SEARCH FOR METHODS OF LOWERING THE CONSUMPTION OF CHLOROSULFONIC ACID IN THE PRODUCTION OF SULFANILAMIDE DRUGS

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In the synthesis of sulfanilamide drugs — active antimicrobial medicament — the starting materials are N-acyl derivatives of aniline, from which the corresponding sulfonyl chlorides are obtained. The latter are converted into sulfanilamide drugs by treatment with various amino derivatives [1].

The first stage of the production of sulfanilamide drugs is the synthesis of p-acylaminobenzenesulfonyl chlorides. Among the known methods for synthesizing sulfonyl chlorides [2-5] in laboratory practice and in industry the main ones used for preparing p-acylaminobenzenesulfonyl chlorides consist in the action of chlorosulfonic acid (I) on acylated anilines [1, 6-18]. There are various opinions in the literature on the question of the mechanism of the interaction of I with aromatic compounds, leading in one stage to arenesulfonyl chlorides. At the present time a two-stage reaction of I with aromatic compounds has been demonstrated [2, 6, 19-21].

$$\mathrm{RH + ClSO_3H \longrightarrow RSO_3H + HCl\uparrow;} \tag{A}$$

$$\mathrm{RSO_3H + ClSO_3H \rightleftharpoons RSO_2Cl + H_2SO_4.} \tag{B}$$

Reaction (A) takes place readily and goes to completion.* Reaction (B) is reversible, and to obtain a good yield of sulfonyl chloride either a considerable excess of reagent must be used or the sulfonyl chloride or the sulfuric acid must be removed from the sphere of the reaction. The possibility is not excluded, either of direct chlorosulfonation taking place in parallel [19].

$$\mathrm{RH + ClSO_3H \rightleftharpoons RSO_2Cl + H_2O.} \tag{C}$$

It is likely that the course of the reaction is even more complex, since it also leads to the formation of a number of byproducts, and especially sulfones, and to a smaller extent polysulfo derivatives, chlorine derivatives, etc. A detailed investigation of the chlorosulfonation of aromatic compounds has shown that, depending on the conditions (temperature, time ratio of the reactants, etc.) the reaction is complicated to a greater or smaller degree by side processes, and the yield of sulfonyl chloride varies within wide limits (from 10-12 to 80-90%) [19-21, 24-30].

An increase in the excess of I and a rise in the temperature makes it possible to obtain high yields of sulfonyl chloride [19, 20]. However, even a two- to threefold excess of I does not enable the sulfonyl chloride to be obtained in quantitative yield because of the equilibrium of reaction (B), which has been studied in detail in a number of investigations [25, 26, 28-30].

The starting material for the production of sulfonilamide drugs is phenylurethylane (II) the action of chlorosulfonic acid on which gives p-methoxycarbonylaminobenzenesulfonyl chloride (III) — the key product in the production of all the sulfanilamide drugs [1]. The simplest representative of this series is sulfanilamide (VI) — streptocid album — and it is desirable to investigate the effectiveness of the use of chlorosulfonic acid with this substance as an example.

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*Reaction (A) is sometimes used to obtain sulfonic acids [6, 22, 23].

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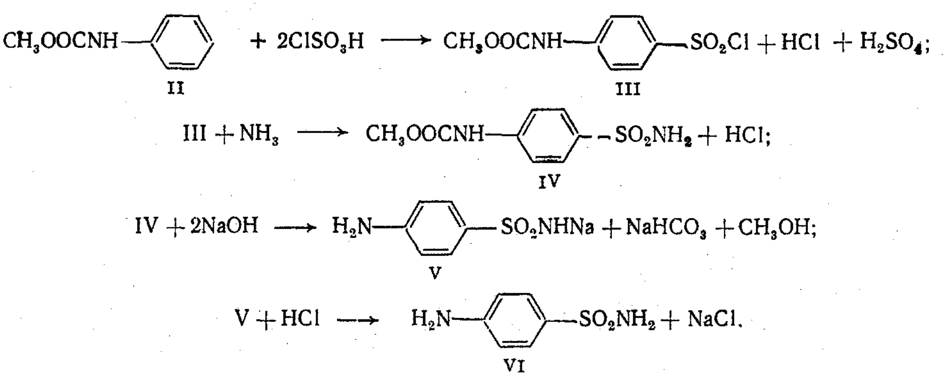
The synthesis of VI is carried out in accordance with the following scheme [1]



