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Synthesis and Properties of Diaminothiadiazoles

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Abstract—Refined synthetic procedure for preparation of 3,5-diamino-1,2,4-thiadiazole and 2,5-diamino-1,3,4- thiadiazole based on the reaction of dithiourea or amidinothiourea with hydrogen peroxide is developed. The optimal reagents ratio was found, and monitoring methods were developed. It resulted in the increase of the target product yield and in a shorter reaction time. On the basis of 2,5-diamino-1,3,4-thiadiazole the alkyl-substituted 1,3,4-diaminothiadiazolidines were synthesized. The compounds prepared were characterized by the elemental analysis data, the IR, ^{1}H NMR, and electronic spectra, and also by mass spectrometry.

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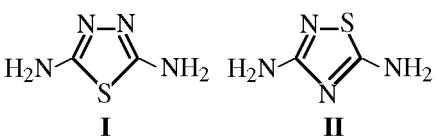
Chemistry of heterocyclic compounds is one of the leading lines of investigations in the organic chemistry. Heterocyclic compounds of different nature underlie many natural and synthetic biologically active compounds. They also exhibit a number of other useful properties. Many of them are used, for example, as organic semiconductors, photoactive materials, antioxidants, additives to fuels and oils, materials for active media of liquid lasers (dye lasers), technical and food dyes, preservatives, etc. [1].

Therefore the development of new synthetic methods or optimization of the previously known procedures is practically important for the chemistry and technology of heterocyclic compounds. The above stated concerns also thiadiazoles, precursors of medicinal preparations [2] and dyes [3].

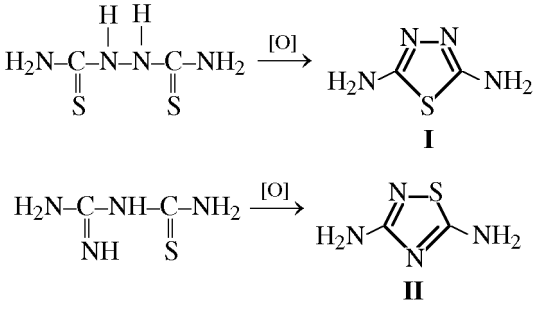
Diamino derivatives of the symmetric 1,3,4-thiadiazole **I** and unsymmetrical 1,2,4-thiadiazole **II** (isothiadiazole) are widely used in the fine organic synthesis, in particular, for preparation of macro-heterocyclic compounds [4–10].



I **II**

Inasmuch as the synthetic procedures for these compounds were developed long ago [11, 12], and they were not up to the modern demands in respect to the quality and the yield of the target products we undertook thorough studies in the series of diaminothiadiazoles.

Analysis of the reported data showed that synthesis of target compounds **I, II** was based on the oxidative condensation of urea derivatives [6, 11, 12].



I

II

Main faults of these procedures are the following:

(1) the yield of the target product does not exceed 40–43% for compound **I** and 32–50% for the compound **II**;

(2) in the course of prepartion compound **I** form many difficultly removable by-products;

(3) synthetic procedures for both compounds are laborious (about 14 operations), and in the case of compound **II** the duration of the process reaches 60 h.

We selected hydrogen peroxide as oxidant [11, 12] for the synthesis of compounds **I, II**.

A series of experiments was carried out to establish the effect of the concentration on the yield of the target products. The results are listed in the table.

It was found that the quality and the yield of the products strongly depended on the concentration of the oxidant. It follows from the data presented that the best results were obtained for the compounds **I, II** when 26% hydrogen peroxide was used.

Further increase in the concentration of hydrogen peroxide significantly decreased the yield of the target product. It is evidently due to the increase in the oxidative activity of the hydrogen peroxide. As known, the highly concentrated solutions can oxidize urea, thiourea, and their derivatives to the simplest final compounds [13]. These side processes of decomposition of the starting substances and further oxidation of compounds **I, II** can take place alongside

$$H_2O_2 + H_2S \rightarrow S\downarrow + 2\,H_2O$$

$$H_2S + Cd(CH_3COO)_2 \rightarrow CdS\downarrow + 2\,CH_3COOH$$

The hydrogen peroxide excess was removed by means of hydrogen sulfide. Appearance of the excess of the latter was controlled by the test with cadmium acetate [14].

