SYNTHESIS OF 1-METHYLPIPERAZINE

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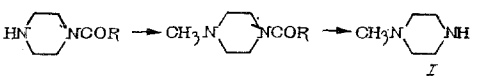
1-Methylpiperazine (I) is a structural component of a number of medicinal preparations (ditrazine, azafen, metrazin, and others) and is a starting material for their synthesis. Consequently, the development of a method for preparing (I) suitable for industrial use appeared of considerable interest.

Of the methods of synthesizing (I) described in the literature [1-8], the most convenient is that which consists in the methylation of monoacyl derivatives of piperazine with the subsequent elimination of the protective group by hydrolysis.



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Protective groups that have been used are the acetyl [4], methoxycarbonyl [5], ethoxycarbonyl [4, 5], butoxycarbonyl [5], and formyl [6] groups.

However, the preparation of these monoacyl derivatives of piperazine in the pure state is associated with difficulties since their synthesis is always accompanied by the formation of 1,4-diacylpiperazines which, just like the monoacyl derivatives, are readily soluble in water and organic solvents.

We have used the method of synthesis shown above to obtain (I), but as the initial monoacylpiperazine we selected 1-benzoylpiperazine (II) [9]. Our selection of this compound was based on the fact that it is easy to separate from the 1,4-dibenzoylpiperazine (III) formed simultaneously because of their different solubilities in water: (II) mixes with water in all proportions, while (III) has a limited solubility (0.53 g/liter at 25°C). Compound (II) was obtained by the benzoylation of piperazine with benzoyl chlorine in aqueous acetone solution with the addition of caustic soda. When benzoylation was performed in the presence of the potassium salt of benzylanilinezobenzene-4-sulfonic acid (pH range of the change of color of the indicator 1.9-3.3), the yield of (II) was about 40% [10], while when the reaction was performed in the presence of Bromocresol Green (pH range of the change of color 3.8-5.4), the yield of (II) was about 76% [11]. The difference in yields permitted the conclusion that the yield of (II) depends on the pH of the reaction medium. Experiments that we performed with the pH-metric control of the benzoylation reaction showed that the maximum yield of (II) is obtained at pH 4.5-5.0 (see Fig. 1).

For this reason it appeared desirable to perform the benzoylation process with the continuous automatic monitoring of the pH. For this purpose we used a pH meter – a type PVU-01 millivoltmeter – coupled to an ÉPP-09 automatic potentiometer and an immersion sensor with glass and silver chloride electrodes.

In actual fact, the continuous monitoring of the pH in the benzoylation of piperazine enabled stable yields of (I) of the order of 75% to be obtained; the yields of (III) were between 15 and 19%. No "poisoning" of electrodes was observed. The accuracy of the measurements on the 0-14 pH scale was ± 0.2 pH units.

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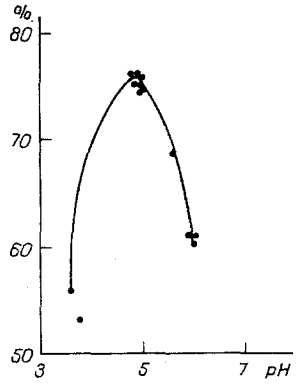


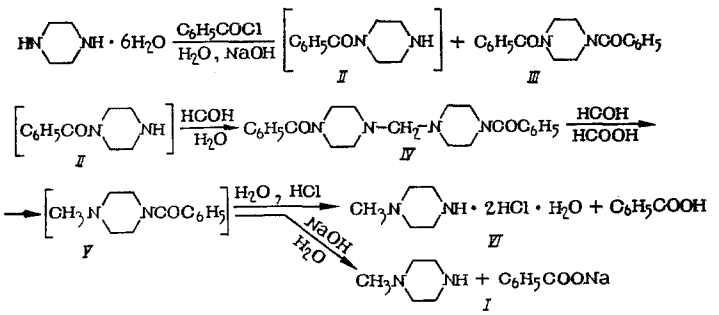
Fig. 1. Yield (in %) of 1-benzoylpiperazine (II) as a function of the pH of the reaction medium.

