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CONVERSION OF HETEROCYCLES OF THE DIHYDROTHIAZINE–THIAZOLINE SERIES IN AQUEOUS SOLUTIONS

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When heterocycles of the dihydrothiazine–thiazoline series are treated with an aqueous solution of base, they undergo ring opening, leading to formation of ureidoalkanethiols. Study of solvolysis of the heterocycles when treated with ammonia permitted us to observe a novel heterocyclic ring opening reaction, occurring with formation of 2(3)-guanidinoalkanethiols. We have developed a novel preparative method for obtaining 2(3)-guanidinoalkanethiols.

Keywords: 2(3)-guanidinoalkanethiols, solvolysis.

S,N-containing compounds such as 2(3)-aminoalkanethiols and their corresponding amidine derivatives guanidinealkanethiols are among the most effective antiradiation drugs. Among the latter, compounds have been observed with pronounced radioprotective activity [1,2]. Accordingly, there is interest in development of new methods for synthesis of previously inaccessible 2(3)-guanidinoalkanethiols and subsequent search among them for effective radioprotectors.

Several methods are known for synthesis of 2(3)-guanidinoalkanethiols. Guanidinoethanethiol is formed as a result of reaction of guanidine and ethylene thioxide [3]. A disadvantage of this method is the fact that guanidinoethanethiol tends toward oxidation under the reaction conditions, as a result of which the target compound is isolated in low yield (10%).

The reaction of aminoethanethiol with S-methylisothiourea makes it possible to obtain the target compound in yields up to 40% [4]. But synthesis of guanidines by this method is accompanied by formation of large amounts of by-products (disulfides, cyanamides), and the reaction product is difficult to isolate in pure form. So this method is only of theoretical interest.

Reaction of S-methylisothiourea and ammonia gives guanidine which is converted to guanidinoalkanebromide on treatment with dibromoalkanes. The obtained compound then reacts with hydrogen sulfide to give guanidinoalkanethiol [5]. But this method makes it possible to obtain derivatives of guanidinoalkanethiols in good yields in the case when the distance between the guanidine and the thiol group is greater than three carbon atoms.

Compounds where the distance between functional groups is no greater than two or three carbon atoms, i.e., 2(3)-guanidinoalkanethiols, are most interesting from the standpoint of synthesis of potential radioprotective drugs. So an important method for obtaining these compounds is intramolecular rearrangement of salts of S-(aminoalkyl)isothioureas, which occurs in neutral or in weakly basic aqueous solutions. Sodium hydroxide [6,7], barium hydroxide [8], and ammonium hydroxide [6, 8, 9, 10] are used for neutralization of the salt and creating the required pH values for the solution.

As a result of the reaction, a mixture of compounds is formed from which it is very difficult to isolate the target compound.

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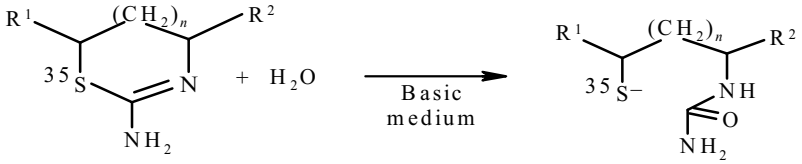
We have shown earlier that 2-amino-2-thiazoline (**1**) and 2-amino-5,6-dihydro-4H-1,3-thiazine (**2**) are stable in aqueous solutions in the pH range 1-7 at 20°C under various conditions [11].

We have investigated conversions of heterocycles of the dihydrothiazine–thiazoline series in basic aqueous solutions. The heterocycles under these conditions can be converted to the corresponding ureidoalkanethiols [12, 13]. Using thin-layer radiochromatography, we quantitatively studied the dependence of the solvolysis rate of the heterocycles on their structure and the temperature in an aqueous (2 mol/l) potassium hydroxide solution (Scheme 1). For these experiments, we synthesized heterocycles labeled with the radionuclide sulfur-35.

Scheme 1



1 – 5

1 R^1 = H, R^2 = H, n = 0; **2** R^1 = H, R^2 = H, n = 1; **3** R^1 = CH_3, R^2 = H, n = 0;
4 R^1 = H, R^2 = CH_3, n = 0; **5** R^1 = H, R^2 = $(CH_3)_2CH$, n = 0

The effective rate constants for the reaction were calculated using the equation for an irreversible first-order reaction (Table 1).