Dependence of the yield of 2,5-diamino-1,3,4- thiadiazole and 3,5-diamino-1,2,4-thiadiazole on the hydrogen peroxide concentration

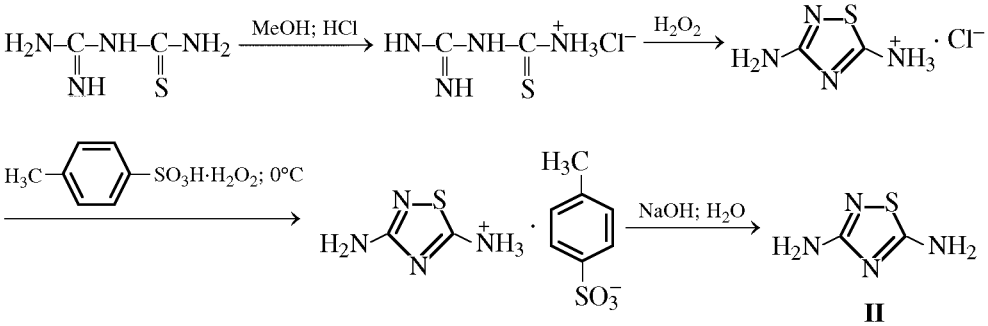
Compound **I**		Compound **II**	
H_2O_2 concentration, %	yield, %	H_2O_2 concentration, %	yield, %
24	79	26	86
25	90	30	69
26	98	35	60
30	70	40	50

Using the analytical monitoring of the reaction progress and increasing the hydrogen peroxide concentration to 26% permitted to improve the yield of compound **I** up to 79–98%.

The development of the synthetic procedure for 3,5-diamino-1,2,4-thiadiazole involved not only the improvement of the yield of the target product, but also reducing the reaction time by decreasing the number of operations.

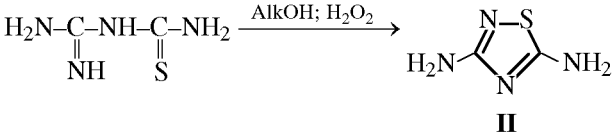
The existing synthesis of compound **II** [6] included the following steps.

The overall time of synthesis and isolation of compound **II** was about 60 h.



We developed a simpler processing including only one stage and thus shortened the reaction time to 2 h.

Hence, rational modification of the previously known synthetic procedures for 2,5-diamino-1,3,4-thiadiazole and 3,5-diamino-1,2,4-thiadiazole permitted the improvement of the yields of the target products.



Alk = Me, C_3H_5.

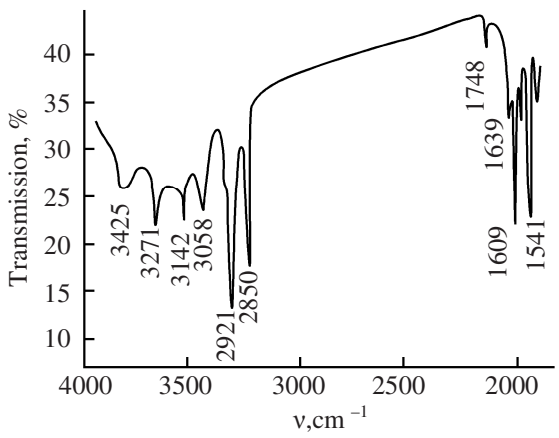
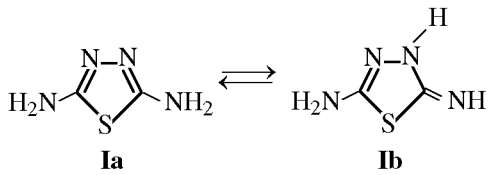


Fig. 1. The IR spectrum of compound **IV**.

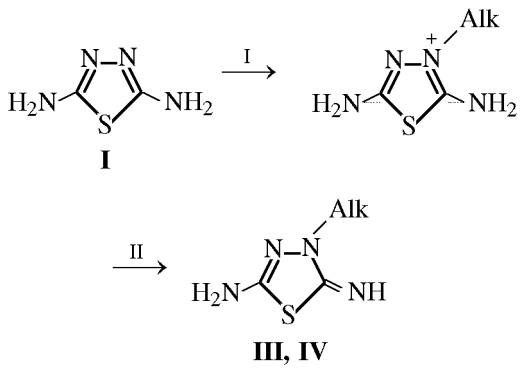
As known [15], compound **I** may exist in two tautomeric forms of the thiadiazole structure **Ia** and the thiadiazoline structure **Ib**.



The thiadiazoline form **Ib** may be fixed by introduction of substituents in the position 3 of the thiadiazole ring. For instance, it was reported [15] on the direct alkylation of the 2-amino derivatives of 1,3,4-thiadiazole leading to the formation of the corresponding 3-alkyl-2-imino-1,3,4-thiazolines. M.K. Islyaikin likewise carried out preparation of 5-amino-3-butyl-2-imino-1,3,4-thiadiazoline **III** by reaction of 2,5-diamino-1,3,4-thiadiazole with butyl bromide in boiling methanol followed by treatment with ammonia [16].[1]

5-Amino-3-dodecyl-2-imino-1,3,4-thiadiazoline **IV** was prepared analogously.

