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SOLVOLYSIS OF 2-AMINO-2-THIAZOLINE DERIVATIVES BY ALIPHATIC AMINO ALCOHOLS

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The opening of the thiazoline ring upon the action of amino alcohols was studied. The effects of the reagent ratio and structures of the heterocycles and amino alcohols on aminolysis were investigated. A new method was developed for the preparative synthesis of a series of N'-(hydroxyalkyl)-2-guanidinoalkanethiols.

Keywords: N'-(hydroxyalkyl)-2-guanidinoalkanethiols, 2-amino-2-thiazoline derivatives, solvolysis.

Thousands of compounds have now been synthesized and tested on mammals, some of which have proved effective radioprotective agents. The most active anti-radiation agents include S,N-containing organic compounds such as 2(3)-aminoalkanethiols and their amidine derivatives, S-(aminoalkyl)isothioureas and guanidinoalkanethiols. There have been only a few studies of the anti-radiation activity of guanidinoalkanethiols, mainly due to the difficulty in preparing these compounds [1].

We have already shown that the introduction of a hydroxy group into 2-amino-2-thiazoline and S-(aminopropyl)isothioureas considerably reduces toxicity with retention of a strong radioprotective effect [2]. The introduction of a hydroxy group into the aminothiol molecule also does not lead to the loss of radioprotective activity. Thus, 3-amino-4-mercapto-2-butanol displays strong activity in mouse experiments [3]. In light of these results, we started work on the preparative synthesis of N'-(hydroxyalkyl)-2-guanidinoalkanethiol derivatives.

In previous work [4], we have shown that dihydrothiazine derivatives can be converted to the corresponding 2(3)-guanidinoalkanethiols in aqueous solution in the presence of ammonia. In the present work, we studied the solvolysis of 2-amino-2-thiazoline derivatives upon the action of various aliphatic amino alcohols. The major reaction products are the corresponding N'-(hydroxyalkyl)-2-guanidinoalkanethiols. The corresponding aminoalkanethiols, their disulfides, and unsubstituted guanidine were found in insignificant amounts as side products. The products of the hydrolytic decomposition of thiazoline derivatives, namely, the corresponding ureidoalkanethiols, are lacking.

The effect of the reagent ratio on the reaction product yield was studied in order to select the optimal conditions for the preparative synthesis of guanidine **5** by the reaction of thiazoline (**1**) with 3-aminopropanol (**18**).

Thus, the yield of guanidine **5** in the reaction of 0.01 mol/l **1** with amino alcohol **18** taken in various mol amounts was as follows (the concentration of **18** is indicated in parentheses: 35 (0.01), 51 (0.02), 55 (0.03), 59 (0.04), 65 (0.05), and 66% (0.06).

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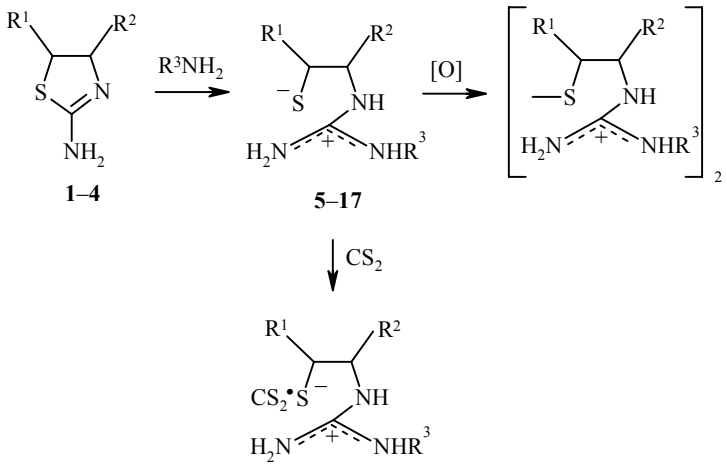


Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
1	H	H		**10**	H	H	$CH_2CH(OH)Me$
2	Me	H		**11**	H	H	$Et(–CH)CH_2OH$
3	H	Me		**12**	H	H	$Me(–CH)CH_2(OH)$
4	H	Et		**13**	H	H	$Me(–CH)CH_2(OH)$
5	H	H	$(CH_2)_3OH$	**14**	Me	H	$(CH_2)_2OH$
6	Me	H	$(CH_2)_3OH$	**15**	Me	H	$Et(–CH)CH_2OH$
7	H	Me	$(CH_2)_3OH$	**16**	H	Me	$(CH_2)_2OH$
8	H	Et	$(CH_2)_3OH$	**17**	H	Me	$Et(–CH)CH_2OH$
9	H	H	$(CH_2)_2OH$				

