SYNTHESIS OF 4-(p-AMINOBENZENESULFAMIDO)-5,6-DIMETHOXYPYRIMIDINE

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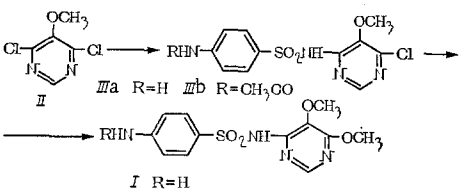
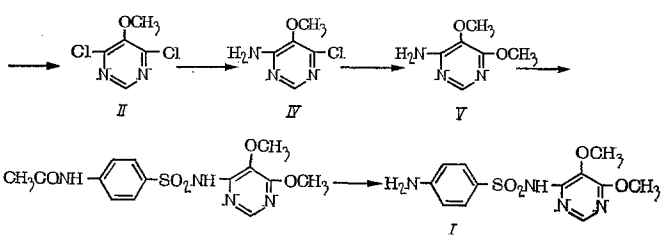
4-(p-Aminobenzenesulfamido)-5,6-dimethoxypyrimidine (I) is a new antibacterial sulfanilamide preparation with ultraprolonged activity. In medicine, the preparation has been introduced by the name Fanasil [1-5]. According to the data available in the literature, the preparation has low toxicity and is well tolerated by the patients; its therapeutic doses are approximately 15 times less than sulfadimezine doses.

The synthesis of I is accomplished by two largely different but well-known alternatives for the synthesis of sulfanilamides for which 4,6-dichloro-5-methoxypyrimidine (II) is used as the starting substance. In the first alternative, II is condensed with sodium sulfanilamide or sodium acetylsulfanilamide [1-3] and the 4-sulfanilamido(acetylsulfanilamido)-5-methoxy-6-chloropyrimidine (IIIa, b) obtained is methoxylated with sodium methylate.



The complexity of the technological design of the processes is a drawback of this alternative. According to the literature [2, 3], the condensation of II with 2 mole of sodium sulfanilamide or sodium acetylsulfanilamide is carried out in dimethylformamide or tetrahydrofuran at 90-105°C. The reaction products IIIa and IIIb are isolated as a difficultly crystallizable oil or as an amorphous viscous mass. We failed to obtain the yield reported by the authors during the preparation of IIIa in laboratory experiments. The chlorine in position 6 of the pyrimidine ring in compounds IIIa and IIIb is not very active; in connection with this, the methoxylation is carried out under drastic conditions (temperature of about 125°C) which requires the use of an autoclave.

In the second alternative, II is subjected to amination by liquid or gaseous ammonia [1-5]; the 4-amino-5-methoxy-6-chloropyrimidine (IV) obtained is methoxylated with sodium methylate [2, 3, 6], and the 4-amino-5,6-dimethoxypyrimidine (V) is condensed in dry pyridine with acetylaminobenzenesulfochloride followed by the saponification of the condensation product with sodium hydroxide.



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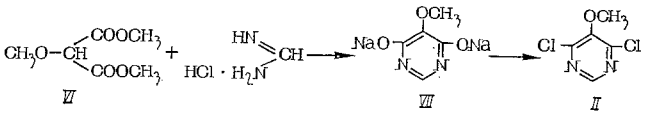
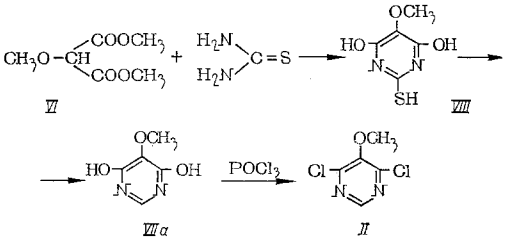
The necessity of using pyridine, which is toxic, expensive, and a difficult-to-recover solvent, is a drawback of this alternative.

