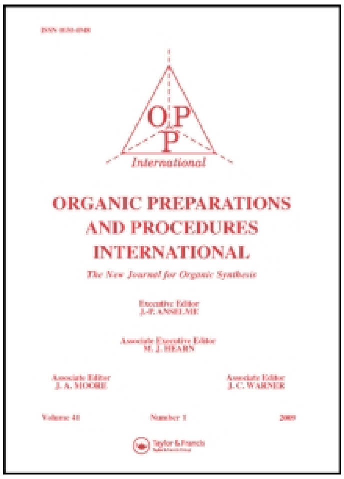

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ETHYL 3,4-DIHYDROXY-5-METHOXYBENZOATE, AN INTERMEDIATE PRODUCT FOR THE SYNTHESIS OF 3,4-DIHYDROXY-5-METHOXYBENZOIC ACID

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hydrazide solution remained green and then became violet. The reaction was allowed to proceed for 2 hrs with stirring. The mixture was then concentrated to a small volume under reduced pressure and the residue was extracted with ether (20 ml), 10% aqueous sulfuric acid (3 x 15 ml) and then 10% aqueous sodium hydroxide (3 x 15 ml). The organic phase was washed with water, dried over sodium sulfate and evaporated under reduced pressure to afford the amide in good purity. Further purification was achieved by usual procedures. The isolated products were identified by comparison with authentic specimens, prepared by standard methods.

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(8/27/80)

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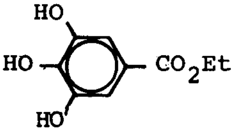
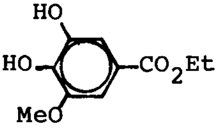
3,4-Dihydroxy-5-methoxybenzoic acid (III) was synthesized by a simple method from methyl gallate.[1]

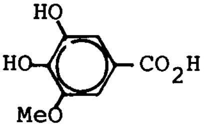
This acid can be obtained by an improved method starting with ethyl gallate (I). Ethyl 3,4-dihydroxy-5-methoxybenzoate (II) has been isolated for the first time in pure state as an intermediate of this procedure. It



I



II



III

is also worth noting that extraction with benzene of the methylated precipitate was not accompanied by the usual contamination of boric acid, whereas, the use of ethyl acetate for the extraction gave products which needed further purification.

EXPERIMENTAL

Ethyl gallate (I) was recrystallized from water ; it showed a dimorphous melting point 146.3-147°/153-154°. It became clear that the discrepancy in the previously reported mps.[2,3] could be attributed to each of the polymorphous forms.

Ethyl 3,4-dihydroxy-5-methoxybenzoate (II).- An aqueous solution (440 ml) of anhydrous sodium borate (20.4 g) and ethyl gallate (I) (5 g) was stirred at room temperature. Dimethyl sulfate (15.3 ml) and aqueous sodium hydroxide (6.7 g in 25 ml H_2O) were alternately added dropwise to the solution over 3 hrs. and the mixture stirred overnight. Acidification with sulfuric acid yielded a white précipitate which was dried *in vacuo* and dissolved into hot benzene. The acidic filtrate was extracted continuously with ethyl acetate, then saturated with sodium chloride. The solvent was evaporated *in vacuo* and the residue was dissolved into hot benzene. The combined benzene solutions were concentrated *in vacuo* and purified by silica gel column chromatography. After recrystallization from benzene, the eluates afforded ethyl 3,4-dihydroxy-5-methoxybenzoate (II), mp. 90-91°, MS: m/e 212 (75%, M^+), 167 (base peak), PMR: δ, ppm in $CDCl_3$, 1.4 (t, J = 7 Hz, CH_3-), 3.88 (s, CH_3O-) 4.33 (q, J = 7 Hz, -CH_2-), 5.82 (s, HO-), 6.04 (s, HO-), 7.14 (d, J = 2 Hz, aromatic H), 7.32 (d, J = 2 Hz, aromatic H).

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70; O, 37.70.
Found: C, 56.62; H, 5.77; O, 37.93.

The crystals which were filtered and air-dried at room temperature had a polymorphous melting point 85-86°/90-91°. Paper chromatographic behavior was observed as follows: Filter paper: Toyo No. 53; solvent: AcOH-H_2O (3 : 17 v/v); temperature: 11-11.7°; Coupler: potassium ferricyanide-ferric chloride; Rfs: 0.48 [3,4-dihydroxy-5-methoxybenzoic acid (III)]; 0.58 [ethyl 3,4-dihydroxy-5-methoxybenzoate (II)]; 0.51 [ethyl gallate (I)]; 0.41 [gallic acid]. This ester had previously been isolated only in a crude liquid state.[4]

3,4-Dihydroxy-5-methoxybenzoic acid (III).- The combined benzene extracts of the original reaction product in which ethyl 3,4-dihydroxy-5-methoxybenzoate had dissolved, was hydrolyzed with aqueous sodium hydroxide. Heating of this material on a water bath for 1 hr, followed by acidification with conc. hydrochloric acid yielded 3.7 g. (77%) of crude 3,4-dihydroxy-5-methoxybenzoic acid. The acid was decolorized by activated charcoal and purified by recrystallization from water to give 3,4-dihydroxy-5-methoxybenzoic acid hemihydrate, mp. 223-223.2°.

Anal. Calcd. for $C_8H_8O_5 \cdot 1/2\ H_2O$: C, 49.74; H, 4.70.
Found: C, 49.61; H, 4.76.

Furthermore, continuous extraction of the acidic filtrate with ether afforded the parent acid (0.07 g) on recrystallization. The acid lost its water of crystallization on heating at 120° and afforded the anhydrous acid, mp. 224-224.7° with slight decomposition; MS: m/e 184 (base peak, M^+), 169 (50%). This material showed no melting point depression on mixing with an authentic specimen.[1]

Anal. Calcd. for $C_8H_8O_5$: C, 52.18; H, 4.38.

Found: C, 52.08; H, 4.21.

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A DETAILED PROCEDURE FOR SYNTHESIS OF 2,3-DIHYDROXYBENZALDEHYDE

Submitted by (7/7/80)

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2,3-Dihydroxybenzaldehyde (II) has been used as an intermediate in organic synthesis[1,2] and as a reagent for enzyme modification.[3] Although II is commercially available, the high cost limits its use. The demethyla-