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SYNTHESIS AND TRANSFORMATIONS OF 2-AMINO-1,3,4-THIADIAZINES

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Depending on the reaction conditions, 2-amino-1,3,4-thiadiazine and 2-hydrazinothiazole derivatives were obtained by cyclization of thiosemicarbazide with ethyl bromopyruvate in concentrated hydrochloric acid. The rearrangements of 5-carbonyl-substituted 2-amino-1,3,4-thiadiazines to thiazole derivatives in an acidic medium were studied.

One of the promising directions in the search for preparations that have biological activity is the synthesis of labile heterocyclic compounds. 2-Amino-1,3,4-thiadiazine derivatives, among which substances that have antibacterial, antiviral, fungicidal, herbicidal, and other types of activity have been observed [1-3], can be classified as compounds of this sort. It is known that 5- and (or) 6-alkyl-substituted 2-amino-1,3,4-thiadiazines react like labile cyclic thiosemicarbazones, undergoing intramolecular rearrangements under the influence of a proton [4]. In this connection the aim of the present research was to synthesize and study the reactivities (primarily the stabilities in an acidic medium) of 2-amino-1,3,4-thiadiazines with a carbonyl group in the 5 position.

We have observed that the structure of the products of cyclization of thiosemicarbazide (I) with ethyl bromopyruvate (II) in concentrated hydrochloric acid depends on the reaction temperature and time. Cyclization at 0°C led to 2-amino-5-ethoxycarbonyl-1,3,4-thiadiazine (III) hydrochloride, while brief heating to the boiling point led to 2-amino-5-carboxy-1,3,4-thiadiazine (IV) hydrochloride. The expected 2-imino-3-aminothiazolines V [4] were not observed.

Prolonged heating of I and II in concentrated HCl gave 2-hydrazino-4-carboxythiazole (VI), which was also isolated from the reaction mixture after prolonged heating of IV in hydrochloric acid. These facts attest to intramolecular rearrangement of 2-amino-5-carboxy-1,3,4-thiadiazine (IV), which includes cleavage of the $N_{(4)}$—$C_{(5)}$ bond of the thiadiazine and subsequent cyclization. This sort of recyclization is not characteristic for 2-amino-1,3,4-thiadiazines with alkyl substituents in the 5 or 6 position of the ring, which under similar conditions are converted to 2-imino-3-aminothiazolines V without opening of the thiadiazine ring [5] (see scheme below).

The structures of the reaction products were confirmed by spectral data and alternative synthesis. In the PMR spectra of thiadiazines III and IV resonance of the protons of the SCH_2 group was observed at 4.0-4.2 ppm, while a singlet of a proton in the 5 position of the thiazole ring at 7.9 ppm was present in the spectrum of thiazole VI.

In the ^{13}C NMR spectrum of IV the triplet at 20.54 ppm with an order I spin-spin coupling constant (SSCC) was assigned to an sp^3-hybridized carbon atom in the 6 position of the thiadiazine ring. A signal at weak field (165.18 ppm, $J_{^{13}C-H} = 5.19$ Hz) is due to resonance of the carbon atom of a carbonyl group. The assignment of the signals of the $C_{(2)}$ (141.67 ppm) and $C_{(5)}$ (162.67 ppm) atoms was accomplished on the basis of a comparison of the SSCC — 5.19 (order III SSCC) and 2.14 Hz (order II SSCC), respectively.

The structure of 2-hydrazinothiazole VI was confirmed by its esterification in absolute ethanol in the presence of thionyl chloride to 2-hydrazino-4-ethoxycarbonylthiazole (VII) and by oxidation with mercuric oxide, as in [6], to 4-carboxythiazole (VIII). The physicochemical characteristics of VII and VIII were in agreement with those presented in [7-9].

