heated for 2 hours at 40°C (for compounds (XIII) and (XIV)) or at 80°C (for compounds (XV) and (XVI)), and cooled, and the precipitate was filtered off and recrystallized from propanol.

Sodium Benzothiazol-2-yl-hydrazinomethanesulfonate (XVII). A mixture of 7.6 g (50 mmole) sodium hydroxymethanesulfonate monohydrate and 8.3 g (50 mmole) of compound (XII) in 70 ml of aqueous ethanol (5:2) was heated at 80°C for 5 h, the ethanol was distilled off, and the precipitate was filtered off and washed with ether.

N-(Benzothiazol-2-yl)-N-(2-cyanoethyl)hydrazine (XVIII). A solution of 8.3 g (50 mmole) of compound (XII) in dioxane was treated with 0.5 ml of 40% aqueous KOH solution and 2.65 g (50 mmole) of acrylonitrile in 10 ml of dioxane, and the mixture was kept for 2 h and was purified by chromatography on a column of Al_2O_3 (with dioxane as eluent). After the addition of hexane, the precipitate was filtered off.

N-(Benzothiazolyl)-N'-(ethoxymethylene)hydrazine (XIX). A mixture of 8.3 g (50 mmole) of compound (XII) and 19.8 g (150 mmole) of ethyl orthoformate was heated at 120°C for 3 h with the simultaneous elimination of ethanol, and then the excess of ethyl orthoformate was distilled off, the residue was treated with hexane, and the precipitate was filtered off and washed with hexane.

2-(3,5-Dimethylpyrazol-1-yl)benzothiazole (XX). A mixture of 5 g (30 mmole) of compound (XII) and 50 ml of acetylacetone was heated at 125°C for 3 h and was cooled, and the precipitate was filtered off and recrystallized from propanol—water (2:1).

1,2,4-Triazolo[4,3-b]benzothiazole (XXI). A mixture of 8.3 g (50 mmole) of compound (XII) and 40 ml of formic acid was heated at 100°C for 2 h 30 min, cooled, and poured into 500 ml of water, and the precipitate was filtered off and washed with water.

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AN INVESTIGATION OF THE TRANSFORMATIONS OF 2-AMINO-2-THIAZOLIN-4-ONE AND ITS DERIVATIVES IN AQUEOUS SOLUTIONS

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It has been shown by thin-layer radiochromatography that the action of an aqueous solution of alkali on 2-amino-2-thiazolin-4-one and its 5-alkyl derivatives leads predominantly to the opening of the ring by a mechanism similar to the opening of lactams in an alkaline medium.

2-Amino-2-thiazolin-4-one and its 5-alkyl derivatives possess a radioprotective action [1]. In aqueous solutions at pH > 7 these compounds decompose with the formation of urea and thiourea and of 2-hydroxy and 2-mercapto carboxylic acids [2-5]. This composition of the reaction products presupposes that an opening of the initial heterocycle at the $S—C_{(5)}$ or $S—C_{(2)}$ bond first takes place (scheme, pathways 1 and 3). The presence of a lactam grouping in the 2-amino-2-thiazolin-4-one molecule permits the assumption that, under the conditions considered, opening of the heterocycle at the $N_{(3)}—C_{(4)}$ bond is also possible (scheme, pathway 2) [6]. We have therefore made a quantitative investigation of the behavior of 2-amino-2-thiazolin-4-one derivatives in aqueous alkaline solutions.

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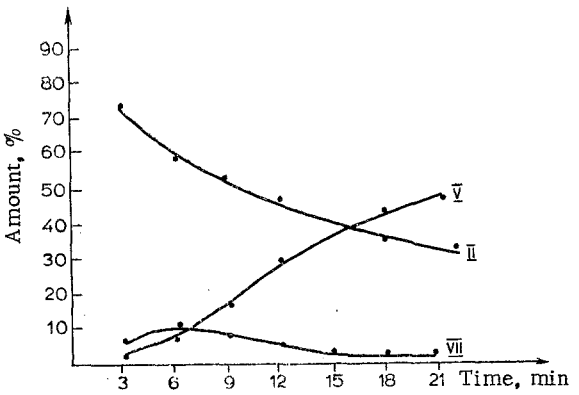
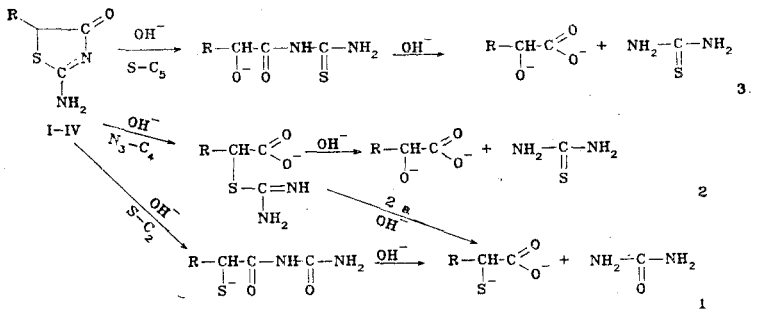


Fig. 1. Change in the amounts of reaction products (II), (V), and (VII) under the action of 2 N KOH on 2-amino-2-thiazolin-4-one (C_0 = 0.01 M) at 70°C.



