. After cooling the solution was filtered to remove stannic chloride which separated during the reaction, diluted with water, and extracted to exhaustion with carbon tetrachloride. The combined extracts were washed with water and evaporated to dryness. A yield of 23 g. (90%) of *o*-methoxyphenylacetic acid was obtained. A portion recrystallized from benzene melted at 124°, the value reported by Pschorr, *et al.*[8]

***o*-Hydroxyphenylacetic Acid.**—Twenty-three grams of *o*-methoxyphenylacetic acid (used directly as obtained above), 70 ml. of glacial acetic acid, 70 ml. of 48% hydrobromic acid, and 7 ml. of hydriodic acid (sp. gr. 1.7) were refluxed sixteen hours. The cooled solution, after dilution with water and addition of a small amount of sodium bisulfite, was extracted first with chloroform and then with ether. The ether extract was washed with water and evaporated; acetic acid in the residue was removed by evaporation with toluene on a steam-bath in a stream of air. The residue was dissolved in ether and sufficient petroleum ether (Skellysolve C) added to form a cloudy solution, from which a small amount of colored gummy material was deposited. The colorless supernatant liquid was decanted and additional petroleum ether added; 15.8 g. (75%) of large snow-white crystals of *o*-hydroxyphenylacetic acid, m. p. 146°–147°, separated; upon recrystallization in the same manner, the m. p. was raised to 149–150° (Czaplicki, *et al.*,[2] reported 147°).

Methyl *o*-Hydroxyphenylacetate.—A solution of 2.0 g. of *o*-hydroxyphenylacetic acid in 20 ml. of methanol and 2 ml. of concentrated sulfuric acid was refluxed for two hours. The cooled solution was diluted with water and extracted with ether. The ether solution, after extraction with sodium bicarbonate solution to remove unreacted acid, was evaporated to dryness. The ester crystallized from petroleum ether as plates (yield, 1.6 g.); upon recrystallization, m. p. 71–72°.

Anal. Calcd. for $C_7H_7OCOOCH_3$: OCH_3, 18.65; sapon. equiv., 166.2. Found: OCH_3, 18.55; sapon. equiv., 163.8.

Summary

o-Hydroxyphenylacetic acid was prepared from *o*-methoxybenzaldehyde (64% over-all yield), *via* the cyanohydrin and *o*-methoxyphenylacetic acid. The methyl ester was prepared.

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(1) "Beilstein," **10**, 187; 1 Erg., **10**, 81; Barnes and McElvain, THIS JOURNAL, **59**, 2350 (1937); Niederl and Roth, *ibid.*, **60**, 2140 (1938); King and McMillan, *ibid.*, **68**, 2335 (1946); Ott, Mattano and Coleman, *ibid.*, **68**, 2633 (1946).

(2) Czaplicki, von Kostanecki and Lampe, *Ber.*, **42**, 827 (1909).

(3) Heller, *ibid.*, **46**, 288 (1913).

(4) Nozu, Hamada, Hosino and Kinosita, *J. Chem. Soc. Japan*, **60**, 1189 (1939); *C. A.*, **36**, 6513 (1942).

(5) "Organic Syntheses," Coll. Vol. II, 1943, p. 619.

(6) Voswinckel, *Ber.*, **15**, 2025 (1882).

(6a) All m. p.'s determined on a Fisher–Johns apparatus.

(7) Buck, THIS JOURNAL, **55**, 2593 (1933).

(8) Pschorr, Wolfes and Buckow, *Ber.*, **33**, 167 (1900).