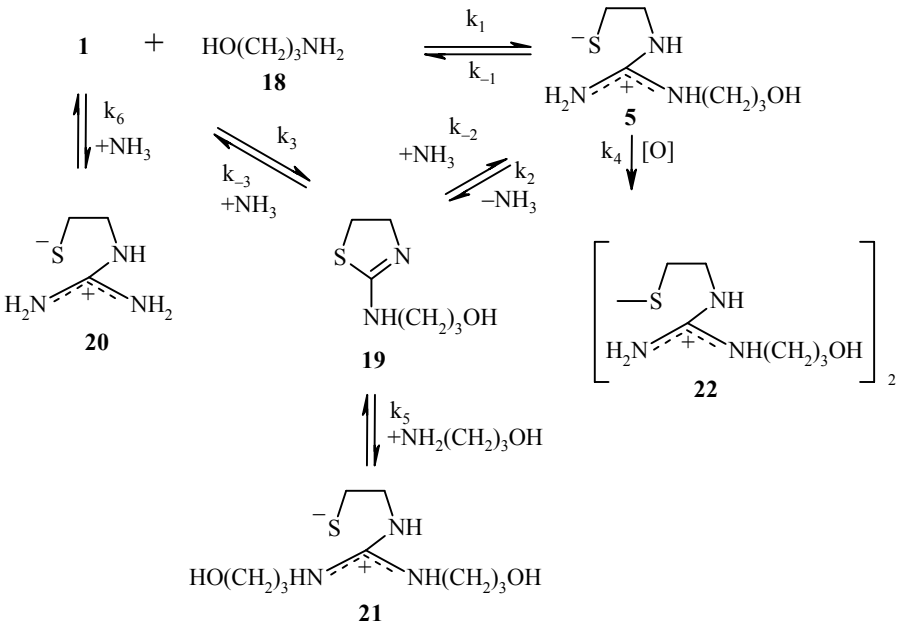
Guanidine **5** here and subsequently was isolated from the reaction medium and identified as the corresponding trithiocarbonate obtained by the reaction of guanidine with carbon disulfide.

A four- or five-fold excess of amino alcohol **18** is required to obtain a suitable yield of guanidine **5**. However, a further increase in the amine concentration does not give a significantly enhanced yield of guanidine. Furthermore, the yield of the desired compound drops with increasing duration of the reaction.

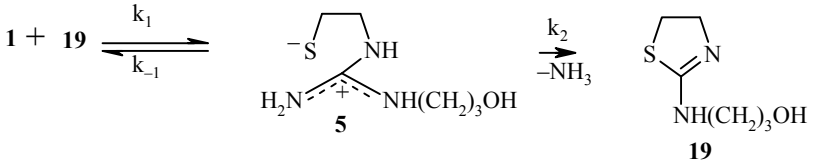
We have already found that 2(3)-guanidinoalkanethiols in aqueous solution at pH 2.5-9.8 are converted irreversibly into the corresponding derivatives of dihydrothiazine and thiazoline [5]. Hence, it appeared that the lack of effect of the reaction time and increase in the concentration of amino alcohol **18** on the yield of the solvolysis product, guanidine **5**, is related to cyclization of guanidine **5** under the aminolysis conditions.

A more detailed study of the mechanism of the reaction of thiazoline **1** with amino alcohol **18** was required. This study was carried out using thin-layer chromatography and heterocycle **1** labeled with carbon-14.

