Hindawi Publishing Corporation
Journal of Chemistry
Volume 2013, Article ID 635079, 4 pages
http://dx.doi.org/10.1155/2013/635079

Research Article

Synthesis and Biological Activity of 2,5-Bisubstituted Derivatives of 1,3,4-Thiadiazol-2,5-dithiol

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Received 18 July 2012; Revised 10 January 2013; Accepted 5 February 2013

Academic Editor: Mehmet Emin Duru

By reaction of 1,3,4-thiadiazol-2,5-dithiol with different organohalogens, chlorides of carboxylic acids, acrylic acid derivatives, alkaloids, and secondary amines, various derivatives of 2,5-bi-substituted 1,3,4-thiadiazole were synthesized, and biological properties of some of them were studied.

Substances containing a fragment of the structure of 1,3,4-thiadiazole have different physiological activity [1–4]. However, it is worth noting the small amount of 1,3,4-thiadiazol-2,5-dithiol, in spite of the availability and simplicity of its synthesis [5]. 1,3,4-Thiadiazol-2,5-dithiol due to the presence in its structure along with thiadiazol cycle, which is characterized by the presence of three donor centers—two atoms of nitrogen and sulfur heterocyclic atom—two equivalent sterically accessible thiol groups, has a high nucleophilicity and reactive ability and is an interesting object for chemical modification, which allows to introduce other functional groups and pharmacophore and synthesis of various 2,5-bisproizvodnye 1,3,4-thiadiazoles. In addition, data on the combination in one molecule thiadiazol cycle and alkaloid fragments are not accessible.

In order to obtain new biologically active substances with 1,3,4-thiadiazol fragment processes of alkylation and acylation, electrophilic and nucleophilic addition of 1,3,4-thiadiazol-2,5-dithiol to the α,β-unsaturated compounds were studied, the oxidation of thiol groups of 1,3,4-thiadiazol-2,5-dithiol into 1,3,4-thiadiazol-2,5-disulfonic acid was carried out. In addition, chelate salts of 1,3,4-thiadiazol-2,5-disulfonic acid and the initial 1,3,4-thiadiazol-2,5-dithiol with alkaloids and cyclic secondary amines were obtained. The combination of fragments of 1,3,4-thiadiazole, alkaloids and their structural analogues—piperidine and morpholine—according to our assumptions, should lead to a wide range of biologically active substances.

The alkylation reaction of 1,3,4-thiadiazol-2,5-dithiol by ¡?bhlt?¿organohalogens was carried out in two ways: in an alcohol medium in the presence of triethylamine as an acceptor of hydrogen halogens in the presence of sodium ethoxide. Alkylation takes place only on the thiol groups through S_N2 mechanism with the formation of biproducts (1–4). Yield of final products (1–4) during the alkylation in the presence of triethylamine constitutes 35–55% and, in the presence of sodium ethoxide, 58–80%. The increase in output (1–4) by about 25% indicates that the intermediate sodium salt is stronger electrolyte compared to the ammonium salt or initial 1,3,4-thiadiazol-2,5-dithiols.

Acylation of 1,3,4-thiadiazol-2,5-dithiol by chlorides of carboxylic acids was carried out in the presence of triethylamine with a slight warming of the reaction mixture for 6–20 hours with the formation of bis(acyl) derivatives (5–9). Outputs of final products (5–9) depended on the nature of the acylating reagent and ranged from 43 to 97%. The lowest yield of acylated product (9) is obtained by using butyric acid chloride, which is explained by electron donor influence of alkyl radical on the magnitude of the positive charge on the carbonyl atom of carbon in the initial chloride. Outputs of acylated products (5–8) are sufficiently high, but