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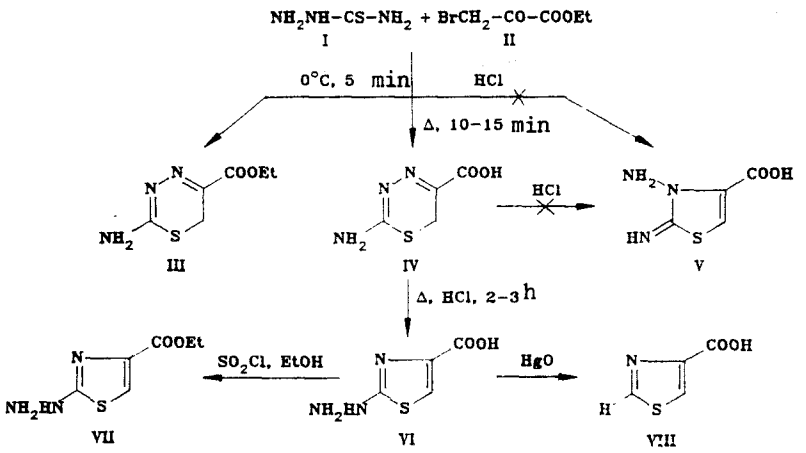
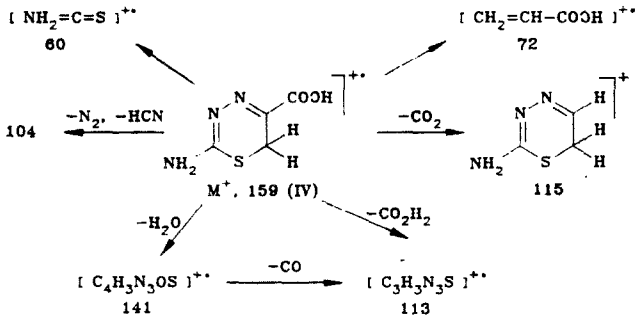


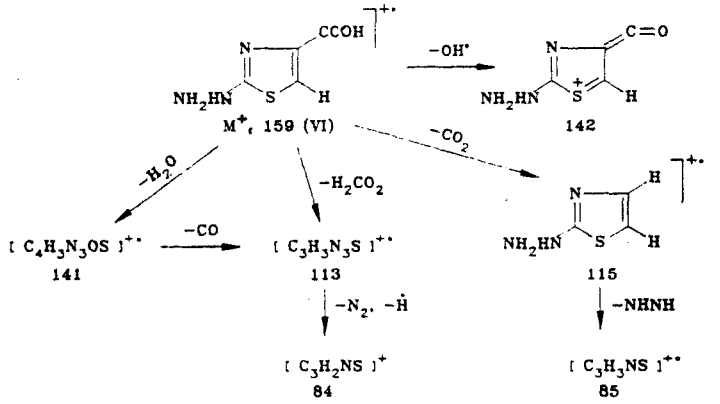
The mass spectra of the isomeric five- and six-membered heterocycles (see Table 1) make it possible to reliably distinguish between these compounds. In the case of thiazoles V and VII the signals of fragments at 141, 113, and 84* dominate in the spectra. In the spectra of thiadiazines III and IV, in addition to molecular-ion peaks (M^+), one observes peaks of intense fragments with low masses, and the maximum peaks are those of ions at 60 and 72, the intensities of which are an order of magnitude lower in the spectra of the isomeric thiazoles. These data attest to greater lability of the 1,3,4-thiadiazine ring as compared with the thiazole ring

The fragmentation of isomeric acids IV and VI under the influence of electron impact is shown in Schemes 1 and 2. The elementary compositions of all of the ions were proved by means of high-resolution mass spectrometry.

Scheme 1



Scheme 2



Intramolecular rearrangement of thiadiazine IV to a thiazole structure was also observed when other mineral acids were used. Thus the formation of 2-azido-4-carboxy- and 2-azido-4-ethoxycarbonylthiazole (IX and X) was observed in the action of dilute nitric acid on thiadiazines IV and III. The IR spectra of IX and X (in pellets and in chloroform) contained an intense band at 2135 cm^{-1} (stretching vibrations of an azido group). Singlets at 8.0 ppm, which are

*In the text and in the schemes the numbers that characterize the ions are the m/z values.

TABLE 1. Mass Spectra of Thiadiazines III and IV and Thiazoles VII and VI

Compound	Intensities (% of total ion current) of peaks of characteristic fragment ions													
	187	159	154	143	142	141	115	113	100	85	84	73	72	60
III	6,3	0,5	0,4	1,5	0,8	0,8	0,7	0,4	0,7	0,7	0,6	3,6	3,2	8,7
IV	—	7,4	—	—	0,4	4,2	10,3	0,8	—	0,9	0,6	—	19,6	13,7
VII	10,7	0,4	—	0,2	3,0	25,4	0,7	10,2	—	0,5	3,1	1,3	1,5	1,0
VI	—	8,2	—	—	1,0	25,0	1,3	8,8	—	5,2	6,1	—	2,7	0,7

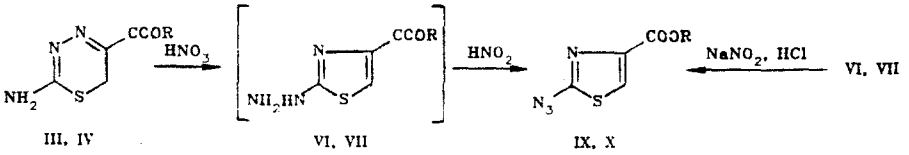
TABLE 2. Characteristics of the Compounds Obtained

