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REGIOSELECTIVITY OF ALKYLATION OF 3-SUBSTITUTED 5-AMINO-1,2,4-THIADIAZOLES

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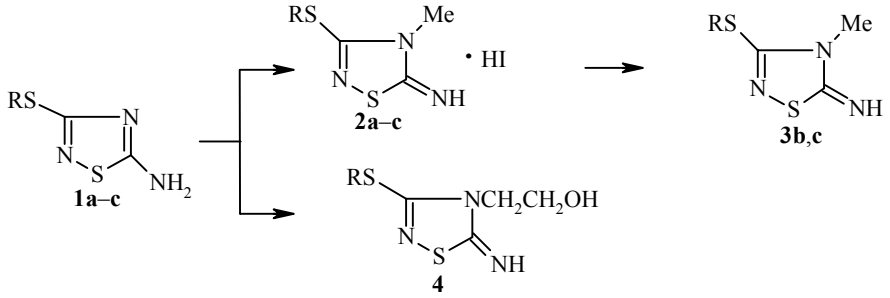
We have synthesized 3-substituted 4-alkyl-5-imino-4,5-dihydro-1,2,4-thiadiazoles by reaction of 3-alkyl(benzyl)thio-5-amino-1,2,4-thiadiazoles with methyl iodide or ethylene chlorohydrin. In the reaction with epichlorohydrin, addition of an oxirane molecule occurs with formation of tetrahydropyrimido[2,1-b]-1,2,4-thiadiazoles.

Keywords: 4-alkyl-5-imino-4,5-dihydro-1,2,4-thiadiazoles, 5-amino-1,2,4-thiadiazoles, tetrahydropyrimido[2,1-*b*]-1,2,4-thiadiazoles, ethylene chlorohydrin, epichlorohydrin, X-ray diffraction.

Despite the fact that the chemistry of 5-amino-1,2,4-thiadiazoles has been rather widely studied [1], the alkylation of these compounds by alkyl halides has been described only in isolated cases, and no information is available in the literature about reactions with halohydrins and oxiranes. Furthermore, we know that in the series of 1,2,4-thiadiazole derivatives, we find compounds with pharmacological [2, 3] and other types of biological [4, 5] activity; and even compounds that are rather similar structurally differ, for example, in the nature of their pesticidal activity [6].

With the aim of studying the reaction of ambident 5-amino-1,2,4-thiadiazoles with alkylating agents and also obtaining new, potentially physiologically active substances based on them, we carried out reactions of 3-alkyl(benzyl)thio-5-amino-1,2,4-thiadiazoles **1** with methyl iodide, ethylene chlorohydrin, and epichlorohydrin.



a R = Me, **b** R = Bu, **c** R = Bn

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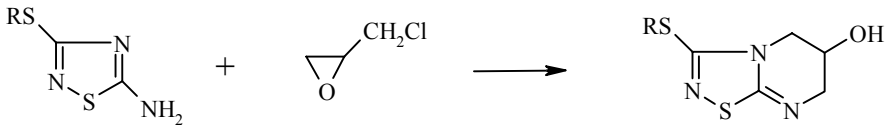
Alkylation of amines **1a-c** with methyl iodide leads to hydroiodides **2a-c**. From the literature, we know that to isolate the free bases, quaternary salts of 5-amino-1,2,4-thiadiazoles are treated with silver oxide in methanol [7] or suspended in anhydrous pyridine [8]. We neutralized the hydroiodides **2b,c** with ammonia solution and isolated the bases **3b,c**.

In the case of the methyl derivative **2a**, the corresponding base could not be isolated in pure form either when treated with ammonia solution or when suspended in pyridine.

Boiling compound **1b** with ethylene chlorohydrin leads to synthesis of amino alcohol **4**, i.e., in reactions of ambident nucleophiles **1a-c** with methyl iodide and ethylene chlorohydrin, the products of alkylation at the endocyclic nitrogen atom of the heterocycle are formed. When we reacted amines **1a-c** with epichlorohydrin in glacial acetic acid, we isolated derivatives of tetrahydropyrimido[2,1-*b*]-1,2,4-thiadiazole **5a-c**, the products of alkylation at the exocyclic amino group and the ring nitrogen atom in the position 4 of the thiadiazole system.



