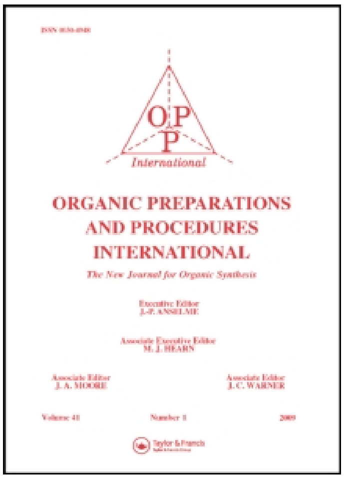

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THE SYNTHESIS OF METHYL 2-HYDROXY-5-METHOXY-3-METHYLBENZOATE

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THE SYNTHESIS OF METHYL 2-HYDROXY-5-METHOXY-3-METHYLBENZOATE

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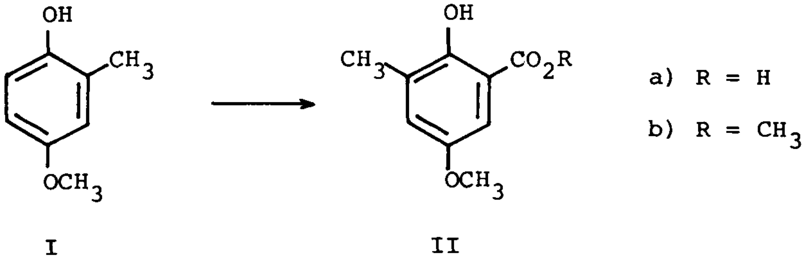
The most likely route to methyl 2-hydroxy-5-methoxy-3-methylbenzoate (IIb), needed in a multistep synthesis seemed to be the reaction of a salt of 4-methoxy-2-methylphenol (I) with carbon dioxide. Such carboxylations (the Kolbe-Schmitt reaction) have most frequently been carried out[1] at high temperatures and under high pressure of CO_2 in solvents in which the salt was relatively insoluble.[2] Later, carboxylations were tried in a number of solvents, of which dimethylacetamide (DMA) at 180° for relatively short times without high pressure of CO_2 was best.[3]

We have carboxylated a solution of the sodium salt of I by bubbling in CO_2 in refluxing bis-(2-methoxyethyl)ether (bp. 162°) and obtained high yields of the unknown 2-hydroxy-5-methoxy-3-methylbenzoic acid (IIa). This route has some advantages over the above routes because of simplicity of operations.



4-Methoxy-2-methylphenol (I) was prepared by a Reimer-Tiemann reaction[4] on 4-methoxyphenol followed by a Wolff-Kishner reduction[5] of 2-hydroxy-5-methoxybenzaldehyde.[6]

EXPERIMENTAL[7]

2-Hydroxy-5-methoxy-3-methylbenzoic Acid (IIa).- To the stirred solution at the bp formed by adding 33.1 g (0.24 mole) of I in 100 ml of diglyme to a suspension of 5.8 g (0.24 mole) of sodium hydride in 25 ml of dry diglyme at room temperature was added carbon dioxide gas over a period of 9 hrs. The mixture was cooled to room temperature, diluted with water and neutralized with dilute HCl. A solution of the product in 1:1 ether-benzene was washed with $NaHCO_3$, water, saturated NaCl and was dried over Na_2SO_4. From the ether-benzene there was recovered some I (19%). The $NaHCO_3$ extract was treated with charcoal (Darco-G-60) and acidified. The crude acid (34.9 g, 80%) isolated by ether-benzene extraction was suitable for esterification. A pure sample, mp. 148.5-149.5°, was more easily obtained pure by hydrolysis of the distilled ester IIb (see below), than by recrystallization of the crude acid.

Anal. Calcd for $C_9H_{10}O_4$: C, 59.3; H, 5.5.

Found: C, 59.5; H, 5.6.

Methyl 2-Hydroxy-5-methoxy-3-methylbenzoate (IIb).- A solution of 71 g of thionyl chloride in 25 ml of CH_2Cl_2 was added during 30 min to a solution of 72.4 g of IIa in 300 ml of CH_2Cl_2 containing 5.3 g of suspended $AlCl_3$ at room temperature. After stirring overnight the solvent and $SOCl_2$ were removed by rotary evaporation. A solution of the product in a small amount of CH_2Cl_2 was added to 450 ml of dry methanol. The mixture was slowly heated to, and maintained at, reflux until the evolution of HCl ceased (1 hr). After removing solvents an ether-benzene solution of the product was washed with $NaHCO_3$, saturated NaCl, and dried with Na_2SO_4. Distillation afforded 63.4 g (82%) of IIb, mp 79-81.0°, lit.[8] mp. 78-79°.

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.2; H, 6.2.
Found: C, 61.4; H, 6.1.

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