HYDROLYSIS OF CARBOMETHOXYSULFANILAMIDE DERIVATIVES.
HYDROLYSIS OF p-CARBOMETHOXYAMINOBENZENESULFONYLGUANIDINE

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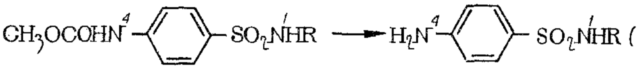
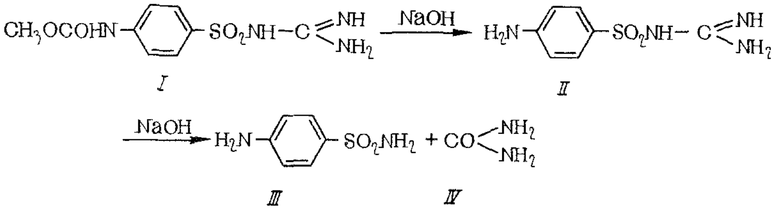
The last chemical stage in the production of many sulfonamide compounds is the hydrolysis of substituted carbomethoxysulfanilamide derivatives:



(1)

The hydrolysis can take place at not only the carbonamide (N^4) group with the formation of the main sulfanilamide product, but also at the sulfonamide group (N^1) with the formation of side products. For example, during the hydrolysis of p-carbomethoxyaminobenzenesulfonylguanidine (I), N^1-carbamidosulfanilamide (sulfanilylurea) can be formed as a side product. Also, the compounds (II) or (III) can hydrolyze to form a sodium salt of sulfanilic acid:



The urea formed at a high temperature (about 100°) in an alkaline solution decomposes with evolution of CO_2 and NH_3 [1].

TABLE 1. Influence of the Duration of the Reaction and the Concentration of the Alkali on the Hydrolysis of (I)

Duration of reaction (min)	Concentration of alkali (N)	% of hydrolysis at N^1		% of hydrosis at N^4	
		of sulfaguine	I	I	V
15	0,25	0,31	1,8	63	93
15	0,50	5,1	6,5	97	97
15	1,00	14,7	11,3	97	99
30	0,25	12,7	6,0	88	98
30	0,50	17,4	15,2	97	97
30	1,00	34,3	28,0	100	100
45	0,25	17,3	11,0	100	100
45	0,50	31,1	27,7	98	100
45	1,00	49,6	42,7	100	100
60	0,25	22,7	17,0	100	100
60	0,50	39,0	30,5	100	100
60	1,00	56,8	52,5	100	100

TABLE 2. Influence of the Time of Holding the Reaction Mixture at 100° on the Content of Diazotizable Substances

Time of holding (min)	Content of diazotizable substances	
	experiment 1	experiment 2
10	82,8	82,0
15	83,0	81,0
25	83,0	80,2
35	81,5	79,5
60	75,9	69,5

EXPERIMENTAL*

Starting Materials: p-Aminobenzenesulfonylguanidine (II) (sulfaguine GFIX); p-carbomethoxyaminobenzenesulfonylguanidine (I) commercial (96%); p-carbomethoxyaminobenzenesulfonylguanidine (I) purified (for preparation, see below).

The pH of the reaction mixture was measured by a LPU-01 pH-meter. The electrodes system consisted of a type ShchVT glass electrodes in conjunction with a dropping mercury electrode.

The rate of the hydrolysis at N^4 was found by withdrawing a sample of the reaction mixture at given intervals of time and titrating an aliquot portion with sodium nitrite [2].

The hydrolysis at N^1 was found by distilling ammonia (through a Kjeldahl apparatus) from the reaction mixture under a slightly reduced pressure, at given intervals of time, and neutralizing the ammonia with a standardized solution of sulfuric acid.

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*With the participation of T. A. Dubinina.