1a–c **5a–c**

A similar course of the reactions of some ambifunctional heterocyclic amines with epihalohydrins, with formation of bis-heterocyclic structures, has been reported already in [9-11], and we have described it earlier in [12].

All the synthesized compounds are stable crystalline substances (Table 1) which remain unaltered during prolonged storage (in contrast to 5-imino-4-methyl-4,5-dihydro-1,2,4-thiadiazoles [13], which on standing rearrange to the amino isomers).

The structure of compounds **2-5** has been established by means of IR and ^{1}H NMR spectroscopy and mass spectrometry (Table 2). Alkylation of amines **1a-c** at the position 4 of the heterocycle has been confirmed by the presence in the IR spectra of compounds **2-4** of the exocyclic C=N bond absorption band in the 1620-1610 cm^{-1} region.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f	Yield, %
		C	H	N			
2a	$C_4H_7N_3S_2 \cdot HI$	16.39 / 16.67	2.40 / 2.42	14.62 / 14.53	228-230	0.17	41
3b	$C_7H_{13}N_3S_2$	41.55 / 41.38	6.38 / 6.40	20.41 / 20.69	61-62*	0.49	43
3c	$C_{10}H_{11}N_3S_2$	50.68 / 50.63	4.49 / 4.64	17.52 / 17.72	71-73*[2]	0.43	36
4	$C_8H_{15}N_3OS_2$	41.25 / 41.20	6.60 / 6.44	18.25 / 18.03	93-96	0.84	35
5a	$C_6H_9N_3OS_2$	35.47 / 35.45	3.87 / 4.46		225-227	0.40	25
5b	$C_9H_{15}N_3OS_2$	43.92 / 44.08	6.23 / 6.12	17.30 / 17.14	140-142	0.44	51
5c	$C_{12}H_{13}N_3OS_2$	51.68 / 51.61	4.53 / 4.66	14.98 / 15.05	169-173	0.5	42

* mp of hydrochloride, 135-137°C.

*[2] mp of hydrochloride, 200-203°C.

TABLE 2. Spectral Characteristics of Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm	Mass spectrum, *m*/*z* (I_{rel}, %)	
			M^+	fragmentary ions
2a	3224, 3168, 3062, 2605, 1623, 1562	2.68 (3H, s, CH_3S); 3.57 (3H, s, CH_3–N);	161 (100)	146 (15), 139 (9), 128 (6), 105 (91), 90 (23), 88 (50)
3b	3197, 1614, 1592	0.85 (3H, t, CH_3C); 1.35 (2H, m, C–CH_2–C); 1.61 (2H, m, C–CH_2–C); 3.11 (2H, t, CH_2S); 3.20 (3H, s, CH_3N); 5.52 (1H, br. s, NH)	203 (41)	149 (10), 139 (100), 143 (20), 90 (13), 88 (56), 74 (10), 69 (13)
3c	3179, 1589, 1536	3.20 (3H, s, CH_3N); 4.37 (2H, s, CH_2); 5.45 (1H, br. s, NH); 7.20-7.50 (5H, m, H_{arom})	237 (68)	222 (2), 204 (5), 177 (3), 160 (3), 148 (19), 144 (13), 121 (7), 91 (100)
4	3213, 1610, 1530	0.83 (3H, t, CH_3C); 1.38 (2H, m, C–CH_2–C); 1.60 (2H, m, C–CH_2–C); 3.18 (2H, t, CH_2S); 3.70 (2H, q, CH_2O); 3.83 (2H, q, CH_2N); 4.79 (2H, br. s, NH, OH)	233 (24)	189 (24), 160 (9), 147 (26), 142 (42), 133 (100), 130 (34), 105 (11), 101 (17), 91 (20), 85 (32), 69 (23)
5a	3030, 1619, 1538	2.55 (3H, s, CH_3); 3.41 (2H, t, CH_2N); 3.76 (2H, t, CH_2N); 4.02-4.18 (1H, m, CH)	203 (62)	186 (7), 160 (13), 158 (100), 157 (51), 146 (18), 130 (19), 121 (13), 112 (15), 107 (83), 80 (34), 69 (38)
5b	3105, 1626, 1523	0.89 (3H, t, CH_3); 1.20-1.85 (4H, m, CH_2–CH_2); 3.14 (2H, t, CH_2S); 3.30-3.80 (5H, m, $2CH_2N$, OH); 4.20 (1H, m, CH)	245 (93)	207 (100), 189 (16), 172 (19), 159 (21), 154 (41), 146 (46), 145 (57), 141 (44), 115 (22), 97 (11), 85 (48), 72 (40)
5c	3063, 1615, 1525	3.51-3.83 (4H, m, $2CH_2N$); 4.15 (1H, m, CH); 4.32 (2H, s, CH_2Ph); 5.00 (1H, br. s, OH); 7.10-7.40 (5H, m, H_{arom})	279 (20)	236 (9), 202 (10), 160 (7), 149 (7), 135 (10), 105 (7), 91 (100), 85 (16), 75 (15), 69 (24)