According to literature procedures [10, 11], after separation from the (III) the (II) was extracted from an alkaline aqueous solution by repeated treatment with chloroform, and then the solvent was distilled off. We have found that the use of chloroform or of methylene chloride for the extraction of (II) is undesirable, since in the heating and distillation process the (II) partially reacts with these solvents with the formation of its hydrochloride.

The use of benzene or ethyl acetate for extraction proved undesirable because of the low partition coefficient of (II) in these solvents in relation to water.

Consequently, to isolate (II) from aqueous solution we developed a method of precipitating the (II) in the form of the sparingly water-soluble 4,4'-methylenebis(1-benzoylpiperazine) (IV), which can be used directly for the preparation of (I) without the isolation of the (II) in the individual state. To obtain (IV), formalin at the rate of 1 mole of formaldehyde per 2 moles of (II) was added at pH 10.0-10.2 to the mother solution after the (III) had been filtered off [12]. To obtain crystalline, well-filtered (IV) it was necessary to add the formalin gradually at a temperature of 30-50°C. The yield of (IV) amounted to 75% of theoretical, calculated on piperazine hexahydrate.

To prepare (I), the methylene derivative of (IV) was boiled with formalin and formic acid until the evolution of carbon dioxide ceased. The water with the excess of formaldehyde and formic acid was distilled off from the reaction mixture (to avoid the formation of 1,4-dimethylpiperazine on acid hydrolysis). The still residue, consisting of 1-benzoyl-4-methylpiperazine formate (V), was either subjected to hydrolysis by being boiled with 20% hydrochloric acid [13] or was first converted into the free base (V), which was then hydrolyzed by being heated with 33-35% caustic soda solution:



The benzoic acid formed on acid hydrolysis was separated by filtration, the filtrate was evaporated, and 1-methylpiperazine dihydrochloride containing a molecule of water of crystallization (VI) was isolated from the residue.

The yield of (VI) amounted to 90% of theoretical calculated on the (IV) or 67.5 calculated on the piperazine hexahydrate.

For the production of some drugs, such as ditrazine, it is unnecessary to isolate the crystalline dihydrochloride: a 60% aqueous solution of the dihydrochloride can be used.

On hydrolysis in an alkaline medium, the (I) was distilled off in vacuum together with the water and was obtained in the form of a 24-25% aqueous solution. The yield of (I) (as 100% material) amounted to 80% calculated on the (IV), or 60% calculated on the piperazine hexahydrate. In order to obtain a purer material from the aqueous solution of (I), solid caustic soda was added to its aqueous solution and the organic layer was separated off and distilled, giving (I) with a purity of 88-90%. To obtain a still purer product, the operations of salting-out and distillation were repeated. The losses in the purification of the (I) amounted to about 15%.

Piperazine can be regenerated from the (III) obtained as a byproduct in the benzoylation of piperazine. For this purpose, the (III) was subjected to hydrolysis with hydrochloric acid, the benzoic acid was separated off, the aqueous mother solution was evaporated, the residue was made alkaline, and aqueous piperazine was distilled off and returned to the first stage.

EXPERIMENTAL

4,4'-Methylenebis(1-benzoylpiperazine) (IV). An apparatus with a stirrer, thermometer, two dropping funnels, and electrodes for pH measurements was charged with 550 ml of water, 300 ml of acetone, 97 g of piperazine hexahydrate, and hydrochloric acid to pH 4.5-5.0. One dropping funnel contained 77 g of benzoyl chloride and the other contained 64 ml of a 44% solution of caustic soda. With stirring, the benzoyl chloride and the caustic soda were added simultaneously from the dropping funnels, the rates of addition being adjusted so that the pH of the reaction mixture was between 4.5 and 4.8 and the time of addition was $3\frac{1}{2}$-4 h. A precipitate of (II) began to form about an hour after the beginning of the reaction. After the end of the reaction, caustic soda was added to pH 6.5-7.0 and a mixture of acetone and water was distilled off. The residue was cooled to 15-20°C and made alkaline (pH 10.0-10.2). The precipitate was filtered off, washed with water, and dried, giving 15 g of (III). The filtrate was heated to 40°C and, with stirring, 15 ml of 37% formalin was added in 2.5-ml portions every 10 min. The mixture was kept for 30 min, cooled to 5-10°C, and stirred for 2 h. The precipitate was filtered off, washed with water, and dried, to give 73.5 g of (IV). The yield amounted to 75% of theoretical, calculated on the piperazine hexahydrate. The compound obtained consisted of a colorless crystalline substance with mp 131-132°C, sparingly soluble in water, moderately in ethanol and acetone, and readily in chloroform and methanol. Under the action of mineral acids it decomposes into formaldehyde and the corresponding salt of 1-benzoylpiperazine. Found, %: C 70.32; H 7.20; N 14.25; $C_{23}H_{28}N_4O_2$. Calculated, %: C 70.37; H 7.19; N 14.20.

