A STUDY OF THE PROCESS OF HYDROLYSIS OF p-CARBOMETHOXYSULFANILAMIDE DERIVATIVES (COMMUNICATION III)

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The effect of amount of alkali, temperature, length of heating, and product quality on the process of hydrolysis of 2-(p-carbomethoxyaminobenzenesulfonamido)-5-ethyl-1, 3, 4-thiadiazole (I) and of 4-(p-carbomethoxyaminobenzenesulfonamido)-2,6-dimethoxypyrimidine (II) has been examined.

EXPERIMENTAL

Materials Studied. 2-(p-Aminobenzenesulfonamido)-5-ethyl-1, 3, 4-thiadiazole (I') conforming to GFKh (State Pharmacopeia) standards; I, purified (for method of preparation, see below); I, technical, content of main compound, 97.5%; II, purified (for method of purification, see below); mp 212-213°; II, technical, main component content 99.7%, mp 196-200°.

The methods of pH measurement and measuring rate of hydrolysis at the N^4 and N^1 nitrogens, and of determining by-products by thin-layer chromatography have been given in [1].

Preparation of Purified I. To a solution of 100 g of technical p-carbomethoxyaminobenzenesulfonyl chloride (III) in 250 ml of acetone was added 5 g of activated charcoal, the mixture was stirred for 1 h and filtered, and the filtrate was poured into 1000 ml of ice water. The precipitate which fell was washed with water (five times with 100 ml portions) and dried. The compound III obtained (80 g, mp 113-115°) was dissolved in 100 ml of dichloroethane, the soltuion was warmed with 3 g of charcoal, filtered, and cooled: the precipitate which separated was filtered off, washed with dichloroethane (three times with 10-ml portions), and dried. The yield of pure III obtained was 70 g, mp 117-118°. Condensation of it with purified 2-amino-5-ethyl-1, 3, 4-thiadiazole (IV), mp 194-195°, led to I, mp 218-219°, content of main component, 99.98% (for

TABLE 1. Effect of Amount of Alkali and Temperature on Process of Hydrolysis of I (reaction time, 30 min)

Sodium hydroxide (moles/mole of I)	Hydrolysis at N^4 (%)			ΔpH at 80°
	70°	80°	90°	
3,0	—	—	91	—
3,2	72	92	96	0,60*
3,5	80	93	98	0,30
4,0	84	96	100	0,30

Change in pH because of lower buffer capacity.

TABLE 2. Rate of Hydrolysis of I (temperature 90°; 3.2 moles of sodium hydroxide/mole of I)

Duration (min)	Hydrolysis (%)
10	79
20	93
30	97
40	99
50	100

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TABLE 3. Results of Hydrolysis of Pure and of Technical I

Sample	Temperature (in deg)	Sodium hydroxide (moles/mole of I)	Yield of I' (%)	Content of I' in mother liquor (%)	mp of I' (deg)
Pure	90	3,2	97	1,20	186
"	90	3,2	98	1,54	186
Technical	80	3,2	88,2	11,12	185
"	90	3,5	87,4	11,8	186

TABLE 4. Effect of Heating Time and Amount of Alkali on Rate of Hydrolysis of II (at 90°)

Heating time (min)	Hydrolysis at N^4 (%)		
	alkali (moles/mole of II)		
	4,0	4,1	4,3
10	41,0	47,5	58,0
20	58,3	75,6	80,0
30	73,4	86,4	90,0
40	84,2	97,2	99,0
50	90,7	99,4	100,0
60	97,2	99,9	
70	100,0	99,8	

TABLE 5. Effect of Temperature on Rate of Hydrolysis of II

Heating time (min)	Hydrolysis at N^4 (%)					
	4.1 moles of NaOH per mole of II			4.3 moles of NaOH per mole of II		
	85°	90°	95°	85°	90°	95°
10	33,2	47,5	—	45,4	58,0	62,8
20	63,0	—	69	69,2	80,0	84,2
30	73,5	82,1	82,1	79,9	90,0	95,0
40	79,8	90,2	99,7	88,6	99,0	99,4
50	86,1	99,4	99,7	95,0	100,0	100,0
60	92,4	99,9	99,9	99,4	—	—
70	100,0	99,8	99,9	—	—	—