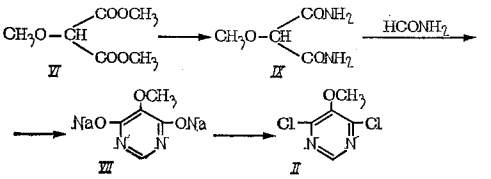
Three ways of preparing (II) from dimethyl methoxymalonate (VI), which are quite complex [1-3], have been described in the literature. Cyclization of VI with formamidine in the presence of sodium methylate leads to the formation of sodium 4,6-dihydroxy-5-methoxypyrimidine (VII), which is converted into II in high yield by reacting it with phosphorus oxychloride in the presence of dimethylaniline. This method cannot be of practical use because there is no industrial production of formamidine salts.



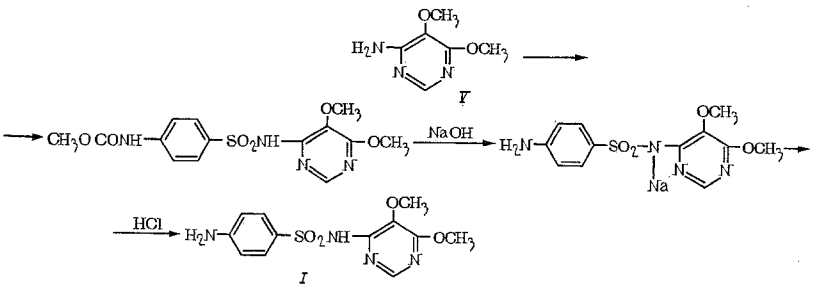
When VI is condensed with thiourea in the presence of sodium methylate at 20°C, 2-mercapto-4,6-dihydroxy-5-methoxypyrimidine (VIII) is obtained which, when treated with Raney nickel in an aqueous medium in the presence of ammonia at 90-95°C, is converted into 4,6-dihydroxy-5-methoxypyrimidine (VIIa). About four parts by weight of Raney nickel paste is used for each part by weight of VIII. Compound VIIa is very highly soluble in water and its isolation from aqueous solutions is connected with great difficulty and product loss. On the basis of what has been reported above, this method of preparing II is not of practical interest.



According to the literature [3], the amidation of VI is carried out with liquid ammonia in an autoclave at room temperature. Methoxymalonamide (IX) is condensed with formamide in alcohol in the presence of sodium alcoholate and the sodium salt, VII, obtained is treated with phosphorus oxychloride in the presence of dimethylaniline.



After a detailed investigation of the literature, practical testing, and comparison of the existing synthesis schemes, we decided on a third alternative for the synthesis of II. Compound I was prepared by condensing V with p-phenylurethylanesulfochloride, an intermediate in the synthesis of many sulfanilamide preparations. In the development process, we considerably modified in a chemical and technological sense a number of the steps in preparing I, which have been described in the literature.

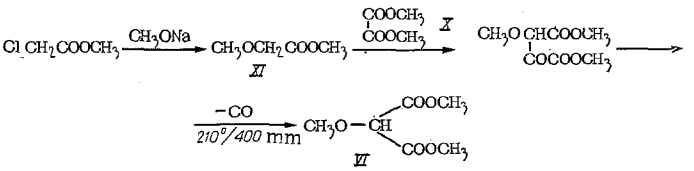


Several methods of synthesizing diesters of alkoxymalonic acids [3, 7, 8] have been described in the literature. Diethyl methoxymalonate [7] is prepared by treating ethyl methoxyacetate with a suspension of sodium ethylate in dry diethylcarbonate and slowly distilling off the ethyl alcohol formed through a column. The diethyl methoxymalonate we obtained this way had a refractive index higher than that indicated by the authors of the method (n_D^{23}=1.4316 instead of 1.4229) and, according to gas-liquid chromatography,

was a mixture of five products; the main one was diethyl methoxymalonate (72-74%), the others were found in amounts from 1.1 to 15% in the mixture. During the development of the process, we established that the reaction of alcoholic or aqueous ammonia with diethyl methoxymalonate does not lead to the formation of methoxymalonamide, whereas the dimethyl ester reacts forming the expected product. Confirmation of this fact exists in the literature [9]. It is reported that even when liquid ammonia is used and when it is heated to 140°C with alcoholic ammonia, only tiny amounts of the diamide were obtained, whereby the purer the ester used the lower the diamide yield. At higher temperatures of up to 170°C, considerable decomposition set in with the formation of ammonium carbamate.

