METHYLATION OF 3-METHYLXANTHINE

WITH METHYL BENZENESULFONATE

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In the preparation of theobromine from 3-methylxanthine, methyl benzenesulfonate has been used as the methylating agent.

As is well known [1-3], to obtain theobromine, 3-methylxanthine is generally methylated with dimethyl sulfate in an aqueous ethanolic solution of caustic potash. However, if in the reaction the pH exceeds 8.0, the methylation of 3-methylxanthine leads to caffeine, which forms a by-product. The methylation of xanthine derivatives can also be carried out with methyl benzenesulfonate [4], but it takes place in a considerably more complicated way than with dimethyl sulfate.

We have developed conditions for the methylation of 3-methylxanthine with methyl benzenesulfonate in analogy with methylation by means of dimethyl sulfate. Since methyl benzenesulfonate, unlike dimethyl sulfate, undergoes practically no decomposition in neutral and weakly acidic media while methylation does not take place at a pH below 7.0-7.5, an excess of the methyl ester in the reaction mixture remains unchanged until the pH reaches the necessary figure. This considerably simplifies the performance of the methylation reaction.

Since the technical methyl benzenesulfonate contains diphenyl sulfone, this impurity complicates the purification of the theobromine obtained. Because of its solubility in hot water, in the filtration of the solution of the calcium salt of theobromine the diphenyl sulfone passes into the solution with it and contaminates the final product. We have eliminated this defect by a process that we have developed which involves the reprecipitation of the technical theobromine via the potassium salt, whereupon the necessity for heating before filtration vanishes [5].

EXPERIMENTAL

Thirty grams of 3-methylxanthine was dissolved in 127 g of an 8% solution of caustic potash at 65°C and 120 ml of methanol was added; then, at the same temperature, 30 ml of 95.5% methyl benzenesulfonate was added over 45 min; towards the end of the addition the pH became 7.5-8.0. The mixture was stirred for 20 min, the pH being maintained by the addition of an 8% solution of caustic potash, and then 19.5 ml of the ester was added over 15 min, the pH being kept within the same limits during an hour. Methylation was complete when 3-methylxanthine was no longer present in the reaction mixture, which was established by test with cobalt chloride. The mass was kept at 20-25°C for 8 h, and then the theobromine was filtered off, washed with cold water, and mixed with 300 ml of water. A 20% solution of caustic potash was added to the suspension until the solid matter dissolved and then 2.5 g of activated carbon. After 30 min, the solution was filtered and the theobromine was precipitated by the addition of 10% hydrochloric acid to pH 4.0, after which it was separated from the mother liquor and washed with water. Yield 24.5 g (75.4%); the material satisfied the requirements of the pharmacopoeia. The mother liquor from the technical product contained 4.25 g of caffeine (12.1%).

LITERATURE CITED

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