Compound	Empirical formula	mp, °C	R_f (system)	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm	Yield, %
III	$C_6H_9N_3O_2S \cdot HCl$	198...200 (202 [7])	0,73 (B)	1750, 1635, 1585	4,45 (2H, q., CH_2); 4,2 (2H,s, SCH_2); 1,3 (3H, t., CH_3)	47
IV	$C_4H_5N_3O_2S \cdot HCl$	220	0,2 (B)	1740, 1635, 1580	4,02 (s, SCH_2)	85
VI	$C_4H_5N_3O_2S \cdot HCl$	208...210 (207...208 [10])		1730, 1685	7,9 (s, 5-H)	95
IX	$C_4H_2N_4O_2S \cdot 2H_2O$	160 (expl.)	0,55 (B)	2215, 2135, 1685	8,0 (s, 5-H)	34*, 58**
X	$C_6H_6N_4O_2S$	Oil	0,85 (A)	2135, 1735	8,0 (1H,s, 5-H); 4,25 (2H,q, CH_2); 1,25 (3H,t, CH_3)	30*, 67**
XIa	$C_{11}H_9N_3O_2S$	292...295 (dec.)	0,12 (A)	1720, 1680, 1615, 1595	8,02 (1H,s, CH=N); 7,7...7,3 (5H,m, Ph); 7,69 (1H,s, 5-H)	85
XIb	$C_{12}H_{11}N_3O_2S$	290...291	0,59 (A)	1710, 1685, 1620, 1580	7,9...7,6 (2H,m, Ph); 7,7 (1H,s, 5-H); 7,57...7,3 (3H,m, Ph); 2,35 (3H,s, CH_3)	80
XId	$C_{14}H_{15}N_3O_2S$	110...113	0,95 (A)	1735, 1585	7,9...7,6 (2H,m, Ph); 7,75 (1H,s, 5-H); 7,55...7,3 (3H,m, Ph); 4,25 (2H,q, CH_2); 2,35 (3H,s, CH_3); 1,26 (3H, t, CH_3)	77

*By method A.

**By method B.

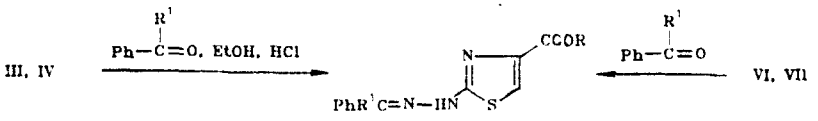
related to the resonance of a proton in the 5 position of the thiazole ring, were present in the PMR spectra of azides IX and X. The high-resolution mass spectrum of acid IX contained an M^+ peak and $[M - N_2]^+$, $[M - N_2, - CO_2]^+$, $[M - N_2, - H_2O]^+$, and $[M - N_2, - CO]^+$ ion peaks. Compounds IX and X were obtained by alternative synthesis by the action of nitrous acid on 2-hydrazinothiazoles VI and VII.



III, VII, X R=Et, IV, VI, IX R=H

The hypothetical reaction pathway includes recyclization of 2-amino-1,3,4-thiadiazines IV and III to 2-hydrazinothiazoles VI and VII, which react with nitrous acid to give 2-azidothiazoles IX and X. The nitrous acid probably develops in the reaction mixture as a result of a redox reaction with the participation of the hydrazino group of VI and VII and nitric acid.

1,3,4-Thiadiazines IV and III also undergo the characteristic (for thiadiazines [4]) intramolecular rearrangement in acidified alcohol solution under the influence of aromatic aldehydes and ketones to give 2-hydrazonothiazoles XIa-d. The hypothetical reaction mechanism includes hydrolytic cleavage of the thiadiazines at the $N_{(4)}$—$C_{(5)}$ bond, condensation of the intermediate isothiosemicarbazide derivative with the aldehyde, and subsequent ring closure to give the 2-hydrazonothiazole [4].



IV, VI, XI a, b R=H; III, VII, XI c, d R=Et; XIa, c R^1=H, b, d R^1=Me

Our studies showed that 5-carbonyl-substituted 2-amino-1,3,4-thiadiazines, inasmuch as they are labile compounds, differ from 5-alkylthiadiazines with respect to the character of the transformations in an acidic medium.

