1,2,4-THIADIAZOLE DERIVATIVES OF CYTISINE

V. A. Saprykina,[1] V. I. Vinogradova,[1] R. F. Ambartsumova,[1] T. F. Ibragimov,[1] A. Sultankulov,[2] and Kh. M. Shakhidoyatov[1]

UDC 547.945+547.79

Several new derivatives were prepared by reaction of 3-alkylthio-5-chloroacetamido-1,2,4-thiadiazoles with cytisine.

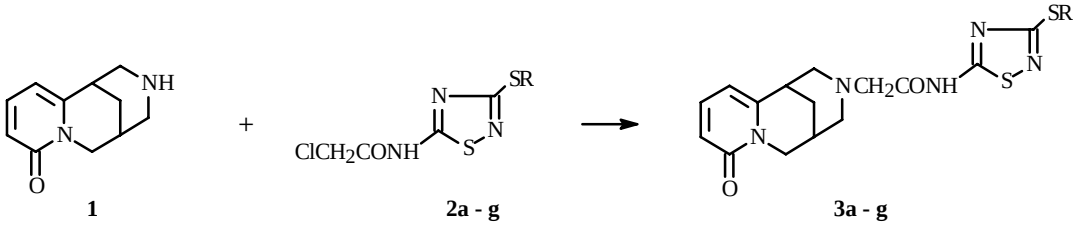
Key words: cytisine, alkylation, 3-alkylthio-5-chloroacetamido-1,2,4-thiadiazoles.

Cytisine (**1**) and its derivatives possess a wide spectrum of biological activity [1]. Therefore, many publications are appearing on the chemical modification of **1** and the study of structure—activity relationships [2, 3].

On the other hand, most natural compounds that are important for life (amino acids, antibiotics, proteins, etc.) that contain a sulfur atom play a significant role in the exchange of compounds in living organisms. Therefore, S-containing compounds, especially heterocyclic ones, may have properties that are valuable in medicine. Derivatives of 5-amino-1,2,4-thiadiazole, one of the promising classes of heterocyclic compounds, many of which are biologically active [4], are of great interest. It would be interesting to combine the cytisine molecule with 5-amino-1,2,4-thiodiazoles, for which we studied amidoalkylation of cytisine with 5-chloroacetyl-1,2,4-thiadiazoles (**2a-g**).

Compounds **2a-g** readily form via acylation of 3-alkylthio-5-amino-1,2,4-thiadiazoles with chloroacetyl chloride.

The condensation was carried out by boiling **1** with **2a-g** in absolute benzene for 4 h in a 2:1 ratio.



1 + **2a - g** → **3a - g**

R = CH_3 (**a**), C_2H_5 (**b**), C_3H_7 (**c**), C_4H_9 (**d**), C_5H_{11} (**e**), C_6H_{13} (**f**), C_7H_{15} (**g**)

The analytical results showed that the yield of **3a-g** slightly decreased as the alkyl chain became longer in **2a-g**.

Compounds **3a-g** are white crystals that crystallize well from the appropriate organic solvents.

The structures of **3a-g** were confirmed by IR and PMR spectra.

The IR spectra of **3a-g** have absorption bands at 1639-1651, 1520-1555, and 798-799 cm^{-1} that are characteristic of an α-pyridone ring. The amide carbonyl absorption (N–CH_2–CO–NH) occurs at 1692-1698 cm^{-1} in the products and at 1687-1691 cm^{-1} in the starting compounds **2b**, **2e**, and **2g**. Stretching vibrations of the exocyclic C=N bond are found in the range 1562-1564 cm^{-1}. The NH group has the characteristic frequencies 3317-3323 cm^{-1}.

The chemical shifts of protons in the PMR spectra of **2a-g** and **3a-g** are similar. However, the NCH_2CO methylene protons are shifted to stronger field (3.32-3.43 ppm) compared with those of the starting materials (4.42-4.46 ppm).

1) S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (99871) 120 64 75; 2) Tashkent Pharmaceutical Institute. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 479-480, November-December, 2004. Original article submitted July 5, 2004.

 0009-3130/04/4006-0582

EXPERIMENTAL

IR spectra were obtained on a Model 2000 Fourier—IR spectrometer (Perkin—Elmer); PMR spectra, on a Tesla instrument at working frequency 100 MHz with HMDS internal standard. The purity of products was monitored by TLC on Silufol UV-254 (Czech Rep.) plates using C_6H_6:$CHCl_3$:$(CH_3)_2CO$ (2:2:1, system A) with development by $KMnO_4$ in dilute H_2SO_4 (**2a-g**) and $CHCl_3$:CH_3OH (10:1, system B) with develoment by iodine and Dragendorff's reagent (**3a-g**).

Compounds **2a-g** were synthesized by the literature method [5].

Elemental analyses of the prepared compounds agreed with those calculated.

3-Amylthio-5-amino-1,2,4-thiadiazole was prepared as before [5]. Yield 60%, R_f 0.69 (system A), mp 93-94°C (ethanol:water, 1:1), $C_7H_{13}N_3S_2$.

