SYNTHESIS OF 4-(p-AMINOBENZENESULFONAMIDO)-6-METHOXYPYRIMIDINE

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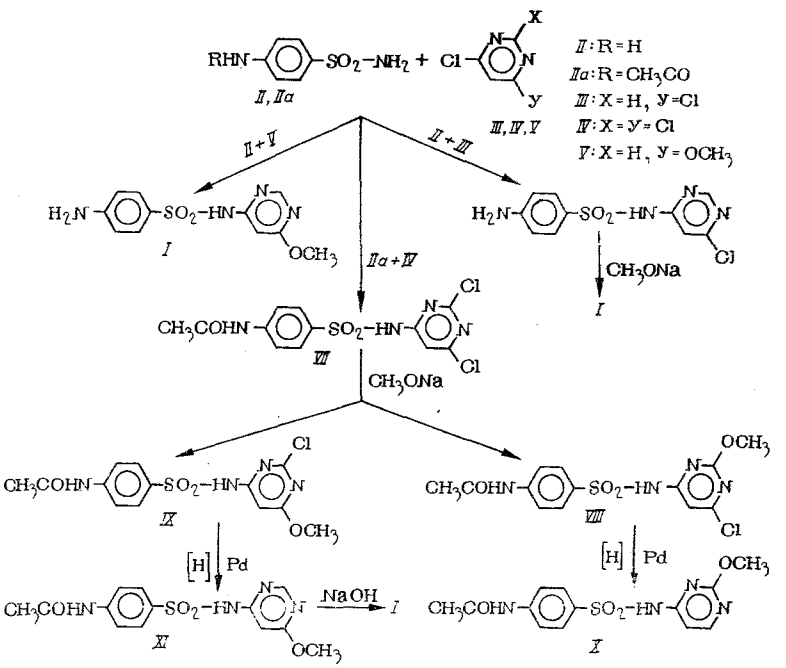
4-(p-Aminobenzenesulfonamido)-6-methoxypyrimidine (I) is a new long-acting antibacterial sulfanilamide. It is known under the names of "sulfameter," "sulfamonomethoxine," and "daimeton."

Compound (I) has a stronger sterilizing action in experimental pneumococcal infection in mice than any other sulfanilamide [1], and it creates a high concentration in brain tissue [2]. The known methods of preparing (I) [3-5] are based on the condensation of sulfanilamide (II) or its acetyl derivative (IIa) with 4,6-dichloropyrimidine (III), 2,4,6-trichloropyrimidine (IV), or 4-chloro-6-methoxypyrimidine (V). The reaction is performed in the presence of alkali-metal carbonates in suitable solvents. The condensation of (II) with (V) gives (I) with a yield of 25%. When (II) and (III) or (IIa) and (IV) are used the corresponding chloro- or dichloro(sulfanilamido)pyrimidines (VI and VII) are obtained. The methoxylation of (VI) with sodium methoxide forms (I) with a yield of 54%, calculated on the (III). The methoxylation of (III) yields a mixture of (chloro)(methoxy)(sulfanilamido)pyrimidines (VIII and IX). They have been dehalogenated by hydrogenation in the presence of palladium, and the resulting methoxy(sulfanilamido)pyrimidines (X and XI) have been separated by fractional crystallization, after which the (XI) was hydrolyzed to (I)



The methods for the synthesis of (I) that have been mentioned could not form the basis of the development of an industrial method for its production for the following reasons. Methods for obtaining the heterocyclic components, which is the most complex problem in industrial syntheses of sulfanilamide compounds containing heterocyclic systems, have not been developed. In the condensation of (II) or (IIa) with (III, IV,

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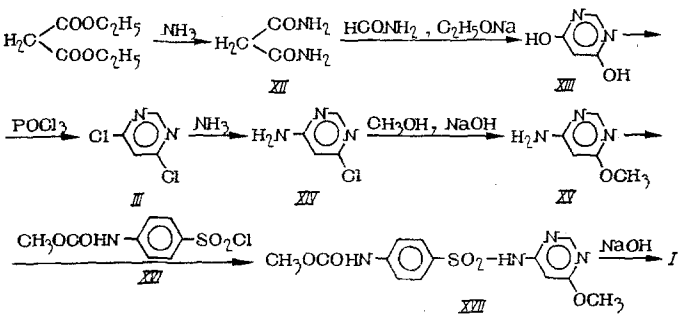
or V), in order to obtain more or less satisfactory yields the necessity arises for using the (II) or (IIa) in 2- to 3-fold excess with respect to the chloropyrimidine derivatives, which substantially complicates the isolation of the desired product from the reaction mixture. Compound (IV) has pronounced vesicant properties. In the last variant, palladium, which is in short supply, is used for dehalogenation.

