ISSN 1070-3632, Russian Journal of General Chemistry, 2016, Vol. 86, No. 6, pp. 1274–1281. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © A.V. Erkin, I.V. Klaptyuk, V.V. Gurzhii, O.S. Yuzikhin, V.I. Krutikov, 2016, published in Zhurnal Obshchei Khimii, 2016, Vol. 86, No. 6, pp. 944–951.

Aryl Ethers of 4-[(2-Hydroxyethyl)sulfanyl]pyrimidine Derivatives: Pathways of Synthesis and Fungicidal Activity of Their Salt Forms

A. V. Erkin[a], I. V. Klaptyuk[b], V. V. Gurzhii[c], O. S. Yuzikhin[d], and V. I. Krutikov[a]

[a] *St. Petersburg State Institute of Technology (Technical University), Moskovskii pr. 26, St. Petersburg, 190013 Russia e-mail: kruerk@yandex.ru*

[b] *St. Petersburg University of State Fire Service at the Emergency Situations Ministry of Russian Federation, St. Petersburg, Russia*

[c] *St. Petersburg State University, St. Petersburg, Russia*

[d] *Kirov St. Petersburg State Forest Technical University, St. Petersburg, Russia*

Received December 17, 2015

Abstract—2-Amino-4-[(2-aryloxyethyl)sulfanyl]-6-methylpyrimidines were obtained by *S*-alkylation of 2-amino-6-methylpyrimidin-4(3*H*)-thione with 2-aryloxyethyl chlorides. Since 2-amino-4-[(2-chloroethyl)sulfanyl]-6-methylpyrimidine is prone to in situ intramolecular cyclization it cannot be used in Claisen reaction. The bromination of the target compounds provided 5-bromo derivatives; some of their hydrochlorides exhibited fungicidal activity.

Keywords: 2-amino-6-methylpyrimidin-4(3*H*)-thione, *S*-alkylation, 2-aryloxyethyl ethers, bromination, fungicidal activity

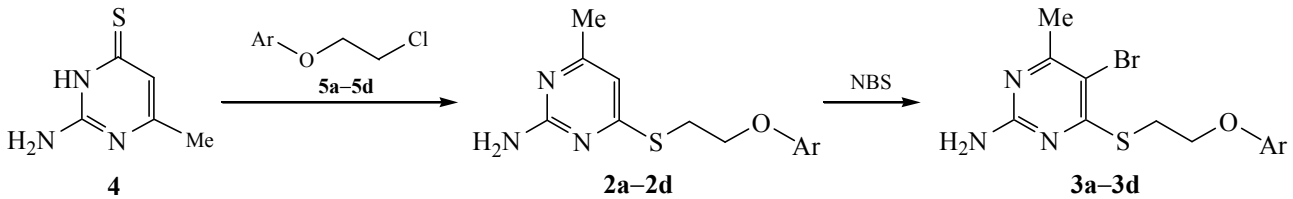
DOI: 10.1134/S1070363216060098

Azoles are ranked as most important among the medicines for the treatment of candidiasis, an infectious disease caused by pathogenic strains of *Candida* yeasts [1]. New generation antifungals includes 2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butane-2-ol which under the name Voriconazole has passed phase III of clinical trials [2]. Hydrochlorides of benzyl ethers of 2-amino-6-methylpyrimidin-4(3*H*)-thione are capable of 100% in vitro inhibiting the growth of *Candida albicans* cells (strain 15) in low (≤0.093 mmol/L) concentrations [3]. The introduction of halogen atoms into the aromatic moiety of compound **1** caused a decrease in the inhibition concentrations of above species.

Here we aimed to synthesize analogs of benzyl ethers of **1** such as 2-amino-4-[(2-arylhydroxyethyl)sulfanyl]-6-methylpyrimidines **2a**–**2d** and 2-amino-4-[(2-aryloxyethyl)sulfanyl]-5-bromo-6-methylpyrimidines **3a**–**3d**, including those containing halogen atoms in aromatic ring, and to study the antifungal activity of their hydrochlorides.

Thioethers **2a**–**2d** were prepared by *S*-alkylation of 2-amino-6-methylpyrimidin-4(3*H*)-thione **4** [4] with 2-

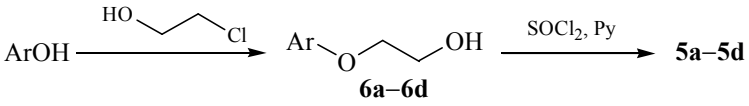
Scheme 1.



