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REACTION OF 1,3,4-THIADIAZOL-2,5-DITHIOL WITH *N*-ACRYLOYL-SUBSTITUTED DERIVATIVES OF SEVERAL ALKALOIDS

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Potentially bioactive 2,5-bis derivatives of 1,3,4-thiadiazole with alkaloid moieties were synthesized by reaction of 1,3,4-thiadiazol-2,5-dithiol with N*-acryloyl-substituted derivatives of the alkaloids anabasine, cytisine, and D-pseudoephedrine.*

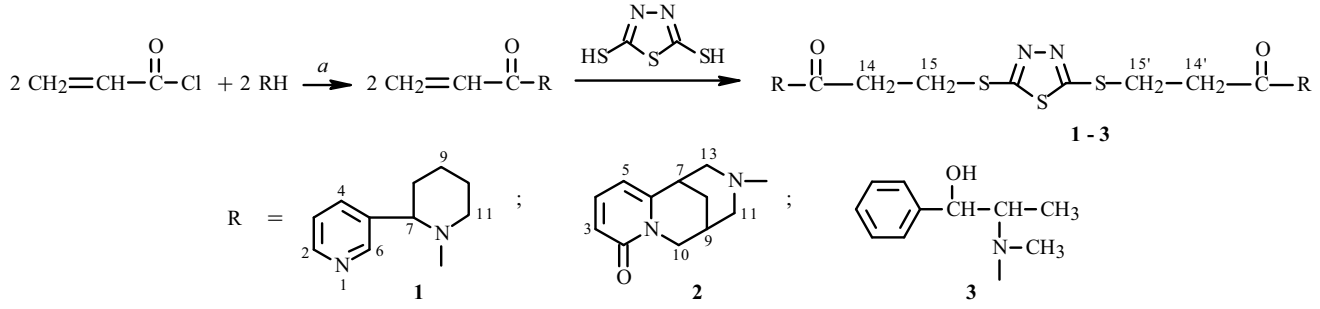
Key words: 1,3,4-thiadiazol-2,5-dithiol, alkaloids, *N*-alkaloid-substituted acrylamides.

Compounds with the 1,3,4-thiadiazole moiety exhibit various physiological activities [1–5]. However, it is worth mentioning that few derivatives of 1,3,4-thiadiazol-2,5-dithiol are known despite its availability and the simplicity of its synthesis [6]. 1,3,4-Thiadiazol-2,5-dithiol is highly nucleophilic because of the thiadiazole ring, which has three donor centers from the two N atoms and the heterocyclic S atom, and two equivalent sterically available thiols. It is interesting as a subject of chemical modification to introduce other functional groups and pharmacophores and to synthesize various 2,5-bis derivatives of 1,3,4-thiadiazoles.

Structural modification of natural biologically active compounds, in particular alkaloids, is a promising area in the synthesis of new potentially biologically active compounds. Combination of alkaloids and 1,3,4-thiadiazole is promising and could according to our hypotheses produce new compounds with a broad spectrum of biological activity.

The high nucleophilicity and steric availablity of the thiols in 1,3,4-thiadiazol-2,5-dithiol suggests that it should add readily to *N*-alkaloid-substituted acrylamides synthesized by the literature method [7].

The reactions of 1,3,4-thiadiazol-2,5-dithiol and *N*-alkaloid-substituted acrylamides was carried out in two steps according to Scheme 1.



Scheme 1

Nucleophilic addition of 1,3,4-thiadiazol-2,5-dithiol to *N*-substituted acrylamides occurred against the Markovnikov rule, i.e., 1,3,4-thiadiazol-2,5-dithiolate anion attacked the β-C atom of the double bond and the labile proton added to the α-C atom of the vinyl group.

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The yields of final products **1**–**3** were 36–75% and depended not so much on the electron-donating properties of the alkaloid moiety in the amide as on the conformational rigidity of the rings in the starting alkaloids that prevented the β-C atom of the double bond from being shielded. Compound **2** was obtained in the highest yield. This was explained by the conformational rigidity of the cytisine rings compared with the conformational flexibility of anabasine and D-pseudoephedrine.

Products **1**–**3** were powdery and oily compounds that were soluble in EtOH and $CHCl_3$ with heating. Their structures and compositions were proved using IR and PMR spectroscopy and elemental analysis.