We found that the six-membered heterocycle **2** under these conditions is less stable than the five-membered heterocycles **1, 3-5**. The strength of the S–$C_{(2)}$ bond of the thiazoline ring under solvolysis conditions is affected by the alkyl substituents. A methyl substituent in the 5 position of the ring destabilizes the compound. At the same time, introducing alkyl substituents into the 4 position has practically no effect on the rate of solvolysis of the heterocycle.

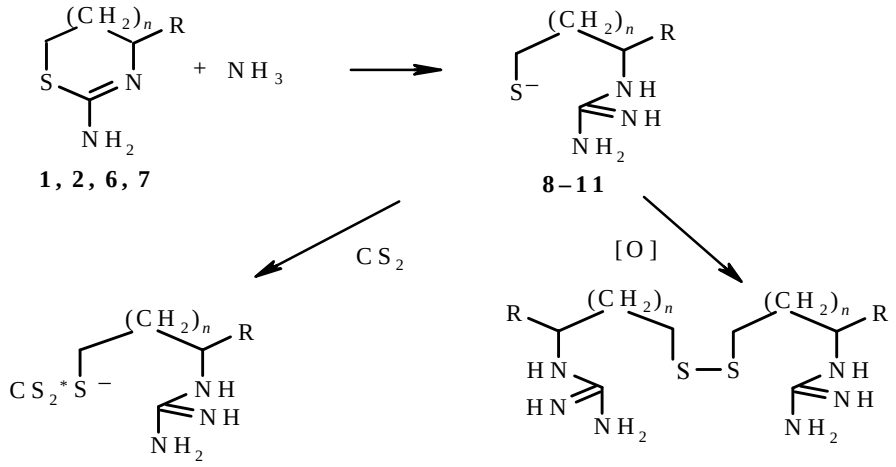
We also investigated the solvolysis of heterocycles **1, 2**, 2-amino-4-methyl-5,6-dihydro-4H-1,3-thiazine (**6**) and 2-amino-4-ethyl-2-thiazoline (**7**) in aqueous solutions in the presence of an excess of ammonia (Scheme 2). The major reaction products under these conditions are the corresponding 2(3)-guanidinoalkanethiols. The ammonolysis products of the heterocycles were isolated from the reaction mixture by preparative paper chromatography in the form of disulfides, and also guanidinoalkanetrithiocarbonates. Their spectral and chromatographic characteristics matched the corresponding physical and chemical parameters of guanidinoalkanethiols obtained by an alternate synthesis from the corresponding S-aminoalkylisothioureas.

Among the byproducts of the ammonolysis reaction of the heterocycles, we detected the corresponding aminoalkanethiols and guanidine in insignificant amounts. The products of alkaline hydrolysis of derivatives of the heterocycles (the corresponding ureidoalkanethiols) were not detected in this case.

TABLE 1. Effective Rate Constants ($k \cdot 10^4$, sec^{-1}) for Solvolysis of Heterocycles **1-5** (C_0 = 0.01 mol/l) in water (2 mol/l KOH)

Compound	T, °C	k	E_a, kJ
1	40	0.061 ± 0.005	88
	55	0.35 ± 0.02	
	70	1.8 ± 0.1	
	85	7.0 ± 0.4	
2	40	0.38 ± 0.02	69
	55	2.0 ± 0.1	
	70	4.7 ± 0.2	
	85	18.3 ± 1.5	
3	70	0.82 ± 0.05	—
4	70	1.6 ± 0.1	—
5	70	1.7 ± 0.1	—

Scheme 2



1 R = H, *n* = 0; **2** R = H, *n* = 1; **6** R = CH_3, *n* = 1; **7** R = C_2H_5, *n* = 0;
8 R = H, *n* = 0; **9** R = H, *n* = 1, **10** R= CH_3, *n* = 1; **11** R = C_2H_5, *n* = 0

With the goal of developing a novel preparative method for obtaining 2(3)-guanidinoalkanethiols, we studied the dependence of the yield of guanidines on the reaction time and temperature, the structure of the starting heterocycles, and also on the concentration of ammonium hydroxide present in solution.

In connection with the fact that 2(3)-guanidinoalkanethiols are easily oxidized by oxygen in the air, it is expedient to conduct their synthesis under an inert gas atmosphere. Table 2 shows the yields of 2(3)-guanidinoalkanethiols in ammonolysis of the heterocycles as a function of the reaction time, the temperature, and the structure of the starting heterocycle.