The structure of the compounds obtained was established from the elemental analysis, the IR, ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry. For instance, the mass spectra contain peaks with *m/e*



172.2 and 284 corresponding to the molecular ions $[M]^+$ of compounds **III, IV** respectively. The fragmentation peaks of these compounds were also observed.

The ^{1}H NMR spectrum of compound **III** contains a broad signal at 5.92 ppm characteristic of the imino group proton. The singlet at 4.22 ppm corresponds to the protons of the amino group. Two triplets at 3.71 ppm and 0.93 ppm, and two multiplets at 1.68 ppm and 1.35 ppm belong to the alkyl chain protons. The ^{13}C NMR spectrum of these compound contains the signals of carbon atoms at 162.0 and 146.1 ppm belonging respectively to the atom bound to the primary amino group and that adjacent to the imino group. Four upfield signals in the range 46.8–13.8 ppm originate from the *n*-butyl group carbon atoms.

In the IR spectra of compounds **III, IV** a series of bands originating from different types of vibrations of the functional groups of substituents were observed. The bands at 3311–3425 and 3271 cm^{-1} correspond to the frequences of asymmetric and symmetric stretching vibrations of the N–H bonds of the primary amino group.

The broad band at 3058-3076 cm^{-1} belongs to the imino group N–H bond stretching vibrations. The set of bands at 2961, 2921–2933 and 2850–2863 cm^{-1} is characteristic of the asymmetric and symmetric stretching vibrations of C–H bonds in the alkyl chain.

The bands at 1633–1639, 1609, and 1641–1544 cm^{-1} may be attributed to the bending skeleton vibrations and stretching vibrations of the C=N bonds (Fig.1).

Inspite of resemblance in the pattern of the IR spectra of compounds **I, II**, **IV** (Fig. 2) they contain significant differences arising from the transition of the thiadiazole into the thiadiazoline form. Introduction of the alkyl substituent increases the solubility of

[1]Compound **III** was prepared within the framwork of the international collaboration agreement between the Ivanovo State University of Chemical Technology and the Madrid Autonomic University in the laboratory of Prof. T. Torres.

compounds in the organic solvents. Therefore compounds **III, IV** dissolve well in alcohols and dichloroethane, but are insoluble in water.

Hence, introducing alkyl substituent in 2,5-diamino-1,3,4-thiadiazole permits to fix the thiadiazoline form.

EXPERIMENTAL

The electron absorption spectra of the compounds obtained were registered on a HITACHI U-2001 spectrophotometer at room temperature in the range 250–800 nm. Ethanol and water were used as solvents. The IR spectra were measured on an AVATAR 360 FT-IR ESP spectrometer from KBr pellets. The elemental analyses were carried out on a CHNS-O Flash E A, 1112 series analyzer. The ^{1}H and ^{13}C NMR spectra were taken on a Bruker WM-200 SY, Bruker AC-300, and Bruker DRX-500 spectrometers, internal reference TMS. LSIMS and MALDI-TOF (ditranol matrix) mass spectra were registered on a VG Autospec and Bruker Reflex III devices respectively. GC-MS measurements were performed on a SATURN chromato-mass spectrometer.

2,5-Diamino-1,3,4-thiadiazole (I). Dithiourea, 5 g, and 114 ml of distilled water were heated to complete dissolution of dithiourea. To the solution obtained was gradually added 24–26% hydrogen peroxide until the test showed the formation of a clear brown spot on the iodostarch paper. Under treating with water the spot became blue. The reaction flask was vigorously shaken to cause the coagulation of the obtained sulfur. The sulfur lump formed was filtered off, and the hydrogen sulfide flow was passed through the clear filtrate until the appearance of the sulfide ion excess in the solution. It was controlled by the test reaction with cadmium salt (formation of yellow cadmium sulfide). Then the flow of hydrogen sulfide was stopped, the solution obtained was evaporated to ¼ of its volume, and left standing in a cup. During the night white needles of mp 211–213ºC were formed in 79–98% yield. The IR spectrum (KBr), ν, cm^{-1}: 3356 (ν_{sym} 354.5 + 0.876ν_{ass}), 3439, 1307, 1164, 1115, 1005. The electron absorption spectrum (H_2O), λ_{max}, nm: 248. Found, %: C 20.66; H 3.6; N 48.33; S 27.29. $C_2H_4N_4S$. Calculated, %: C 20.69; H 3.47; N 48.28; S 27.56.

