IMPROVED METHOD OF PREPARING 4,4-DIETHOXYTHIOCARBANILIDE (ETHOXIDE)

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In 1959, N. B. Galstukhova and M. N. Shukina, co-workers at the S. Ordzhonikidze All-Union Scientific-Research Chemico-Pharmaceutical Institute, developed a method of preparing 4,4-diethoxythiocarbanilide (ethoxide) by heating p-phenetidine hydrochloride with ammonium thiocyanate for 4 h at 148-150° [1]. As a reaction medium the authors used vaseline oil, a mixture of diphenyl ether and vaseline oil, or p-phenetidine.

The technological production process consists of preparing p-phenetidine sulfate and condensing it with ammonium thiocyanate in a mixture of kerosene and diphenyl ether, with subsequent recrystallization of the technical production from isopropyl alcohol. The use of kerosene and diphenyl ether in the heating medium and the use of large amounts of isopropyl alcohol for recrystallization of the product are undesirable, since they are substances which offer fire and explosion hazards.

We have found conditions for preparing a preparation conforming to the pharmacopeia using only small amounts of glycerin as reaction medium in the condensation stage. The use of p-phenetidine hydrochloride which has been recrystallized from water and of pure ammonium thiocyanate permits obtaining a product whose pharmacopeia purity is limited only by its washing with isopropyl alcohol.

EXPERIMENTAL

A. p-Phenetidine Hydrochloride. To 60 g of 19% hydrochloric acid (chemically pure) in the course of 30-40 min, with stirring, was added 20 g (0.146 mole) of freshly distilled p-phenetidine, maintaining the temperature in the mixture not above 20°; the mixture was cooled to 8° and was kept at this temperature for 2 h, with stirring. The precipitate which fell was filtered off and dried at a temperature not over 80°. There was obtained 24.6 g (97.4%) of p-phenetidine hydrochloride which was recrystallized from water as follows. A suspension of 24.6 g of p-phenetidine hydrochloride in 50 ml of water was heated in a hot water bath until the solid completely dissolved. Sodium hydrosulfite and activated charcoal (0.5 and 2% by weight of the p-phenetidine hydrochloride taken, respectively) were added to the solution, and it was filtered after it had been kept at 80° for 20 min. The filtrate was cooled to 8° and was kept at this temperature for 2 h. The p-phenetidine hydrochloride which separated as a precipitate was filtered off and dried at 80°. There was obtained 20.95 g (85%) of white-colored p-phenetidine hydrochloride, mp 234°, calculated on the distilled p-phenetidine, or 82.7% if one does not take into account utilization of the mother liquors.

B. Ethoxide. Into a round-bottom flask of 250-ml capacity, provided with an air reflux condenser and a stirrer, was placed 18 g (0.104 mole) of p-phenetine hydrochloride, ground to a powder, 4 g (0.052 mole) of ammonium thiocyanate, and 2 ml of distilled glycerin. The reaction mixture was kept at 148-152°, with stirring, for $1\frac{1}{2}$ h, in an oil bath (bath temperature, 150-154°). At the end of this period, the bath was removed, and 100-150 ml of boiling distilled water was poured in rapidly to avoid clumping. The ethoxide, in the form of flakes, was distributed throughout the whole liquid volume; it was filtered off, and then was twice washed by suspension and thorough trituration in 20-25 ml of isopropyl alcohol at room temperature, and was filtered. The solid was washed liberally with hot water and then with cold water until chlorides were absent, after which it was dried at 70-80°.

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There was obtained 14.7 g (89.6%) of ethoxide, mp 168-171°, or 74.2% based on the distilled p-phenetidine.

LITERATURE CITED

1. N. B. Galstukhova and M. N. Shukina, Med. Prom. SSSR, No. 8, p. 15 (1960).