PREPARATION OF 3,5-DINITROBENZOIC ACID FROM meta-NITROBENZOIC ACID

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3,5-Dinitrobenzoic acid (3,5-DNBA) is the starting material for the synthesis of the x-ray contrast preparation "triombrast" and a series of other x-ray contrast reagents.

The two methods known for obtaining 3,5-DNBA are by the oxidation of 3,5-dinitrotoluene [7] and 1,5-dinitronaphthalene [2], and by the nitration of benzoic or meta-nitrobenzoic acids [1, 4, 5, 8]. The disadvantages of these methods of obtaining 3,5-DNBA are related to the inordinately high proportion of acid (20-60 parts by weight), the low yield (6-50%), and the presence of major impurities, including isomers of dinitrobenzoic acid, mononitrobenzoic acid, and products from the partial oxidation of these substances, tetranitromethane, etc. Moreover, the duration of the syntheses indicated was at times very long (up to 72 h).

From an examination of information in the literature, together with the demand for 3,5-DNBA, it can be concluded that, at present, the production of this acid would be carried out most expediently on the basis of nitration of benzoic acid by sulfuric/nitric acid mixtures, however simple from the point of view of practical implementation.

Previously, it was shown [3] that the first stage of nitration of benzoic acid to mononitrobenzoic acid in a medium of concentrated nitric acid combined with sulfuric acid proceeds sufficiently quickly, ending with the formation of o-, m-, and p-isomers in the ratio 16:82:2 in quantitative yield. In the course of subsequent nitration the ortho- and para-isomers were completely oxidized.

We studied the nitration of meta-nitrobenzoic acid to 3,5-DNBA, varying the basic parameters of the process on which the rate was dependent: the concentration of sulfuric acid, the temperature of nitration, the excess of nitric acid, and the equivalence, defined as the weight ratio, of the acid mixture to the nitrated compound. The stage of conversion of m-NBA to 3,5-DNBA was defined by the melting point of the nitro-product, corresponding to the fusibility diagram of the system m-NBA–3,5-DNBA (Fig. 1).

Secondary reaction during the nitration of deactivated aromatic carbons usually leads to the destruction of the substrate molecule and the formation of low-molecular-weight compounds, which are volatile. Therefore, the precipitated, solid products separated from the reaction during the course of the process should represent a dual mixture of nitrated substrate and nitro-product. This kind of reaction scheme is realized during the nitration of m-NBA, confirmed by us through analysis of the nitro-product using thin-layer chromatography, and permits, in this instance, the composition to be determined using the phase diagram of the system m-NBA–3,5-DNBA (see Fig. 1).

As a preliminary, we established that, parallel with the main nitration reaction, there is also oxidative degradation of the m-NBA, the latter reaction accounting for about 30%. Notably, this situation gives rise to increased consumption of nitric acid in the given process – 1.5 parts to 1 part by weight of m-NBA (Fig. 2), or 4 moles nitric acid to 1 mole m-

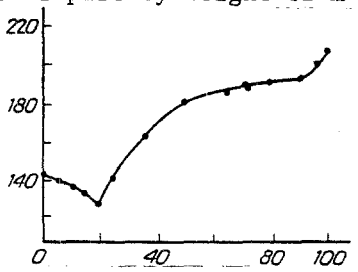

Fig. 1. Fusibility diagram of the system m-NBA–3,5-DNBA: x-axis) proportion of 3,5-DNBA in the mixture (in %); y-axis) temperature (in °C).

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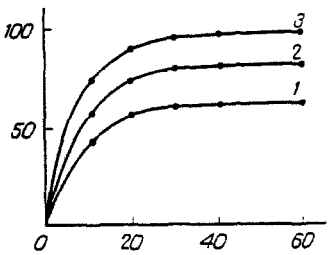

Fig. 2

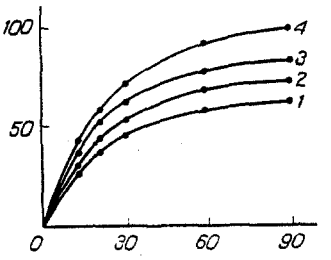

Fig. 3

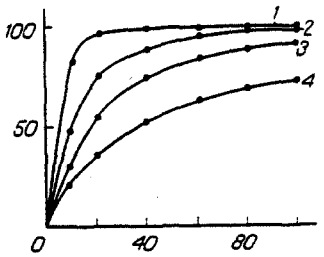

Fig. 4

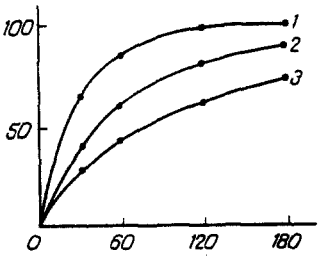

Fig. 5

Fig. 2. Rate of conversion of m-NBA in nitrating mixtures with variable concentration of nitric acid. Temperature 95°C, equivalence 10, initial concentration of sulfuric acid 104.5%. Concentration of nitric acid and ratio by weight of nitric acid/ m-NBA: 1) 5% and 0.5:1; 2) 10% and 1:1; 3) 15% and 1.5:1. Here and in Figs. 3-5: on x-axis, time (min); on y-axis, concentration of m-NBA (%).