(1)

(2)

(3)

(4)

In one of the first investigations devoted to the sulfonation of II [10], it was proposed to carry out this process at 0-5°C with a molar ratio of II to I of 1:5. The yield of III was 60-65% and of VI 50% of theoretical calculated on the II. In a subsequent improvement of this process [1, 11], it was proposed to take 5.2-5.5 moles of I per mole of II and to perform the chlorosulfonation at 40-51°C.

The present paper gives the results of an investigation of methods of lowering the consumption of chlorosulfonic acid and improving the quality of the effluents while retaining a high yield of the intermediates and required products in the manufacture of sulfanilamide drugs.

In the first place we made an attempt to determine the dependence of the yield of III on the number of moles of I taken per mole of II. In view of the lower accuracy of the analysis of III, this relationship was evaluated not only with respect to the yield of II but also with respect to the yield of VI, only the conditions of reaction (1) being varied and all the subsequent stages (2)-(4) being performed under standard conditions. Table 1 gives the results obtained at various molar ratios of II to I. As follows from Table 1, high yields of III and VI are achieved at a ratio of 5.34, a further increase in the relative amount of I having little effect on the yield of VI. On the other hand, even a slight decrease in the amount of I considerably reduces the yield of III and VI.

In the literature there are statements relating to possible methods of reducing the amount of I for producing various sulfonyl chlorides. The fact that the action of I aromatic compounds forms sulfonyl chloride in the first stage (A) has led a number of authors to replace I by other sulfonating agents (sulfur trioxide, oleum) [31-35]. On the other hand, to displace the equilibrium to the right in reaction (B), in addition to the usual method — a large excess of I — the chemical elimination of the sulfuric acid by binding it in sulfates with the addition of alkali-metal chlorides has also been proposed [6, 34, 36].

The replacement of part of the I by oleum or sulfur trioxide may be promising. There are various statements concerning the proportions of SO_3, I, and aromatic compound in the literature. Some authors recommend taking 1 mole of aromatic compound and 1 mole of SO_3, and reducing by one mole the amount of I that is required in the absence of SO_3 [32]. Others propose to take ~1 mole of I and ~0.5 mole of SO_3 per mole of ArH [31] or to replace 17-20% of I by the same amount of SO_3 [35].

We have performed two variants [32, 35]. The use of oleum in admixture with I (4.55 mole of I and 0.38 mole of SO_3 per mole of II led to a fall in the yield of VI by 2.5% (see Table 1) as compared with chlorosulfonation performed with I alone at the same ratio between I and II.

When the synthesis of VI was carried out with a mixture of 1 mole of liquid sulfur trioxide and 4.38 mole of I, the yield of VI increased from 62.5 to 65.7% (see Table 1), but it was 5.1% lower than at a ratio of 5.34. It follows from literature information that the addition of mineral salts in chlorosulfonation raises the yield of sulfonyl chlorides either through lowering the amount of sulfone impurities formed in a reaction competing with the formation of sulfonyl chloride [21, 37] or by shifting the equilibrium in (B) to the right as a consequence of the binding of the sulfuric acid in sulfates [6, 36], chlorosulfonation being performed, in the investigation known to us, with a mixture of I and a salt.

