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NEW METHOD FOR THE SYNTHESIS OF N'-MONODERIVATIVES OF 2(3)-GUANIDINOALKANETHIOLS BY THE AMINOLYSIS OF HETEROCYCLES

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A study of the solvolysis of heterocycles under the influence of amines uncovered a new ring-opening reaction of heterocyclic rings to give N'-monoderivatives of 2(3)-guanidinoalkanethiols. A new preparative method for N'-monoderivatives of 2(3)-guanidinoalkanethiols is developed.

Keywords: N'-monoderivatives of 2(3)-guanidinoalkanethiols, aminolysis, solvolysis of heterocycles.

Thiols and similar compounds have a special place among biologically active substances. The interest in these compounds stems from the fact that many aminoalkanethiols and their derivatives possess notable radioprotective activity. 2-Guanidinoalkanethiols and 3-guanidinoalkanethiols are known as highly effective materials in the radioprotection of mammals [1, 2]. In this connection it was of interest to develop new methods for the synthesis of 2(3)-guanidinoalkanethiols (we have previously described methods for the preparation of unsubstituted guanidinoalkanethiols [3]). In this paper a new method for the synthesis of N'-monoderivatives of 2(3)-guanidinoalkanethiols with the aim of finding effective radioprotective agents among them.

N'-Methylguanidino- [4] and N'-ethylguanidinoethanethiols [5] have been obtained by "transguanidination" of the corresponding N-derivatives of S-(2-aminoethyl)isothiourea in neutral aqueous solutions. A mixture of substances is formed from which it is very complex to isolate the required substances. Consequently the yields of the guanidines are low.

With the objective of new methods for preparing N'-monoderivatives of 2(3)-guanidionalkanethiols we have studied conversions of 2-amino-2-thiazoline (**1**) and 2-amino-5,6-dihydro-4H-1,3-thiazine (**2**) in aqueous solutions in the presence of amines. The principal products under these conditions are the corresponding N'-monoderivatives of 2(3)-guanidinoalkanethiols. Small quantities of the corresponding aminoalkanethiols and guanidine were observed among the by-products of ammonolysis of the heterocycles. The products of alkaline hydrolytic scission of the derivatives of heterocycles – the corresponding ureidoalkanethiols – were not observed in this case (Scheme 1).

To determine optimal conditions for the preparative synthesis of N'-derivatives of 2(3)-guanidinoalkanethiols we investigated the dependence of the yield of the guanidines on the structure of the heterocycle starting materials, the concentration of the amines, and the influence of the solvent. The results of the investigation of the effect of changing the ratio of the reagents on the yield of reaction products are shown in Table 1. We succeeded in showing that a five-fold excess of amine is required for optimal yield, but a further

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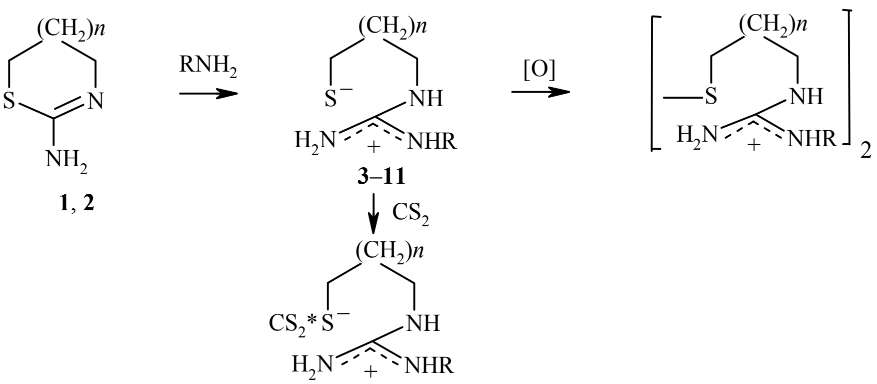
Scheme 1