3,5-Diamino-1,2,4-thiadiazole (II). The amidinothiourea, 0.1 g was dissolved in 2.33 ml of methanol, the reaction mixture was heated to boiling, and 0.1 ml of 26% hydrogen peroxide was added to it. The foam

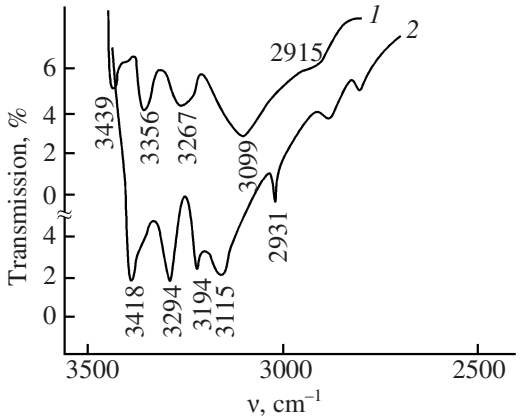


Fig. 2. The IR spectra of compounds **I, II.** (*1*) 2,5-diamino-1,3,4-thiadiazole **I** and (*2*) 3,5- diamino- 1,2,4-thiadiazole **II**.

formation took place. After that the mixture obtained was heated on a water bath for 25–30 min, and the resulting solution was evaporated until dryness. The product obtained was crystallized from ethanol. It was a white powder soluble in water and ethanol and insoluble in chloroform and benzene. Yield 0.0845 g (86%), mp 168–170ºC (published data [6] mp 169–171ºC). The IR spectrum (KBr), ν, cm^{-1}: 3417, 3297, 3115, 2918, 2858, 1629, 1523, 1415, 1106, 948, 836, 735, 702, 481. The electron absorption spectrum (ethanol), λ_{max}, nm (log ε): 256 (3.88). Found, %: C 20.23; H 3.48; N 47.47; S 28.50. $C_2H_4N_4S$. Calculated, %: C 20.69; H 3.47; N 47.28; S 27.56.

5-Amino-3-butyl-2-imino-1,3,4-thiadiazoline (III). A mixture of 2.32 g of 2,5-diamino-1,3,4-thiadiazole **I**, 9.60 g of *n*-butyl bromide, and 80 ml of MeOH was refluxed with stirring for 24 h. After that solvents were removed on a rotory evaporator, and the precipitate obtained was treated with 120 ml of water and 20 ml of 30% ammonia, and the reaction mixture was stirred for 2 h at room temperature. The target product was extracted with chloroform. After removing the solvent on a rotory evaporator at reduced pressure and drying in a vacuum at 60–70ºC a product of white color was obtained. Yield 2.14 g (62.1%). The IR spectrum (KBr), ν, cm^{-1}: 3311 (–NH_2), 3272 (–NH_2); 3076 (=NH); 2961, 2933, 2863 (C–H); 2784; 1633, 1609, 1544 (C=N); 1454, 1430, 1377, 1323, 1218, 1178, 1139, 1071, 687, 597. The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 5.92 br.s (1H, =NH); 4.22 s (2H, NH_2); 3.74, 3.71, 3.67 t (2H, C^1H_2); 1.68 m (2H, C^2H_2); 1.35 m (2H, C^3H_2); 0.96, 0.93, 0.91 t (3H, C^4H_3). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 162.0 (C^a), 146.1 (C^b), 46.8 (C^1), 30.1 (C^2), 19.9 (C^3),

13.8 (C4). Mass spectrum (electron impact, CH_2Cl_2), *m/e*: 172.2 $[M]^+$, 139.2, 130.1, 116.1, 97.1, 88.0, 86.0, 84.0, 74.0, 70.0, 60.0. Found, %: C 42.08, H 7.17, N 32.79, S 19.23. $C_6H_{12}N_4S$. Calculated, %: C 41.84, H 7.02, N 32.53, S 18.61.

5-Amino-3-dodecyl-2-imino-1,3,4-thiadiazoline (IV). A mixture of 2.32 g of 2,5-diamino-1,3,4-thiadiazole **I**, 4.79 ml of dodecyl bromide, and 50 ml of methanol was refluxed with stirring for 24 h. After that solvent was removed at reduced pressure, and the precipitate obtained was treated with 120 ml of water and 20 ml of 30% ammonia. The resulting mixture was stirred for 2 h at room temperature, and the target product was extracted with chloroform. After removing the solvent on a rotory evaporator at reduced pressure and drying in a vacuum at 60–70ºC the cream-colored substance was obtained. It is well soluble in alcohols and dichloroethane, poorly soluble in hot acetone, hexane, and benzene, and insoluble in water. Yield 4.65 g (82%), mp 175ºC. The IR spectrum (KBr), ν, cm^{-1}: 3410, 3270, 3054 (N–H), 2921, 2850 (C–H, alk), 1609, 1541 (C=N). Mass spectrum (electron impact), *m/e*: 284 $[M]^+$.

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