In order to search for the optimal conditions for preparative synthesis of 2(3)-guanidinoalkanethiols, we assessed the dependence of their yield on the amount of ammonium hydroxide present in the reaction mixture (Table 3).

Analysis of the presented data shows that the yield of 2(3)-guanidinoalkanethiols is highest for a 2-2.5-fold excess of ammonium hydroxide. Further increase in the amounts of ammonium hydroxide does not lead to an increase in the yield of 2(3)-guanidinoalkanethiols.

In direct isolation of guanidinoalkanethiols salts obtained as a result of solvolysis of aqueous solutions of the heterocycles, the reaction product contains the heterocycles and inorganic salts as impurities. A method is known for isolation and identification of guanidinoalkanethiols in the form of flavianates [6,7], in connection with the fact that hydrohalides of guanidinoalkanethiols crystallize very poorly. Guanidinoalkanethiols furthermore may be isolated in the form of salicylates [14]. In our case, we found that guanidinoalkanethiols are most conveniently precipitated from aqueous solution by treatment with carbon disulfide. The trithiocarbonate obtained can be stored for 3 years in unchanged form. If a pure guanidinoalkanethiol is required, the corresponding trithiocarbonate is decomposed by strong mineral acid [10,15].

TABLE 2. Yields (%) of 2(3)-Guanidinoalkanethiols in Ammonolysis of Heterocycles (C_0 = 0.01 mol/l) in the Presence of Ammonium Hydroxide (C_0 = 0.025 mol/l) as a Function of Reaction Time (h), Temperature (°C), and the Structure of Heterocycles **1, 2, 10, 11**

Compound	50		70		90		100	
	Time	Yield	Time	Yield	Time	Yield	Time	Yield
1	5	75	4	70	2	60	0.5	65
2	36	20	30	21	18	39	10	60
10	22	18	12	25	8	30	5	45
11	19	40	10	65	9	70	4	65

TABLE 3. Yield (%) of 2(3)-Guanidinoalkanethiols in Ammonolysis of Heterocycles **1** and **2** (C_0 = 0.01 mol/l) as a Function of Ammonium Hydroxide Concentration in Aqueous Solution at 100°C

Compound	Reaction time, h	Ammonium hydroxide concentration, mol/l				
		0.0125	0.025	0.0375	0.05	0.1
1	5	45	75	75	60	55
2	10	40	65	70	67	65

Thus studies of solvolysis of derivatives of the heterocycles allowed us to observe a novel heterocyclic ring opening reaction by treatment with ammonia in aqueous solutions. As a result of these experiments, we have developed a novel synthesis method and have carried out a preparative synthesis for the 2(3)-guanidinoalkanethiol series.

TABLE 4. Constants for Guanidinoalkanetrithiocarbonates **8-11** and Heterocycle **5***

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*[2]	Yield, %
		C	H	N			
8·CS_2	$C_4H_9N_3S$	24.69 / 24.61	4.75 / 4.61	21.42 / 21.54	142, 140-142 [10]	0.51 (1)	80
9·CS_2	$C_5H_{11}N_3S_3$	29.03 / 28.84	4.77 / 4.80	20.51 / 20.19	132-134 133-135 [10]	0.58 (1)	83
10·CS_2	$C_6H_{13}N_3S_3$	32.41 / 32.28	5.91 / 5.83	19.15 / 18.83	140-141	0.67 (1)	74
11·CS_2	$C_6H_{13}N_3S_3$	32.39 / 32.28	5.96 / 5.83	18.89 / 18.83	167-168	0.74 (1)	79
5	$C_6H_{13}BrN_2S$	32.10 / 32.00	5.84 / 5.77	12.29 / 12.44	134	0.68 (2)	40

*Mass spectrum: **10**·CS_2 – 114 ($C_5H_{12}N_3^+$), 86 ($C_3H_8N_3^+$), 76 (CS_2), 44 ($CH_4N_2^+$), 30 (CH_4N^+).
^{13}C NMR spectrum: **8**·CS_2 – 238.48 (CS_3^-), 156.7 (CN_3^+), 40.53 (CH_2N), 38.59 ppm (CH_2S); **11**·CS_2 – 232.5 (CS_3^-), 155.65 (CN_3^+), 52.74 (CH_2N), 44.39 ppm (CH_2S).
IR spectrum: **9**·CS_2 – 3300 (N–H), 1630, 1600, 1570 cm^{-1} (C=N).
*[2] In parentheses: chromatographic systems.