In the mass spectra, there are molecular ion peaks and peaks of their fragmentation products, due to successive splitting off the alkyl groups and cleavage of the thiadiazole ring, and in the case of compounds **5a-c** also of the tetrahydropyrimidine ring. The ^{1}H NMR spectra of compounds **2-5** are completely consistent with their structure. The structure of the bicyclic products **5** for the example of compound **5b** has also been confirmed by X-ray diffraction data (Fig. 1).

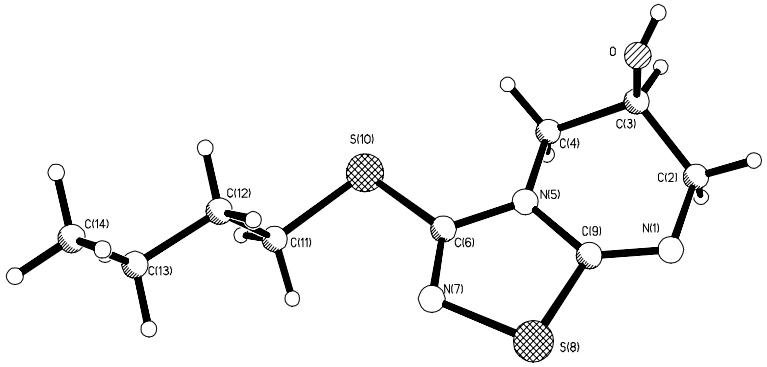


Fig. 1. Spatial structure and numbering of atoms in the molecule of compound **5b**.

TABLE 3. Bond Lengths (*d*) and Bond Angles (ω) in the Molecule of Compound **5b**

Bond	*d*, Å	Angle	ω, deg.
S(8)–N(7)	1.695(5)	N(7)–S(8)–C(9)	94.5(2)
S(8)–C(9)	1.763(4)	C(6)–N(5)–C(9)	113.7(3)
N(5)–C(6)	1.374(5)	C(6)–N(5)–C(4)	126.5(3)
N(5)–C(9)	1.382(5)	C(9)–N(5)–C(4)	119.5(3)
N(5)–C(4)	1.465(5)	C(6)–S(10)–C(11)	100.9(3)
O–C(3)	1.423(5)	N(1)–C(9)–N(5)	128.2(4)
S(10)–C(6)	1.758(5)	N(1)–C(9)–S(8)	126.8(3)
S(10)–C(11)	1.796(6)	N(5)–C(9)–S(8)	105.0(3)
C(9)–N(1)	1.271(5)	C(9)–N(1)–C(2)	116.0(3)
N(1)–C(2)	1.472(6)	C(6)–N(7)–S(8)	108.6(3)
N(7)–C(6)	1.287(6)	N(1)–C(2)–C(3)	113.7(3)
C(2)–C(3)	1.502(6)	N(7)–C(6)–N(5)	118.1(4)
C(4)–C(3)	1.526(6)	N(7)–C(6)–S(10)	125.5(3)
C(11)–C(12)	1.549(10)	N(5)–C(6)–S(10)	116.3(3)
C(12)–C(13)	1.495(8)	N(5)–C(4)–C(3)	107.8(3)
C(13)–C(14)	1.506(9)	O–C(3)–C(2)	110.5(4)
		O–C(3)–C(4)	108.5(4)
		C(2)–C(3)–C(4)	110.0(4)
		C(12)–C(11)–S(10)	111.9(4)
		C(13)–C(12)–C(11)	111.5(5)
		C(12)–C(13)–C(14)	111.7(6)