1-Benzoyl-4-methylpiperazine (V). A flask with a stirrer, reflux condenser, thermometer, and dropping funnel was charged with 66 g of (IV) and 20 ml of 37% formalin. The mixture was heated to 80°C, and 33 ml of 86% formic acid was added over 1 h. The vigorous evolution of carbon dioxide took place. The reaction mixture was boiled for 4 h, and the excess of formalin and formic acid was distilled off under vacuum. The still residue, which consisted of the formate of (V), was used for the production of (I).

Where necessary, the (V) can be isolated from the still residue by making it alkaline, extracting with benzene, evaporating off the solvent, and distilling the residue in vacuum. Compound (V) consists of a viscous yellow oil with bp 147-150°C (2 mm), soluble in water and organic solvents. It is salted out from aqueous solutions by caustic alkalies. According to the literature, bp 114-122°C (0.04 mm) [14].

1-Methylpiperazine (I). A. Hydrolysis of (V) in an acid medium. The formate of (V), obtained in the preceding stage, was treated with 155 ml of 20% hydrochloric acid. The resulting solution was boiled for 3 h and was then cooled, and the benzoic acid was filtered off. The filtrate was treated with activated carbon. The water was distilled off in vacuum from the clarified solution, and the residue was treated with 150 ml of ethanol. The precipitate was filtered off, washed with ethanol, and dried at 50-60°C. This gave 58 g of (VI), mp 80-82°C. The yield was 90% of theoretical, calculated on the (IV). According to the literature, mp 82.5-83°C [5].

B. Hydrolysis of (V) in an alkaline medium. At a temperature not exceeding 40°C, the reaction mixture obtained by the methylation of 6 g of (IV) (without the elimination of the formalin and formic acid by distillation) was gradually added to 24 ml of a 42% aqueous solution of caustic soda. After cooling to 20°C, the upper layer, consisting of the technical base (V) (about 90 g), was separated off and was treated with 55 ml of the 42% solution of caustic soda and 20 ml of water. The resulting emulsion was boiled for 3 h with vigorous stirring. As hydrolysis proceeded, the temperature of the reaction mixture fell from 112 to 106°C. Reduced pressure was applied, and aqueous (I) was distilled off, with a gradual rise of the temperature in the reaction flask and a lowering of the residual pressure from 550 to 200 mm Hg. This gave 108 ml of a solution containing 26.9 g of (I). The yield of (I) as 100% material amounted to 80% of theoretical calculated on the (IV). To obtain high-purity (I), the solution obtained was treated with 50 g of solid caustic soda, the mixture was slowly stirred for 15 min (to avoid the formation of a stable emulsion), and the layers were separated. The organic layer was distilled, a fraction boiling between 105 and 136°C being collected. This amounted to 22-23 g of 88-90% (I). Where it was necessary to obtain absolute (I), the drying with solid caustic soda was repeated, and the (I) was redistilled, the 133-136°C fraction being collected. According to the literature, bp 135-137°C [2].

Regeneration of Piperazine from (III). A mixture of 29.4 g of (III) and 65 ml of 20% hydrochloric acid was boiled with stirring for 5 h. After cooling, the benzoic acid was filtered off. The filtrate was neutralized to pH 6.5-7.0 and the water was distilled off in vacuum. The residue was treated with 18 ml of a 42-44% solution of caustic soda and aqueous pyrazine was distilled off, the 105-125°C fraction being collected. This gave 19 g of a product containing about 94% of piperazine hexahydrate. The yield of regenerated piperazine hexahydrate amounted to 92% of theoretical, calculated on the (III).

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