1 $n = 0$; **2** $n = 1$; **3** R = CH_3, $n = 0$; **4** R = C_2H_5, $n = 0$; **5** R = $HO(CH_2)_2$, $n = 0$;
6 R = $HO(CH_2)_3$, $n = 0$; **7** R = $H_2N(CH_2)_5$, $n = 0$; **8** R = CH_2COOH, $n = 0$; **9** R = CH_3, $n = 1$;
10 R = C_2H_5, $n = 1$; **11** R = $HO(CH_2)_3$, $n = 1$

increase in amine concentration lead to a decrease in yield of guanidine. In addition it was established that an increase in the duration of the reaction led to a notable decrease in the yield of the required compound. Addition of acetonitrile to the reaction mixture showed no noticeable effect on the yield of reaction products, but its presence noticeably accelerated the formation of the crystalline products isolated after addition carbon disulfide.

Since thiols are readily oxidized by aerial oxygen and this process is significantly catalyzed by ions of iron, copper, and other metals, syntheses of guanidine derivatives were carried out in an inert gas atmosphere and using deionized water.

Direct isolation of salts of N'-monoderivatives of 2(3)-guanidinoalkanethiols from the reaction mixtures is difficult in the presence of amines, inorganic salts, and the initial heterocycle. The most suitable method for isolating the guanidines from the reaction mixture is the addition of carbon disulfide to the cooled reaction mixture. In this case the well crystallized clear yellow N'-derivatives of 2(3)-guanidinoalkanetrithiocarbonates are formed which are readily identified. If It is necessary to have the salt of the guanidine derivative, the corresponding trithiocarbonate is decomposed by strong mineral acid [7, 8].

We investigated the possibility of solvolysis of heterocycles by aminolysis of the latter under the influence of different amines under the same conditions. The yields of N'-monoderivatives of 2(3)-guanidinoalkanetrithiocarbonates and their physico-chemical characteristics are given in Table 2.

TABLE 1. Yield (%) of N'-Monoderivatives of 2(3)-Guanidinoalkanetrithiocarbonates on Aminolysis of Heterocycles **1** and **2** (C_o = 0.01 mol/l) Depending on the Concentration of Amines in Aqueous Solution at 100°C for 1 h

Compound	Concentration of methylamine (3-aminopropanol) (mol/l)							
	0.001	0.02	0.03	0.04	0.05	0.055	0.06	0.07
1	25	30	50	89	86/85*	90/88*	79	70
2	20	25	47	52	60	70/75*	62	55
	(35)	(51)	(55)	(59)	(75)	(60)	(54)	(49)

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* Solvent water–acetonitrile, 1:3.

TABLE 2. Characteristics of N-Derivatives of 2(3)-Guanidioalkanethiols

Compound ($\cdot CS_2$)	Empirical formula	Found, % / Calculated, %			mp, °C	^{13}C NMR spectra, δ, ppm					IR spectra, ν, cm^{-1}		Yield, %
		C	H	N		CH_3	CN^+_3	CH_2N	CH_2S	R	N–H	C=N	
3	$C_5H_{11}N_3S_3$	28.63 28.71	5.37 5.26	20.17 20.10	166-168	239.10	156.24	40.70	38.45	28.01 (CH_3)	3200	1650, 1630, 1570	86
4	$C_6H_{13}N_3S_3$	32.24 32.26	5.98 5.87	18.58 18.87	154-156	238.87	155.43	40.73	38.51	36.13 (CH_2N); 14.33 (CH_3)	3200	1660, 1640, 1600	90
5	$C_6H_{13}N_3OS_3$	29.93 30.10	5.52 5.47	17.21 17.55	162-164	238.87	156.10	40.85	38.87	43.89 (CH_2N); 59.52 (CH_2O)	3200	1670,1610	69
6	$C_7H_{15}N_3OS_3$	33.01 33.20	5.94 5.93	16.60 16.81	145-147	238.50	155.65	40.73	38.44	31.47 (CH_2O); 57.93 (CH_2O)	3200	1670, 1620	89
7	$C_9H_{20}N_4S_3$	38.57 38.71	6.96 7.07	19.77 20.00	120	238.70	156.10	40.77	38.67		3200	1630, 1590	47
8	$C_6H_{10}N_3NaO_2S_3$	26.45 26.18	3.48 3.30	15.05 15.27	185-187	238.83	156.53	40.65	38.35	176.37 (COO^-); 39.79 (CH_2N)	3200	1680, 1610, 1570	72
9	$C_6H_{13}N_3S_3$	32.22 32.26	5.92 5.87	18.76 18.81	123-125	238.71	156.35	40.78	38.55	28.50 (CH_3)	3200	1650, 1640, 1580	75
10	$C_7H_{15}N_3S_3$	35.41 35.44	6.50 6.33	17.43 17.72	142-144	239.42	155.36	40.83	37.10	35.90 (CH_2N); 28.29 (CH_2); 14.30 (CH_3)	3280 3140	1640, 1620	72
11	$C_8H_{17}N_3OS_3$	35.41 35.46	6.30 6.37	15.40 15.73	121-123	239.38	155.59	40.34	38.31	28.25 (CH_2); 31.45 (CH_2); 57.92 (CH_2O)	3200	1660, 1620, 1600, 1580	75