A method of synthesizing diesters of alkoxymalonic acids [3], which includes the condensation of 1 mole of methyl alkoxyacetate with 1.5 mole of the dialkyl ester of oxalic acid in absolute benzene in the presence of dry sodium methylate, is known. The yield is quoted as being 78% for VI. We reproduced this method of preparing VI, however, the product yield containing not less than 95% of the principal substance (according to gas-liquid chromatography) did not exceed 60%. The necessity of constantly adding dry sodium methylate to the mixture of esters is the main drawback of this method of synthesizing VI.

We succeeded in considerably revising this method of preparing VI, making it suitable for industrial application. Dimethyl oxalate (X) [10] and methyl methoxyacetate (XI) [11-13] are the starting materials for the synthesis of VI. Compound X is obtained by esterifying anhydrous oxalic acid with methyl alcohol in the presence of sulfuric acid. The existing methods of drying oxalic acid are inconvenient in a technological sense; we used the azeotropic distillation of water with toluene and the esterification is carried out in this medium. The use of toluene permits one to avoid sharp jumps in temperature when the sulfuric acid is added; it provides for the safety of the process and permits one to shorten the duration of the process. We succeeded in replacing the dry sodium methylate in the step where X is condensed with XI by a suspension of sodium methylate in benzene or toluene containing no alcohol, in changing the order of addition of the reagents (the solution of the ester mixture in benzene and toluene is added to the sodium methylate suspension), and in reducing the amount of X from 1.5 to 1.05 mole.



The amidation of the diesters of alkoxymalonic acids is carried out with liquid ammonia in an autoclave at room temperature according to the literature [3]. The yield reported for methoxymalonamide was 97%. After taking the complexity of the process with liquid ammonia into account, we carried out the amidation with gaseous ammonia in methyl alcohol at 5-15°C. The methoxymalonamide yield came to 93-94%. It was shown in the same work that the alkoxymalonamides condense with formamide in alcohol in the presence of sodium alcoholate. Attempts to carry out this condensation in methyl alcohol in the presence of sodium methylate were unsuccessful; we succeeded in isolating only traces of VIIa from the reaction mixture. The condensation of IX with formamide in ethyl alcohol in the presence of sodium ethylate was carried out with the formation of VII.

Compound II, according to the literature [2, 3], was prepared by treating VII (1 mole) with phosphorus oxychloride (11 mole) in the presence of dimethylaniline (0.6 mole). The product was extracted from the reaction mixture with ether. The technical product was recrystallized from an ether-petroleum ether mixture. The yield of pure product is not reported. We succeeded in reducing the amount of phosphorus oxychloride to 8 mole after having increased the amount of dimethylaniline to 1.2 mole/mole of VII at the same time. A further decrease in the amount of phosphorus oxychloride leads to a drop in the yield of II. Improvements concerning the isolation of the product from the reaction mixture and its purification are reflected in the experimental section.

During the preparation of IV, which consists of passing ammonia through a solution of II in dimethylformamide, the temperature was lowered from 80 to 25-30°C, which permits one to avoid the partial resinification of the reaction mixture and leads to the yield of a purer product. We succeeded in substituting the alcoholic solution of sodium methylate in the step where IV is methoxylated with an alcoholic solution of sodium hydroxide.

EXPERIMENTAL

Dimethyl Oxalate (X). Oxalic acid (dihydrate), 252 g, and 350 ml of toluene were boiled with agitation and the azeotropic toluene-water mixture was distilled off, 200 ml of absolute methanol was added at 35-40°C and, with good agitation, 70 ml of 98% sulfuric acid was added within 10-20 min. The temperature of the reaction mixture was raised to 60-70°C. The reaction mixture was agitated at 70-72°C for 1 h, cooled to 40°C, the toluene and methanol layer were separated, and cooled to 3-5°C. From the toluene solution was obtained 104 g of product, mp 52-54.5°C, and from the methanol, 55 g of product which was combined with 20 g of the product obtained after evaporating the toluene off; the product was recrystallized from 35 ml of methanol. A yield of 55.1 g of the product was obtained, mp 51-53°C. The yield of X came to 159.1 g or 67.5%.