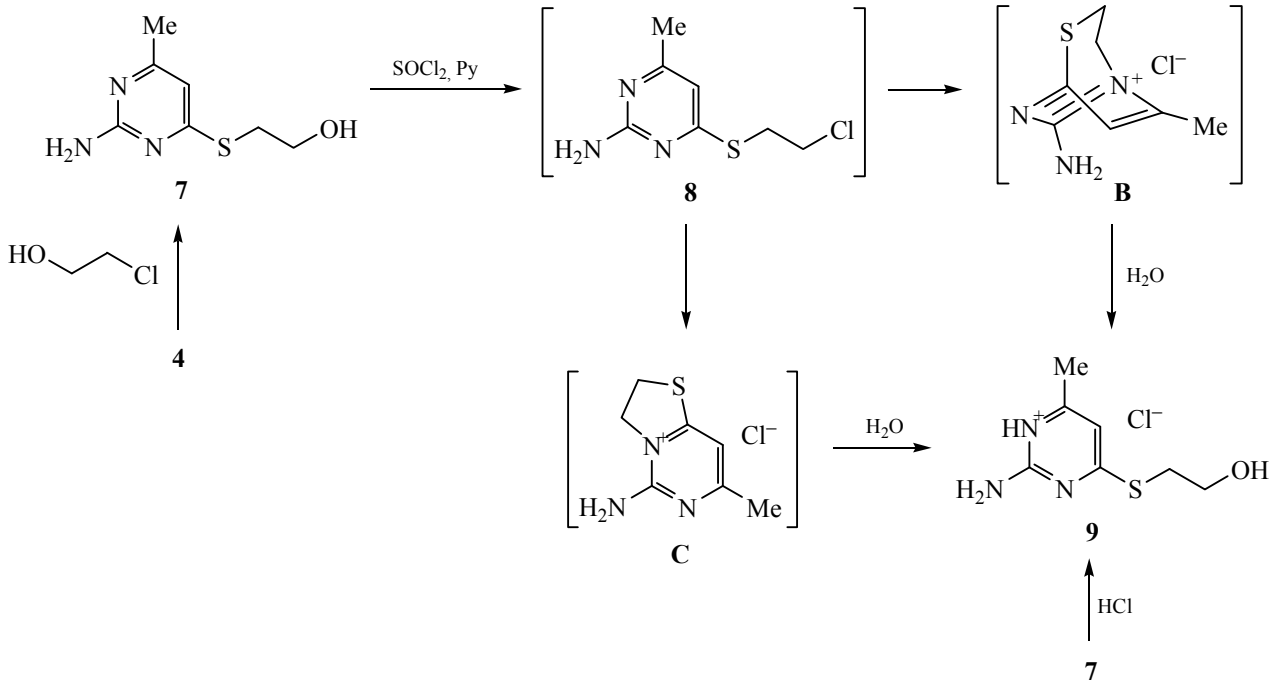
4 **2a–2d** **3a–3d**

Ar = Ph (**a**), 2-FC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 2,4-$Cl_2C_6H_3$ (**d**).

Scheme 2.



Scheme 3.



aryloxyethyl chlorides **5a**–**5d** in DMF in the presence of potassium carbonate at 100°C. Thioethers **3a**–**3d** were obtained through bromination of compounds **2a**–**2d** with *N*-bromosuccinimide (NBS) in boiling chloroform (Scheme 1).

Compounds **5a**–**5d** were synthesized via *O*-alkylation of the corresponding phenols with 2-chloroethanol in aqueous medium in the presence of an equimolar amount of sodium hydroxide at 80°C, followed by chlorination of the intermediate 2-aryloxyethanols **6a**–**6d** with thionyl chloride in chloroform in the presence of pyridine (Scheme 2).

The structure and the composition of the prepared compounds were confirmed by NMR and IR spectroscopy and by elemental analysis (Tables 1, 2). The ^{1}H NMR spectra of thioethers **2a**–**2d** and **3a**–**3d** contained the signals of methyl (2.1–2.3 ppm) and NH_2 groups (6.5–6.8 ppm), as well as the triplets of CH_2CH_2 unit (3.4–4.3 ppm) and multiplets of aromatic protons (6.9–7.5 ppm). In the IR spectra the following absorption bands were attributed to the stretching (3492–3443 cm^{-1}) and bending (1640–1605 cm^{-1}) vibrations of amino group, C=N (1570–1525 cm^{-1}) and C=C (1470–1445 cm^{-1}) vibrations, as well as asymmetrical (1265–1230 cm^{-1}) and symmetric (1060–1010 cm^{-1}) vibrations of C–O–C_{Ar} bond (Table 2).

