PREPARATION OF THE DRUG "ETHOXID"

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Ethoxid [NN'-di-(p-ethoxyphenyl)thiourea] (I) is prepared by condensing p-phenetidine (II) hydrochloride or sulfate with ammonium thiocyanate [1]. The reaction is carried out at 148-150° in a mixture of diphenyl ether and petroleum oil, or diphenyl ether and kerosene. The yield of I does not usually exceed 64%.

Attempts have been made to increase the yield in this reaction by fusing II hydrochloride with ammonium thiocyanate in the presence of small amounts of glycerin [2], and by heating II thiocyanate with free II in xylene [3]. In developing a method for the preparation of I which could be used industrially, we also used xylene as the reaction medium. However, we avoided the isolation of the intermediate II thiocyanate from the reaction mixture, and, moreover, the xylene was removed by distillation with live steam rather than by filtration. This resulted in a significant improvement in the technology of production of I, and it enables the use of such solvents as diphenyl ether and petroleum oil to be avoided with a consequent marked improvement in working conditions with regard to health. The use of this method substantially improved the quality of the final product, and it gave an increase in yield of approximately 12%. The hydrochloride and sulfate of II were used as starting materials for the condensation with ammonium thiocyanate. The sulfate was especially convenient to use, and it could be obtained by reaction of II with the calculated amount of concentrated sulfuric acid in xylene immediately before carrying out the condensation, without isolating the salt from the reaction mixture. Using this method, the yield of technical I calculated on the initial amount of II was close to theoretical. Recrystallization of technical I from 2-propanol gave 76-77% of product which complied with the requirements of the GFKh State Pharmacopoeia (m.p. 171-172°).

EXPERIMENTAL

II Hydrochloride. To 57 ml of hydrochloric acid (1 : 1) was added 28 ml of II with vigorous stirring at 20-22° over a period of 30 min. The viscous mixture obtained was stirred at this temperature for 1 h, cooled to 8-10°, kept for 1 h, and filtered. The II hydrochloride thus obtained was dried at a temperature not exceeding 80°. Weight of salt 34.6 g (95.1% calculated on starting II). The content of pure material in the salt was 99.9%.

Condensation of II Hydrochloride with Ammonium Thiocyanate in Xylene. A mixture of 72 ml of xylene, 34.6 g of II hydrochloride, and 8 g of ammonium thiocyanate was heated at 130° for 3 h. The xylene was then removed by distillation with live steam, and the aqueous suspension was cooled to room temperature and filtered. The solid was washed on the filter with 100 ml of hot water. Weight of dry product 31-32 g, m.p. 165-167°. The technical I was recrystallized from a 26-fold quantity of 2-propanol to give 23.3 g of pure product, m.p. 171-172°. The yield of I was 71.2%, calculated on starting II.

Condensation of II Sulfate with Ammonium Thiocyanate in Xylene. To a solution of 26 ml of II in 100 ml of xylene was added 6 ml of concentrated sulfuric acid dropwise with vigorous stirring over a period of 30 min, the temperature of the reaction mixture being kept below 40-45°. After adding the sulfuric acid, the mixture was kept at room temperature for 1 h, and 8.3 g of finely ground ammonium thiocyanate was added. The mixture was heated to 130° and stirred at this temperature for 3 h. The xylene was then distilled off with live steam, and the technical I which separated was filtered off and washed on the filter with 200 ml of hot water. The weight of technical product was 31.75 g, m.p. 166-168°. Recrystallization of the product

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from a 25- to 26-fold quantity of 2-propanol gave 24.3 g of I, m.p. 170-172° (76.9%, calculated on starting II).

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