S 16.17%. $C_8H_{10}N_2O_2S$. Calculated: N 14.15; S 16.19%.

2-Acetylimino-3,3'-diallyl-4,2'-dioxo-5,4'-dithiazolidinylidene. A. To a solution of 1.56 g (10 mmole) compound V in 10 ml acetic anhydride was added 1.56 g (10 mmole) 3-allylthiazolidin-2,4-dione (IV), and the reaction mixture was heated for 4 h with constant stirring. After being cooled the reaction mixture was poured into ice water, and the precipitate was filtered, dried, and crystallized from isopropyl alcohol. Yield 1.73 g (54%), mp 150-151°C. Found: N 12.40; S 19.01%. $C_{14}H_{15}N_3O_3S_2$. Calculated: N 12.45; S 19.00%.

B. To a solution of 1.98 g (10 mmole) compound VI in 10 ml acetic anhydride was added 1.56 g (10 mmole) compound IV; the mixture was further worked up according to the above procedure. Yield 2.05 g (61%), mp 150-151°C.

2-Acetylimino-3,3'-diallyl-4,2'-dioxo-5'-benzylidene-5,4'-dithiazolidinylidene (VIII). To a solution of 1.68 (5 mmole) compound VII in 10 ml acetic acid was added 0.5 g (5 mmole) benzaldehyde and 2 drops of 25% aqueous methylamine solution. The mixture was heated in an oil bath at 110-120°C for 2 h with constant stirring. After being cooled the reaction mixture was poured into water and filtered. The product was washed on the filter with ether and dried. Yield 1.6 g (76%), mp 211-212°C (acetic acid). Found: N 10.02; S 14.98%. $C_{21}H_{19}N_3O_3S_2$. Calculated: N 9.89; S 15.06%.

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INTRAMOLECULAR CYCLIZATION OF GUANIDINOALKANETHIOLS IN AQUEOUS SOLUTION

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We have demonstrated the basic possibility of cyclizing guanidinoalkanethiols of different structure to thiazolines and thiazines. The rate of reaction depends on the pH of the medium. The concentration of buffer and the addition of heavy water and α-D,L-alanine have virtually no effect on the rate of reaction.

Methods are known for obtaining dihydrothiazines and thiazolines by the reaction of potassium thiocyanate with suitable haloaminoalkanes [1] as well as by cyclization of derivatives of S-2(3)-aminoalkylisothioureas in acid solution [2].

We have studied the behavior of 2-guanidinoethanethiol (I), 3-guanidinopropanethiol (II), 3-guanidinobutanethiol (III), and 2-guanidinobutanethiol (IV) in aqueous solution. When compounds I-IV are heated in water without admission of oxygen, dihydrothiazine or

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TABLE 1. Rate Constants for Cyclization of Compounds I-IV (c_0 = 0.05 moles, k × 10^5, sec^{-1}, 80°C, in 0.2 M aqueous phosphate buffers in 1 N KCl)

Compound	pH 6,2	pH 6,8	Compound	pH 6,2	pH 6,8
I	6,2±0,6	7,2±0,6	III	0,79±0,09	0,95±0,10
II	0,70±0,06	0,78±0,07	IV	9,1±1,0	11,1±1,2

TABLE 2. Rate Constants for Cyclization of Compounds I and II*

Buffer solution	I		II	
	pH	$k \times 10^5$, sec^{-1}	pH	$k \times 10^6$, sec^{-1}
Acetate	2,55	4,25±0,25	3,8	2,5±0,3
	3,75	8,40±0,27		
	5,20	10,5±0,5		
	5,90	17,7±0,2		
Diphthalate			4,5	3,1±0,3
Phosphate	7,0	29,8±2,5	5,1	4,1±0,5
	7,45	19,7±0,3	6,2	7,0±0,6
			6,8	7,8±0,7
			7,4	7,1±0,8
Borate	8,4	12,7±0,3	8,6	4,4±0,7
	9,8	6,83±0,67		

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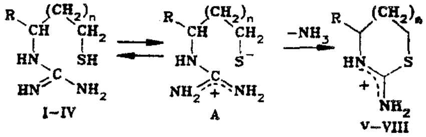
*In 0.2 M aqueous buffer solutions in 1 N KCl; for compound I c_0 = 0.05 moles, 100°C, for compound II c_0 = 0.05 moles, 80°C.

thiazoline derivatives V-VIII are formed in 75-90% yield. The structure and composition of the initial and final compounds have been proved by counter-synthesis, and the data of elemental analysis, mass spectrometry, and ^{13}C NMR. It was found that compounds I-IV are irreversibly converted to derivatives V-VIII and the rates of cyclization are given by kinetic equations for first-order irreversible reactions.