We studied the change in the relative concentrations of heterocycle **1** (c_0 = 0.01 mol/l) over time in the reaction of amino alcohol **18** (c_0 = 0.02 mol/l) in water at 100°C. Guanidine **5** was found to accumulate during the course of the reaction and then was consumed in the formation of an additional product, N'-(3-hydroxypropyl)-2-amino-2-thiazoline (**19**). This heterocycle was isolated from the reaction medium and identified. Furthermore, guanidine **5** is partially oxidized over time under the reaction conditions to give disulfide **22**. These results indicated the following reaction mechanism:



Analysis of these data taking account of a series of limitations permitted us to simplify this scheme. Thus, the extent of oxidation of guanidine **5** (step k_4) was less than 10%, which could be considered negligible, under conditions excluding oxygen. Substituted thiazolines such as **19** are known to be more stable under solvolysis conditions than unsubstituted heterocycles such as **1** [4-6]. Thus, at the reaction onset, reaction through step k_1 is favored over reaction through step k_5. The unlikely reactions proceeding through steps k_{-2}, k_{-3}, and k_6 may also be excluded from consideration without major error. This is permissible since the ammonia concentration in the reaction mixture at the onset is much lower than the concentration of amino alcohol **18**. Thus, if we consider mainly the initial periods of this reaction, the aminolysis may rather correctly be described by the following simplified scheme:



A kinetic study of the aminolysis of thiazoline **1** was carried out to evaluate the cyclization rate constants for guanidine **5** to give thiazoline **1** (k_{-1}) and substituted thiazoline **19** (k_2). For this purpose, a sample of carbon-14-labelled guanidine **5** was prepared. In order to obtain comparable conditions for the aminolysis of the heterocycles by amino alcohols, we studied the solvolysis of [^{14}C]-**5** in a reaction mixture consisting of alcohol **18** and N,N-dimethylaminopropanol (**23**). The first-order rate constants of the parallel reactions given in Table 1 indicate a preference for cyclization of guanidine **5** under the given conditions to give thiazoline **19**. We should note that the hydrolysis of thiazoline **1** to N-mercaptoethylurea does not proceed under the aminolysis reaction conditions. Thus, heating an aqueous solution of **23** with thiazoline **1** for 2 h at reflux showed the latter is stable under these conditions.

TABLE 1. Rate Constants for the Cyclization of Guanidine **5** (c_0 = 0.1 mol/l) to Heterocycles **1** and **19** at 100°C in Water

19, mol/l	**24**, mol/l	$k_{-1}\cdot10^5$, s^{-1}	$k_2\cdot10^5$, s^{-1}
—	0.2	6.2±0.8	13.1±1.8
0.1	0.2	6.9±1.1	13.8±2.2

Comparison of the rate constants for the cyclization of guanidine **5** (k_2 and k_{-1}) clearly shows that the aminolysis should be carried out over the optimal, experimentally determined time period to achieve the maximum yield of N'-substituted guanidines.

Following the our previous study of ammonolysis reactions [4] and the present kinetic data, we attempted to find a preparative synthesis for N'-(hydroxyalkyl)-2-guanidinoalkanethiol derivatives. The reaction of the heterocycles with amino alcohols was carried out at 100°C with a five-fold molar excess of amine without solvent to select the optimal conditions for obtaining guanidines.

The results of our study of the reactivity of 4- and 5-substituted thiazolines in their reaction with amino alcohol **18** are given in Table 2.

We found that unsubstituted thiazoline has the greatest reactivity and the greatest yield of the reaction product is reached 30 min after onset of the reaction. The introduction of a methyl group at $C_{(5)}$ of the heterocycle somewhat reduces the reactivity of thiazoline **2**. However, the reaction time to obtain the maximum yield is unchanged. The introduction of alkyl substituents at $C_{(4)}$ of the thiazoline ring in **3** and **4** alters the time for the optimal synthetic procedure for the corresponding guanidine. On the other hand, the times required for maximum product yields when using heterocycles **3** and **4** are much less than in the reaction with thiazoline **1**.

It was of interest to study the effect of the nucleophile structure on the maximum yield of guanidines **5** and **9-13**. For this purpose, we studied the reaction of thiazoline **1** with various amino alcohols under comparable conditions (see Table 3).

