THE PROBLEM OF IMPROVING THE QUALITY OF PHENACETIN

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Phenacetin (p-acetylaminoethoxybenzene) is widely used as a sedative and an antiphlogistic medium.

Impurities of small amounts of chlorine-containing products are tolerated in phenacetin: thus, 0.05% according to GFIKh, 0.03% according to GFKh, and 0.02% according to the 1965 British pharmacopoeia, recalculated to chlorine; recalculated to p-chloroacetanilide [1] these indices are 4.8 times higher.

Of the various methods of preparing phenacetin (IV), the most economic method used is starting with p-nitrochlorobenzene (I) by the following scheme (I-IV) [2, 3]:



The presence of chlorine-containing products in phenacetin is due to unreacted p-nitrochlorobenzene (I) (up to 5%), which upon reduction of p-nitrophenetole (II) to p-phenetidine (III) is simultaneously converted to p-chloroaniline (VI) and is then acetylated to p-chloroacetanilide (VII), which is similar to (IV) in its properties. We have developed a variation of the synthesis of phenacetin, in which the amount of chlorine-containing impurities in the final product does not exceed acceptable norms.

For this, (I) which remains unreacted during ethoxylation is removed from the reaction medium by conversion to p,p'-dichloroazoxybenzene(V). It is known that the reaction of (I) with alcoholic base in the presence of manganese dioxide at 85-115°C leads to formation of (V) together with p-nitrophenetole [4]. The same compounds are also formed upon reaction of an alcoholic solution of potassium hydroxide and p-nitrochlorobenzene without a catalyst in the course of a lengthy (140-170 h) heating at 60° [5, 6].

We have established that upon reaction of an alcoholic solution of sodium hydroxide and (I) without a catalyst at the boiling temperature of the alcohol, (I) is virtually completely transformed into (V). It was also established that samples of (II), containing an impurity of (I), after treatment in this way contained chlorine-containing compounds only in the form of (V). Analagous results were obtained upon working with wet samples of (II), isolated from the reaction mixture with water. At the same time, the following were also established. To successfully carry out the process, the moisture in the product must not exceed 15% and the base concentration must not be less than 30 g/liter. Experiments in which the reaction mixture was separated from the catalyst after ethoxylation, sodium hydroxide was added to a concentration of 30 g/liter, the mixture was heated at 78-80° for $1-1^{1}/_{2}$ h, and then treated by the known method, were carried out with positive results.

It was also necessary to clarify what chemical transformation (V) can undergo in the step of reduction of (II) to (III). Upon reduction in basic media azoxy compounds can form azo compounds and primary

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amines [7]. It was found that upon boiling a mixture of (II) and (V) with a 22-25% solution of sodium sulfite, (V) is completely reduced to p,p'-dichloroazobenzene, and upon distillation of (III) p,p'-dichloroazobenzene remains in the flask residue.

Samples of p-nitrophenetole (II) obtained by the described method were converted into phenacetin (IV) by the usual method. The chlorine content in (IV) did not exceed 0.02% and in a series of cases was completely undetected. The work was controlled by analysis by thin layer chromatograph*.

EXPERIMENTAL

<u>p-Nitrophenetole (II).</u> A. To 178 ml of ethyl alcohol at a temperature not exceeding 30° was gradually added 16.15 g of sodium hydroxide. After solution the content of base in the alcoholic solution should be 8-9 vol.%. To the solution were added 5.05 g of manganese dioxide and, at a temperature not exceeding 35°,55 g of p-nitrochlorobenzene. The reaction mixture was heated over 3 h to boiling, refluxed with stirring for 17 h, filtered free from catalyst, and the precipitate was washed with 30 ml of hot ethyl alcohol. To the solution was added an amount of sodium hydroxide such that its content amounted to 30 g/liter. The mixture was boiled for 2 h, diluted to 500 ml with water, and cooled to 20-25°; the precipitate was filtered and washed with water. The precipitate was dried at 40°. We obtained 51-52 g (87-89%) of (II) having mp 56-60° (in the range of 1-2°), which contained chlorine only in the form of p,p'-dichloroazoxybenzene.

B. We dissolved 45 g of sodium hydroxide with stirring in 1500 ml of ethyl alcohol and added 750 g of dry[†] p-nitrophenetole (technical sample having a chlorine content of 1.4%, mainly in the form of p-nitro-chlorobenzene). The mixture was heated to boiling and refluxed for 1 h, poured into 3300 ml of water, and cooled to $20-25^{\circ}$; the precipitate was filtered and washed with water. We obtained 723 g of (II) having mp $56-58^{\circ}$. Yield 96.5% based on p-nitrophenetole or 88.5% based on starting p-nitrochlorobenzene.

The obtained p-nitrophenetole (II) was converted to phenacetin (IV) by the known method. The chlorine content in phenacetin was 0.005-0.01% (analysis was carried out according to the British pharmacopoeia and chromatographically in a thin layer).

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^{*} Developed by A. A. Chemerisskii and M. R. Bagreev (All-Union Scientific Research Pharmaceutical Chemistry Institute).

[†] Wet p-nitrophenetole can be used (not more than 12% moisture), in which case the concentration of base should be 50 g/liter.