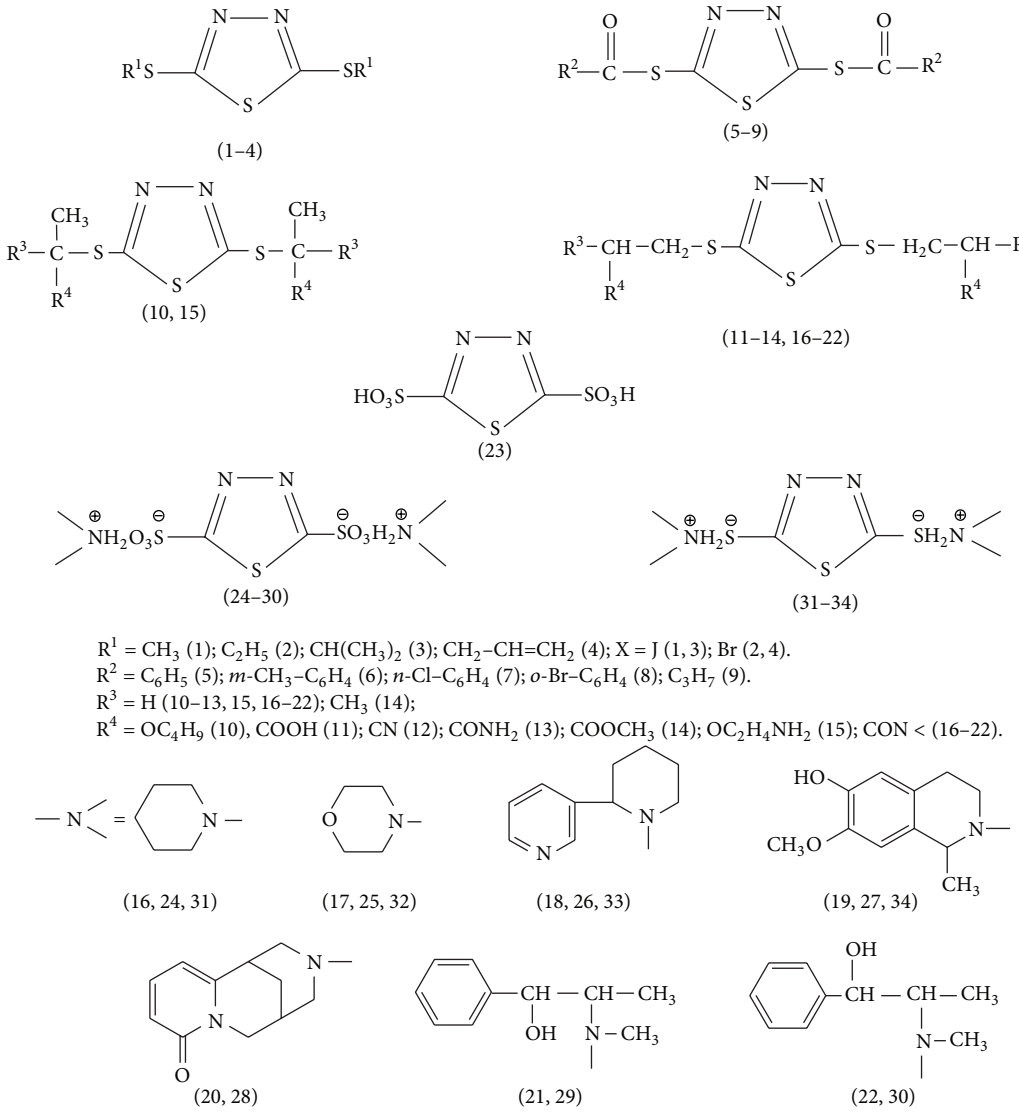

Figure 1

they depend on the nature of the substituent and its position in the benzene ring of the chloride (see Figure 1).

Depending on the nature of the substituent in the α-position of double bond the joining of 1,3,4-thiadiazol-2,5-dithiol to compounds containing a double bond may take place both by Markovnikov's rule and against it.

As the compounds containing the vinyl fragment acrylic acid, acrylamide, acrylonitrile, methyl methacrylate, vinyl ether of monoethanolamine, vinylbutyl ether, and N-substituted acrylamides were used, synthesis of compounds (10–22) was carried out in an alcoholic or aqueous-alcoholic medium with moderate heating and vigorous stirring of the reaction medium for 6–12 hours.

The presence of electron-withdrawing substituents in the α-position of the double bond (acrylic acid, acrylonitrile, acrylamide, acrylic acid methyl ester, and N-substituted acrylamides) leads to the fact that the electrophilic attack center of dithiol anion is β-carbon atom in double bond. The formation of carbanion and subsequent addition of a proton on the α-carbon atom occurs; that is, accession takes place against the Markovnikov rule with the formation of compounds (11–14, 16–22).