TABLE 2. Dependence of the Yield of Trithiocarbonates from Guanidines **5-8** on the Time of Reaction of Thiazolines **1-4** with **18** at 100°C (Mol Ratio of the Reagents was 1:5)

Compound	Yield, %, by *t*, min				
	10	20	30	60	90
5	80	85	95	65	51
6	68	72	83	57	55
7	78	63	55	49	51
8	66		59		21

TABLE 3. Yield of Trithiocarbonates from Guanidines **5** and **9-13** obtained in the Reaction of Thiazoline **1** with Various Amino Alcohols (Mol Ratio 1:5) at 100°C

Compound	t_{opt}, min	Yield, %	Compound	t_{opt}, min	Yield, %
5	30	95	**11**	30	44
9	45	92	**12**	30	61
10	15	51	**13**	30	58

TABLE 4. Yield of Trithiocarbonates from Guanidines **6-8** and **14-17** obtained in the Reaction of Thiazolines **2-4** with Various Amino Alcohols at 100°C (Mole Ratio 1:5, t = 30 min)

Heterocycle	$HO(CH_2)_2NH_2$	$HO(CH_2)_3NH_2$	$HOCH_2CH(NH_2)Et$
2	45	66	33
3	66	63	51
4	—	65	—

The optimal reaction time depends significantly on the amino alcohol structure. The highest guanidine yields are obtained in the reaction with amino alcohol **18** and 2-aminoethanol. The lower reactivity of amino alcohols with the amino group at a secondary carbon atom may be related to steric hindrance.

The aminolysis of substituted thiazolines **2-4** was studied with the most reactive amino alcohols (Table 4). The highest guanidine yield is observed for unsubstituted thiazoline **1** (Table 3). Substituents introduced at $C_{(4)}$ and $C_{(5)}$ in heterocycles **2-4** lead to a marked decrease in the yield of the desired product.

Further investigation of the aminolysis of thiazoline derivatives permitted us to select the optimal conditions for obtaining new N-(hydroxyalkyl)guanidinoalkanethiols and then develop preparative syntheses of these compounds in high yield.

We should note that the use of the starting heterocycles as salts or bases has no effect on the yield of the desired products and the reaction conditions. The selection of the heterocycles or their salts was made solely on the basis of synthetic availability. The preparation of guanidines should be carried out in an inert gas atmosphere since these compounds are readily oxidized by atmospheric oxygen at 100°C. For identification and subsequent preparation of various salts, N'-(hydroxyalkyl)guanidinoalkanethiols are conveniently isolated as trithiocarbonates, which have low solubility in water and are stable upon storage. These products precipitate out when carbon disulfide is added to the reaction mixture [7]. Then, the trithiocarbonate solution was decomposed by the action of the required acid [8].

The products of the solvolysis of thiazolines **1-4** were isolated and identified (see Table 5).

Thus, we have studied the opening of the thiazoline ring upon the action of aliphatic amino alcohols. The effects of the reagent ratio and structures of the heterocycles and amino alcohols on the aminolysis reaction were studied. These results suggested a new preparative synthesis of a series of new N'-(hydroxyalkyl)-guanidinoalkanethiols.

EXPERIMENTAL

The mass spectra were taken on a Varian MAT-III mass spectrometer with direct introduction of the sample into the ionization chamber. The ^{13}C NMR spectra were taken in methanol on a Bruker HX-80 spectrometer at 80 MHz with TMS as the internal standard. The IR spectra were taken on a Perkin–Elmer 457 spectrometer for KBr pellets. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates.

Guanidinoalkanetrithiocarbonates of 5-17. A sample of corresponding hydrobromide salt of heterocycle **1-4** (0.01 mol) was dissolved in amino alcohol (0.01-0.06 mol). The solution was placed in an ampule and flushed with argon. The ampule was sealed and heated at the optimal temperature for a given period. After cooling to 0°C, the ampule was opened. Then, carbon disulfide (2 ml) was added with stirring and left for 12 h at 0°C. The residue was filtered off and washed with water, 2-propanol, and ether. The physicochemical and spectral indices of these compounds are given in Table 5.