As we see from Fig. 1, the condensed bicyclic system is practically flat within 0.042 Å. The exocyclic S(10) atom deviates from this plane slightly (0.19 Å) but deviation of the endocyclic C(3) atom from the plane (0.63 Å) is rather appreciable, which leads to a change in the shape of the ring: the tetrahydropyrimidine ring takes on a sofa conformation. The hydroxyl group in this position is located axially. The practically flat alkyl group (torsional angles around the C(11)–C(12) and C(12)–C(13) bonds equal to 175.1° and 179.4° respectively) is located perpendicular to the plane of the bicyclic system (89.9°) (the bond lengths and bond angles are presented in Table 3). Analysis of the bond lengths shows that the formal double bond C=N in the bicyclic system [C(9)–N(1) 1.271(5) Å and C(6)–N(7) 1.287(6) Å] is slightly lengthened while the single bond Csp^2–N [C(6)–N(5) 1.374(5) Å and C(9)–N(5) 1.382(5) Å] is shortened in comparison with the standard values [14]. This fact indicates some redistribution of electron density in the hetero bonds as a result of conjugation of the π-electron system of the double bonds with the unshared electron pairs of the N(5), S(8), and S(10) atoms, which is also reflected in a change in the lengths of the S–C hetero bonds. The apparent shortening of the Csp^3–Csp^3 bonds [C(12)–C(13) 1.495(8) Å and C(13)–C(14) 1.506(9) Å] is apparently due to strong thermal vibrations of the terminal alkyl groups (Table 4). The other hetero bonds and valence bonds in the hydrogenated pyrimidothiadiazole system do not differ from the standard values within 3*s* [14].

EXPERIMENTAL

The IR spectra were taken on a Perkin Elmer spectrometer (System 2000 FT-IR) in KBr pellets. The ^{1}H NMR spectra of solutions of compounds **2a, 4, 5a** in CD_3OD, compounds **3b,c** and **5b** in deuterochloroform, and compound **5c** in C_5D_5N were recorded on a Tesla BS-567 instrument with operating frequency of 100 MHz, internal standard HMDS. The mass spectra were obtained on a Kratos MS-25RF spectrometer with direct

TABLE 4. Coordinates of Atoms ($\times 10^4$) and Their Equivalent Thermal Parameters ($Å^2 \times 10^3$) for the Molecule of Compound **5b**

Atom	*x*	*y*	*z*	U_{eq}
O	-3660(3)	4240(3)	7235(4)	53(1)
N(1)	-921(3)	4691(3)	6869(4)	46(1)
C(2)	-1956(5)	5119(4)	5957(6)	53(1)
C(3)	-3065(4)	4364(4)	5839(4)	43(1)
C(4)	-2628(4)	3248(3)	5311(5)	44(1)
N(5)	-1598(3)	2895(2)	6274(4)	38(1)
C(6)	-1204(4)	1845(3)	6498(5)	45(1)
N(7)	-249(4)	1686(3)	7348(5)	55(1)
S(8)	298(1)	2908(1)	7925(2)	54(1)
C(9)	-838(3)	3663(3)	6943(4)	38(1)
S(10)	-2013(1)	833(1)	5510(2)	70(1)
C(11)	-1042(6)	-331(4)	5883(8)	80(2)
C(12)	-1475(6)	-942(4)	7288(9)	74(2)
C(13)	-733(7)	-1961(5)	7518(8)	77(2)
C(14)	-1142(6)	-2552(6)	8891(8)	76(2)