Fig. 3. Rate of conversion of m-NBA in nitration mixture at 95°C. Initial concentration of sulfuric acid and equivalence: 1) 93.5% and 11; 2) 100% and 11; 3) 93.5% and 22; 4) 100% and 22.

Fig. 4. Effect of equivalence on rate of nitration of m-NBA. Temperature 95°C, initial concentration of sulfuric acid 104.4%, weight ratio of nitric acid/m-NBA 1.5:1. Equivalence value: 1) 22; 2) 11; 3) 8; 4) 6.6.

Fig. 5. Effect of temperature or rate of nitration of m-NBA. Equivalence 10, initial concentration of sulfuric acid 104.5%, weight ratio of nitric acid/m-NBA 1.5:1. Nitration temperature: 1) 95°C; 2) 85°C; 3) 75°C.

NBA, corresponding to the value calculated from the data of [6]. Strong oxidation processes are usually accompanied by the formation of significant amounts of water and nitrogen oxides, leading to a dilution of the sulfuric acid and a reduction in nitrating activity of the system. This dilution has such a significant effect on mixtures of low concentration that complete conversion of the m-NBA is not even achieved by using a significant excess of nitrating mixture containing the necessary quantity of nitric acid (Fig. 3, curves 1, 3).

The results obtained, taking into account economic considerations and raw material resources, show that nitrating mixtures based on 20% fuming sulfuric acid (104.5% sulfuric acid) are the only acceptable ones for the industrial production of 3,5-DNBA. The minimal consumption of such mixtures was verified in special experiments on the nitration of m-NBA (Fig. 4).

The influence of temperature on the rate of nitration of m-NBA is shown in Fig. 5.

The optimum conditions for nitration of m-NBA ensuring not less than 98% conversion according to the results of laboratory experiments are the following: consumption of nitrating mixture of composition 15% nitric acid and 85% 20% fuming sulfuric acid 8 parts to 1 part by weight of m-NBA; temperature of nitration 95°C; duration of nitration 1.5 h. In this case the yield of 3,5-DNBA is 72-73%.

EXPERIMENTAL

A preweighed amount of nitrating mixture of known composition was stirred in a thermostatted glass nitration vessel, capacity 150 ml. At the predetermined temperature, and with vigorous stirring, a weighed quantity of m-NBA was added over a period of 1-3 min. Samples were removed at intervals of 5-10 min. The sample was added to 2 volumes of water and cooled to 10-15°C. The precipitated product was filtered, washed with water until the pH was not less than 6.0, and was dried at 90°C to a constant weight. The composition of the nitration product was determined from its melting point corresponding to the fusibility diagram of the system m-NBA–3,5-DNBA (see Fig. 1). The diagram was constructed using temperatures of crystallization of mixtures of predetermined composition measured using a DSM-2M calorimeter (USSR).

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SYNTHESIS OF N-ACETYL-ε-AMINOCAPROIC ACID

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An effective stimulator of wound healing and bone knitting, N-acetyl-ε-aminocaproic acid (AACA) can be produced by acetylation of ε-caprolactam (CL), followed by hydrolysis of N-acetyl-ε-caprolactam (ACL) or by hydrolysis of CL to ε-aminocaproic acid (ACA) or its salt and acetylation of the reaction product.

Along the first line we studied and developed a technology for the production of AACA with a yield of 45-47% of the theoretical [1, 2].

We were interested in developing a technology for AACA production such as to significantly increase the yield of the product. We used the insufficiently studied second approach to the process. The main attention was paid to the acetylation of ACA, since the hydrolysis of CL has been described in sufficiently great detail [3]. To exclude losses associated with isolation of the intermediate product, we developed a method of acetylation of ACA directly in the reaction mass after hydrolysis of CL, which is based on the substantially more pronounced nucleophilic properties of amines in comparison with the properties of water in interaction with Ac_2O. A combination of conditions of conducting the hydrolysis of CL, acetylation of ACA, and isolation of AACA that were permitted realized a rechnologically one-step method of production of AACA, corresponding to the requirements of All-Union Pharmaceutical Standard 42-837-79, with a yield of 85%, on one apparatus.

EXPERIMENTAL

A mixture of 56.5 g (0.5 mole) CL, 40 g (1 mole) NaOH, and 100 ml of water was heated with mixing to 105-111°C and exposed at this temperature for 1 h. The solution was cooled to room temperature, and 52 ml (0.53 mole) of 95% Ac_2O was gradually added with mixing at a rate such that the temperature did not rise above 40°C; the reaction mass was exposed at 55-60°C for 1 h, cooled to 20-25°C, and acidified with 65 ml of 33.8% HCl (0.7 mole). The prod-

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