SYNTHESIS OF BENZYL p-HYDROXYBENZOATE

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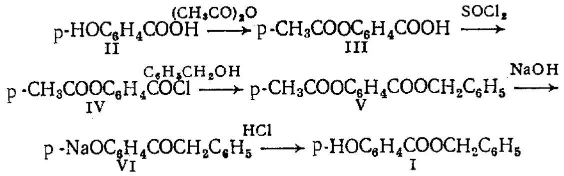
Benzyl p-hydroxybenzoate is of interest as a medium for the preparation of medicinal [1] and cosmetic [2] agents. According to the literature, it can be obtained by the direct esterification of p-hydroxybenzoic acid (II) with benzyl alcohol in the presence of concentrated sulfuric acid [2], by heating an aqueous alkaline solution of (II) with benzyl chloride [3], or by the transesterification of methyl p-hydroxybenzoate with benzyl alcohol in the presence of aluminum benzyloxide [4].

As our observations have shown, it is impossible to reproduce Krajkemann's results [2]: under all the conditions studied, the reaction of (II) with benzyl alcohol in the presence of sulfuric acid gave, instead of the expected (I), a substance with a melting point above 200°C, the structure of which was not investigated.

The production of (I) by the method of Covallito and Buck [3] is complicated by the high toxicity of benzyl chloride and the low yield of products [~30%, calculated on the initial (II)] and synthesis by the last-mentioned method [4] requires the organization of the production of methyl benzoate and aluminum benzyloxide.

We have obtained (I) by the following route:



$$\underset{\text{II}}{\text{p-HOC}_6\text{H}_4\text{COOH}} \xrightarrow{(\text{CH}_3\text{CO})_2\text{O}} \underset{\text{III}}{\text{p-CH}_3\text{COOC}_6\text{H}_4\text{COOH}} \xrightarrow{\text{SOCl}_2}$$

$$\underset{\text{IV}}{\text{p-CH}_3\text{COOC}_6\text{H}_4\text{COCl}} \xrightarrow{\text{C}_6\text{H}_5\text{CH}_2\text{OH}} \underset{\text{V}}{\text{p-CH}_3\text{COOC}_6\text{H}_4\text{COOCH}_2\text{C}_6\text{H}_5} \xrightarrow{\text{NaOH}}$$

$$\underset{\text{VI}}{\text{p-NaOC}_6\text{H}_4\text{COCH}_2\text{C}_6\text{H}_5} \xrightarrow{\text{HCl}} \underset{\text{I}}{\text{p-HOC}_6\text{H}_4\text{COOCH}_2\text{C}_6\text{H}_5}$$

The reliable yield of (I) by this route is about 60% of theoretical.

EXPERIMENTAL

p-Acetoxybenzoic Acid (III). According to the literature [5], this substance can be obtained with a yield of ~50% by treating an aqueous alkaline solution of (II) with acetic anhydride. We have obtained it by acetylating (II) with acetic anhydride in glacial acetic acid in the presence of catalytic amounts of sulfuric acid.

A mixture of 138 g of (II), 350 ml of glacial acetic acid, and 138 ml of acetic anhydride was stirred until a homogeneous suspension had been formed, and then 7 ml of concentrated sulfuric acid was added in one portion. The temperature of the reaction mixture rose spontaneously to 50-60°C and the bulk of the solid phase passed into solution. The mixture was heated to 70-75°C, stirred until the solid matter had gone into solution completely, left to cool for 1 h, cooled further to room temperature, and poured into a 10-fold volume of cold water. The precipitate of (III) was filtered off, washed with water until the mineral acid had been eliminated (pH 4.0-4.5 according to universal indicator), and dried first in the air and then in the drying cabinet at 80-100°C. Yield 171-172 g (~95%), mp 195-196°C (which agrees with the literature figure [5]).

p-Acetoxybenzoyl chloride (IV). In a patent [5], (IV) is obtained by treating (III) with phosphorus pentachloride. According to our observations, it is more convenient to perform this synthesis with thionyl chloride in chlorobenzene.

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Over 30-35 min, 60 ml of thionyl chloride was added to a suspension of 54 g of dry (III) in 210 ml of chlorobenzene heated to 80-82°C, after which the mixture was heated to 95-98°C (at this temperature, the solid phase passed into solution after 10-15 min) and was kept there until the evolution of hydrogen chloride had ceased completely (~3 h). The excess of thionyl chloride was distilled off at atmospheric pressure, and then the chlorobenzene at a residual pressure of 70-80 mm, and, finally, pure (IV) was collected at 155-160°C (12-13 mm). Yield 51-52 g (~87%). In agreement with the literature [5], the substance solidified at ~30°C.

Benzyl-p-Acetoxybenzoate (V). To a mixture of 21.6 g of benzyl alcohol in 50 ml of dry pyridine at 20-25°C was added 39.7 g of (IV), and the mixture was heated to 60-62°C, stirred for 2 h, cooled to room temperature, and poured into a 10-fold volume of ice water. The oil that separated out crystallized rapidly on stirring. The crystals of technical (V) were filtered off, washed with ice water until the smell of pyridine had disappeared, dried in a desiccator over phosphorus pentoxide, and recrystallized from diethyl ether (1:3). Yield 48-48.5 g (89-90%), mp 46°C. Found, %: C 70.98; H 5.23. $C_{16}H_{14}O_4$. Calculated, %: C 71.10; H 5.21.

Benzyl p-Hydroxybenzoate (I). A mixture of 48-48.5 g of (V) and 200 ml of 8% aqueous caustic soda was stirred at 40-45°C until dissolution was complete, which took 35-40 min. The solution was filtered and the clear filtrate was treated at 10-15°C with 20% hydrochloric acid to pH 6.0-6.5 by a universal indicator. The precipitate of technical (I) was filtered off, washed with 50 ml of 1% sodium bicarbonate solution and then with water to neutrality, carefully pressed out, and recrystallized from a mixture of 100 ml of methanol and 50 ml of water. Yield 33-33.5 g (81-82%), mp 109-111°C (which agrees with the literature value [1]). A mixture with a sample of (I) obtained by the method of Covallito and Buck [3] melted without depression.

LITERATURE CITED

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4. K. W. Rosenmund, F. Zimabrowski, and E. Güssow, Arch. Pharm. (Weinheim), 286, 324 (1953).