TABLE 1. Dependence of the Yields of p-Methoxycarbonylaminobenzenesulfonyl Chloride (III) and Technical Sulfanilamide (VI) on the Conditions of Performing the Stage of the Chlorosulfonation of Phenylurethylane (II) with Chlorosulfonic Acid (I)*

Molar ratio 100% I/100% II	Chlorosulfonation conditions	Yield of II, % of theoretical, calc. on II	Yield of VI, % of theoretical, calc. on II
8	Typical experiment	—	68,8
7	" "	—	70,6
6	" "	—	71,0
5,34	" "	77,0	70,8
4,87	" "	74,4	68,2
4,75	" "	72,9	65,5
4,55	" "	—	65,2
4,44	" "	—	62,5
4,55	Mixture of oleum with I	—	62,7
4,38	" of liquid SO_3 with I		65,7
4,87	Addition of KCl to I	77,2	68,6
4,87	Dosed charge (1st variant)	76,0	69,5 69,0
4.75	Dosed charge (2nd variant)	75,7	69,0
4.87	Dosed charge (1st variant) at an elevated temperature	77,3	71,0

*In each series not less than three to four parallel experiments were performed; the mean results are given.

In attempts to reproduce literature methods, the yield III obtained was considerably lower than at a ratio of I to II of 5.34. In view of the fact that the second stage of reaction during which sulfuric acid is liberated is slower, the inorganic salts were during the hour before the end of chlorosulfonation. The yield III at a molar ratio between I and II of 4.87 was raised by the addition of 0.09 mole of potassium chloride per mole II to 77.2% and was close to the yield (77%) at a ratio of I to II of 5.34 (see Table 1). Under these conditions the yield of VI was 68.6%.

Since in the first stage of chlorosulfonation the main product is the sulfonic acid, and the aromatic compound and the I are usually taken in a molar ratio of 1:1 [22, 23, 25], we decided to investigate the possibility of reducing the amount of I in the chlorosulfonation on II by reducing its consumption in the first stage.

Initially, to part of the total amount of I taken in a proportion of 2.3-3 moles per mole of II* at a temperature of 30-32°C the whole amount of II was added in portions. After the reaction mixture had been kept at 30-32°C for 40-60 min, the remainder of the I, in an amount such as to give a total ratio of 4.65-4.89 moles per mole of II, was added. After the reaction mixture had been stirred at 40-42°C for 90-120 min, the III was isolated by a known method (first variant).

The charging of the components in chlorosulfonation can also be performed by alternating the addition of II and I. In this case, to part of the I is added part of the II in such amount that at the beginning of II the excess of I amounts to 5-6 moles and then, after the temperature has been kept at 30-35°C for 10-20 min, the remainder of the II and then the I are added in such a way that the total amount of I per mole of II does not exceed 4.65-4.89 moles, after which the reaction mixture is stirred at 40-48°C for 80-120 min, and the III is isolated by a known method (second variant).

As can be seen from Table 1, the yields of III and VI on working by the first variant of dosed addition at a molar ratio of I to II of 4.87 practically correspond to the yields on working at a ratio of 5.34. By the second variant, the yields of III and VI at a molar ratio of I to II of 4.75 are somewhat lower. A change in the temperature and time conditions of the process of chlorosulfonation by the method of dosed additions gave satisfactory results. Thus, at a ratio of 4.87 moles of I to 1 mole of II, raising the temperature during the time of addition of the II from 30-32 to 40-42°C and raising the holding temperature from 40-42 to 47-48°C while shortening the time of the process to one half enabled III to be

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*It was impossible to achieve a smaller amount of I per mole of II in view of the high viscosity of the reaction mixture.

obtained with a yield of 77.3%, and VI with a yield of 71%.

A decrease in the amount of I in the chlorosulfonation of II also enabled the quality of the III to be improved through a decrease in the probability of occurrence of side reactions. The amount of impurities in the technical III obtained by the first variant of dosed addition at an elevated temperature was 7-7.5% as compared with 12-13% on working with a molar ratio of I to II of 5.34.