For industrial use, we have developed a complete scheme for the synthesis of (I) consisting of the following reactions:



In the main, well-known methods were used for the synthesis of the intermediates (XII, XIII, III, XIV, and XV), but each stage of the preparation of a particular substance was carefully studied in order to put it into the technologically most suitable form. The practical importance of the proposed method is that it has much that is similar to the methods for obtaining products of similar structure – sulfadimethoxide and ortosulfin – that we have developed previously [6, 7]. Thanks to this similarity, the production of all three drugs can be organized in modern equipment using a number of common types of raw materials.

According to the literature, malonamide (XII) is obtained by treating malonic ester with aqueous ammonia solution. This process is described in most detail in [8], the yield amounting to 70-72%. On repeating this procedure with some modifications, we increased the yield of (XII) to 82-84%. We obtained the highest yield of (XII) (96%) by treating malonic ester with a solution of ammonia in methanol.

The production of 4,6-dihydroxypyrimidine was performed [9] by condensing (XII) with formamide in the presence of sodium ethoxide. The optimum ratios of the reactants have been determined more accurately. The yield of (III) amounted to 83-86% at a molar ratio of (XII) to formamide to sodium ethoxide of 1:2:3.

4,6-Dichloropyrimidine was obtained by the action on (XIII) of phosphorus oxychloride in the presence of dimethylaniline. In this stage, it was found that the yield of (III) can be raised to 80% and more, and the quality of the product be improved, by performing the process in dichloroethane. The use of this solvent permits the employment of a relatively small excess of phosphorus oxychloride (~4 moles per mole of (XIII)).

4-Amino-6-chloropyrimidine (XIV) can be obtained by the action of gaseous ammonia on a solution of (III) in dimethylformamide with a yield of 85-87% or by the action of aqueous ammonia on (III) [10] with a yield of about 91%.

4-Amino-6-methoxypyrimidine (XV) is obtained by the action of sodium methoxide on (XIV) in absolute methanol [11]. We performed this stage by treating (XIV) with a methanolic solution of caustic soda. The yield of (XV) was 82%.

The stage of preparing 4-(p-methoxycarbonylaminobenzenesulfonamido)-6-methoxypyrimidine (XVII) and (I) was performed under the conditions for obtaining sulfadimethoxide [6]. The present synthesis of (I) was performed with the technical grades of the raw materials used in the Soviet pharmaceutical chemicals industry.

EXPERIMENTAL

Malonamide (XII). a. In an aqueous medium. At 13-16°C, 576 ml of 25% ammonia solution was added to 245 g of malonic ester (98% pure). The mixture was stirred at 13-16°C for 2 h, and was then cooled to 5°C, and the precipitate of (XII) was filtered off, washed with ethanol, and dried. Yield 104-105 g (67.9-68.7%), mp 167-168°C (for a purified sample, 171°C). The mother solution was evaporated at 20-30 mm to small volume. The residue was cooled to 5°C, and the crystals of (XII) were filtered off, washed with eth-

anol, and dried. This gave 21-24.7 g of a product with mp 163-167°C. The total yield was 126-129 g (82.5-84.1%).

b. In methanol. At 10-14°C, 102 ml of methanol was saturated with ammonia to a concentration of 18-19%. To this solution was added 61.2 g of malonic ester and the mixture was left for four days. The resulting precipitate of (XII) was filtered off, washed with methanol, and dried, giving 37 g of (XII) (yield 95%), mp 169-170°C.

4,6-Dihydroxyprimidine (XIII). At 30°C, 51 g of (XII) and 45 g of formamide (97% pure) were added to a solution of sodium ethoxide prepared from 750 ml of absolute ethanol and 34.5 ml of metallic sodium. The mixture was boiled for 2 h and it was then cooled to 5°C and the white precipitate of the sodium salt of (XIII) was filtered off. This precipitate was dissolved in 200 ml of water and the solution was acidified with concentrated hydrochloric acid to pH 3.0-3.5 at 5-10°C. After 1 h the precipitate was filtered off and was dried at 50°C. The yield of (XIII) was 46.6 g (83.2%), mp ~300°C.

4,6-Dichloropyrimidine (III). At 35°C, 26.8 ml of dimethylaniline was slowly added to a mixture of 22.8 g of (XIII), 46 ml of dichloroethane, and 56 ml of phosphorus oxychloride. The mixture was boiled for $3^1/_2$ h, cooled to 25°C and poured onto 400 g of ice. The lower layer was separated off. The upper layer was extracted with 100 ml of dichloroethane and the extracts were combined. The dichloroethane was distilled off at 90-100 mm, and the residue was dried in a vacuum desiccator. The yield of (III) was 24.4 g (81.1%), mp 64-66°C.

