EFFECT OF CARBOMETHOXYSULFANILIC ACID ON THE SYNTHESIS OF CERTAIN SULFANILAMIDE PREPARATIONS

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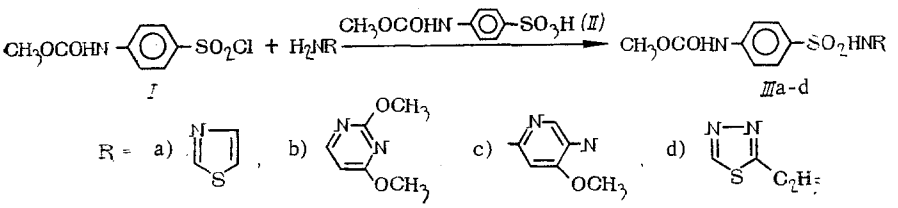
A series of sulfanilamide preparations, large-capacity preparations (etazole, sulfadimethoxine, sulfamonomethoxine, etc.) also among them, are manufactured using pyridine as the solvent at the stage of condensation of phenylurethylanesulfochloride (I) with the aminoheterocyclic component. If pure (recrystallized) (I) is used for this reaction, then the yields of carbomethoxy-substituted sulfanilamides (III) are very high and close to quantitative. If technical (dried) (I) is used, then yields of the corresponding condensation products are significantly lower and are not constant. We have established that one of the impurities in technical (I) is carbomethoxysulfanilic acid (II), which is not normalized and is not determined analytically by the existing standard for technical (I).

During the investigation of a series of samples of technical (I) we showed that the content of (II) varies in the range of from 3 to 10%. The presence of (II) can be a result of partial hydrolysis of (I) due to moisture, particularly during its prolonged storage at a temperature above 20°, or be a result of incomplete realization of the sulfochlorination reaction of phenylurethylane and also partial hydrolysis of (I) at the stage of decomposition of the reaction mass with water during separation of (I) after its synthesis. The effect of impurity (II) in condensation reactions of (I) with a series of aminoheterocyclic compounds in a pyridine medium was studied in this research.

The method of obtaining (II) and a description of its properties are absent in the literature.

We obtained (II) by hydrolysis of pure (recrystallized) samples of (I) by heating them with water at boiling. The initial materials were: pure (I) (recrystallized from dichloroethane), pure (II); the aminoheterocyclic compounds: 2-aminothiazole, 4-amino-2,6-dimethoxypyrimidine, 4-amino-6-methoxypyrimidine, and 2-amino-5-ethylthiadiazole. In control experiments 1.1 moles of (I) was taken per 1 mole of aminoheterocyclic compound and their condensation was carried out in pyridine according to the procedures developed and described earlier [1-4]. In experimental runs, as in control runs, 5 and 10% (II) of weight of loaded (I) was added to the reaction mass.



It was established as a result of the executed experiments that introduction of (II) to the reaction mass decreases the yields of the carbomethoxy derivatives of sulfanilamides (II) significantly and that the decrease in yields is proportional to the amount of added (II). Experimental results are presented in Table 1.

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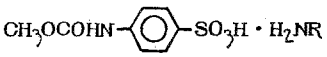
TABLE 1. Effect of Additions of (II) on Yield of (IIIa-d)

Compound	Amount of (II) [% of (I)]	Yield of (III) (% based on R–NH_2)	Literature
IIIa	0	91,8	
	5	88,0	[1]
	10	85,5	
IIIb	0	94,5	
	5	88,3	[2]
	10	81,5	
IIIc	0	93,3	
	5	82,6	
	10	76,8	[3]
IIId	0	98,5	[4]
	10	84,2	

TABLE 2. Salts of Carbomethoxysulfanilic Acid with Heterocyclic Amines (IVa-d)



R	Yield (% on H_2NR)	mp (deg)	pH of 0.1 N solution	Solubility in 100 ml (g)			Found (%)	
				water 20°	water 100°	pyridine 20°	C	H
IVa	90,6	195—7	3,47	10,0	22,3	5,0	39,91	3,89
IVb	93,6	175—6	2,87	0,8	10,0	85,0	43,86	4,55
IVc	88,0	194,5	2,65	5,0	43,0	10,0	43,87	4,26
IVd	41,0	150—3	2,3	25,0	—	27,0	39,80	4,47

R	Found (%)		Empirical formula	Calculated (%)			
	N	S		C	H	N	S
IVa	12,50	19,34	$C_{11}H_{13}N_3O_5S_2$	39,88	3,93	12,28	19,36
IVb	14,25	8,02	$C_{14}H_{18}N_4O_7S$	43,43	4,66	14,53	8,18
IVc	15,83	8,83	$C_{13}H_{16}N_4O_6S$	43,79	4,49	15,71	8,99
IVd	15,60	17,98	$C_{12}H_{16}N_4O_5S_2$	39,96	4,58	15,54	17,76