An attempt to obtain compounds **2a**–**2d** by Claisen reaction failed. Exchange chlorination of 2-amino-4-[(2-hydroxyethyl)sulfanyl]-6-methylpyrimidine **7** with thionyl chloride in chloroform in the presence of pyridine provided chromatographically pure product (R_f 0.26, mp 181ºC) (eluent **A**). Aqueous solution of the latter showed positive test for the presence of chloride ion when treating with silver nitrate. The ^{1}H NMR spectrum of compound **A** contained no signals of OH group in the range of 4–6 ppm. The signal of amino group appeared as two broadened singlets about 7.8 and 8.7 ppm. In the ^{13}C NMR spectrum the signals of methyl group and heterocyclic moiety were shifted upfield [$\Delta\delta_C$ 4.8 (Me), 7.8–11 ppm ($C^{2,6}$)] and downfield [$\Delta\delta_C$ 9.9 ppm (C^4)] relative to the signals of identical atoms in compound **7**. According to the facts

Table 1. Yields, melting points, R_f values, and elemental analysis data of 2-amino-4-[(2-aryloxyethyl)sulfanyl]-6-methylpyrimidines (**2a–2d**) and 2-amino-4-[(2-aryloxyethyl)sulfanyl]-5-bromo-6-methylpyrimidines (**3a–3d**)

Comp. no.	Yield,[a] %	mp, °C	R_f (A)	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
2a	62	135	0.60	59.46	5.69	15.81	$C_{13}H_{15}N_3OS$	59.75	5.79	16.08
2b	55	127	0.57	55.67	5.13	14.82	$C_{13}H_{14}FN_3OS$	55.90	5.05	15.04
2c	57	128	0.65	52.37	4.51	14.11	$C_{13}H_{14}ClN_3OS$	52.79	4.77	14.21
2d	51	141	0.63	46.85	3.65	12.53	$C_{13}H_{13}Cl_2N_3OS$	47.28	3.97	12.72
3a	41	146	0.74	46.02	3.84	12.27	$C_{13}H_{14}BrN_3OS$	45.89	4.15	12.35
3b	44	163	0.63	43.33	3.72	11.57	$C_{13}H_{13}BrFN_3OS$	43.59	3.66	11.73
3c	44	151	0.69	41.26	3.41	10.86	$C_{13}H_{13}BrClN_3OS$	41.67	3.50	11.21
3d	43	152	0.71	37.85	2.76	10.33	$C_{13}H_{12}BrCl_2N_3OS$	38.16	2.96	10.27

[a] After recrystallization.

Table 2. ^{1}H NMR and IR spectral data of 2-amino-4-[(2-aryloxyethyl)sulfanyl]-6-methylpyrimidines (**2a–2d**) and 2-amino-4-[(2-aryloxyethyl)sulfanyl]-5-bromo-6-methylpyrimidines (**3a–3d**)

Comp. no.	δ, ppm[a]						ν, cm^{-1}		
	Me	CH_2	CH_2	C^5H	NH_2	Ar	NH_2[b]	C=N, C=C	C–O–C_{Ar}[c]
2a	2.14 s	3.48 t	4.17 t	6.43 s	6.57 s	6.92–7.27 m	3475 s, 1633 s	1569 s, 1463 s	1232 s, 1029 s
2b	2.14 s	3.50 t	4.25 t	6.42 s	6.56 s	6.92–7.37 m	3465 s, 1629 s	1570 s, 1470 s	1261 s, 1018 s
2c	2.14 s	3.46 t	4.17 t	6.41 s	6.55 s	6.96, 6.98 d, 7.30, 7.32 d	3461 s, 1637 s	1560 s, 1467 s	1241 s, 1035 s
2d	2.15 s	3.50 t	4.27 t	6.40 s	6.50 s	7.19, 7.21 d, 7.33–7.50 m	3443 s, 1631 s	1556 s, 1463 s	1265 s, 1016 s
3a	2.31 s	3.49 t	4.19 t	–	6.74 s	6.92–7.29 m	3468 s, 1633 s	1527 s, 1463 s	1238 s, 1026 s
3b	2.30 s	3.51 t	4.26 t	–	6.76 s	6.92–7.12 m	3471 s, 1629 s	1527 s, 1467 s	1255 s, 1012 s
3c	2.30 s	3.48 t	4.19 t	–	6.77 s	6.97, 6.99 d, 7.31, 7.33 d	3477 s, 1633 s	1527 s, 1463 s	1262 s, 1012 s
3d	2.31 s	3.52 t	4.28 t	–	6.75 s	7.19, 7.21 d, 7.34–7.37 m	3492 s, 1606 s	1535 s, 1446 s	1242 s, 1057 s

[a] Integral intensity of the signals corresponded to the protons number. [b] Stretching and bending vibrations. [c] Asymmetric and symmetric vibrations.

mentioned above, compound **A** can be identified [5] as 7-amino-8-methyl-4-thia-6-azabicyclo[3.2.2]nona-5,7,8-triene-1-azonium chloride **B** (Scheme 3).

When recrystallizing compound **A** from acetonitrile–95% ethanol mixture (2 : 1), neither melting point nor character of melting were not changed; another behavior was observed when using other solvents. Thus, the treatment of **A** with 98% methanol resulted in the formation of pyrimidylthioethanol hydrochloride **9**, whose structure was confirmed by X-ray diffraction data (Table 3). This unexpected result indicated that compound **A** was prone to hydrolysis with the residual water contained in organic solvents which did not form azeotropes with it. In this case the presented ^{1}H and ^{13}C NMR spectral data may correspond to hydrochloride **9**. If this did occur, then along with bicyclic compound **B** 5-amino-7-methyl-2,3-dihydro[3,2-*c*]pyrimidinium chloride **C** should be regarded as an alternative product of intramolecular cyclization of compound **8**. According to quantum-chemical calculations, the charges at the ring hetero atoms of compound **8** are of close values [q N^1/N^3 –0.323/–0.347 (MNDO), –0.237/–0.252 (AM1) and –0.174/–0.190 (PM3)].