TABLE 6. Results of Hydrolysis of II (conditions: 90°; 4.1 moles of NaOH per mole of II)

Sample of II	Yield of II' (%)	Content of II' in mother liquor (%)	Overall yield, calc. on II (%)	mp of II' (deg)
Pure	96,0	2,7	98,7	198
"	96,0	1,4	97,4	198
Technical	92,0	5,5	97,5	193
"	92,0	7,6	99,6	192

method of determination, see [2]). Found, %: C 42.30; H 4.10; N 15.70; S 18.60. $C_{12}H_{14}N_4O_4S_2$. Calculated, %: C 42.20; H 4.12; N 16.37; S 18.71.

Preparation of Purified II. Technical II (20 g) was dissolved in 200 ml of acetone, the solution was heated at the boiling point for 30 min with 3 g of activated charcoal, it was filtered, 200 ml of water was poured into the filtrate with stirring, the mixture was cooled, and the precipitate was filtered off. After three such crystallizations, the purified II had mp 212-213°, and a content of main compound of 99.7-100.2% (for method of determination, see [2]). Found, %: C 45.81; H 4.55; N 14.94; S 8.53. $C_{14}H_{16}N_4O_6S$. Calculated, %: C 45.55; H 4,61; N 15.17; S 8.67.

Results of Experiments on Hydrolysis of I. From Table 1 it follows that, at 90° and a reaction time of 30 min, an increase in the amount of alkali over 3.2 moles per mole of I essentially does not affect the hydrolysis results.

The rate of hydrolysis of technical I differs little from that for pure I. Results of determining the rate of hydrolysis of I are shown in Table 2. The data obtained indicate stability of compounds I and I' to hydrolysis at N^1. The percent content of a solution of I' in 0.5 N sodium hydroxide solution did not change after heating it for 1 h at 100°.

In Table 3 we give the results of hydrolysis of samples of pure and technical I. Just as in previously described cases [1], the yield of I' depends on the purity of the starting I. Raising the hydrolysis temperature to 90° and increasing the amount of alkali (more than 3.2 moles per mole of I) does not affect the yield of I'.

The use of mother liquors does not greatly raise the yield of I' (2% in all). Only traces of sulfanilic acid or sulfanilamide were detected in the mother liquors after isolating I' in the hydrolysis of pure I. In the case of isolating I' from technical I (manufacturing concentrations), one substance was detected in a concentration equal approximately to the solubility of I' in the mother liquor; it had an R_f which was close to that of I'. Chromatography showed that this substance is not IV. In view of the fact that the content of this impurity was slight, we did not identify it.

Hydrolysis of II. Data on the effect of heating time, temperature, amount of alkali, and purity of product on the course of hydrolysis of II are given in Tables 4-6.

Investigation of the possibility of hydrolysis at N^1 demonstrated the stability of the amide part of the molecule under the conditions used (see chromatographic studies). After 3-h boiling of II or II' with alkali (4.5 moles per mole of II or II'), analysis of the solutions showed that the content of the main material (for method of determination, see [2]) had not changed.

In Table 6 we give the results of experiments on hydrolysis of pure and technical II.

In work with technical II, a certain lowering of the yield of technical II' is observed, plus an increase in the content of II' in the mother liquor (see Table 6). Experiment 4 was carried out in the mother liquor from experiment No. 3. In this case, no increase in yield was observed, and the quality of the technical II' was not impaired.

Chromatographic (thin-layer chromatographic) studies showed that the mother liquors obtained as a result of hydrolysis of pure II give a single spot.

CONCLUSIONS

1. The optimum conditions for hydrolysis of I should be considered 80°, 3.2 moles of caustic soda per mole of product to be hydrolyzed, at a reaction time of 40 min; for II, these are respectively 90°, 4.1 moles of alkali per mole of product to be hydrolyzed, and a reaction time of 60 min.

2. Chromatographic studies have shown that under the optimum conditions hydrolysis at N^1 and destruction of the pyrimidine or thiadiazole ring do not take place.

3. The possibility of recycling the mother liquors after isolating a technical sulfanilamide compound has been demonstrated.

4. Hydrolysis of a purified carbomethoxy derivative makes it possible to raise the yield by 4-10%.

LITERATURE CITED

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