IR spectra of **1**–**3** contained absorption bands at 780–730 cm^{-1} (C–Sh), 1060–1040, 1160–1120, 1270–1250 (S–C–S, N=C–S, N–N), and 1460–1390 (N=C) that were identified as absorption bands of the thiadaizole ring [8, 9]. Other functional groups of **1**–**3** appeared in characteristic regions of the spectrum at 1695–1624 (C=O), 1480–1440 (–CH_2–), and 705–680 (C–S–) [10].

EXPERIMENTAL

The course of reactions and purity of **1**–**3** were monitored using TLC on Silufol UV-254 standard plates with elution by propan-2-ol:NH_4OH:H_2O (7:2:1) and detection by iodine vapor. Elemental analyses of all compounds agreed with those calculated. Melting points were determined on a Boetius apparatus. IR spectra in KBr disks were recorded on an Avatar-320 spectrometer; PMR spectra in DMSO-d_6, on a Bruker AC-300 spectrometer at operating frequency 300 MHz relative to TMS internal standard.

2,5-Bis(1-(anabasin-1-yl)propan-1-on-3-thio)-1,3,4-thiadiazole (1). A solution of anabasine (1.62 g, 0.01 mol) in benzene was cooled, stirred vigorously in the presence of triethylamine (1.01 g, 0.01 mol), treated dropwise with acryloylchloride (0.91 g, 0.01 mol) over an hour, and stirred at room temperature for 2 h. The resulting precipitate of triethylammonium hydrochloride was filtered off. The filtrate was cooled, stirred, treated dropwise with a solution of 1,3,4-thiadiazol-2,5-dithiol (0.75 g, 0.005 mol) in anhydrous EtOH over an hour, and stirred at room temperature for 2 h. The resulting precipitate was filtered off to afford a white powdery compound (1.3 g, 44%), mp 89–90°C (EtOH), R_f 0.82, $C_{28}H_{34}N_6O_2S_3$. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.81 (4H, m, H-9,9′), 2.08 (4H, m, H-8,8′), 2.50 (4H, m, H-10,10′), 2.81 (4H, t, $J_{14,15}$ = 6.0, H-14,14′), 3.27 (2H, m, H-7,7′), 3.32 (4H, t, $J_{15,14}$ = 6.0, H-15,15′), 3.71 (4H, m, H-11,11′), 7.15 (2H, q, H-3,3′), 7.58 (2H, q, H-4,4′), 8.31 (2H, d, H-6,6′), 8.50 (2H, d, H-2,2′).

2,5-Bis(1-(cytisin-1-yl)propan-1-on-3-thio)-1,3,4-thiadiazole (2) was synthesized analogously to **1** from cytisine (1.9 g, 0.01 mol) to afford a white powdery compound (2.4 g, 75%), mp 121–122°C (EtOH), R_f 0.53, $C_{30}H_{34}N_6O_4S_3$. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.92 (4H, m, H-8,8′), 2.81 (4H, t, $J_{14,15}$ = 6.0, H-14,14′), 2.90 (4H, m, H-11,11′), 2.98 (2H, m, H-9,9′), 3.10 (2H, m, H-7,7′), 3.30 (4H, t, $J_{15,14}$ = 6.0, H-15,15′), 3.36 (4H, m, H-13,13′), 3.80 (2H, m, H_{ax}-10,10′), 4.36 (2H, m, H_{eq}-10,10′), 5.98 (2H, dd, H-5,5′), 6.33 (2H, dd, H-3,3′), 7.23 (2H, dd, H-4,4′).

2,5-Bis(1-(D-pseudoephedrin-1-yl)propan-1-on-3-thio)-1,3,4-thiadiazole (3) was synthesized analogously to **1** from D-pseudoephedrine (1.65 g, 0.01 mol) to afford an oily compound that was purified by column chromatography over silica gel with elution by benzene:EtOH (2:1), R_f 0.78, $C_{28}H_{36}N_4O_4S_3$. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.98 (6H, d, 2CH–C$\underline{H}_3$), 2.48 (2H, m, 2C$\underline{H}$–N), 2.65 (6H, s, 2N–CH_3), 2.80 (4H, t, $J_{14,15}$ = 6.0, H-14,14′), 3.40 (4H, t, $J_{15,14}$ = 6.0, H-15,15′), 4.68 (2H, d, C$\underline{H}$–OH), 5.35 (2H, s, 2OH), 6.28, 7.34 (10H, m, 2ArH).

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