It is remarkable that a similar feature, the absence of the signal of OH group, was observed in the ^{1}H NMR spectrum of compound **9** obtained by passing dry hydrogen chloride through a suspension of pyrimidylthioethanol **7** in benzene. This feature can be ex-plained only by assuming the identical character of hydrogen bonding both in the crystal (Fig. 1) and in DMSO-d_6 solution.

The analysis of compound **A** by HPLC-MS using aqueous organic eluent allowed to identify several products of its degradation. Among them chloride **8** was detected as monoprotonated molecule $[M + H]^+$

(*m*/z 204, I_{rel} 5%); the most intensive peak (*m*/z 186) in the spectrum belonged to molecular ion $[M + H]^+$ of pyrimidylthioethanol **7**. The presence of isotopic peak $[M + 2 + H]^+$ (*m*/*z* 206) in the cluster of molecular ion peak confirmed undoubtedly the structure of compound **8**. Owing to the presence of chlorine and sulfur atoms in the molecule of **8**, the ratio of $[M + 2 + H]^+$ and $[M + H]^+$ peaks intensities was 0.4 : 1. Using procedure of direct admission of compound **A**, we managed to detect the molecular ion peak $[M]^+$ (*m*/*z* 168) corresponding to the structures **B** or **C** in the mass spectrum recorded in a positive ion electrospray ionization (HESI) mode.

Pyrimidylthioethanol **7** was synthesized via *S*-alkylation of compound **4** with 2-chloroethanol in DMF in the presence of potassium carbonate at 100°C. A partial desulfurization of thione **4** occured when replacing the used solvent and a basic agent with 10% aqueous sodium hydroxide and reducing the reaction temperature to 80°C. Polyethylene sulfide C_2H_4S was isolated from the hot reaction mixture. Its melting point (~154ºC) was close to that of one of the polymer modifications [6]. After polyethylene sulfide separation and neutralization of the filtrate with acetic acid the formed precipitate was filtered off and recrystallized from water. The analysis of this precipitate by HPLC-MS method showed the presence of 2-amino-6-methylpyrimidin-4(3*H*)-one and of unreacted thione **4** identified as monoprotonated molecules $[M + H]^+$ (*m*/*z* 126 and 142, respectively).

The presumable mechanism of thione **4** desulfurization involves several steps: nucleophilic addition of the anion **D** to oxirane formed from 2-chloroethanol in the presence of alkali, intramolecular cyclization of the anion **E** to ionized spiro compound **F**, following opening of the five-membered ring as a result of redistribution of electron density, and the elimination of thiirane from anion **G** with the final formation of anion **H**.

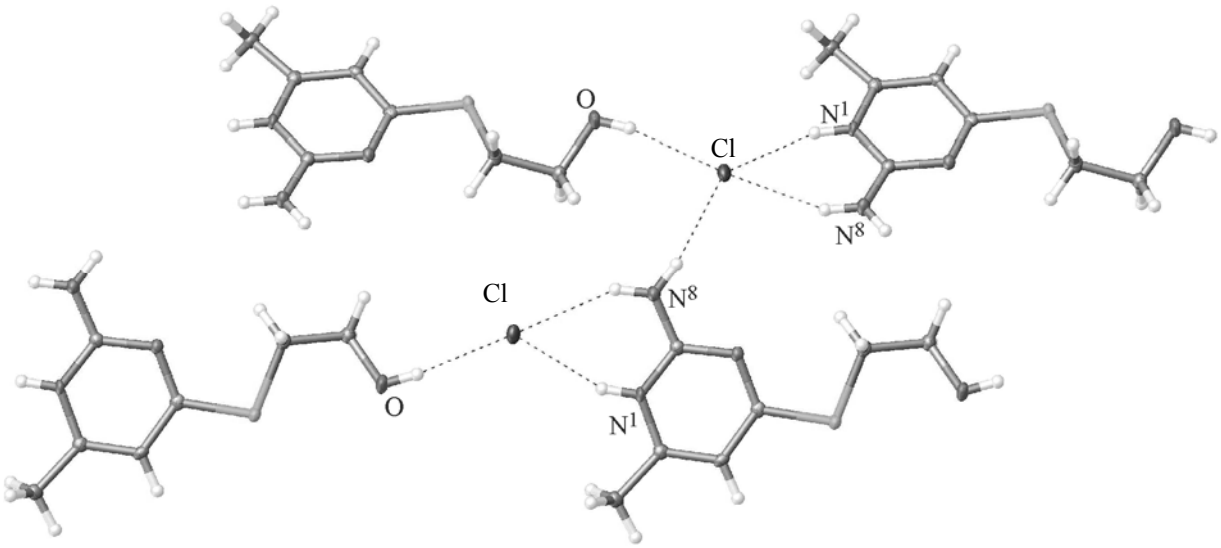
A similar mechanism has been proposed for desulfurization of 2-thioxo-1,2-dihydropyrimidin-4(3*H*)-ones by the action of oxiranes [7], which underlies the modern procedure of uracil derivatives synthesis [8] (Scheme 4).

