Chemistry of Heterocyclic Compounds, Vol. 44, No. 6, 2008

SPECIAL FEATURES OF THE NUCLEOPHILIC SUBSTITUTION OF HALOGEN IN ALKYL AND BENZYL HALIDES WITH ANIONS GENERATED FROM 4-HYDROXY-2-MERCAPTO-6-METHYL-PYRIMIDINE

A. I. Rakhimov[1], E. S. Titova[1], R. G. Fedunov[2], and V. A. Babkin[3]

*The nucleophilic substitution of halogen (chlorine, bromine, and iodine) in alkyl and benzyl halides has been effected in aqueous dioxane media with S- and O-anions generated from 4-hydroxy-2-mercapto-6-methylpyrimidine. Under these conditions replacement of halogen proceeds by an S_N2 mechanism and the reactivity of S-anions is 10 times greater than that of O-anions, which is in agreement with the results of ab initio quantum-chemical calculations of the electronic structure and total energy of transition states, carried out within the framework of the restricted Hartree-Fock method, basis 6-31G**.*

Keywords: 2-alkyl(benzyl)thio-6-methylpyrimidin-4(3*H*)-one, S-, O-anions, 4-hydroxy-2-mercapto-6-methylpyrimidine, charges on atoms, quantum-chemical calculations, *ab initio* method, electron density.

Derivatives of 4-hydroxy-2-mercapto-6-methylpyrimidine (**1**) are widely used as medicinal preparations for the treatment of cerebrovascular illnesses [1], hyperthyroidism [2], HSV-1 virus [3, 4], thyroid gland hyperfunction [5], neurological illnesses, hypoglycemia, Alzheimer's disease, Huntington's disease, Parkinson's disease, migraine, depression, memory impairment [6], and as tranquillizers [7]. Derivatives of compound **1** are inhibitors of the reverse transcriptase of human immunodeficiency virus (HIV-1) and display powerful inhibitory properties in relation to HIV-1 *in vitro* [8-21].

We have developed a method of synthesizing S-mono derivatives of compound **1** by the nucleophilic substitution of halogen in halogen derivatives by the S-anion generated from the sodium thiolate, which is formed by the action of an equimolar amount of sodium hydroxide on compound **1** in aqueous dioxane medium. The reaction involving the S-anion proceeds under mild conditions (30-50°C) after a short time interval (15-60 min) and enables S-mono derivatives to be synthesized in high yield (72-99%).

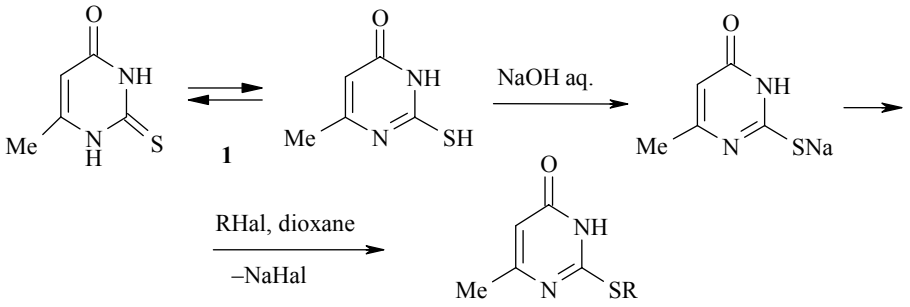
---

[1]Volgograd State Technical University, Volgograd 400131, Russia; e-mail: organic@vstu.ru; [2]Institute of Enviromental Chemical Problems, Russian Academy of Natural Sciences, Volgograd 400131; [3]Volgograd State University of Architecture, Sebyakov Branch, Mikhailovka 403330, Volgograd region, Russia; e-mail: sft@reg.avtlg.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 874-883, June, 2008. Original article submitted February 14, 2006; revision submitted January 12, 2007.

 0009-3122/08/4406-0700©2008 Springer Science+Business Media, Inc.

The aqueous dioxane solution of the S-sodium salt of compound **1** was prepared at room temperature. The S-sodium salt isolated from the solution is a white crystalline substance of mp 370-372°C (decomp.). The structure of the salt was demonstrated by ^{1}H NMR spectroscopy, δ, ppm: 2.1 (3H, s, CH_3); 5.95 (1H, s, H-5); 12.2 (1H, s, NH). The S-sodium salt obtained in aqueous dioxane solution (salt concentration 0.5 M) was treated with alkyl or benzyl halides.

