IMPROVED METHOD OF PRODUCING p-AMINOMETHYLBENZOIC ACID (AMBENE)

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p-Aminomethylbenzoic acid (I) is used under the name of "PAMBA" or Ambene in medical practice as an effective antifibrinolytic substance [1, 2]. This compound can also be used for obtaining the corresponding ethyl ester, i.e., trans-1-aminomethyl-4-carboxylhexane and its various other esters, which are also powerful antifibrinolytic agents [3].

Several methods for the synthesis of I are known, but the most widely used is the reduction of cyanobenzoic acid (II) under various conditions [4-8] in which a Raney nickel catalyst is generally used, and hydrogenation is carried out in aqueous ammonia at a pressure of up to 100 atm or under atmospheric pressure. The technological solution of the problem of preparing I therefore depends as a whole on the method of preparing II.

One convenient method of synthesizing aryl nitriles, and II in particular, is the reaction of diazonium salts with solutions of Cu cyanide in the presence of an excess of alkali metal cyanides, in accordance with the Sandmeyer reaction.

Although the reaction for preparing II from p-aminobenzoic acid (III) has been well studied [9-10], in developing an industrial method of preparing II, we tried to exclude the difficulties associated with the use of highly toxic alkali metal cyanides, and also with the complexity of the isolation of II from the reaction mixture in a pure form.

In order to prepare the solution of Cu cyanide we used acetone cyanohydrin, which has previously been successfully used as a substitute for alkali metal cyanides [11]. This method as also the classical method, requires the use of a monovalent copper salt, which complicates the preparation of cyanide derivatives by the Sandmeyer reaction in high yields.

We suggested that it might be possible to prepare a solution of a complex salt without previously preparing a monovalent copper salt by the reducing action of acetone cyanohydrin in alkali medium. In fact, with gradual addition of 4 mole of alkali to an aqueous solution of 1 mole of $CuSO_4$ and 4 mole of acetone cyanohydrin, a clear solution of light yellow color is obtained, which is stable on storage.

Accordingly, in contrast to the known reaction [12],

$$2Cu^{+2} + 10CN^- = 2\,[Cu\,(CN)_4]^{-3} + (CN)_2,$$

a complex can easily be prepared by the method which we developed, using acetone cyanohydrin and $CuSO_4$ [13] as the starting materials. This has the great advantage that toxic dicyanogen is not evolved. The method can be applied to the synthesis of any aryl nitriles by the Sandmeyer reaction.

In the Sandmeyer reaction, 1 mole of diazonium salt is generally taken per 1 mole of complex copper salt.

As a result of these experiments it was shown that in preparing II a decrease in the quantity of copper complex to 0.5 mole per mole of diazonium salt does not lead to a decrease in the yield of aryl nitrile.

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The reaction with the ethyl ester of p-aminobenzoic acid (Anesthesin, IV) was carried out under similar conditions, but in this case the yield of the ethyl ester of p-cyanobenzoic acid (V) was 68% as against 23.6% with the classical method [14].

We have significantly simplified the method of isolating the final products. Thus, II can be conveniently isolated by salting out from the reaction mixture in the form of an intermediate complex with Cu cyanide, which is then decomposed by heating in water. Also, a more convenient method of isolating V is steam distillation of the latter directly from the reaction mixture after the reaction has finished.

The main difficulty in preparing I from II is the necessity of careful and painstaking purification of the final product from the heavy metals copper and nickel. This leads to greater complication in the technique used, i.e., the necessity of using ion-exchange resins, with a corresponding drop in yield.

In order to avoid these disadvantages, to simplify the method, and to make use of more easily accessible and cheaper raw materials we developed a method of preparing I from V, which consisted in hydrogenating the latter under mild conditions (1-5 atm, 40-50°) with Raney Ni catalyst in an aqueous alcohol solution of ammonia, and subsequent saponification without isolating the intermediate product, i.e., the ethyl ester of p-aminomethylbenzoic acid (VI), to give a valuable product [15]. Commercial I, which already had a purity of 98-99%, was additionally purified by dissolving in aqueous ammonia and vacuum distillation to small volume. The yield of the very pure I (without using special purification methods) was about 80%.