I, II R=H; III R=CH_3; IV R=C_2H_5

With this aim, we synthesized [2-^{14}C]-2-amino-2-thiazolin-4-one (I), and also [^{35}S]-2-amino-2-thiazolin-4-one (II) and its 5-methyl and 5-ethyl derivatives (III and IV). To separate the reaction products and estimate their concentrations quantitatively, we used the method of thin-layer radiochromatography.

The use of 2-amino-2-thiazolin-4-one containing carbon-14 permitted separate determinations of the amounts of thiourea and urea in the reaction mixture. However, on the radiochromatograms it was possible to record only a single transformation product — thiourea.

Under the conditions of performing kinetic experiments, thiourea is fairly stable [7]. We have shown that under these conditions its decomposition does not exceed 10%. In a special experiment with nonradioactive 2-amino-5-methyl-2-thiazolin-4-one under the conditions of kinetic experiments, the end products of its cleavage — thiourea (V) and lactic acid (VI) — were isolated in good yield and identified.

Thus, the experiments performed with the use of compound (I) permit the possibility of the transformation of 2-amino-2-thiazolin-4-one by pathway 1 under our conditions being excluded, although this could not have been expected on the basis of literature statements [2].

The appearance of thiourea and of 2-hydroxy carboxylic acids among the transformation products of the heterocycles studied could take place as the result of cleavage of the S—$C_{(5)}$ bond [2, 3] (with subsequent decomposition of the N-glycolylthiourea or its analogs) or also at the $N_{(3)}$—$C_{(4)}$ bond (with the subsequent splitting out of thiourea from the S-(1-carboxylalkyl)-isothiourea [8]). The latter direction of the reaction (scheme, pathway 2) is possible because of the presence of a lactam grouping in the 2-amino-2-thiazolin-4-one molecule and can take place by a known mechanism of alkaline hydrolysis [6].

To determine whether the opening of the ring at the $N_{(3)}$—$C_{(4)}$ bond does actually take place, we studied the composition of the products formed under the action of 2 N KOH on [^{35}S]-2-amino-2-thiazolin-4-one at 70°C.

TABLE 1. Rate Constants (min^{-1}) of the Hydrolytic Cleavage of Some 2-Amino-2-thiazolin-4-ones (C_0 = 0.01 M, 70°C) as Functions of the Concentration of Alkali

Compound	Experimental conditions		
	2 N KOD in D_2O	2 N KOH in H_2O	0.1 N KOH in H_2O
II	0,018±0,001	0,037±0,002	0,033±0,001
III	—	0,028±0,002	0,019±0,001
IV	—	0,018±0,001	0,0059±0,0002

It was found that as early as the sixth minute the reaction mixture contained about 12% of S-(1-carboxymethyl)isothiourea (VII), which by the twentieth minute had undergone further transformation completely (Fig. 1). The rate constant of the transformation of compound (VII) under identical conditions was six times greater ($k = 0.194 \pm 0.006$ min^{-1}) than the rate constant of the opening of the ring of 2-amino-2-thiozolin-4-one ($k = 0.037 \pm 0.002$ min^{-1}). It is obvious that the heterocycle is converted into the isothiourea compound irreversibly.

The absence from the reaction mixture of other compounds containing radioactive sulfur is one more confirmation that under our conditions the conversion of 2-amino-2-thiazolin-4-one by pathways 1 and 2a does not take place.

However, the investigations performed do not permit us to deny the possibility of the formation of the end products of the reaction by pathway 3. Consequently, using information on the composition of the reaction mixture under the action of 2 N KOH on ^{35}S-labeled 2-amino-2-thiazolin-4-one at 70°C, we calculated the rate constant of the formation of thiourea. Within the limits of experimental error, this magnitude agreed with the value of the rate constant of the accumulation of thiourea calculated from the results of the conversion of the isothiourea (VII) under similar conditions. Thus, the formation of thiourea in the transformation of 2-amino-2-thiazolin-4-one takes place practically completely as the result of the opening of the ring by direction 2.

In order to evaluate the rate of splitting out of N-glycolylthiourea, we synthesized an analog of it — N-acetylthiourea labeled with sulfur-35 — and studied the stability of this compound in 2 N KOH at 70°C and 20°C. It was found that in the first case the time of complete conversion did not exceed 30 sec ($k > 1.4$ min^{-1}), and in the second case 6 min ($k > 0.1$ min^{-1}). We also considered the behavior of 2-amino-2-thiazolin-4-one in 2 N KOH at 20°C. However, it was impossible to detect the acyl derivative. For the N-acyl derivative to accumulate, it would be necessary that the rate of its further transformation determined the rate of the whole reaction. Consequently, the cleavage of $S-C_{(5)}$ bond would have to take place at an even greater rate, which is unlikely.