I, V R=H, n=0; II, VI R=H, n=1; III, VII R=CH_3, n=1; IV, VIII R=C_2H_5, n=0

In order to investigate the form of cyclization we varied the structure of the initial compounds, the pH value of the aqueous solution, and the concentration of buffer, and we examined the effect of adding heavy water and α-D,L-alanine on this process. We showed that an increase in the distance between the functional groups in the molecule leads to a substantial slowing down of the rate of reaction (Table 1). For example, when changing from guanidine I to II, cyclization is inhibited approximately by a factor of ten. The introduction of alkyl substituents into the carbon skeleton of the guanidinoalkanethiol molecule increases the rate of cyclization, evidently by producing conformations that allow a favorable configuration of thiol and guanidine groups. Thus the rate of cyclization of compound IV is higher than the rate of cyclization of I, and the rate of cyclization of III is higher than that for II.

The rate-determining stage of the overall reaction, in our opinion, is attack of the nucleophilic mercapto anion on the amidine fragment of the molecule. Subsequent stabilization of the structures formed is determined by the pH of the medium (Table 2), an increase in the apparent rate constants of cyclization occurring as the pH of the aqueous solution increases within the limits 3 < pH < 7.

We have established that the concentration of the components of the buffer systems does not have any significant effect on the rate of reaction (Table 3). Inhibition of the

TABLE 3. Rate Constants for Cyclization of Compound I (c_0 = 0.05 moles, in aqueous buffer solutions in 1 N KCl)

Buffer solution	pH	Buffer concentration, moles	T, °C	$k \times 10^5$, sec^{-1}
Acetate	5,9	0,25	20	17,7±0,2
		0,15		16,3±1,1
Phosphate	6,2	0,2	80	6,2±0,6
		0,1		5,6±0,6
		0,2*		5,3±0,7
		0,2**		6,3±0,7
	6,8	0,2	80	7,2±0,6
		0,1		6,5±0,7
	7,0	0,25	100	29,8±2,5
		0,15		30,0±3,0

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*In D_2O.

**In the presence of 0.02 moles of α-D,L-alanine.

TABLE 4. Constants of Guanidinoalkanetrithiocarbonates of I-IV and Hydrobromides of V-VIII

Compound*	T_{mp}, °C	R_f	Found, %			Empirical formula	Calculated, %			Yield, %*
			C	H	N		C	H	N	
$I \cdot CS_2$	142	0,51								80
	140—142 [8]									
$II \cdot CS_2$	132—134	0,58								83
	133—135 (8)									
$III \cdot CS_2$	140—141	0,67	32,7	5,1	19,1	$C_6H_{13}N_3S_3$	32,3	5,8	18,8	74
$IV \cdot CS_2$	143—142	0,74	32,0	5,6	19,1	$C_6H_{13}N_3S_3$	32,3	5,8	18,8	79
V	175—176	0,26	20,0	3,5	15,7	$C_3H_7BrN_2S$	20,0	3,5	15,7	61 (50)
	175—176 [5]						19,7	3,8	15,3	
VI	132—134	0,33	24,1	4,2	14,6	$C_4H_9BrN_2S$	24,4	4,6	14,2	48 (45)
	134 [5]									
VII	147—149	0,34	28,2	5,1	13,4	$C_5H_{11}BrN_2S$	28,5	5,2	13,3	55 (50)
VIII	101—103	0,47	28,7	4,8	13,6	$C_5H_{11}BrN_2S$	28,4	5,2	13,2	60 (49)
	102—104 [7]									

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*Mass spectrum of $III \cdot CS_2$: 114 ($C_5H_{12}N_3^+$), 86 ($C_3H_8N_3^+$), 76 (CS_2^+), 44 ($CH_4N_2^+$), 30 (CH_4N^+); $IV \cdot CS_2$: 114 ($C_5H_{12}N_3^+$), 100 ($C_4H_{10}N_3^+$), 76 (CS_2^+), 44 ($CH_4N_2^+$), 30 (CH_4N^+). ^{13}C NMR spectrum of V: 31.69 ($C_{(6)}$), 49.24 ($C_{(4)}$), 175.54 ($C_{(2)}$); VI: 26.55 ($C_{(6)}$), 27.29 ($C_{(5)}$), 38.73 ($C_{(4)}$), 171.04 ($C_{(2)}$).