The structures and compositions of the synthesized compounds were demonstrated by IR, ^{1}H NMR, and mass spectroscopy and by data of elemental analysis.



1 **2–4**

Hal = I, Cl, Br; **2** R = Bn; **3** R = Et, **4** R = Pr

The kinetics of the processes occurring with the participation of S-anion were studied from the change in concentration of the S-sodium salt. The change in concentration of the S-sodium salt on interaction with halogen derivatives was studied by potentiometric titration with 0.1 N H_2SO_4 solution, and the reaction rate constants were calculated by the method of differentiation of kinetic curves (Table 1).

We have determined the order of the reactions being studied, which for all halogens was close to 2, indicating a mechanism of bimolecular nucleophilic substitution (S_N2).

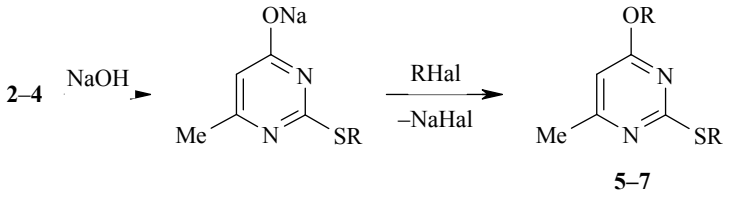
The O-sodium salts of 2-alkyl(aralkyl)thio-4-hydroxy-6-methylpyrimidine were obtained by the interaction of equimolar amounts of the S-derivatives with sodium hydroxide. The compositions and structures of the O-sodium salts were demonstrated by ^{1}H NMR and IR spectroscopy, and data of elemental analysis. Peaks were absent from the NMR spectrum in the 12 ppm region characteristic of the NH group in position 3 of the heterocycle. Absorption bands were absent from the IR spectrum for the carbonyl group at 1644-1712 and

TABLE 1. Yields and Rate Constants for the Reactions Making Compounds **2-4**

RXal	Reaction product	Temperature, °C	*k**, l/mol·sec	Yield, %
$PhCH_2Br$	**2**	50	0.055	99
		40	0.038	96
		30	0.025	95
$PhCH_2Cl$	**2**	50	0.035	92
		40	0.025	87
		30	0.012	82
PrI	**3**	50	0.005	88
		40	0.0025	90
		30	0.001	85
EtBr	**4**	50	0.003	84
		40	0.001	82

*k – rate constant.

the NH group at 3100-3450 cm^{-1}, which indicates the formation of the O-sodium salt. The obtained salt was treated with alkyl and benzyl halides in aqueous dioxane solution with the formation of S- and O-diderivatives of compound **1**.



5–7

Hal = Cl, Br, I; **5** R = Bn, **6** R = Et, **7** R = Pr

The kinetics of the processes involving O-anions were studied by the change in concentration of the O-sodium salts of 2-alkyl(benzyl)thio-4-hydroxy-6-methyl-pyrimidines. The concentration of O-sodium salt was determined by potentiometric titration with a standard 0.1 N H_2SO_4 solution.

The rate constants for the reactions of 2-alkyl(aralkyl)thio-4-hydroxy-6-methylpyrimidines with alkyl and benzyl halides were determined by the differential graphical method. These reactions also proceed by a bimolecular nucleophilic substitution mechanism.

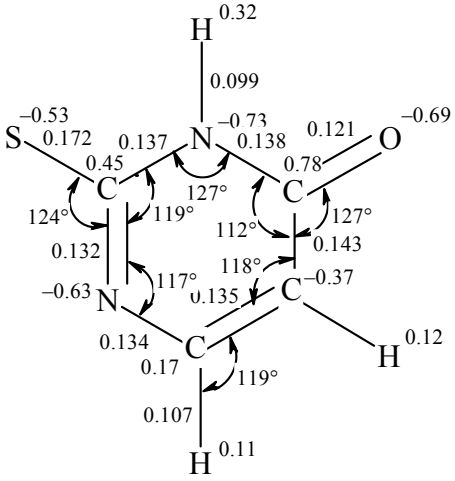
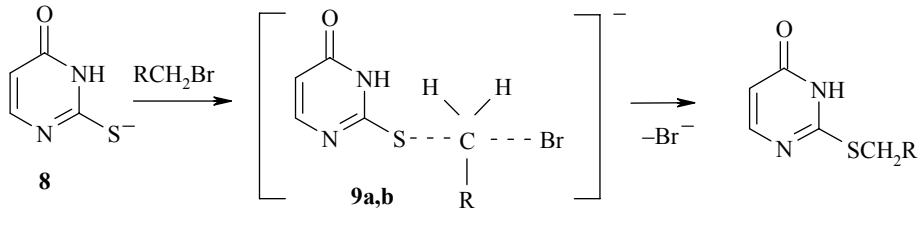


Fig. 1. Geometric and electronic structure of S-anion **8**.