The presence of electron-donating substituents in vinylbutyl ether and vinyl ether of monoethanolamine significantly reduces the positive charge on the β-carbon atom of the double bond and leads to the fact that hydrogen atom attacks it, and a dithiol anion attaches to the α-carbon atom; that is, 1,3,4-thiadiazol-2,5-dithiol serves as the electrophile and joins to vinyl ethers with Markovnikov's rule with the formation of compounds (10, 15). Yields of compounds (10, 15) are 27 and 79%, respectively. The reactivity of monoethanolamine vinyl ether is significantly reduced due to the presence of intramolecular hydrogen bond in its molecule. The reaction rate and yields of compounds (11–14)

Table 1: Antioxidant activity of compounds (23–26, 28, and 29).

Compound number	Compound	C_{MDA}, nmol/L (30 min incubation)	Decrease of C_{MDA} in comparison to control level, %
Control	—	30,01	—
Ionol	2,6-Di-*tert*-butylphenol	9,32	68,94
23	1,3,4-Thiadiazol-2,5-disulfonic acid	15,16	50,52
24	Piperidine salt	4,58	84,74
25	Morpholine salt	14,68	51,08
26	Anabasine salt	20,68	31,09
28	Cytisine salt	14,68	51,08
29	*l*-ephedrine salt	14,05	53,18

(42–93%) depend on the electronic and steric factors that determine the activity and the availability of β-carbon atom in an acrylic system.

Despite the voluminous amide fragment in the alkaloids of N-alkaloid(amino)-substituted acrylamides, compared with acrylamide yields of final products (16–22) were 25–65%. Outputs (16–22) depend on the electron properties of the alkaloid (amino) amide fragment in the balance and on the conformational rigidity of the initial cycles of secondary amines and alkaloids, which does not allow to escape β-carbon atom of the double bond. The highest yield of obtained compounds (16, 17, 20) is due to the greater basicity and conformational rigidity of the initial cycles of piperidine, morpholine, and cytisine compared with the conformationally unstable anabasine, *l*-ephedrine, and *d*-pseudoephedrine. The low yield of compound (19) can be explained by spatial inaccessibility of the reaction center due to close proximity to fragment of salsoline undergoing nucleophilic attack by a double bond.

Oxidation of 1,3,4-thiadiazol-2,5-dithiol with an aqueous solution of potassium permanganate takes place only at the thiol groups without affecting the heterocyclic sulfur atom and leads to the formation of 1,3,4-thiadiazol-2,5-disulfonic acid (23) with the yield of about 98%. The reaction of the latter with the alkaloids and secondary amines complex salts (24–30) was synthesized with 50–77% yield. Similarly, the salt of 1,3,4-thiadiazol-2,5-dithiol (31–34) was obtained with yield of 78–94%. Synthesis was carried out in alcoholic medium by heating and stirring the reaction mixture for 5-6 hours. The outputs of salts (24–30) and (31–34) are in the same dependency on basicity and conformational rigidity of the cycles of the secondary amines and alkaloids (16–22).

The composition and structure of all synthesized compounds (1–34) were proved by IR, NMR ^{1}H, and ^{13}C spectroscopy.

In IR spectrums of all the synthesized compounds (1–34), there are absorption bands at 780–730 (C–S_r), 1060–1040, 1160–1120, 1270–1250 (S–C–S, N=C–S, N–N), 1460, and 1390 (N=C) cm^{-1}, which are assigned to thiadiazol cycle. In spectrums of ^{13}C NMR of compounds (1–34) signals of thiadiazol carbon cycle appear as a singlet in the range 168.0–140.0 ppm depending on the nature of the substituent at the sulfur atom of the thiol groups. Spectrums of ^{1}H NMR confirm the presence of proton signals in the substituents of compounds (1–34) in their characteristic regions of the spectrums.