Methyl Methoxyacetate (XI). To sodium methylate (from 23 g of metallic sodium and 240 ml of absolute methanol) was added dropwise 108.5 g of methyl monochloroacetate with agitation at 20-25°C over a 2 h period; the mixture was kept at 20-25°C for 3 h. On the following day, the sodium chloride was filtered off, washed with 20 ml of methanol, and about 200 ml of methanol was distilled from the filtrate with agitation using a rod-and-disk type fractionating column (about 25 cm long). The remainder was fractionated. Fractions No. 1 with a bp of 105-125°C (6-10 g, n_D^{20}=1.3870-1.3950) and No. 2 with a bp of 125-132°C (72.9 g, n_D^{20}=1.3964) were collected. The yield of XI was 75% based on the methyl monochloroacetate and taking into account the product obtained during the distillation of fraction No. 1.

Methyl Methoxymalonate (VI). To sodium methylate (from 19.1 g of metallic sodium and 225 ml of absolute methanol) was added 750 ml of absolute benzene. The methyl alcohol-benzene mixture was azeotroped off with agitation until the vapor temperature reached 72-76°C (about 705 ml of the mixture was distilled off), 150 ml of absolute benzene was added, and the mixture was cooled to 16-18°C. A benzene solution of a mixture of 93 g of (X) and 78 g of (XI) was added in a stream of nitrogen to the suspension over a 30-40 min period at 16-20°C. At the end of the addition of the mixture, the reaction mass was agitated at 18-20°C for 3-4 h and allowed to stand overnight under nitrogen without agitation. The reaction mixture was acidified at 4-6°C with dilute hydrochloric acid (1:1) until acid to Congo red (about 150 ml of the acid was consumed), the sodium chloride was filtered off, the benzene layer was separated, and the aqueous layer was extracted with 450 ml of methylene chloride. The methylene chloride was distilled off (about 400 ml), the benzene solution was added, and the benzene was distilled off. Traces of the solvents and X were distilled out of the residue (about 164 g) at 10-20 mm until the vapor temperature just attained 90-95°C. The residue, dimethyl methoxyoxalacetate, was subjected to decarbonylation at 200-210°C in an oil bath and at a residual pressure of 400 mm for 3 h, compound VI which formed was vacuum distilled at 10-20 mm. Compound VI, 66.4 g, was obtained, bp 117-119°C (17 mm), n_D^{20} 1.4229-1.4235. The yield was 54.5% based on XI.

Methoxymalonamide (IX). Into a solution of 64.8 g of VI in 195 ml of methanol at 5-15°C with slight agitation was passed ammonia for 3 h. The precipitate, IX, was filtered off and washed with cold methanol. After drying at 70-80°C, 49.6 g of IX was obtained (yield 94%), mp 208-212°C (within 2°C).

Sodium 4,6-dihydroxy-5-methoxypyrimidine (VII). To sodium ethylate (from 19.1 g of metallic sodium and 385 ml of absolute ethanol) at 20°C was added with agitation over a 25-30 min period 39.6 g of IX, and then 18.9 g of formamide, the mixture was boiled for 3 h, cooled to 15°C, the precipitate, VII, was filtered off, and washed with 50 ml of cold absolute ethanol. The product, 67-69 g, which was dried in vacuo to constant weight, was used to prepare II without further purification.

4,6-Dichloro-5-methoxypyrimidine (II). To 150 ml of dry methylene chloride with agitation was added the dry sodium salt, VII, obtained as described above from 0.3 mole of IX, and at a temperature not higher than 30°C over a 1 h period was added dropwise 232 ml of phosphorus oxychloride, and then 45.6 ml of dry dimethylaniline. The reaction mixture was gradually heated and the methylene chloride was completely evaporated off so that the temperature just had not as yet reached 98-100°C, then the mixture was boiled for 3 h at 102-107°C, and cooled to 18-20°C. The reaction mixture was added to a mixture of 600 ml of water and 600 g of ice with agitation while keeping the temperature no higher than 35°C; this mixture was cooled to 20°C, and II was extracted from the acid solution with 1800 ml of methylene chloride. The extract was clarified with 25 g of activated carbon, filtered, and the methylene chloride was distilled from the filtrate. The traces of solvent were evaporated off in vacuo at 10 mm, the remainder was cooled to 0°C, and allowed to remain at this temperature for 10-12 h. The residue, II, was filtered off, washed with 20 ml of cold ethanol, and dried in a vacuum desiccator. The dry product, 20.9-22 g, was obtained, mp 54-