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TABLE 3. Influence of the Amount of Alkali on the Yield of Sulfaguine

NaOH (% of theoretical)	pH of solution at 98°	% of hydrolysis at N^1	Yield of sulfaguine (% of theoretical)
None added	7.8	0	0
100	11.4	2.7	8
122	12.1	3.5	12
148	12.5	10.6	68

TABLE 4. Influence of Temperature on the Hydrolysis of (I)

Duration of hydrolysis (min)	Conversion, %		
	70°	80°	99°
15	35.4	45.6	96.0
30	43.6	73.0	98.0
45	62.6	82.0	100.0
60	73.9	88.0	100.0
90	92.0	97.0	–
105	95.0	100.0	–
120	98.0	–	–

The side products were chromatographed as follows: on paper (n-butanol - water system, developer - the Ehrlich reagent); thin-layer chromatography, 200 × 100 mm plates with a fixed silica gel layer (type KSK with a 5% admixture of calcium sulfate); the plates were activated for 30 min at 120°, developer - the Ehrlich reagent.

Preparation of Purified (I). A solution of 50 g of commercial p-carbomethoxyaminobenzenesulfonyl chloride in 150 ml of acetone was treated with 2 g of activated charcoal, stirred for 1 h, and filtered. The filtrate was poured into ice-water (750 ml); the precipitate that separated was washed four times with water (150 ml) and dried. The yield of purified sulfonyl chloride was 44 g, mp 117-118°.

A 32 ml portion of a 40% sodium hydroxide solution was added to a solution of 20 g of guanidine nitrate in 160 ml of acetone, and this solution of the base was treated in small portions with cooling (the temperature of the reaction mixture was 12-15°) with 40 g of the purified sulfonyl chloride. The reaction mixture was stirred for 1 h, and filtered. The precipitate was washed until the washings gave no chloride ion reaction, and dried (80-85°) to constant weight. The yield of purified (I) was 40 g. Found, %: C 39.89; H 4.42; N 20.80; S 11.86. $C_9H_{12}N_4SO_4$. Calculated, %: C 39.70; H 4.41; N 20.60; S 11.78.

Results of the Experiments and Discussion. The data on the influence of the concentration of the alkali and the duration of the reaction on the hydrolysis at N^4 and at N^1 of carbomethoxyaminobenzenesulfoxylguanidine (I) are given on Table 1. The data on the hydrolysis of sulfaguine (II) at N^1 under the same conditions, and of carbomethoxysulfanilamide p-$CH_3OCONHC_6H_4SO_2NH_2$ (V) at N^4 are shown on the same table for comparison.

These data show that in a 0.5 N sodium hydroxide (2% excess of alkali) at 100° the hydrolysis at N^4 is complete after 15 min. Further holding of the reaction mixture under the same conditions leads to a decrease of the sulfaguine content (hydrolysis at N^4).

It was found (Table 2) that during the hydrolysis of (I) in an alkaline medium at 100° the content of diazotizable substances in the reaction mixture gradually decreases.

The data on the influence of the concentration of alkali on the yield of sulfaguine are shown on Table 3. It was found that after the hydrolysis the minimal pH value of the mother liquors was 11.6 (at 25°).

Data on the influence of temperature on the hydrolysis process are shown on Table 4.

It has already been shown that at a temperature of about 100° the rate of hydrolysis is high, and a short exposure (about 15-20 min) can not always be realized under industrial conditions. Therefore, further experiments on the hydrolysis of purified (I) were carried out at 80° with a reaction time of 90 min. Under optimal conditions and with repeated use of the mother liquor the yield reached 94%. It should be noted that in the hydrolysis of commercial (I) containing 96% of the basic substance the yield of sulfaguine in our experiments did not exceed 79%, i.e., it was lower than in the hydrolysis of purified (I) under the same conditons.

After sulfaguine (II) had separated, sulfanilamide (III) and sulfanilic acid (VI) were also detected in the mother liquors in a ratio of 10:1.

No satisfactory results were obtained with thin-layer chromatography for a quantitative determination of the side products (III) and (VI), since desorption during the extraction of these substances from the silica gel layer is not complete, and the amount of admixtures left is not always constant.

LITERATURE CITED

1. J. Wolker, and J. Hambly, J. Chem Soc., 67, 747 (1895).
2. M. A. Portnov, T. A. Veselitskaya, and V. A. Mikhalev, Med. prom. SSSR, No. 12, 27 (1962).