We studied the influence of alkyl substituents in position 5 of the heterocyclic ring and of the concentration of alkali on the stability of the $N_{(3)}-C_{(4)}$ bond. The results obtained are given in Table 1. It was found that the introduction of alkyl substituents appreciably increases the stability of the heterocycles.

The decrease in the values of the rate constant of the reaction on passing from 2 N to 0.1 N potassium hydroxide and from water as solvent to D_2O confirms that the hydroxyl ion takes part in the reaction at the rate-determining stage. It is obvious that the primary attack of the hydroxyl ion takes place at the carbon atom of the carbonyl group. The greater rate of conversion of (VII) as compared with (II) permits the assumption that in the case of the opening of the heterocycle at the $N_{(3)}-C_{(4)}$ bond the attack of the hydroxyl ion on the carbon atom in position 4 is the limiting stage.

Thus, it may be concluded that under the action of an aqueous solution of alkali on 2-amino-2-thiazolin-4-one and its 5-alkyl derivatives the predominant reaction is the opening of the ring at the $N_{(3)}-C_{(4)}$ bond (pathway 2) by a mechanism similar to the alkaline opening of lactam rings.

EXPERIMENTAL

The kinetic experiments with labeled compounds were carried out at 20°C and 70°C with C_0 0.1 M in 0.1 N and 2 N solutions of KOH in water and 2N solutions of KOD in D_2O. The specific radioactivities of the solutions used in the kinetic experiments amounted to 1.85 mBq/ml.

TABLE 2. Physicochemical Characteristics and Chemical and Radiochemical Yields of 2-Amino-2-thiazolin-4-one and Its 5-Alkyl Derivatives and Their Transformation Products

Compound	mp, °C	Yield, %[a]		Specific radioactivity, mBq/mole	R_f in systems[b]		
		A	B		1	2	3
I, II	206	71	60	28	0,35	0,45	0,50
III	205	65	50	28	0,50	0,55	0,60
IV	208	61	52	28	0,60	0,70	0,70
V	176	73	—	—	0,80	0,50	0,70
VI	124[c]	74	—	—	0,75	0,60	0,65[d]

[a] A — Unlabeled compound; B — labeled compound. [b] For the solvent systems, see the Experimental part. [c] Bp at 15.6 hPa; n_D^{20} 1.4390. [d] In system 4.

Three independent runs were carried out in parallel in each individual experiment. In each experiment, at predetermined intervals of time 24 successive samples were taken from the reaction mixture, and these were deposited on Silufol UV-254 plates or on plates coated with cellulose ("LT," Czechoslovakia). The plates were run in n-butanol saturated with 12% hydrobromic acid (system 1) and the products were fixed with Grote's reagent [10]. The radioactivities of the corresponding zones were determined with the aid of a Mark-II liquid scintillation counter (Nuclear Chicago, USA). The results were treated by the method of least squares. The overall rate constants for the cleavage of the heterocycles were calculated by means of the equation for irreversible reactions of the first order. Table 2 gives the characteristics of the 2-amino-2-thiazolin-4-ones synthesized and some of their transformation products. The purity of the compounds synthesized and those isolated were checked by the TLC method in the following systems: 2) the organic layer of butanol—acetic acid—water (4:1:3); 3) butanol—acetone—85% formic acid (1:1:1); and 4) ethanol—ammonia—water (16:1:3).

The labeled compounds (I-V) and (VII) were obtained by the method used for synthesis without a radioactive label [9].

Isolation of the Conversion Products of 2-Amino-5-methyl-2-thiazolin-4-one. After the preparation of 1.5 liters of a 0.01 M solution of 2-amino-5-methyl-2-thiazolin-4-one in 2 N KOH, it was thermostated at 70°C for 1 h, by which time the initial compound had undergone complete conversion (check by TLC). Then it was neutralized with 48% hydrobromic acid, and further 48% hydrobromic acid was added to give a weakly acid reaction (pH 2). After the solvent had been driven off in vacuum, the dry residue was treated with anhydrous acetone (5 × 100 ml) to extract the thiourea (until the reaction with an ammoniacal solution of silver nitrate was negative). Vacuum distillation of the extract gave 1 g (74%) of lactic acid (identified by IR spectra, the coincidence of R_f values in three different systems, and its refractive index, Table 2). The distillation residue, on recrystallization from 2-methylpropan-2-ol, gave thiourea. Its yield was 0.8 g (identified by IR spectra, coincidence of R_f values in three different systems, and the melting point, Table 2).

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