We have studied the geometric and electronic structure of S-anion **8** (Fig. 1) with the aid of *ab initio* quantum-chemical calculations (restricted Hartree-Fock method, basis 6-31G**) with the GAMESS set of programs series 6.0 [22].

The total energy of the S-anion was less than the isomeric O-anion by 55.9 kJ/mol, which makes the formation of the latter not very likely under otherwise similar conditions. We have established experimentally that all the studied reactions proceed according to a bimolecular mechanism, consequently the electronic structure of the transition state determining S_N2 substitution of halogen in halogen derivatives involving anion **8** was calculated. In the case of methyl bromide and benzyl bromide the reaction proceeds according to the Scheme:



8 **9a,b**

9 **a** R = H, **b** R = Ph

Depending on the proximity of anion **8** to the methyl group carbon atom the negative charge on the bromine atom is increased in the transition state **9a** (initial value of charge is -0.32). At a spacing of 0.24 nm at the barrier point the ionization of bromine reaches -0.78, and then at further proximity of the carbon and sulfur atoms to 0.22 nm the charge on the bromine atom reaches -0.92. Simultaneously with the ionization of bromine a covalent bond is formed between the sulfur atom and the carbon atom of methyl bromide, which is accompanied by a reduction in the negative charge on the sulfur atom. At the barrier point the charge on the sulfur atom is equal to -0.34. Directly after the barrier point at a spacing of 0.22 nm of the interacting C and S atoms a sudden reduction in the charge on the sulfur atom to -0.14 is observed (initial value of charge -0.53), and further at a spacing of 0.20 nm the charge on the sulfur atom becomes positive, but the bromide ion is practically removed with a charge of -0.96. The nucleophilic substitution, as the calculation showed, proceeds with the evolution of 16.3 kJ/mol energy.

On changing from methyl bromide to benzyl bromide the ionization of the carbon–halogen bond grows significantly depending on the proximity to the electrophilic center of anion **8**. The charge on the bromine atom is increased to -0.87 at a spacing of 0.24 nm in the region of the barrier point, the charge on the sulfur atom is equal to -0.27. At the same time, in difference to methyl bromide, for benzyl bromide in the transition state **9b** in the vicinity of the barrier point at a spacing of 0.20 nm the charge on the sulfur atom is 0.18, which is 9 times greater than the charge in the transition state **9a**. The reaction of benzyl bromide with anion **9** is accompanied by a gain of energy equal to 50.6 kJ/mole, which is 3 times greater than for methyl bromide (Fig. 2).