4-Amino-6-chloropyrimidine (XIV). A. A current of dry ammonia was passed through a bubbler into a solution of 44.7 g of (III) in 300 ml of dimethylformamide at 28-30°C for 5 h. The solution was filtered from ammonium chloride and the dimethylformamide was distilled off at 100 mm. The recovery of dimethylformamide was 90-95% (for reuse). The precipitate was treated with 50 ml of water at 15-20°C and the light-brown precipitate of (XIV) was filtered off and dried at 50°C. Yield 33.4 g (85.8%), mp 193-195°C.

B. To 50 ml of 25% aqueous ammonia was added 14.9 g of (III). A gentle current of ammonia was passed into the reaction mixture through a bubbler at 60°C with stirring for 4-5 h. The end of the reaction was determined by means of thin-layer chromatography. The precipitate of (XIV) was separated off and dried. Yield 10.93-11.3 g (84.7-91%).

4-Amino-6-methoxypyrimidine (XV). To a solution of 24.14 g of caustic soda (98.4% pure) in 450 ml of methanol was added 38.9 g of (XIV). The mixture was boiled for 20 h. The solvent was distilled off finally at a pressure of 90 mm. The yellowish crystals were filtered off, washed with ice water to pH 7.5-7.7, and dried. The yield of (XV) was 29.5-32.4 g (78.4-86.2%), mp 155-156°C.

4-(p-Methoxycarbonylaminobenzenesulfonamido)-6-methoxypyrimidine (XVII). For 30-35 min, 71.7 g of 4-(methoxycarbonylamino)benzenesulfonyl chloride that had been recrystallized from dichloroethane was added to a solution of 31.4 g of (XV) in 146 ml of dry pyridine at 15°C. The mixture was stirred at 20°C for 2 h and was then heated to 55-57°C and kept for 2 h. After cooling to 20°C, 225 ml of water was added and the mixture was acidified with 10% hydrochloric acid to pH 3.0. The precipitate of (XVII) was filtered off and washed with water. The yield of dry (XVII) was 76.4-81.9 g (90.3-96.8%, calculated on the (XV)), mp 228-230°C. Found, %: C 45.73; H 4.33; N 15.09; S 8.69. $C_{13}H_{14}N_4O_5S$. Calculated, %: C 45.6; H 4.35; N 15.2; S 8.69.

4-(p-Aminobenzenesulfonamido)-6-methoxypyrimidine (I). To 932 ml of a 4% solution of caustic soda was added 101.5 g of (XVII), and the mixture was heated at 88-90°C for 1 h. Then, at 20°C, the solution was neutralized with 10% hydrochloric acid to pH 5.5-6.0. The light-cream-colored crystalline precipitate of (I) was filtered off and was purified by reprecipitation through the sodium salt with the use of activated carbon. The yield of purified (I) was 71 g (84.4%, calculated on the (XV)), mp 204-205°C. Found: %: C 47.33; H 4.50; N 20.00; S 11.65. $C_{11}H_{12}N_4O_3S$. Calculated, %: C 47.13; H 4.32; N 19.99; S 11.44.

LITERATURE CITED

1. E. N. Padeiskaya and L. M. Polukhina, in: Collection of Papers from the All-Union Scientific-Research Institute of Pharmaceutical Chemistry Vol. 2 [in Russian], (1971), p. 129.
2. E. N. Padeiskaya, L. M. Polukhina, and G. N. Pershin, Farmakol. i Toksikol., No. 4, 472 (1966).
3. R. Shepard and W. Taft, J. Org. Chem., 26, 2764 (1961).
4. British Patent No. 886,693; Chem. Abstr., 57, 2234 (1962).
5. S. Rossi, F. Pisseli, and O. Piroba, Farmaco. Ed. Sci., 18, 499 (1963).

6. V. A. Zasosov, N. M. Kolgina, K. S. Bushueva, et al., Med. Prom. SSSR, No. 4, 9 (1966).
7. V. A. Zasosov, T. N. Nikulina, L. S. Blinova, et al., Khim.-Farmats. Zh., No. 3, 29 (1972).
8. S. S. Radle-Desyatnik, Methods of Obtaining Chemical Reagents, No. 6 [in Russian], Moscow (1962), p. 101.
9. German Federal Republic Patent No. 1,200,308; Chem. Abstr., 63, 16364 (1965); German Democratic Republic Patent No., 32,753; Chem. Abstr., 65, 727 (1966); French Patent No. 1,424,940; Chem. Abstr., 65, 8930 (1966).
10. H. Goldner, Chem. Technik, 21, 495 (1969).
11. D. Brown, J. Chem. Soc., 1238 (1961).