

TECHNOLOGY

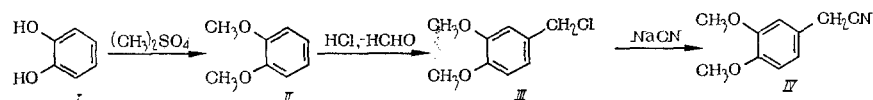
PREPARATION OF 3,4-DIMETHOXYPHENYLACETONITRILE

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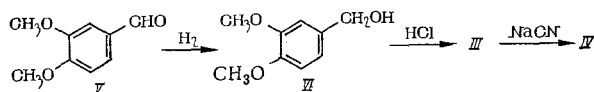
3,4-Dimethoxyphenylacetoneitrile ("homonitrile," IV) is an important intermediate in the synthesis of papaverine.

Compound (IV) is synthesized from pyrocatechol (I) according to one of the methods currently used in the pharmaceutical chemistry industry via the scheme:



The last two steps are carried out without isolating the intermediates, and the technical IV obtained is purified by distillation in vacuo. The yield of pure IV in this process is 43 to 45% of the theoretical yield based on veratrole (II) or ~39% based on I.

The low yields of IV compelled us to seek other routes for its preparation. One of the promising routes was a scheme involving synthesis of IV from veratraldehyde (V) [1, 2] which is obtained in industry by methylation of vanillin (92-93% yield).



3,4-Dimethoxybenzyl alcohol (veratric alcohol, VI) can be obtained from V by the Cannizzaro reaction [1] or by catalytic hydrogenation [3-7]. We found that hydrogenation over Raney nickel has a number of advantages over the Cannizzaro reaction: 1) the yield of (VI) reaches 97% (~90.92% by the Cannizzaro reaction); 2) the (VI) form can be subsequently processed without additional purification; 3) the solvent (ethanol) and the catalyst can be used repeatedly.

The conversion of (VI) to 3,4-dimethoxybenzyl chloride (III) is accomplished by the action of thionyl chloride [2, 8] or dry hydrogen chloride [9, 10]. Our laboratory testing indicated that high yields of (III) (92-95%) can be obtained when thionyl chloride is used in charges of the order of 20-50 g, but these yields are not reproduced when the experiments are carried out on a larger scale (1-2 kg). In addition, a number of side products, whose presence significantly decreases the yield in the ensuing step and hinders purification of (IV) [11, 12], are formed when thionyl chloride is used. Hydrogen chloride turned out to be more successful for this end. In the presence of moisture, this reaction is accompanied by the formation of a number of side products: in particular, we isolated 2,3,6,7-tetramethoxy-9,10-dihydroanthracene, and the literature also describes the formation of diveratric ether [13]. In order to exclude the formation of these side products we introduced anhydrous sodium sulfate into the reaction mixture to combine with the water evolved, and excess hydrogen chloride was neutralized with dry soda ash [14]. Under these conditions, sufficiently pure (III) is formed in high yield (~90%) in trichloroethylene or toluene and is then subjected to cyanation without isolation under the usual conditions [15]. The technical IV obtained is a crystalline substance with 89.9% content of pure substance and mp 53-55°C. The yield of the technical product, reck-

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oned for 100% substance, is 70% based on (VI). Compound (IV) is purified by recrystallization from aqueous methanol, and the (IV) remaining in the mother liquor is used to obtain "homoveratric acid," another intermediate product in the synthesis of papaverine.

EXPERIMENTAL

3,4-Dimethoxybenzyl Alcohol (Veratric Alcohol, VI). A solution of 47 g of 98% technical (V) in 93 ml of ethanol was stirred at room temperature for 15 min with 1 g of activated charcoal. The purified solution of (V) was mixed with 5 ml of a Raney nickel paste and 45 ml of ethanol and hydrogenated in an autoclave at 50 gage atm and 100° for 3 h. After cooling, the reaction mixture was filtered from the catalyst, and the ethanol was evaporated in vacuo to give 45.2 g of (VI) with 100% content of major product. The yield of (VI) was 97% based on 100% V.

3,4-Dimethoxyphenylacetonitrile (IV). A mixture of 147 ml of dry trichloroethylene and 17 g of anhydrous sodium sulfate was cooled to 0°, and a stream of dry hydrogen chloride was passed through it with stirring and simultaneous, slow addition of 38.1 g of (VI) at such a rate that the temperature did not exceed 5 to 7°. The reaction mixture was stirred for another 15 min with passage of hydrogen chloride through the mixture, and 3 g of soda ash was then added to combine with the excess hydrogen chloride. After 30 min the solution was filtered from the precipitate of mineral salts, and the precipitate was washed with trichloroethylene. A solution of 15.7 g of sodium cyanide in 42 ml of water was added to the combined trichloroethylene filtrates, containing ~38 g of (III), and the mixture was heated at 78-80° with vigorous stirring for 8 h. The trichloroethylene solution was removed, washed with water, and the solvent was evaporated to give 31.1 g of technical (IV). This was purified by recrystallization from 50 ml of 70% aqueous methanol to give 18.6 g of recrystallized (IV) with a 95.5% pure product content. The yield of (IV) was 44.5% based on (VI).

Sodium hydroxide (20 ml of a 20% solution) was added to the mother liquor, containing ~9 g of (IV), the solution was refluxed for 10 h, cooled to 20°, and then neutralized with concentrated hydrochloric acid up to pH 7. The solution was filtered, the filtrate was refluxed for 15 min with 0.5 g of activated charcoal, and the charcoal was filtered off and washed with hot water. The aqueous solution was cooled to 10° and acidified with hydrochloric acid up to pH 3. The precipitate of "homoveratric acid" was filtered and washed with water to give 4.6 g (10.4%) of a product with mp 93-95°. The overall yield of 100% IV and "homoveratric acid" was ~55% based on (VI) [53% based on (V) or 49.3% based on vanillin].

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