IR spectrum (KBr, ν, cm^{-1}): 3324, 3108, 2952, 1638, 1532, 1466, 1251.

PMR spectrum (DMSO-d_6, δ, ppm): 0.83 (t, 3H, CH_3), 1.28 (m, 4H, two CH_2), 1.60 (t, 2H, CH_2), 3.03 (t, 2H, S–CH_2), 7.90 (s, 2H, NH_2).

3-Ethylthio-5-chloroacetamido-1,2,4-thiadiazole (2b) was synthesized as before [6]. Yield 90%, R_f 0.75 (system A), mp 185-186°C, $C_6H_8ClN_3OS_2$.

IR spectrum (KBr, ν, cm^{-1}): 3140, 3033, 2968, 2941, 2839, 1687, 1567, 1405, 1381, 1243.

PMR spectrum (DMSO-d_6, δ, ppm): 1.30 (t, 3H, CH_3), 3.11 (m, 2H, S–CH_2), 4.42 (s, 2H, CH_2–CO), 8.03 (s, 1H, NH).

3-Amylthio-5-chloroacetamido-1,2,4-thiadiazole (2e) was synthesized as before [6]. Yield 66%, R_f 0.77 (system A), mp 139-140°C (petroleum ether), $C_9H_{14}ClN_3OS_2$.

IR spectrum (KBr, ν, cm^{-1}): 3445, 3144, 3034, 2961, 2855, 1688, 1565, 1402, 1380, 1247.

PMR spectrum (DMSO-d_6, δ, ppm): 0.83 (t, 3H, CH_3), 1.31 (m, 4H, two CH_2), 1.65 (t, 2H, CH_2), 3.12 (t, 2H, S–CH_2), 4.45 (s, 2H, CH_2–CO), 7.95 (s, 1H, NH).

3-Heptylthio-5-chloroacetamido-1,2,4-thiadiazole (2g) was prepared as before [6]. Yield 56%, R_f 0.95 (system A), mp 114-115°C (petroleum ether), $C_{11}H_{18}ClN_3OS_2$.

IR spectrum (KBr, ν, cm^{-1}): 3139, 2924, 2855, 1691, 1570, 1404, 1378, 1247.

PMR spectrum (DMSO-d_6, δ, ppm): 0.80 (t, 3H, CH_3), 1.23 (m, 6H, $3CH_2$), 1.60 (t, 2H, CH_2), 3.12 (t, 2H, S–CH_2), 4.44 (s, 2H, CH_2–CO), 7.95 (s, 1H, NH).

N-(3-Alkylthio-5-acetamido-1,2,4-thiadiazolyl)cytisines (3a-g). A mixture of cytisine (2 mmol) and **2a-g** (1 mmol) was boiled for 4 h in absolute benzene (15 mL). The solvent was evporated. The solid was washed with water and recrystallized from hexane.

N-(3-Methylthio-5-acetamido-1,2,4-thiadiazolyl)cytisine (3a). Yield 93%, R_f 0.60 (system B), mp 171-173°C, $C_{16}H_{19}N_5O_2S_2$.

IR spectrum (KBr, ν, cm^{-1}): 3143, 3047, 2930, 2807, 1652, 1639, 1564, 1520, 1406, 1234, 810, 801, 798.

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 1.68 (H-8, J = 12.5, 2.5), 2.54 (S–CH_3), 2.62, 2.78, 2.86, 2.96 (H-7, 11, 13), 3.33 (N–CH_2–CO), 3.68 (H_{ax}-10), 3.74 (H_{eq}-10), 6.01 (d, J = 6.5, H-5), 6.15 (d, J = 9, H-3), 7.26 (d, J = 9, J = 6.5, H-4), 12.62 (NH).

N-(3-Ethylthio-5-acetamido-1,2,4-thiadiazolyl)cytisine (3b). Yield 82%, R_f 0.87 (system B), mp 115-117°C, $C_{17}H_{21}N_5O_2S_2$.

IR spectrum (KBr, ν, cm^{-1}): 3323, 3128, 3047 2938, 2797, 1694, 1639, 1563, 1553, 1531, 1404, 1226, 811, 798.

PMR spectrum (DMSO-d_6, δ, ppm): 1.26 (t, CH_3), 1.68 (H-8), 2.34 (H-9), 3.10 (S–CH_2), 3.32 (N–CH_2–CO), 3.70 (H_{ax}-10), 3.75 (H_{eq}-10), 6.04 (d, J = 6.5, H-5), 6.14 (d, J = 9, H-3), 7.26 (dd, J = 6.5, J = 9, H-4), 12.08 (NH).

N-(3-Propylthio-5-acetamido-1,2,4-thiadiazolyl)cytisine (3c). Yield 77%, R_f 0.77 (system B), mp 161-162°C, $C_{18}H_{23}N_5O_2S_2$.

IR spectrum (KBr, ν, cm^{-1}): 3124, 3032, 2960, 2932, 2819, 1696, 1651, 1563, 1548, 1537, 1406, 1027, 798.