The preparation of hydrochlorides of thioethers **2a**–**2d** and **3a**–**3d** was accomplished by their treating with dry hydrogen chloride in anhydrous ethanol or benzene at room temperature. The calculation of the pK_a values of their conjugate acids formed by the proton addition to the atom N^1 showed that they had a less pronounced ability to dissociate [pK_a 4.66 (**2a**), 3.98 (**3a**)] compared with the acids formed by the proton addition to the atom N^3 [pK_a –1.26 (**2a**), –1.98 (**3a**)]. For comparison, the pK_a value for 2-amino-4-(methylsulfanyl)pyrimidinium cation determined by potentiometric titration was 4.75 [9].

Table 3. Crystal data of 2-amino-4-[(2-hydroxyethyl)sulfanyl]-6-methylpyrimidine hydrochloride **9**

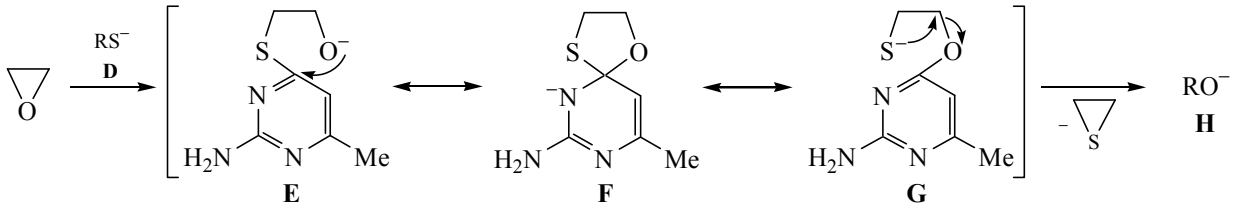
Parameter	Value
Formula	$C_7H_{12}N_3OS{\cdot}Cl$
Crystal system	Monoclinic
M	221.71
Space group	$P2_1/n$
a, Å	5.1668(4)
b, Å	20.8004(13)
c, Å	9.3735(6)
α, deg	90
β, deg	97.584(6)
γ, deg	90
V, Å^3	998.57(12)
μ, mm^{-1}	0.557
T, K	100(2)
Z	4
d_{calc}, g cm^{-3}	1.475
Crystal size, mm	0.10 × 0.05 × 0.02
Radiation	MoK_α
Reflections collected	7800
Independent reflections	2291
2θ range, deg	5.88–55.00
Reflections with $\|F_0\| \geq 4\sigma_F$	1780
R_{int}	0.0588
R_σ	0.0816
R_1 ($\|F_o\| \geq 4\sigma_F$)	0.0425
wR_2 ($\|F_o\| \geq 4\sigma_F$)	0.0667
R_1 (all data)	0.0638
wR_2 (all data)	0.0745
S	1.052
ρ_{min}, ρ_{max}, *e*/Å^3	–0.312, 0.356

The quaternization of compounds **2a**–**2d** and **3a**–**3d** involving the N^1 atom was confirmed by ^{13}C NMR spectroscopy data [5] for some of hydrochlorides **10a**–**10d** and **11a**–**11d**. In the spectra of compounds **10a** and **11a** of the signals of methyl group, C^2 and C^6 atoms of the pyrimidine ring were significantly shifted to the strong field; the signal of C^4 atom was shifted downfield relative to the signals of the mentioned atoms of thioethers **2a** and **3a** (Table 4, Scheme 5).



Crystal packing in compound **9**.

Scheme 4.



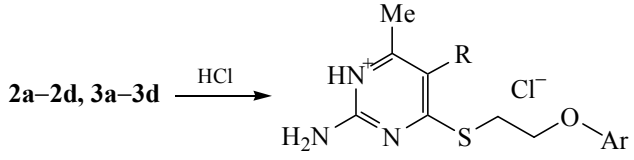
R = 2-amino-6-methylpyrimidin-4-yl.