TABLE 5. Physicochemical Indices of N-Derivatives of 2(3)-Guanidinoalkanethiols

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	^{13}C NMR spectrum, δ, ppm.					Yield, %
		C	H	N		CS_3	CN^+_3	CH_2O	CH_2S	Other groups	
5·CS_2	$C_7H_{15}N_3OS_3$	33.01 / 33.20	5.94 / 5.93	16.81 / 16.60	145-147	238.50	155.65	57.93	38.44	40.73 (C^4H_2N); 31.74 (C^6H_2N); 30.78 (CH_2)	95
6·CS_2	$C_8H_{17}N_3OS_3$	35.71 / 35.95	6.37 / 6.15	15.64 / 15.74	145-146	238.67	155.77	57.90	46.95	46.22 (C^5H_2N); 38.38 (C^3H_2N) 31.41 (CH_2); 16.30 (CH_3)	63
7·CS_2	$C_8H_{17}N_3OS_3$	35.62 / 35.95	6.10 / 6.37	15.48 / 15.73	142-143	238.71	155.01	57.91	45.74	47.38 (CH); 38.37 (CH_2N); 31.43 (CH_2); 19.74 (CH_3)	60
8·CS_2	$C_9H_{19}N_3OS_3$	37.84 / 38.43	6.43 / 6.76	14.53 / 14.95	170-172	238.98	155.50	57.93	44.34	38.42 (C^3H_2N); 10.06 (CH_3); 52.92 (CH)	66
9·CS_2	$C_6H_{13}N_3OS_3$	29.84 / 30.12	5.10 / 5.45	17.50 / 17.57	162-164	238.87	156.10	59.52	38.70	48.89 (C^5H_2N); 40.85 (C^3H_2N)	92
10·CS_2	$C_7H_{15}N_3OS_3$	32.41 / 32.20	5.90 / 5.77	16.85 / 16.60	155-157	238.43	155.60	57.82	38.38	48.89 (C^5H_2N); 38.33 (C^3H_2N); 38.38 (CH_2S); 31.39 (CH_3)	51
11·CS_2	$C_8H_{17}N_3OS_3$	35.54 / 35.93	5.99 / 6.37	15.66 / 15.73	141-143	238.42	155.75	62.55	39.35	40.72 (CH_2N); 54.87 (CHN); 2.71 (CH_2); 10.14 (CH_3)	44
12·CS_2	$C_7H_{15}N_3OS_3$	33.71 / 33.20	5.42 / 5.93	16.44 / 16.60	156-158	238.53	155.72	55.66	38.36	35.90 (C^6H_2N); 28.29 (CH_2); 14.30 (CH_3)	61
13·CS_2	$C_8H_{17}N_3OS_3$	35.31 / 35.93	6.21 / 6.37	15.82 / 15.73	148-150	238.24	155.56	63.61	38.38	40.66 (C^4H_2N); 38.43 (CH_2), (CH), 223.73 (CH_3)	58
14	$C_7H_{15}N_3OS_3$	32.95 / 33.20	5.35 / 5.93	16.75 / 16.60	160-163	238.56	156.15	59.40	46.94	46.29 (C^5H_2N); 43.74 (C^3H_2N); 16.33 (CH_3)	66
15·CS_2	$C_9H_{19}N_3OS_3$	38.19 / 38.43	6.55 / 6.76	14.41 / 14.95	128-130	238.46	155.90	62.70	46.80	54.95 (C^5H_2N); 46.30 (C^3H_2N); 23.76 (CH_2); 10.10 (CH_3)	51
16·CS_2	$C_7H_{15}N_3OS_3$	32.97 / 33.20	5.71 / 5.93	16.70 / 16.60	167-168	238.83	155.34	59.42	45.73	47.48 (CH); 43.85 (CH_2N); 19.76 (CH_3)	45
17·CS_2	$C_8H_{17}N_3OS_3$	38.03 / 38.43	6.10 / 6.76	14.80 / 14.95	130-132	238.69	155.10	63.52	45.72	54.89 (C^5H_2N); 47.30 (C^3H_2N); 23.72 (CH_2); 10.13 (CH_3)	33
19*	$C_6H_{12}N_2OS$	44.80 / 45.00	7.82 / 7.50	17.28 / 17.50	139-141	—	—	—	—		62

* IR spectrum, ν, cm^{-1}: 3250 (=NH); 1650, 1620, 1570, 1430 (=C=N–); 1000, 960, 860, 800 (≡C–S–C≡).

Hydrochlorides 5-17 were obtained as aqueous solutions by decomposition of the corresponding guanidinoalkanetrithiocarbonates upon adding an equivalent amount of hydrochloric acid at 20°C in an argon stream required to prevent oxidation of the thiols formed.

The kinetic studies were carried out using thin-layer chromatography (see Table 1). A sample of carbon-14-labelled guanidine **5** was prepared according to the method of the unlabelled compound. The synthesis of carbon-14-labelled thiazoline **1** was described in our previous work [4].

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