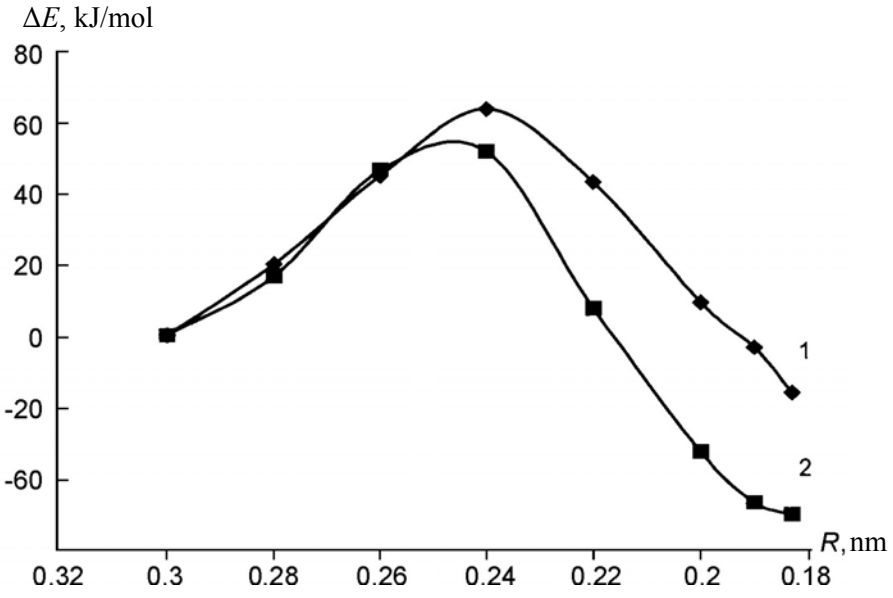
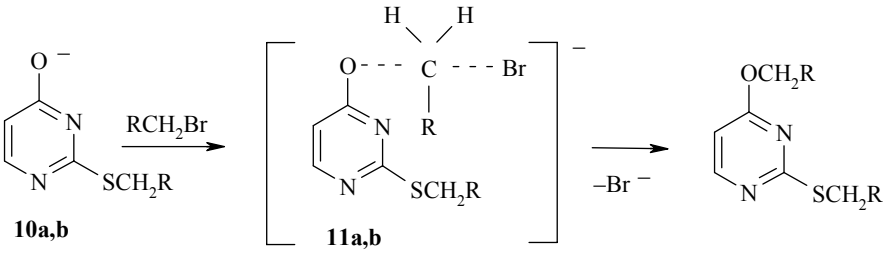


Fig. 2. Change of energy in the reaction of 4-hydroxy-2-mercapto-6-methylpyrimidine with methyl bromide and benzyl bromide. 1 – methyl bromide; 2 – benzyl bromide. Change of energy $\Delta E = E_0 - E_i$; R is bond length.

The results of the quantum-chemical calculations are in agreement with the kinetic parameters of an S_N2 substitution reaction (Table 1).

The S_N2 substitution rate constant for ethyl bromide (closest homolog of methyl bromide) is 17 times less at 50°C than for benzyl bromide.

The *ab initio* quantum-chemical method was also used to study the reactivity of O-anions generated from 2-alkyl(aralkyl)thio-4-hydroxy-6-methylpyrimidines in a S_N2 substitution reaction with methyl and benzyl bromides according to the Scheme:



10, 11 a R = H, **b** R = Ph

The polarization of the carbon–bromine bond in methyl bromide proceeds to a lesser extent than in benzyl bromide on approach of anion **10a** to the electrophilic center. For transition state **11a** the charge on bromine is -0.76, and for **11b** the charge is equal to -0.84. The increase in reaction rate constant for benzyl bromide of 16 times in comparison with the constant for ethyl bromide is explained by the greater extent of ionization of bromine in **11b** and its departure as an ion (Table 2). The order of the covalent C–S and C–O bonds being formed and of the polar covalent C–Br bonds being broken (Tables 1, 2) in the reaction process is changed in a different way in the first and second stages of the process. In the first stage at the barrier point 0.24 nm a sharp strengthening of the C–S bond occurs concomitantly with a sharp weakening of the C–Br bond, and at a spacing of 0.2 nm the C–Br bond is completely broken and a simple covalent C–S bond is formed. The less reactive O-anions (**10a**,**b**) participate in the formation of a covalent bond while approaching to a closer spacing to the electrophilic center of 0.20 nm and are characterized by a slower growth of bond order.

The thermodynamics of the reaction of benzyl bromide with anion **10b** are also favorable for it, the reaction proceeds with a liberation of energy of 51.4 kJ/mol, and are close to the thermodynamics for benzyl bromide and anion **8**. The higher reactivity of anion **8** than anion **10b** is explained by the lower energy barrier necessary for the reaction to proceed, *viz*. 51.9 kJ/mol, the energy barrier for anion **10b** amounts to 64 kJ/mol. This is in agreement with the fact that the rate constant for the S_N2 substitution reaction for benzyl bromide involving anion **10b** is 10 times less than the S_N2 substitution rate constant for anion **8**.

The experimentally found values for the energy of activation (E_a) for the S_N2 substitution of bromine in methyl bromide (52.35 kJ/mol) and benzyl bromide (32.83 kJ/mol) by the 6-methyl-substituted anion **8** and the 6-methyl-substituted anions **10a** and **10b** (E_a = 41.13 kJ/mol for benzyl bromide), in accordance with the Arrhenius equation, correlate with the values of the energy barriers calculated by the *ab initio* method (Fig. 2).

