

AN UNAMBIGUOUS SYNTHESIS OF  
2,6-DIMETHOXY-3-METHOXYCARBONYLBENZOIC ACID\*

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In our recent work on bayin<sup>1</sup> it became necessary to prepare authentic 2,4-dihydroxyisophthalic acid derivatives for comparison with degradation products of the naturally occurring compound. Several literature references<sup>2</sup> claiming to describe syntheses of 2,4-dihydroxyisophthalic acid or its derivatives were found actually to deal with the more common 4,6-isomer. The first authentic synthesis of 2,4-dihydroxyisophthalic acid and its esters and ethers appears to be that of Radha and Shah.<sup>3</sup> They initially prepared the dimethoxy acid, which was demethylated to give the free dihydroxy acid. The dimethoxy acid was also treated with methanol and sulphuric acid when it gave a mixture of the monomethyl and dimethyl esters; the authors assumed that the monomethyl ester was esterified at position 1, due to steric hindrance of the carboxyl group in position 3. Essentially the same method for the synthesis of 2,4-dimethoxyisophthalic acid derivatives was also used at about the same time by Gruber.<sup>4</sup> We report now an unambiguous synthesis of 2,6-dimethoxy-3-methoxycarbonylbenzoic acid, the properties of which closely resemble those of the above monomethyl ester reported by Radha and Shah.

2-Methylresorcinol was carboxylated<sup>5</sup> to 2,4-dihydroxy-*m*-toluic acid. This was converted into 2,4-dimethoxy-*m*-toluic acid and then methylated with diazomethane to give methyl 2,4-dimethoxy-*m*-toluate, which on neutral permanganate oxidation in aqueous acetone gave 2,6-dimethoxy-3-methoxycarbonylbenzoic acid.

### *Experimental*

Melting points were determined on a Kofler block, and are uncorrected.

#### *2,4-Dihydroxy-m-toluic Acid*

2-Methylresorcinol (1 g) was carboxylated<sup>5</sup> with potassium hydrogen carbonate (5 g) in water (20 ml) to give 2,4-dihydroxy-*m*-toluic acid (680 mg), m.p. 199–201·5° (dec.) (lit.<sup>5</sup> 200–201° (dec.)).

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<sup>1</sup> Eade, R. A., Salasoo, I., and Simes, J. J. H., *Chemistry Ind.*, 1962, 1720.

<sup>2</sup> "Beilstein's Handbuch der organischen Chemie." Main Series, Vol. X, p. 553; Birkinshaw, J. H., and Raistrick, H., *Biochem. J.*, 1932, **26**, 441; Marzin, A., *J. prakt. Chem.*, 1933, **138**, 107; Hale, D. K., Hawdon, A. R., Jones, J. L., and Packham, D. I., *J. Chem. Soc.*, 1952, 3503; Wagner, G., *Pharmazie*, 1953, **8**, 1021.

<sup>3</sup> Radha, K. S., and Shah, R. C., *J. Indian Chem. Soc.*, 1942, **19**, 495.

<sup>4</sup> Gruber, W., *Mh. Chem.*, 1946, **76**, 46 (submitted for publication in 1944).

<sup>5</sup> Shah, R. C., and Laiwalla, M. C., *J. Chem. Soc.*, 1938, 1828.

*2,4-Dimethoxy-m-toluic Acid*

A solution of 2,4-dihydroxy-*m*-toluic acid (650 mg) in dry acetone (40 ml) was refluxed for 14 hr while methyl sulphate (2.3 ml) and freshly ignited potassium carbonate (5 g) were added in portions until the ferric chloride test was negative. The product was boiled with aqueous methanolic sodium hydroxide for 30 min, the cooled mixture was extracted with ether, acidified, and the precipitate was collected. 2,4-Dimethoxy-*m*-toluic acid formed colourless needles (563 mg), m.p. 144–146° (lit.<sup>5</sup> 146–147°).

*Methyl 2,4-Dimethoxy-m-toluate*

An ethereal solution of 2,4-dimethoxy-*m*-toluic acid (500 mg) was treated with excess diazomethane and kept in a refrigerator for 20 hr. The solvent was evaporated, the residue was extracted several times with boiling light petroleum (b.p. 50–60°), the extract washed with sodium bicarbonate solution, dried, and evaporated to dryness. Recrystallized from light petroleum, *methyl 2,4-dimethoxy-m-toluate* formed hexagonal leaflets, m.p. 36–38°, b.p. 102–104°/0.5 mm, 109–111°/0.6 mm (Found: C, 62.7; H, 6.7; OCH<sub>3</sub>, 43.9; mol. wt. (Rast), 203. C<sub>11</sub>H<sub>14</sub>O<sub>4</sub> requires C, 62.8; H, 6.7; 3 × OCH<sub>3</sub>, 44.3%; mol. wt., 210); total yield 437 mg.

*2,6-Dimethoxy-3-methoxycarbonylbenzoic Acid*

Methyl 2,4-dimethoxy-*m*-toluate (375 mg) was oxidized with potassium permanganate (675 mg) in aqueous acetone in the presence of magnesium sulphate. Acetone was boiled off, the solution acidified with sulphuric acid, clarified with sulphur dioxide, and the organic material was extracted into ether. The product was separated by aqueous sodium bicarbonate extraction, followed by acidification and ether extraction. The crude product (106 mg) was recrystallized from water to give 2,6-dimethoxy-3-methoxycarbonylbenzoic acid in colourless needles, m.p. 155–156° (lit.<sup>3</sup> 150–151°) (Found: C, 54.8; H, 4.9. Calc. for C<sub>11</sub>H<sub>12</sub>O<sub>6</sub>: C, 55.0; H, 5.0%). The product could also be purified by sublimation.