TABLE 5. Physicochemical Characteristics, Chemical and Radiochemical Yields of Heterocycles **1-5**

Compound	mp, °C	Specific radioactivity, MBq/mole	R_f in systems*			Yield, %*[2]	
			1	2	3	A	B
1	175-176, 175-176 [7]	28	60	55	0.54	60	55
2	134-135 134-135 [6]	20	48	56	0.40	48	56
3	128-129 129-130 [19]	24	80	62	0.63	80	62
4	127-128 128-129 [19]	19	81	75	0.61	81	75
5	134-135	18	0.51	0.68	0.70	40	80

* For chromatographic systems: see Experimental.
*[2] A – unlabeled compound; B – labeled compound.

EXPERIMENTAL

The mass spectra were obtained on a Varian MAT III with injection of the sample directly into the ionizing source. The ^{13}C NMR spectra were obtained on a Brucker HX-80 in methanol, internal standard TMS. The IR spectra were recorded on a Perkin-Elmer 457 in KBr disks. The course of the reaction and the purity of the compounds were monitored by TLC on Silufol UV-254 plates or cellulose-coated plates in the systems: butyl alcohol saturated with 12% hydrobromic acid (system 1), the organic layer of a mixture of 4:1:5 butyl alcohol–acetic acid–water (system 2), and 1:1:1 butyl alcohol–acetone–85% formic acid (system 3), visualization with the Grote reagent [16].

Guanidinoalkanetrithiocarbonates of Compounds 8-11. The corresponding heterocycle hydrobromide (0.01 mol) was dissolved in a 7% aqueous solution of ammonium hydroxide (0.025-0.05 mol, Table 3) (7 ml). The solution was placed into an ampoule, purged with argon and sealed. Then it was heated at the optimum temperature for several hours (Table 2). After cooling down to 0°C, the ampoule was opened, carbon disulfide (2 ml) was added, and it was allowed to stand for 12 h at 0°C. The precipitate was filtered off, washed with water and then with 2-propanol. The yields of the compounds are given in Table 2.

An alternate synthesis for guanidinoalkanethiols was carried out by *trans* guanidination of the corresponding S-aminoalkylisothiourea [6, 7, 17, 18]. The corresponding S-aminoalkylisothiourea dihydrobromide (0.02 mol) was dissolved in a 5% ammonia solution (50 ml) and then cooled down to 0°C. After 15 min, carbon disulfide (8 ml) was added with stirring and then allowed to stand for 12 h at 0°C. The precipitate was filtered off and washed with water and then 2-propanol.

Hydrochlorides 8-11 were obtained as aqueous solutions by decomposition of the corresponding guanidinoalkanetrithiocarbonates with the equivalent amount of hydrochloric acid at 20°C under a stream of argon, required to avoid oxidation of the thiols formed.

2-Amino-4-isopropyl-2-thiazoline Hydrobromide 5. 2-Amino-1-bromo-3-methylbutane hydrobromide (31.50 g, 0.14 mol) was boiled in water with potassium thiocyanate (11.64 g, 0.12 mol) for 50 h [19]. At the end of the reaction, the solution was evaporated down to dryness. Compound **5** was recrystallized from anhydrous ethanol.

The characteristics of the synthesized compounds are given in Tables 4 and 5. Compounds **8-11**, obtained by ammonolysis of heterocycles **1, 2, 6, 7** did not result in depression of the melting point when mixed with guanidinealkanetrithiocarbonates obtained by the methods in [6-9]. The results of elemental analysis confirm the composition of the compounds obtained (Table 4).

Kinetic Studies. We determined the rate constants for opening of the heterocycles by thin-layer chromatography on Silufol plates. For this purpose, we synthesized heterocycles labeled with sulfur-35. The synthesis was carried out by the procedures given for the nonradioactive compounds (Table 5). The kinetic experiments were carried out in capillaries. The capillaries were filled and the chromatographic analysis of the samples was done under a stream of argon. The radiochromatograms were counted by the differential method on a liquid scintillation counter. The data obtained were treated using the kinetic equation for irreversible first-order reactions. Statistical treatment of the experimental data was performed using the standard least-squares method.

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