The O-substitution reaction is energetically more favored than the N-substitution reaction (Fig. 3), which is also in agreement with experimental data, confirming the formation of the S,O-disubstituted derivative. The quantum-chemical calculations by the *ab initio* method have therefore enabled clarification of the reason for the high reactivity of anion **8** and the selectivity of obtaining S-mono- and S,O-di-derivatives of compound **1**.

TABLE 2. Yields and Reaction Rate Constants for S,O-Diderivatives

RXal	Reaction product	Temperature, °C	*k**, l/mol·sec	Yield, %
$PhCH_2Cl$	**5**	30	0.00095	41
		40	0.00190	54
		50	0.00360	84
$PhCH_2Br$	**5**	30	0.00148	43
		40	0.00296	56
		50	0.00560	70
EtBr	**6**	50	0.00020	51

**k* – rate constant.

The differences in absolute values of the energy of activation found experimentally and calculated by the quantum chemical method (Fig. 2), are explained primarily by the different properties of the gaseous and liquid phases, although the relative conformities to principle found by both methods are in complete agreement.

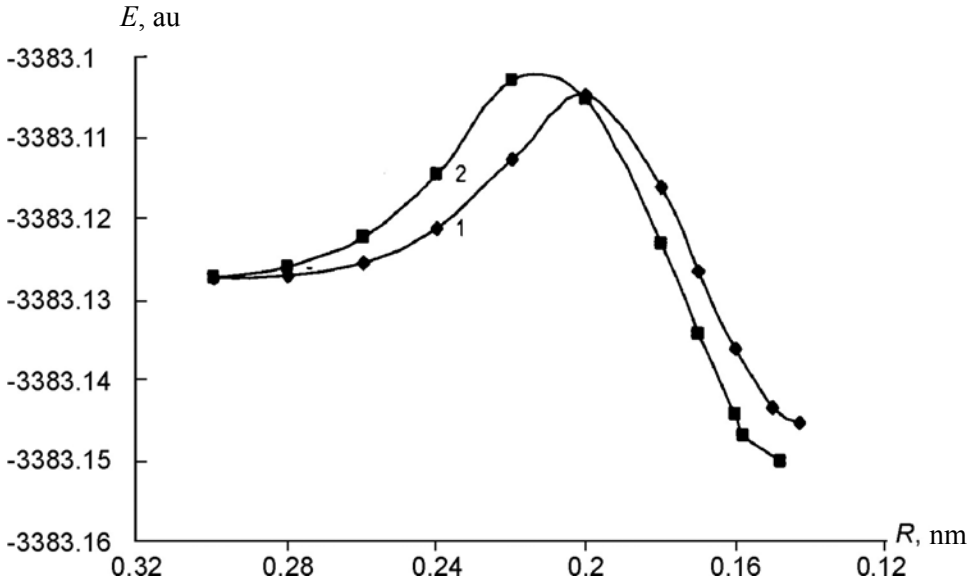


Fig. 3. Energy barriers for nucleophilic substitution at the nitrogen atom in position 3 of the heterocycle and at oxygen on reaction with methyl bromide. 1 – At oxygen; 2 – at nitrogen. *E* is total energy, *R* is bond length.

EXPERIMENTAL

The ^{1}H NMR spectra of substances were taken on a Varian Mercury 300 (300 MHz) instrument in DMSO-d_6, internal standard was HMDS (δ 0.05 ppm). The IR spectra were obtained in nujol suspension on a Specord M 82 instrument with a potassium bromide prism.

Synthesis of 4-Hydroxy-2-mercapto-6-methylpyrimidine S-Sodium Salt. Sodium hydroxide (0.42 g, 10.6 mmol) and 6-methyl-2-thiouracil (1.5 g, 10.6 mmol) were dissolved in water (7 ml). The solution was evaporated and the residue crystallized from ethanol. Yield of salt was 1.7 g (99.9%); mp 370°C. ^{1}H NMR spectrum, δ, ppm: 2.1 (3H, s, CH_3); 5.95 (1H, s, H-5); 12.2 (1H, s, NH). Found, %: N 17.00. $C_5H_5N_2NaOS$. Calculated, %: N 17.12.

Synthesis of S-Monoderivatives of Compound 1 (General Method).