Of the two possible methods of reducing the amount of I in the chlorosulfonation of II that keep the yield of III and VI at the previous level (addition of alkali-metal chlorides and use of dosed addition of the components), dosed addition may be recommended in view of the high suitability for industrial use and economy of this method. Advantages of the proposed method consist in a reduction in the consumption of I, a decrease in the pollution of the effluents from the stage of chlorosulfonating II, and an increase in the yield of III from existing equipment.

The method is being used in industry [38], permitting a saving of 9-10% of I [39].

EXPERIMENTAL

Preparation of p-Methoxycarbonylaminobenzenesulfonyl Chloride (III) and Sulfanilamide (VI) (Typical Experiment). A three-necked flask fitted with a stirrer and thermometer was charged with the calculated amount of technical I. With stirring and external water cooling, 59.5 g (0.39 mole) of technical II was added to the flask at such a rate that the temperature of the reaction mixture did not exceed 30-32°C. Then it was heated to 42-44°C and was kept at this temperature for 2 h. After the end of the holding period, the reaction mixture was cooled to room temperature and poured in a thin stream with stirring into a mixture of 450 g of ice and 730 ml of water at such a rate that the temperature did not rise above 20-22°C. The III that deposited was filtered off and washed to neutrality to Congo Red.

A three-necked flask fitted with a stirrer, thermometer, and reflux condenser was charged with 70-75 ml of 25% aqueous ammonia and 35-40 ml of water and the paste of III obtained above was added, care being taken that the temperature did not rise above 30-35°C. After the charging of all the III, the reaction mixture was heated over 1-1.5 h to 58-60°C and was stirred at this temperature for 2.5 h and it was then cooled to room temperature and filtered, and the precipitate of IV was washed with water. Then it was boiled for 3.5-4 h with 50-55 ml of 44% caustic soda solution and 150-160 ml of water. After this, the reaction mixture was cooled to 80°C, acidified with 32% hydrochloric acid to pH 9.5, heated to a boil, and left to crystallize slowly at room temperature. The precipitate of technical VI that deposited was filtered off, washed with a small amount of water, and dried. After recrystallization from water, VI of pharmacopoeial purity was isolated, mp 165-166°.

Preparation of p-Methoxycarbonylaminobenzenesulfonyl Chloride (III) and Sulfonilamide (VI) by the Dosed Addition of Phenylurethylane (II) and Chlorosulfonic Acid (I). First Variant. A three-necked flask fitted with a stirrer and thermometer was charged with 110.75 g (0.928 mole) of technical I. With stirring and external cooling, 59.5 g (0.39 mole) of technological II was added to the flask at such a rate that the temperature did not exceed 30-35°C. Then 110.75 g (0.928 mole) of technical I was added at a temperature not exceeding 42-44°C, and the reaction mixture was kept at this temperature for 90-120 min. After the end of the holding period, the reaction mixture was cooled to room temperature. Then the III was isolated and it was converted into VI by the method described above.

Second Variant. A three-necked flask fitted with a stirrer and thermometer was charged with 120.98 g (1.0144 mole) of technical I. With stirring and external water cooling, 29.75 g (0.1905 mole) of technical II was added to the flask at such a rate that the temperature of the reaction mixture did not exceed 42-45°C. After the addition of the whole of the II, the reaction mixture was stirred at this temperature for 45-60 min and it was then cooled to 25-30°C and 29.75 g (0.1905 mole) of technical II was added. In this process the temperature of the reaction mixture should not exceed 40-42°C. After the introduction of the whole of the II, 94.72 g (0.7942 mole) of technical I was added at such a rate that the temperature did not exceed 43-45°C, and the mixture was stirred at this temperature for 90-120 min. After the end of the holding period, the reaction mixture was cooled to room temperature and was treated by the above-described method.

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*As in Russian original — Consultants Bureau.