SYNTHESIS OF AMIDOPYRINE AND ANALGIN FROM METHYLENBISMONOMETHYLAMINOANTIPYRINE

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1-Phenyl-2,3-dimethyl-4-dimethylaminopyrazolone-5 (I) (pyramidone, amidopyrine) and 1-phenyl-2, 3-dimethyl-4-methylaminopyrazolone-5-N-methylsulfate sodium – monohydrate (II) (analgin) are valuable drugs. They are close in chemical structure; the scheme of production of these substances is the same up to the next to last steps:



In the industrial production of II from monomethylaminoantipyrine (III), at the next to last step a large amount of a waste product is obtained – an aqueous solution of mineral salts, containing the valuable intermediate product III in amounts of 4-6 g/ liter. However, thus far, no method has been found for utilizing this waste product. In view of the low concentration of III in the waste product, it cannot be converted to I or II by the usual methods without isolation from solution. The utilization of this waste product, however, would be extremely expedient, since with the existing multi-ton productions, this could give an additional several tons of I or II per year.

We have found that it is most convenient to isolate III from dilute aqueous solutions in the form of its sparingly soluble condensation product with formaldehyde – methylenbismonomethylaminoantipyrine (IV) [1, 2]:



Optimum conditions under which IV is isolated almost quantitatively with a yield of 92-95% on the basis of III were selected. IV is isolated most completely and with a smaller amount of contamination, including mineral salts, from dilute solutions containing only 3-6 g/ liter III, using formaldehyde in amounts of 2-3 moles/ mole of the initial substance, at pH 6.0-7.0 and a temperature of $40-50^\circ$. Depending upon the quality of the waste product, IV with mp in the range $163-174^\circ$ (within 2°) is obtained.

Methods of producing I from aminoantipyrine, its sulfate, sulfoaminoantipyrine, and formylaminoantipyrine are known. We have developed a method of producing I by heating IV with a mixture of formic acid and formaldehyde in water.

Amidopyrine is obtained in high yield (79-85%) and good quality. The melting point of the technical product is 103-106°; after two recrystallizations from ethanol or isopropanol, I melts at 108-109° and satisfies the requirements of the State Pharmacopeia of the USSR.

S. Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific Research Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 9, pp. 24-26, September, 1968. Original article submitted March 4, 1968. In industry II is produced by the reaction of III with a formaldehydebisulfite compound in aqueous or alcohol medium. According to the literature data [2,3], II can be produced from IV by the action of bisulfite or a mixture of formaldehyde with bisulfite; however, there is no detailed description of the method, and the yield of II is not indicated.

We established that the conditions used in industry can be used entirely for the production of II from IV; II is obtained in this case in a yield of 80-85% of the theoretical (calculated on the basis of IV), satisfying the requirements of the pharmacopoeia.

EXPERIMENTAL

<u>Methylenbismonomethylaminoantipyrine (IV).</u> A 900-g portion of a 37% aqueous solution of formaldehyde was added at $45-50^{\circ}$ to 480 liters of waste products from the production of analgin – an aqueous solution of mineral salts, possessing pH 6.3 and containing monomethylaminoantipyrine (III) in a concentration of 4.4 g/ liter, or 2.11 kg in the entire volume, and the reaction mixture was mixed at the indicated temperature for 30 min. Then it was cooled to 40°, the crystalline precipitate formed was filtered off, washed with water, and dried. We obtained 2 kg of the dry product with mp 163-165°, yield on the basis of III 92% (IV was produced under industrial conditions).

<u>Amidopyrine (1)</u>. To 1.5 liters of water we added 223 g (0.5 mole) IV with mp 163-165° and 135 g 85% formic acid (115°, calculated on the basis of 100%, or 2.5 moles); the mixture was heated to boiling, and 63.5 g of a 36% aqueous solution of formaldehyde (22 g of a 100% solution, or 0.75 mole) was gradually added ed to it over a period of 1 h 45 min. Then the reaction mixture was boiled with mixing for 11 h, activated charcoal added, mixed for 30 min, and filtered. To the filtrate we gradually added 110 g of calcined soda at 60-65° to pH 6.3; then the mass was heated to 85° (until melting of the precipitated 1), mixed thoroughly, the pH of the mother liquor verified, and the mass cooled to 25°. The I that precipitated in the form of granules was filtered off, washed with water, and dried. Yield 113 g of the technical product with mp 105-106°. I was extracted from the mother liquor with an organic solvent (benzene, dichloroethane, chlorobenzene), the solvent distilled off (benzene) or I extracted from it (chorobenzene, dichloroethane) with dilute sulfuric acid, followed by neutralization of the sulfuric acid solution with calcined soda to pH 6.3. An additional 47 g of the dry product with mp 103-105° was obtained. The total yield of I was equal to 160 g (79% on the basis of IV). The technical product was recrystallized twice from isopropanol (0.25 ml alcohol per g of the substance). Yield 125 g of pure I with mp 108-109°. The yield comprises (without considering the alcohol mother liquors) 78% of that taken for purification or 61% on the basis of technical IV.

Analgin (II). A. To a suspension of 24.5 g technical IV with mp 172-174° in 25 ml of 80% isopropannol we added 14.3 g dry formaldehyde-bisulfite compound. The mixture was heated with mixing at 65-70° for 2 h. Then it was cooled to 10-15°, the precipitate filtered off, washed twice with 90% isopropanol, recrystallized from 80% isopropanol, washed twice with 90% isopropanol, and dried. Since considerable II is carried off in the alcohol mother liquors, to increase the yield the production of II is repeated four times more with the same amount of starting materials, but using the alcohol mother liquors instead of pure alcohol in the reaction and in the crystallization of II, respectively. From five experiments, 160.4 g of pharmacopic II is obtained, comprising 83.2% of the theoretical yield on the basis of IV (without considering the mother liquors from the last experiment).

B. To 21.2 g of IV with mp $171-172.5^{\circ}$, we added 26.4 g of a 50% aqueous solution of the formaldehyde-bisulfite compound (13.2 g of 100% solution) and heated the mixture at 60-65° with mixing for 2 h. Then water was distilled off from the reaction solution under vacuum to dryness (while heating on a water bath). We obtained 29 g of dry technical II. The product was recrystallized from 58 ml of 80% isopropanol, washed twice with 90% isopropanol, and dried. We obtained 21.3 g of pure II, satisfying the requirements of the pharmacopoeia. The yield comprises 63% of the theoretical on the basis of IV. Evaporation of the alcohol mother liquor yielded an additional 7 g (converted to 100% according to analysis) of the technical product. Total yield 82.3% of the theoretical on the basis of IV.

In industry, the aqueous reaction solutions of II are not evaporated, but the pure product is isolated from them by additing sodium chloride. In such isolation of II, to judge the yield it is necessary to use the salt mother liquors in a series of successive experiments. In addition, it is difficult to filter hot solutions of II, saturated with sodium chloride, under laboratory conditions. Therefore, to determine the quality and yield of II obtained from IV in aqueous medium we used different conditions of isolation and purification of II, more accessible in laboratory experiments, analogous to the conditions used when the reaction was conducted in alcohol medium.

CONCLUSIONS

Methods of producing amidopyrine and analgin from methylenbismonomethylaminoantipyrine, isolated from industrial waste products, were developed in order to increase the industrial yields.

LITERATURE CITED

- 1. German Patent No. 421505.
- 2. M. Bockmuhe et al., Zbl. Chem., <u>1</u>, 1367 (1927).
- 3. German Patent No. 476643.