2-Benzylthio-6-methylpyrimidin-4(3H)-one (2). A. Sodium hydroxide (0.42 g, 10.6 mmol) and compound **1** (1.5 g, 10.6 mmol) were dissolved in water (7 ml). Dioxane (7 ml) was added, and then a solution of benzyl bromide (1.4 g, 10.6 mmol) in dioxane (4.2 ml) was added dropwise. The mixture was stirred at 50°C for 15 min. After cooling, the precipitated solid was filtered off, washed with cold water, dried, and recrystallized from benzene. Yield of compound **2** was 2.5 g (99%); white crystals, mp 173-174°C. ^{1}H NMR spectrum, δ, ppm: 2.2 (3H, s, CH_3); 4.3 (2H, s, SCH_2); 5.95 (1H, s, H-5); 7.05-7.39 (5H, m, H arom.); 12.2 (1H, s, NH). Found, %: N 11.77. $C_{12}H_{12}N_2OS$. Calculated, %: N 11.86).

B. Compound **2** (2.3 g, 92%) was obtained analogously to method A from NaOH (0.42 g, 10.6 mmol) and benzyl chloride (1.4 g, 10.6 mmol), as white crystals of mp 173-174°C.

2-Ethylthio-6-methylpyrimidin-4(3H)-one (3) was obtained analogously to compound **2** from compound **1** (1.5 g, 10.6 mmol), NaOH (0.42 g, 10.6 mmol), and ethyl bromide (1.3 g, 11.6 mmol) in a yield of 1.5 g (84%); white crystals, mp 124-125°C. ^{1}H NMR spectrum, δ, ppm: 1.15-1.22 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$); 2.15 (3H, s, CH_3); 2.95-3.05 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$); 5.95 (1H, s, H-5); 12.5 (1H, s, NH). Found, %: N 16.23. $C_7H_{10}N_2OS$. Calculated, %: N 16.46.

6-Methyl-2-propylthiopyrimidin-4(3H)-one (4) was obtained analogously to compound **2** from compound **1** (1.5 g, 10.6 mmol), NaOH (0.42 g, 10.6 mmol), and propyl iodide (1.8 g, 10.6 mmol). Yield was 1.7 g (88%); white crystals, mp 99-100°C. ^{1}H NMR spectrum, δ, ppm: 0.85-0.95 (3H, m, $CH_2CH_2C\underline{H}_3$); 1.5-1.75 (2H, m, $CH_2C\underline{H}_2CH_3$); 2.1 (3H, s, CH_3); 3.0-3.1 (2H, m, $C\underline{H}_2CH_2CH_3$); 5.95 (1H, s, H-5); 12.2 (1H, s, NH). Found, %: N 15.04. $C_8H_{12}N_2OS$. Calculated, %: N 15.20.

Synthesis of 2-Benzylthio-4-hydroxy-6-methylpyrimidine O-Sodium Salt. Sodium hydroxide (0.16 g, 4 mmol) and compound **2** (1 g, 4 mmol) were dissolved in water (7 ml). The solution was evaporated, and the obtained O-sodium salt of compound **2** was recrystallized from ethanol. ^{1}H NMR spectrum, δ, ppm: 2.2 (3H, s, CH_3); 4.3 (2H, s, SCH_2); 5.95 (1H, s, H-5); 7.05-7.39 (5H, m, H arom.). Found, %: N 10.87. $C_{12}H_{11}N_2NaOS$. Calculated, 5: N 11.02.

Synthesis of S,O-Disubstituted Derivatives of Compound 1 (General Method).

4-Benzyloxy-2-benzylthio-6-methylpyrimidine (5). Sodium hydroxide (0.2 g, 5 mmol) and compound **2** (1 g, 4 mmol) were dissolved in water (9 ml). Dioxane (18 ml) and benzyl chloride (0.7 g, 5 mmol) were added to the solution. The mixture was stirred at 50°C for 1 h. After cooling, the precipitated solid was filtered off, washed with cold water, and recrystallized from benzene. The yield of compound **5** was 1.0 g (84%); white crystals, mp 59-61°C. ^{1}H NMR spectrum, δ, ppm: 1.85 (3H, s, CH_3); 4.3 (2H, s, SCH_2); 5.5 (2H, s, OCH_2); 6.1 (1H, s, H-5); 7.05-7.39 (10H, m, H arom.). Found, %: N 8.54; $C_{19}H_{18}N_2OS$. Calculated, %: N 8.60. The filtrate was neutralized with 20% acetic acid acid solution, the precipitated solid was filtered off, washed with cold water, dried, and recrystallized from ethanol. The yield of compound **2** was 0.3 g; white crystals, mp 173-174°C.