Accordingly, the preparation of I from V as starting material, compared with its preparation from II, involves very little complication of the production process. The advantage of the method as a whole is the ready availability of the raw material (Anesthesin) and the easy availability, simplicity of preparation, and safety of the complex salt of Cu cyanide which is used, and the ease of isolating the intermediate ester V in the pure form compared with the free acid II, and also the possibility of preparing the hydrochloride of VI by this method.

EXPERIMENTAL

Preparation of a Complex Salt of Cu Cyanide

Crystalline copper sulfate (20 g) was dissolved in 170 ml of water, and 30 ml of acetone cyanohydrin was added. A solution of 12.8 g of NaOH in 43 ml of water was then added over 30 min with rapid stirring. After the alkali had been added, the reaction mixture became clear, the solution having a light-yellow color.

p-Cyanobenzoic Acid (II)

A 20 g quantity of III was dissolved in 95 ml of water, containing 5.7 g of NaOH and 10.1 g of $NaNO_2$. The solution obtained was added at -3 to $+2°$ to a solution of 32 ml of concentrated HCl in 105 ml of water. The reaction mixture was held at 0° for 30 min, after which it was carefully neutralized with an aqueous solution of NaOH to pH 7.0. The cold solution of diazonium salt obtained was slowly added over 5 min with rapid stirring to the solution of complex (prepared as described above). When nitrogen evolution had ceased, 120 g of NaCl was added to the reaction mixture, and after the salt had dissolved the reaction mixture was held for 3-4 h at 0-5°. The crystalline residue deposited was separated and dissolved in 0.5 liter of water. The solution was heated to boiling, 1-2 g of activatd carbon were added, and the solution was filtered. The clear, colorless solution obtained was cooled and acidified with concentrated HCl to pH 3.0. The white residue deposited was filtered off, washed with water, and dried at 70°, to give 13.2 g (62%), of II, mp 218-219°, as against the published value [4] of 219°.

Ethyl Ester of p-Cyanobenzoic Acid (V)

Compound IV (40 g) was suspended in a mixture of 65 ml of concentracted HCl and 250 ml of water, and the mixture was cooled to 4-7°, after which a solution of 16.8 g of $NaNO_2$ in 70 ml of water was added dropwise with rapid stirring so that the temperature of the reaction mixture never exceeded 8°. The solution of diazonium salt obtained was held for 30 min at 0-5°, and was then carefully neutralized with an aqueous solution of NaOH to pH 5.0-6.0. This was then added fairly rapidly, i.e., over 5 min, with rapid stirring to a solution of copper complex previously heated to 45-50°, the solution of copper complex being obtained from 30.2 g of crystalline copper sulfate, 45 ml of acetone cyanohydrin 7.5 g of NaOH, and 330 ml of water. The reaction product was isolated as a dark oil. When nitrogen evolution had ceased the reaction product was steam distilled from the reaction mass, until the condensate was clear. The

crystalline white residue deposited from the condensate was filtered off and dried in air to give 29 g (68%) of V, mp 51-52°. After recrystallization from petrol ether (bp 40-45°) this gave a product of mp 54°, as against a published value [16] of 54°.

p-Aminomethylbenzoic Acid (I).

A solution of 140 g of V in a mixture of 700 ml of ethanol and 350 ml of concentrated aqueous ammonia was loaded into a 2-liter autoclave, 10 g of Raney Ni catalyst were added, and the mixture was hydrogenated at 40-50° and 1-5 atm pressure. After 30 min, hydrogenation had almost ceased, and after 1 h the catalyst was separated off. Sodium hydroxide (70 g in 250 ml of water) was added to the solution obtained, and this solution was evaporated to 0.5 liter under normal pressure. The residue obtained was filtered off, and the solution was decolorized with activated carbon, after which 200 ml of dilute HCl (1 : 1) was slowly added with rapid stirring to pH 7.5-8.0. The reaction mixture was cooled to 10-15° and held at this temperature for 2-3 h. The crystalline residue obtained was filtered off, and dissolved in 150 ml of concentrated aqueous ammonia and 800 ml of water. The ammonia solution was also decolorized with activated carbon and then filtered and evaporated down to 250 ml, after which the residue was filtered off and dried in air to give 107 g of pure I, mp 347-352°, as against a published value [8] of 350°, i.e., a yield of 81% based on the anhydrous product.

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