Of all the hydrochlorides synthesized only compounds **11a** and **11b** were able to inhibit completely (100%) the growth of *Candida albicans* fungi (strain 15) in vitro in concentrations of 0.066 and 0.127 mmol/L, respectively. It should be noted that hydrochlorides of benzyl ethers of 2-amino-5-bromo-6-methylpyrimidin-4(3*H*)-thione [3], regardless of the nature of the substituent in the aromatic moiety, were inactive with respect to the fungi.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra of solutions in DMSO-d_6 were recorded on a Bruker Avance III-400 spectrometer operating at 400 (^{1}H) and 100 (^{13}C) MHz using as internal reference the residual signals of undeuterated solvent. IR spectra (KBr) were taken on a FSM -1201 FTIR spectrometer. HPLC-MS spectra were registered on a Thermo Scientific TSQ Quantum Access instrument in HESI mode using methanol as a solvent after preliminary chromatographic separation of the samples (column Zorbax CB-C18, 150 × 2.1 mm, 35ºC, 0.1% aqueous solution of trifluoroacetic acid–acetonitrile, 95 : 5). Mass spectrum using the direct admission of the sample was recorded on a tandem quadrupole mass spectrometer Waters XEVO TQD in HESI mode (anhydrous methanol, capillary voltage 4 kV, source temperature 150°C, desolvation gas nitrogen). Elemental analysis was carried out using a Flash EA 1112 analyzer. Elemental analysis of polyethylene sulfide (C 39.36%; H 6.20%; S 52.49%) was performed on a Leco CHNS-932 analyzer. The chlorine content in compound **9** was determined by Schoeniger method. TLC analysis was made using

Scheme 5.



R = H (**10a–10d**), Br (**11a–11d**).

Sorbfil PTLC-AF-V-UV and Silufol UV-254 (**10a**–**10d**) plates and eluting with acetone–hexane, 1 : 1 (eluent A) and 1-butanol–acetic acid–water, 1 : 1 : 1 (eluent B). Visualization of spots was performed with UV light (λ = 254 nm). The charge calculation for the Fletcher–Reeves optimized molecules was done with the use of HyperChem software (Release 8.0.8); ionization constants were calculated using Marvin program [10]. Purification of the solvents was carried out in accordance with the known methods [11].

X-Ray diffraction analysis of the crystals of compound **9** was done at the Resource Center of St. Petersburg State University "X-ray diffraction studies" using an Agilent Technologies Excalibur Eos diffractometer equipped with CCD detector. Diffraction data were measured with monochromatic MoK_α radiation at 100 K. The unit cell parameters (Table 3) were refined by the least-squares method based on 7800 reflections within 2θ 5.88–55.00º. The structure was solved by the direct method and refined till R_1 0.042 (wR_2 0.067) for 1780 independent reflections with $|F_0| \geq 4\sigma_F$ using SHELXL program [12] integrated into the Olex2 software package [13]. The extinction correction was empirically made basing on spherical harmonic functions implemented in SCALE3 ABSPACK scaling algorithm using CrysAlisPro software package [Agilent Technologies, Ver. 1.171.36.20 (Release 27-06-2012)]. Positions of the hydrogen atoms were calculated by means of SHELX program, with U_{iso}(H) = 1.5U_{eq}(C) and C–H 0.96 Å for CH_3 groups, U_{iso}(H) = 1.2U_{eq}(C) and C–H 0.97 Å for CH_2 groups, U_{iso}(H) = 1.2U_{eq}(C) and C–H 0.93 Å for CH groups, U_{iso}(H) = 1.2U_{eq}(N) and N–H 0.86 Å NH and NH_2 groups, U_{iso}(H) = 1.5U_{eq}(O) and O–H 0.82 Å for OH groups. The crystal data of compound **9** has been deposited at the Cambridge Crystallographic Data Center (CCDC 1437521).

2-Amino-4-[(2-aryloxyethyl)sulfanyl]-6-methylpyrimidines (2a–2d). An equimolar amount of the corresponding 2-aryloxyethyl chloride **5a**–**5d** and 0.49 g of calcined potassium carbonate were added to a suspension of 0.5 g (3.54 mmol) of thione **4** in 15 mL of anhydrous DMF. The mixture was stirred at 100°C for 1 h and then cooled. Inorganic salts were filtered off. The filtrate was concentrated in a vacuum. The solid residue was treated with 10% sodium hydroxide, filtered off, washed with water, and dried at 70°C to a constant weight. The product obtained was recrystallized from benzene–cyclohexane mixture [2 : 1 (**2a**–**2c**), 5 : 4 (**2d**)].

Table 4. ^{13}C NMR spectral data of 2-amino-4-[(2-aryloxyethyl)sulfanyl]-5-R-6-methylpyrimidines **2a**, **3a** and their hydrochlorides **10a** and **11a**

Comp. no.	δ_C, ppm		
	Me	C^2, C^6	C^4
2a	23.66	163.1, 166.3	168.3
3a	24.37	161.2, 164.4	167.1
10a	19.06	155.5, 155.8	177.9
11a	22.51	157.7[a]	176.0

[a] One of the signals was not observed due to the low intensity.