EXPERIMENTAL

The individuality of the substances was monitored by TLC on Silufol UV-254 plates in chloroform—ethanol (9:1) (A) and n-propanol—25% ammonia (3:1) (B) systems. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Perkin—Elmer R-12B spectrometer (60 MHz). The ^{13}C NMR spectra were recorded with a Bruker WH-90 spectrometer (22.62 MHz) under conditions of total decoupling and with retention of the spin-spin coupling (SSC) of the protons with the carbon nuclei; the solvent was d_6-DMSO, the internal standard was tetramethylsilane (TMS), and the chemical shifts are presented on the δ scale in parts per million. The mass spectra were obtained with a Finnigan MAT-212 spectrometer using a system for direct introduction of the samples into the ion source; the ionizing-electron energy was 70 eV, the temperature of recording of the samples ranged from 80°C to 150°C, depending on the volatility of the compounds, and the total ion current was reckoned over the range from m/z 50 to the M^+ ion. The high-resolution mass spectra were recorded with the same spectrometer under the same conditions; the precise determination of the masses was performed manually using perfluorinated kerosene as the mass reference point.

The characteristics of the synthesized compounds are presented in Table 2.

2-Amino-5-ethoxycarbonyl-1,3,4-thiadiazine (III) Hydrochloride. A 3.7-ml (33 mmole) sample of ethyl bromopyruvate (II) was added to a cooled (to 0°C) suspension of 3 g (33 mmole) of thiosemicarbazide (I) in 30 ml of concentrated HCl, and the reaction mixture was stirred at 0°C for 5-10 min. The precipitate was removed by filtration and recrystallized from ethanol.

A compound with identical characteristics was obtained by the method in [7].

2-Amino-5-carboxy-1,3,4-thiadiazine (IV) Hydrochloride. A 3.7-ml (33 mmole) sample of II was added to a suspension of 3 g (33 mmole) of I in 30 ml of concentrated HCl, and the mixture was refluxed for 10-15 min. It was then cooled, and the precipitate was removed by filtration and recrystallized from dilute hydrochloric acid.

2-Hydrazino-4-carboxythiazole (VI) Hydrochloride. An 11.3-ml (100 mmole) sample of II was added in portions with stirring to a suspension of 9.1 g (100 mmole) of I in 30 ml of concentrated HCl, and the reaction mixture was refluxed for 3-4 h. The white precipitate of thiadiazine IV that formed 10-15 min after the start of refluxing gradually dissolved on further refluxing. The mixture was then cooled, and the precipitate was removed by filtration and

suspended in chloroform. The suspension was heated up to the boiling point, and the hot suspension was filtered. The product was treated with absolute ether and reprecipitated from absolute ethanol by the addition of dry ether.

A compound with identical characteristics was obtained by the method in [10].

2-Hydrazino-4-ethoxycarbonylthiazole (VII, $C_6H_9N_3O_2S$). This compound was obtained by the method in [10].

2-Azido-4-carboxythiazole (IX) Dihydrate. A. A solution of 1 g (5.1 mmole) of thiadiazine IV in 10 ml of dilute nitric acid was heated to the boiling point. After a vigorous reaction with the evolution of nitrogen oxides commenced, heating was stopped, and the mixture was allowed to stand for 1 h at room temperature and then evaporated. The resulting oil was extracted with ether, and the extract was dried with calcium chloride and evaporated to dryness. The residue was recrystallized from water.

B. A solution of 0.12 g (1.68 mmole) of sodium nitrite in 2 ml of water was added with stirring at 0°C to a solution of 0.3 g (1.53 mmole) of thiazole VI in 5 ml of 1 N HCl, and the reaction mixture was maintained at 0°C for 30 min. It was then extracted with ether, and the extract was dried with calcium chloride and evaporated. The product was crystallized from water. Mass spectrum, m/z (I, percent of the total ion current): 170 (4.3), 142 (9.8), 124 (2.4), 114 (4.2), 98 (2.7), 96 (6.8), 72 (6.5).

2-Azido-4-ethoxycarbonylthiazole (X). This compound was obtained as an oil in the same way as IX from thiadiazine III by method A and from thiazole VII by method B.

2-Benzylidenehydrazino-4-carboxythiazole (XIa). A 1-g (5.11 mmole) sample of thiadiazine IV was dissolved by heating in a mixture of 10 ml of ethanol and 15 ml of water, 5 ml of concentrated HCl and 0.57 ml (5.6 mmole) of benzaldehyde were added, and the mixture was refluxed for 2 h. The solution was cooled, and the precipitate was removed by filtration and recrystallized from DMF—water.

The reactions of acid IV with acetophenone and of ester III with benzaldehyde and acetophenone, which lead to 2-hydrazonothiazoles XIb-d, were carried out similarly. With respect to its physicochemical characteristics, thiazole XIc was identical to a genuine sample [7].

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