PMR spectrum (Py-d_5, δ, ppm): 0.81 (t, 3H, CH_3), 1.48 (CH_2), 1.68 (H-8), 2.45-2.89 (H-7, 9, 11, 13), 3.12 (S–CH_2), 3.43 (N–CH_2–CO), 3.85 (H_{ax}-10), 4.17 (H_7-10), 5.84 (dd, J = 6.5, H-5), 6.37 (dd, J = 9, H-3), 7.12 (dd, J = 6.5, J = 9, H-4).

N-(3-Butylthio-5-acetamido-1,2,4-thiadiazolyl)cytisine (3d). Yield 70%, R_f 0.79 (system B), mp 164-166°C, $C_{19}H_{25}N_5O_2S_2$.

IR spectrum (KBr, ν, cm^{-1}): 3123, 3033, 2955, 2933, 1698, 1647, 1562, 1548, 1537, 1408, 1225, 799.

PMR spectrum (Py-d_5, δ, ppm, J/Hz): 0.76 (t, CH_3), 1.38 (CH_2) 1.46 (CH_2), 2.01 (H-8), 2.54-2.82 (H-7, 9, 11, 13), 3.16 (S–CH_2), 3.42 (N–CH_2–CO), 3.86 (H_{ax}-10), 4.14 (H_{eq}-10), 5.77 (dd, J = 2, J = 6.5, H-5), 6.37 (dd, J = 2, J = 9, H-3), 7.08 (dd, J = 6.5, J = 9, H-4).

N-(3-Amylthio-5-acetamido-1,2,4-thiadiazolyl)cytisine (3e). Yield 68%, R_f 0.76 (system B), mp 152-153°C, $C_{20}H_{27}N_5O_2S_2$.

IR spectrum (KBr, ν, cm^{-1}): 3116, 3031, 2931, 2859, 1698, 1651, 1564, 1548, 1536, 1406, 1224, 798.

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 0.8 (CH_3), 1.30 (CH_2), 1.54 (CH_2), 1.68 (CH_2), (2H-8), 2.3-3.02 (H-7, 11, 13), 3.10 (S–CH_2), 3.32 (N–CH_2–CO), 3.70 (H_{ax}-10), 3.76 (H_{eq}-10), 6.06 (dd, J = 2, J = 6.5, H-5), 6.16 (dd, J = 2, J = 9, H-3), 7.16 (dd, J = 6.5, J = 9, H-4).

N-(3-Hexylthio-5-acetamido-1,2,4-thiadiazolyl)cytisine (3f). Yield 65%, R_f 0.74 (system B), mp 123-124°C, $C_{21}H_{29}N_5O_2S_2$.

IR spectrum (KBr, ν, cm^{-1}): 3120, 3034, 2933, 2869, 1698, 1645, 1563, 1552, 1537, 1408, 1227, 798.

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 0.82 (CH_3), 1.22, 1.68 (8H, CH_2), 2.55-3.03 (H-7, 11, 13), 3.10 (S–CH_2–CO), 3.68 (H_{ax}-10), 3.73 (H_{eq}-10), 5.98 (dd, J = 2, J = 6.5, H-5), 6.13 (dd, J = 2, J = 9, H-3), 7.23 (dd, J = 6.5, J = 9, H-4).

N-(3-Heptylthio-5-acetamido-1,2,4-thiadiazolyl)cytisine (3g). Yield 62%, R_f 0.75 (system B), mp 127-128°C, $C_{22}H_{31}N_5O_2S_2$.

IR spectrum (KBr, ν, cm^{-1}): 3122, 3033, 2930, 2855, 1698, 1651, 1564, 1548, 1537, 1407, 1227, 798.

PMR spectrum (Py-d_5, δ, ppm, J/Hz): 0.66 (CH_3), 1.04 (6H, $3CH_2$), 1.77 (4H, CH_2), 2.08, 2.48-3.10 (H-7, 11, 13), 3.18 (S–CH_2), 3.42 (N–CH_2–CO), 3.80 (H_{ax}-10), 4.12 (H_{eq}-10), 5.78 (dd, J = 2, J = 6.5, H-5), 6.35 (dd, J = 2, J = 9, H-3), 7.06 (dd, J = 6.5, J = 9, H-4).

REFERENCES

1. A. M. Gazaliev, M. Zh. Zhurinov, and S. D. Fazylov, *New Bioactive Alkaloid Derivatives* [in Russian], Gylym, Alma-Ata (1992), pp. 88-133.
2. T. V. Khakimova, O. A. Pukhlyakova, G. A. Shavaleeva, A. A. Fatykhov, E. V. Vasil′eva, and L. V. Spirikhin, *Khim. Prir. Soedin.*, 301 (2001).
3. K. A. Krasnov, V. G. Kartsev, A. S. Gorovoi, and V. N. Khrustalev, *Khim. Prir. Soedin.*, 367 (2002).
4. F. Kurtzer, *Adv. Heterocycl. Chem.*, **5**, 200 (1965).
5. J. Goerdeler and P. Linden, *Chem. Ber.*, **89B**, No. 12, 2742 (1956).
6. M. M. Khakimov, R. F. Ambartsumova, V. A. Saprykina, and Kh. M. Shakhidoyatov, *Uzb. Khim. Zh.*, No. 2, 33 (2000).