2-Amino-4-[(2-aryloxyethyl)sulfanyl]-5-bromo-6-methylpyrimidines (3a–3d). A mixture of 0.3 g of thioether **2a**–**2d** and an equimolar amount of NBS [14] in 15 mL of chloroform was refluxed for 1 h. Then the solvent was removed in a vacuum, and the residue was treated with 10% sodium hydroxide. The solid residue was filtered off, washed with water, and dried at 70°C to a constant weight. The product obtained was recrystallized from benzene–cyclohexane [5 : 2 (**3a**)], 3 : 2 (**3b**), 5 : 3 (**3c**)], or water–ethanol mixture, 1 : 3 (**3d**).

2-(2-Fluorophenoxy)ethyl chloride (5b). To a solution of 0.85 g of freshly distilled thionyl chloride in 15 mL of anhydrous chloroform precooled to 0–5ºC was successively added 0.56 g of anhydrous pyridine. Next a solution of 12.7 g of 2-(2-fluorophenoxy) ethanol **6b** in 15 mL of anhydrous chloroform was added dropwise with vigorous stirring within 1 h, maintaining the temperature of the reaction mixture below 10°C. The resulting mixture was slowly heated in a water bath to 60–65ºC and kept at this temperature until gas evolution ceased. After distilling off the volatiles, the residue was treated with 20 mL of water and 20 mL of benzene, and the organic layer was separated and dried over calcium chloride. Benzene was distilled off, the residue was distilled, collecting the fraction with bp 124–127ºC (35 mmHg). Yield 7.50 g (53%). Found, %: C 54.67; H 4.41. C_8H_8ClFO. Calculated, %: C 55.03; H 4.62.

Compounds **5a**, **5c** and **5d** were prepared similarly. Their physicochemical characteristics coincided with those given in [15, 16]. 2-Aryloxyethanols **6a**–**6d** were synthesized by the procedure reported in [17]. Physicochemical characteristics of the compounds obtained coincided with those given in [18, 19].

2-Amino-4-[(2-hydroxyethyl)sulfanyl]-6-methylpyrimidine (7). To a suspension of 4 g of thione **4** in 20 mL of anhydrous DMF were added 0.57 g of 2-

chloroethanol and 1 g of calcined potassium carbonate. The mixture was vigorously stirred at 100°C for 1 h and then cooled. Inorganic salts were filtered off. The filtrate was concentrated in a vacuum. The oily residue was treated with 5% sodium hydroxide. The precipitate formed was filtered off, washed with water, and dried at 70°C to a constant weight. Yield 0.82 g (62%), mp 118ºC, R_f 0.37 (A). An analytical sample was prepared by recrystallization from water, mp 119ºC. ^{1}H NMR spectrum, δ, ppm: 2.14 s (3H, Me), 3.14 t (2H, CH_2, J = 6.5 Hz), 3.58 q (2H, CH_2, J = 5.7 Hz), 4.86 s (1H, OH), 6.33 s (1H, C^5H), 6.40 s (2H, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 23.67 (Me), 31.33 (CH_2), 60.54 (CH_2), 106.4 (C^5), 162.9, 166.1 ($C^{2,6}$), 169.2 (C^4). Found, %: C 44.79; H 5.68; N 22.31. $C_7H_{11}N_3OS$. Calculated, %: C 45.39; H 5.99; N 22.68.

2-Amino-4-[(2-hydroxyethyl)sulfanyl]-6-methylpyrimidine hydrochloride (9). Through a suspension of 0.20 g of pyrimidylthioethanol **7** in 6 mL of anhydrous benzene dry hydrogen chloride was bubbled to saturation. The precipitate was filtered off, washed with benzene, recrystallized from benzene–ethanol mixture (5 : 3), and dried at 70°C to a constant weight. Yield 60 mg (27%), mp 189ºC, R_f 0.49 (A). ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, Me), 3.28 t (2H, CH_2, J = 6.3 Hz), 3.64 t (2H, CH_2, J = 6.3 Hz), 6.84 s (1H, CH), 7.90 br.s (1H, NH_2), 8.59 br.s (1H, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 18.98 (Me), 32.76 (CH_2), 59.63 (CH_2), 107.4 (C^5), 155.2, 155.4 ($C^{2,6}$), 178.9 (C^4). Found Cl, %: 15.57. $C_7H_{11}N_3OS\cdot HCl$. Calculated Cl, %: 15.99.

2-Amino-4-[(2-aryloxyethyl)sulfanyl]-6-methylpyrimidine hydrochlorides (10a–10d). Through a solution of 0.2 g of thioether **2a**–**2c** in 10–15 mL of anhydrous benzene or ethanol (**2d**) dry hydrogen chloride was bubbled to saturation. The solvent was removed in a vacuum, and the residue was triturated with 10 mL of cyclohexane (**10a**–**10c**) or diethyl ether (**10d**). The precipitate was filtered off, washed with cyclohexane or diethyl ether, and dried at 70°C to a constant weight to yield 0.17 g (74%) of compound **10a** [mp 158ºC, R_f 0.73 (B)], 0.16 g (74%) of compound **10b** [mp 167ºC, R_f 0.71 (B)], 0.17 g (77%) of compound **10c** [mp 165ºC, R_f 0.72 (B)] and 0.10 g (45%) of compound **10d** [mp 183ºC, R_f 0.70 (B)].