injection of the sample into the ion source, temperature of the ionization chamber 250°C, ionizing electron energy 70 eV. The purity of the products and the course of the reactions were monitored using TLC (Silufol UV-254, benzene–chloroform–acetone, 1:1:2 (compounds **2a, 3bc**) and methanol–chloroform, 1:1 (compounds **4, 5a-c**), detection with a solution of $KMnO_4$ in dilute H_2SO_4 or under UV light).

3-Alkyl(benzyl)thio-5-amino-1,2,4-thiadiazoles **1a-c** were synthesized according to the procedure in [15].

5-Imino-4-methyl-3-R-4,5-dihydro-1,2,4-thiadiazole hydroiodides (2a-c). CH_3I (20 mmol) was added to solution of amine **1a-c** (10 mmol) in absolute ethanol (3-4 ml) and then boiled for 10 h. The reaction mixture was cooled, the precipitate was filtered off, washed with dry acetone, and recrystallized from absolute ethanol.

In the case of amine **1b**, the reaction mixture was evaporated down to dryness on a rotary evaporator, the residue was triturated with diethyl ether, washed with acetone, and recrystallized from ethanol.

5-Imino-4-methyl-3-R-thio-4,5-dihydro-1,2,4-thiadiazoles (3b,c). Hydroiodide **2b,c** was dissolved in a minimal amount of water and neutralized on cooling by 25% ammonia solution. The precipitate was filtered off and recrystallized from benzene–heptane mixture, 1:2.

3-Butylthio-4-hydroxyethyl-5-imino-4,5-dihydro-1,2,4-thiadiazole (4). Amine **1b** (2.39 g, 12 mmol) and ethylene chlorohydrin (3.36 g, 48 mmol) were boiled for 4-6 h. The reaction mixture was evaporated down to dryness, the residue was extracted with water, the aqueous extract was neutralized with ammonia solution. The precipitate was filtered off and recrystallized from heptane. Yield 0.98 g (35%).

3-Hydroxy-6-R-thio-2,3,4,5-tetrahydropyrimido[1,2-*b*]-1,2,4-thiadiazoles (5a-c). Aminothiadiazole **1a-c** (10 mmol) was dissolved in glacial CH_3COOH (12 ml); epichlorohydrin (22 mmol) was added and the mixture was stirred for 10 h at 60°C to 80°C. Acetic acid was evaporated, the oily residue was extracted with water, the aqueous solution was neutralized with ammonia solution. The precipitate was filtered off and recrystallized from methanol or acetone.

X-ray Diffraction Study of Compound 5b. Single crystals were obtained by growing up from methanol. The unit cell parameters and the intensities of 1872 independent reflections were measured on a CAD-4 Nonius diffractometer (MoKα, graphite monochromator, $\theta/2\theta$ scanning, $\theta < 25.1$). The crystals are rhombic, $a = 10.598(2)$, $b = 12.310(3)$, $c = 9.070(2)$ Å; $V = 1183.3(4)$; $d_{calc} = 1.372$ g/cm^3; $Z = 4$ ($C_9H_{14}S_2N_3O$); space group $Pca2_1$. The structure was solved by the direct method and refined by the full-matrix least-squares

method in the anisotropic approximation for the nonhydrogen atoms. The hydrogen atom coordinates were assigned geometrically and located using the "rider" model. The calculations used 1377 reflections with $I > 2\sigma(I)$. The final R factors were $R = 0.0462$ and $R_w = 0.1289$. The coordinates of the atoms are presented in Table 4. All the calculations were done on an IBM 486 PC using the program packages SHELXTL and SHELXL-95.

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