Antibacterial and insecticidal activity of the original 1,3,4-thiadiazol-2,5-dithiol was detected. Studies on the antibacterial activity were carried out by conventional methods used for antibiotics [6]. We determined the sensitivity of microorganisms to a medicine by using method of serial dilutions (8.0, 4.0, 2.0, 1.0, 0.5, 0.25, and 0.125 mg/mL) in liquid medium. For these studies we have used cultures of microorganisms: *S. aureus 505, P. vulgaris 1, P. aeruginosa ATC 464, E. coli M-17, B. subtilis ACCC 6633*, as well as clinical strains of *S. agalactiae* and *C. albicans*.

The minimum bactericidal concentration (MBC) was determined by reseeding from the liquid medium, where there was no visible growth, on solid nutrient medium. The minimum bacteriostatic concentration (MSC) was evaluated by using turbidimetric method by comparing the intensity of microbial growth in liquid nutrient media. The results were recorded on a spectrophotometer, a control culture medium with the appropriate concentration of the drug experience was used.

It was determined that 1,3,4-thiadiazol-2,5-dithiol has antibacterial (MBC from 0.25 to 0.5 mg/mL; MSC from 0.125 to 0.25 mg/mL) (on all subjected strains of microorganisms) and antifungal (MBC 0.25 mg/mL, MSC 0.125 mg/mL) (on a clinical strain of *C. albicans*) activity.

Studies of pesticide (insecticide and aphicide) activity of 1,3,4-thiadiazol-2,5-dithiol were conducted in accordance with the methodological instructions [7]. Insecticidal activity of 1,3,4-thiadiazol-2,5-dithiol was studied in relation to the apple moth (*Hyponomeuta malinellus* Z.), while aphicide one to the apple aphid (Aphis pomi De Geez) and compared with those of standard preparations of Sumi-Alpha and Carbophos. 0,2% aqueous solution of 1,3,4-thiadiazol-2,5-dithiol was used for spraying. Aqueous solutions of reference substances were prepared according to the instructions for use. Average damage of plants before and after processing was registred and effectiveness of drugs calculated. The data obtained were processed statistically; the criterion of reliability was calculated by nonparametric methods [8].

As a result of the tests it was determined that 1,3,4-thiadiazol-2,5-dithiol has insecticidal activity against the

apple moth, exceeding the level of reference preparations of Sumi-Alpha and Carbophos. The mean value of efficiency for 1,3,4-thiadiazol-2,5-dithiol is 43,3%, for sumi-alpha: 38,0%, and carbophos: 19,3%. 1,3,4-thiadiazol-2,5-dithiol has also shown aphicidic activity against apple aphid, but the effectiveness of it is inferior to reference drugs.

According to the results of the primary biotrials 1,3,4-thiadiazol-2,5-dithiol can be recommended for in-depth studies to explore the possibility of its application in agriculture as a pesticide.

Antioxidant activity of 1,3,4-thiadiazol-2,5-disulfonic acid (23) and its salts (24–26, 28, 29) were tested to determine the effect of the thiadiazol ring and sulfonic groups in the structure of nitrogen-containing heterocyclic compounds on the antioxidant activity (AOA) of the latter.

Despite the fact that antioxidants are traditionally considered to be a substance of phenolic nature [9], nitrogen heterocycles containing piperidine, pyridine, pyrimidine, thiazole and other fragments found to have anti- or prooxidant action [10]. Antioxidant activity of 1,3,4-thiadiazol-2,5-disulfonic acid (23) and its salts (24–26, 28, 29) were studied using a model of liposomic oxidation of phosphatidylcholine with the test of thiobarbituric acid [11]. The inhibition of oxidation processes was assessed by measuring concentrations of malondialdehyde (MDA) after 10, 15, 20, and 30 minutes after the start of the reaction. Table 1 shows the antioxidant activity of compounds (23–26, 28, 29) compared to the comparison drug—a synthetic antioxidant ionol 30 minutes after the start of the reaction.

Thus, all studied compounds in varying degrees have shown antioxidant properties. Given the fact that anabasine and *l*-ephedrine by themselves do not exhibit antioxidant properties and cytisine is prooxidant [10], we can assume that it is the introduction of sulfonic acid groups, and thiadiazol fragment in the structure of alkaloids and secondary amines leads to occurrence of antioxidant abilities.

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