Hence an investigation of the solvolysis of heterocycles has permitted the observation of a new ring opening reaction of the heterocycles under the influence of amines. As a result of these experiments a new method for the preparative synthesis of new N'-monoderivatives of 2(3)-guanidinoalkanethiols has been developed.

EXPERIMENTAL

^{13}C NMR spectra of methanol solutions with TMS as internal standard were recorded with a Bruker HX-80 instrument. IR spectra of KBr disks were recorded with a Perkin-Elmer 457 machine.

Guanidinoalkanetrithiocarbonates of Compounds 8-11. The corresponding heterocycle hydrobromide (0.01 mol) was dissolved in water or 60% acetonitrile in water (10 ml), the corresponding amine was added in a heterocycle–amine ratio of 1:1 - 1:6 (**7**). The solution was placed in an ampule, flushed with argon, sealed, and heated at 100°C for 1 h. After cooling to 0°C, the ampule was opened, water (15 ml) and carbon disulfide (2 ml) were added with stirring, and the mixture was kept at 0°C for 12 h. The clear yellow solid was filtered off, washed successively with ethanol and ether, and dried. The yields are recorded in Table 2.

Hydrochlorides of 8-11 were obtained in aqueous solution by decomposition of the corresponding guanidinoalkanetrithiocarbonates with an equivalent amount of hydrochloric acid at 20°C in a stream of oxygen, which was necessary to prevent oxidation of the thiols formed.

REFERENCES

1. V. G. Vladimirov, I. I. Krasil'nikov, and O. V. Arapov, *Radioprotective Agents: Structure and Function* [in Russian], Nauk. Dumka, Kiev (1989), 263.
2. A. A. Mandurgin, V. M. Fedoseeva, O. V. Dubova, A. A. Rodunin, M. M. Konstantinova, and G. V. Dontsova, *Radiats. Biol. Radioekol.,* **39**, 256 (1999).
3. A. A. Mandurgin, V. M. Fedoseev, M. N. Semenko, and S. M. Khomutov, *Khim. Geterotsikl. Soedin.,* 1550 (2000).
4. D. J. Doherty, R. Shapira, and W. T. Burnett, *J. Amer. Chem. Soc.,* **79**, 5567 (1957).
5. A. Hanaki, *Chem. Pharm. Bull.,* **19**, 1223 (1971).
6. F. Yu. Pachinski, A. S. Mozzhukhin, and M. M. Slavachevskaya, *Usp. Khim.,* **28**, 1488 (1959).
7. W. O. Foye, T. Mickels, R. Duval, and T. R. Marshall, *J. Med. Chem.,* **6**, 509 (1983).
8. E. D. Manolov, *Farmatsiya*, **15**, 271 (1965).