2-Amino-4-[(2-aryloxyethyl)sulfanyl]-5-bromo-6-methylpyrimidine hydrochlorides (11a, 11b). Through a solution of 0.1 g of thioether **3a** or **3b** in 10 mL of anhydrous benzene preheated to 50°C dry hydrogen chloride was bubbled to saturation. The resulting slurry was cooled and kept at room temperature for 20 h. The precipitate was filtered off, washed with benzene, and dried at 70°C to a constant weight to yield 90 mg (82%) of compound **11a** [mp 164ºC, R_f 0.71 (B)] or 70 mg (63%) of compound **11b** [mp 130°C, R_f 0.61 (B)].

2-Amino-4-[(2-aryloxyethyl)sulfanyl]-5-bromo-6-methylpyrimidine hydrochlorides (11c, 11d) were prepared similarly from 60 mg of thioether **3c** or **3d**. Yield 55 mg (83%) [**11c**, mp 179ºC, R_f 0.69 (B)], 50 mg (77%) [**11d**, mp 142ºC, R_f 0.66 (B)].

ACKNOWLEDGMENTS

The authors are grateful to V.V. Tets and coworkers (Pavlov First Saint-Petersburg State Medical University) for performing the microbiological tests, as well as T.V. Artamonova (St. Petersburg State University of Technology and Design) for performing elemental analysis of polyethylene sulfide.

REFERENCES

1. Geronikaki, A., Fesatidou, M., Kartsev, V., and Macaev, F., *Curr. Top. Med. Chem*., 2013, vol. 13, no. 21, p. 2684. DOI: 10.2174/15680266113136660195.
2. Sharma, V., Chitranshi, N., and Agarwal, A.K., *Int. J. Med. Chem*., 2014, vol. 2014, p. 1. DOI: 10.1155/2014/202784.
3. Erkin, A.V., Krutikov, V.I., and Tets, V.V., Abstracts of Papers, *I Russian-Korean Conf. "Current Issues of Biologically Active Compounds Chemistry and Biotechnology,"* Novosibirsk, 2015, p. 173.
4. Erkin, A.V., Gurzhii, V.V., and Krutikov, V.I., *Russ. J. Gen. Chem*., 2015, vol. 85, no. 1, p. 79. DOI: 10.1134/S107036321501014.
5. Brown, D.J., Evans, R.F., Cowden, W.B., and Fenn, M.D., *The Pyrimidines*, New York: John Wiley & Sons, 1994, p. 867.
6. Zander, M., *Usp. Khim.*, 1968, vol. 37, no. 3, p. 433.
7. Gerasimov, E.N., *Candidate Sci. (Chem.) Dissertation*, Volgograd, 2013.
8. Novakov, I.A., Orlinson, B.S., and Navrotskii, M.B., *Russ. J. Org. Chem*., 2005, vol. 41, no. 4, p. 607. DOI: 10.1007/s11178-005-0211-1.
9. Brown, D.J. and Teitei, T., *Austral. J. Chem*., 1965, vol. 18, no. 4, p. 559.
10. Zevatskii, Yu.E. and Samoilov, D.V., *Russ. J. Org. Chem*., 2011, vol. 47, no. 10, p. 1445. DOI: 10.1134/S1070428011100010.

11. Gordon, A.J. and Ford, R.A., *The Chemist's Companion*, New York: Wiley, 1972.
12. Sheldrick, G.M., *Acta Crystallogr. (A)*, 2008, vol. 64, no. 1, p. 112. DOI: 10.1107/S0108767307043930.
13. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K., and Puschmann, H., *J. Appl. Crystallogr.*, 2009, vol. 42, no. 2, p. 339. DOI: 10.1107/S0021889808042726.
14. Weygand, C. and Hilgetag, G., *Organisch-chemische Experimentierkunst*, Leipzig: Johann Ambrosius Barth Verlag, 1964.
15. Foldeak, S., Czombos, J., Matkovics, B., and Porszasz, J., *Acta Phys. Chem*., 1963, vol. 9, nos. 3–4, p. 134.
16. Hanreich, R.G., Eur. Patent 306453, 1989; *C. A*., 1989, vol. 111, p. 96822 d.
17. Vasarhelyi, E., Hegedus, I., and Nyikos, E., Hungary Patent 157457, 1970; *C. A.*, 1970, vol. 73, p. 76853 h.
18. Bliznyuk, N.K., Kolomiets, A.F., Kvasha, Z.N., Levskaya, G.S., and Zhemchuzhin, S.G., *Zh. Obshch. Khim.*, 1966, vol. 36, no. 3, p. 480.
19. Joshi, K.C. and Bahel, S.C., *J. Indian Chem. Soc*., 1962, vol. 39, no. 1, p. 5.