**Yields obtained by cyclization of guanidinoalkanethiols are given in brackets.

reaction in heavy water is also insignificant. Addition of α-D,L-alanine does not affect the rate of cyclization.

The intramolecular cyclization of compounds I-IV does not show the effect of general acid catalysis. It evidently does not appear against the background of high catalytic activity of the hydronium ion, which is characteristic of a similar type of reaction in aqueous solution [3].

EXPERIMENTAL

Mass spectra were recorded on a Varian MAT-111 instrument with direct introduction of the sample into the source, with ionizing voltage 70 eV. ^{13}C NMR spectra were obtained on a Bruker HX-80 instrument. ^{13}C shifts were measured relative to methanol as the internal standard and given in ppm relative to TMS. The course of the reactions and the purity of the products were monitored by means of TLC on Silufol UV-254 plates in a system of C_4H_9OH saturated with a 12% aqueous solution of HBr.

Synthesis of guanidinoalkanethiols was carried out by transguanidation of the corresponding S-aminoalkylisothioureas [4-7]. The properties of the products synthesized are given in Tables 4 and 5.

TABLE 5. Constants of Labeled Compounds

Compound	Specific radioactivity, mBq/mmole	R_f*	Radiochemical yield, %
I	20	0,51	72
II	12	0,58	75
III	16	0,67	65
IV	17	0,74	70

*Data given for hydrochlorides of I-IV.

Guanidinoalkanetrithiocarbonates. The appropriate S-aminoalkylisothiourea dihydrobromide (0.02 mole) was dissolved in 50 ml of a 5% aqueous solution of ammonia cooled to 0°C. After 15 min 8 ml of CS_2 was added with agitation and the mixture was left for 12 h at 0°C. The solid residue was filtered off and washed with water followed by 2-propanol.

Hydrochlorides of I-IV. These were obtained in the form of aqueous solutions by decomposition of the respective guanidinoalkanetrithiocarbonates with an equivalent quantity of hydrochloric acid at 20°C in a current of argon, which was necessary to prevent oxidation of the thiols formed.

Hydrobromide of 1-Amino-5,6-dihydro-4H-1,3-thiazine (VI). S-(3-Aminopropyl)isothiourea dihydrobromide (0.2 mole) was boiled in water for 30 h. The solution was evaporated to dryness and the product recrystallized from anhydrous ethanol.

The hydrobromide of 1-amino-4-methyl-5,6-dihydro-4H-1,3-thiazine (VII) was obtained in a similar manner from S-(3-aminobutyl)isothiourea dihydrobromide.

Hydrobromide of 2-Amino-2-thiazoline (V). Bromoethylamine hydrobromide (0.14 mole) was boiled in water with potassium thiocyanate (0.12 mole) for 50 h. When the reaction was complete the solution was evaporated to dryness. The product was recrystallized from anhydrous 2-propanol.

The hydrobromide of 2-amino-4-ethyl-2-thiazoline (VIII) was obtained in a similar manner.

Cyclization of Guanidinoalkanethiols. An aqueous solution (0.01 mole) of the hydrochloride of I-IV was neutralized to pH 7 with a 0.2 M aqueous solution of NaH_2PO_4 and the mixture was heated to boiling in a current of argon for 20 h. The solution was evaporated and then dissolved in 10 ml of a 2 N aqueous solution of KOH. The solution was treated 3 times with 10 ml portions of diethyl ether. The ether fractions were combined and gaseous hydrogen bromide was passed through the mixture. The precipitate formed was filtered off and the product recrystallized from butanol.

Compounds V-VIII obtained by cyclization of guanidinoalkanethiols did not depress the melting point when mixed with the heterocyclic compounds obtained by other methods [5, 7]. The results of the analyses confirmed the composition of the compounds obtained (see Table 4).

Kinetic Studies. The rate constants for cyclization were determined by means of thin layer radiochromatography on Silufol plates. For these experiments guanidinoalkanethiols labeled with ^{35}S were synthesized. The synthesis was carried out according to the methods reported for the nonradioactive compounds (Table 5). The kinetic experiments were conducted in capillary tubes. Filling of the capillaries and the chromatographic analysis of the samples were carried out in a current of argon. The radiochromatograms were counted by a differential method on a liquid scintillation counter. Calculation of the data obtained was carried out according to the kinetic equation for first-order irreversible reactions. Statistical treatment was carried out using a standard method [9].

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