The following hypothesis was made to explain this effect: (II), being a strong acid, forms salts (IV) with aminoheterocyclic compounds, dissociated little in pyridine, which leads to a decrease in amount of free amines in the reaction solution, and consequently, to a decrease in yield of (III). We synthesized salts (IV) with the heterocyclic amines indicated above for the first time. Salts (IV) were obtained by heating equimolecular amounts of amine and (II) in aqueous medium. Data on their synthesis and properties are presented in Table 2. To confirm the hypothesis stated above experiments on obtaining (III) were carried out by condensation of (I) with salts (IV) in pyridine. The following results were obtained: yields of (III) amounted to 61% for 2-aminothiazole, 63.7% for 4-amino-2,6-dimethoxypyrimidine, 31.4% for 4-amino-6-methoxypyrimidine, and 75.5% for 2-amino-5-ethylthiadiazole.

EXPERIMENTAL

Carbomethoxysulfanilic Acid (II). We boiled 50 g of (I), purified by recrystallization from dichloroethane, with 500 ml of water until complete solution of the precipitate for approximately 1 h. The solution was clarified with carbon and filtered; the filtrate was evaporated in vacuum (10-15 mm) to dryness. The residue was treated with acetone and dried. Yield was quantitative. Compound (II) is a finely crystalline hygroscopic white powder with a cream tint; mp 189-190°. It is very highly soluble in water, pyridine, and insoluble in acetone, benzene, dichloroethane. An aqueous 0.1 N solution has pH 1.2. After drying at 105° for 2 h (II) contains 0.5 mole of water of crystallization. Found: C 39.62; H 4.26; N 6.28; S 13.3. $C_8H_9NO_5 \cdot {}^1/_2\ H_2O$. Calculated, %: C 40.02; H 3.78; N 5.85; S 13.35. Upon drying (II) at 115° for 4 h the anhydrous product was obtained. Found, %: C 4.15; H 4.03; N 6.17; S 13.74. $C_8H_9NO_5S$. Calculated, %: C 41.6; H 3.89; N 6.06; S 13.88.

Salt of Carbomethoxysulfanilic Acid and 2-Aminothiazole (IVa). We dissolved 2.62 g of (II) in 2 ml of water. To the filtered solution was added 1 g of 2-aminothiazole. A crystalline precipitate separated from solution upon prolonged standing, which was filtered after 1 h by suction, washed with cold water, and dried. Yield was 3 g (90.6%).

Salt of Carbomethoxysulfanilic Acid and 4-Amino-6-methoxypyrimidine (IVc). We dissolved 7.86 g of (II) in 7 ml of water. To the solution was added 3.75 g of 4-amino-6-methoxypyrimidine. The mixture was heated to 50° until the precipitate dissolved, filtered, and cooled to 20°; the precipitate was filtered, washed with water, and dried. Yield was 9.41 g (88%).

Salts with 4-amino-2,6-dimethoxypyrimidine (IVb) and 2-amino-5-ethylthiadiazole (IVd) were obtained analogously (see Table 2).

LITERATURE CITED

1. V. I. Khmelevskii and O. I. Sinegubova, Med. Prom. SSSR, No. 3, 12-16 (1953).
2. V. A. Zasosov, N. M. Kolgina, et al., Med. Prom. SSSR, No. 4, 9-14 (1966).
3. V. A. Zasosov, N. M. Kolgina, and A. M. Zhelokhovtseva, Khim.-Farmats. Zh., No. 2, 28-32 (1974).
4. M. V. Rubtsov and A. G. Baichikov, Synthetic Chemical-Pharmaceutical Preparations [in Russian], Moscow (1971), pp. 126-127.

OPTIMIZATION OF THE INSULIN SALTING-OUT PROCESS

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The process of salting out insulin from solution belongs to complex biochemical and physical processes. Theoretical premises existing at the present time do not make it possible to obtain a mathematical description of all aspects occurring during this effect [1].

The creation of a general theory of the process would make it possible to carry out an optimal selection of parameters of the process at the planning stage and to achieve optimal control of the process under production conditions in the presence of perturbing factors. The absence of a phenomenological model and the importance of optimization of the problem cause us to turn to methods of experimental optimization of the insulin salting-out process [2].

The effect of three factors on the optimization criterion was examined in this paper: specific weight of the solution going for salting out (x_1), pH of solution (x_2), and its temperature (x_3). The optimization criterion is the maximum activity of solution. Activity was measured by the method of radial paper chromatography [3]. Effect of other factors was not studied because of restrictions of technological character and they were held constant.

A complete factoral experiment and second-order composition plans were used during the development of a mathematical model of the process, describing the stage of salting out, and the search for optimal conditions of occurrence of the processes.

The response surface was restricted by a linear approximation at the first stage of investigation and experiments were carried out by a scheme of a complete factoral experiment (Table 1, experiment Nos. 1-8). Statistical treatment of data of experiment Nos. 1-8

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