58°C (within 2°C). The filtrate was evaporated in vacuo at 100-200 mm, and after treating it in the same way as described above, another 6 g of product was obtained, mp 43.5-51°C (within 2°C). The yield of II was 50-52% based on IX.

4-Amino-5-methoxy-6-chloropyrimidine (IV). Gaseous ammonia was passed into a solution of 35.8 g of II in 215 ml of dimethylformamide using slight agitation at a temperature of 25-30°C for 10 h, the reaction mixture was cooled to 10°C, and the ammonium chloride was filtered off. About 215 ml of the dimethylformamide was distilled in vacuo at 10-20 mm from the filtrate, the remainder was cooled to 0-5°C, the precipitate, IV, was filtered off, washed with 25 ml of ethanol cooled to 0-5°C, and dried at 70-80°C. Compound IV, 23.3 g, was obtained, mp 174.5-177°C (within 2°C). The yield was 73% based on II.

4-Amino-5,6-dimethoxypyrimidine (V). To an alcoholic solution of sodium hydroxide (from 8.8 g of sodium hydroxide and 200 ml of methanol) was added 31.9 g of IV and the reaction mixture was boiled for 12 h with agitation, cooled to 10°C, the sodium chloride was filtered off, and washed with 20 ml of cold methanol. The methanol (about 200 ml) was distilled from the filtrate, the remainder was dissolved in 100 ml of water, and V was extracted out with 300 ml of methylene chloride. The solvent was evaporated off first at atmospheric pressure then in vacuo. Compound V, 29.4 g, was obtained, mp 85-88°C (within 2°C). The yield of V was 95% based on IV.

4-Sulfanilamido-5,6-dimethoxypyrimidine (I). To a solution of 29.4 g of V in 76 ml of dry pyridine was added in portions 66.1 g of p-phenylurethylanesulfochloride with agitation at 10-15°C, the reaction mixture was agitated at 20-22°C for 2.5 h, then at 50-55°C for 5 h, 165 ml of water was added, the mixture was carefully stirred, acidified with concentrated hydrochloric acid until acid to Congo red (to a pH of about 3.0), and cooled to 20°C. The cream-colored precipitate, 4-carbomethoxyaminobenzosulfamido-5,6-dimethoxypyrimidine, was filtered off and washed with water until neutral. About 85 g of the wet or 61.5 g of the dry substance was obtained (yield 88.0% based on V); it was added to a solution of 50 g of sodium hydroxide in 470 ml of water with agitation, heated at 80-90°C for 30-40 min, cooled to 50°C, neutralized with concentrated hydrochloric acid to pH 9.0, and 2.8 g of activated carbon was added. The reaction mixture was stirred at 70-75°C for 30 min, filtered, acidified to pH 6.0 at 35-40°C with 10% hydrochloric acid. I was filtered off, and washed with water. After drying at 70-80°C, 46.8 g of technical (grade) I was obtained, mp 195-197°C (yield 79.4% based on V).

The substance, 46.8 g, was dissolved with agitation in a solution of 8.6 g of sodium hydroxide in 300 ml of water, heated to 65-70°C, 2 g of activated carbon was added, the mixture was stirred at this temperature for 20-30 min, and filtered. Compound I was isolated from the filtrate at 65-70°C by adding a 25% acetic acid solution to pH 6.0, the precipitate was filtered off, washed with water, and dried at 70-80°C to constant weight. Compound I, 44 g, was obtained, mp 196.5-198°C (yield 94% based on technical grade I; 74.6% based on V).

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