4-Ethoxy-2-ethylthio-6-methylpyrimidine (6) was obtained analogously to compound **5** from NaOH (0.24 g, 6 mmol), compound **3** (1 g, 5.5 mmol), and ethyl bromide (1 g, 6 mmol) in water (8 ml) and dioxane (13 ml). Yield was 2.4 g (51%); white crystals, mp 124-125°C. ^{1}H NMR spectrum, δ, ppm : 1.15-1.22 (3H, m, $SCH_2C\underline{H}_3$); 1.30-1.35 (3H, m, $OCH_2C\underline{H}_3$); 2.15 (3H, s, CH_3); 2.95-3.05 (2H, m, $SC\underline{H}_2CH_3$); 3.40-3.60 (2H, m, $OC\underline{H}_2CH_3$); 5.95 (1H, s, H-5). Found, %: N 13.56. $C_9H_{14}N_2OS$. Calculated, %: N 13.83.

6-Methyl-4-propoxy-2-propylthiopyrimidine (7) was obtained analogously to compound **5** from NaOH (0.24 g, 6 mmol), compound **4** (1 g, 5.4 mmol), and propyl iodide (1 g, 6 mmol) in a yield of 1.1 g (69%); white crystals, mp 83-85°C. ^{1}H NMR spectrum, δ, ppm: 0.85-0.95 (6H, m, $CH_2CH_2C\underline{H}_3$); 1.5-1.75 (4H, m, $CH_2C\underline{H}_2CH_3$); 2.1 (3H, s, CH_3); 3.00-3.10 (2H, m, SCH_2); 3.35-3.45 (2H, m, OCH_2); 5.9 (1H, s, H-5). Found, %: N 11.87. $C_{11}H_{12}N_2OS$. Calculated, %: N 11.98.

Kinetic Investigations of Nucleophilic Substitution Reactions of Halogen in Pyrimidine Derivatives by S-Anion. Reactions were carried out in a thermostatted three-necked reactor fitted with a stirrer, thermometer, and a neck for removing samples.

The amount of compound **1** monosodium salt was determined after every 2 min, taking a test sample of V = 1 ml from the reactor and transferring it to a small beaker containing distilled water (30 ml). The amount of monosodium salt in the test sample (ω) was determined by potentiometric titration with 0.1 N H_2SO_4 solution in a universal EV 74 ionomer instrument using a calomel reference electrode and a glass electrode as measuring (indicator) electrode according to the following formula:

$$\omega = V_к \cdot V_р \cdot 0.1/1000,$$

where V_K is the volume of H_2SO_4 consumed in the titration of **1** monosodium salt in ml; V_P is the volume of the reaction mass in ml.

The concentration of monosodium salt (c) at each point in time was determined from the formula:

$$c = \omega/V_p.$$

At the end of the experiment the reaction mixture was cooled, the reaction products were filtered off, washed with cold water, and recrystallized.

Investigation of nucleophilic substitution reactions proceeding at the oxygen atom were carried out analogously.

Quantum-Chemical Calculations. For the calculation of model molecules the *ab initio* quantum-chemical restricted Hartree-Fock method, basis 6-31G**, was used with the GAMESS version 6.0 set of programs. Minimization of the total energy of a system was carried out by the gradient method with optimization of all geometric parameters at a frozen reaction coordinate. Calculation was carried out in the classical approximation of an isolated molecule in the gas phase. For reproduction of a reaction barrier the standard method was used for minimizing the energy of a geometric structure from the previous calculation at a new value for the fixed coordinates. Choice of basis was caused by the presence in the molecular system of elements of the third and fourth rows of the Mendeleev Periodic Table with clearly expressed long-acting interactions due to elongated *d*-orbitals, which may be discounted on inclusion in the basis of polarization exponents (asterisks in the designation of the basis). The precision of calculating the total energy is determined by the virial coefficient, which amounts to ~2.005 for systems including bromine, and ~2.002 for the remaining systems.

REFERENCES

1. S. Chokai, Y. Ukai, T. Aoki, and K. Ideguchi, US Pat. 5945426 (1999); *Ref. Zh. Khim.*, 19O102 (2000).
2. E. Rabusic, Danish Pat. 77130 (1994); *Ref. Zh. Khim.*, 17O53 (1995).
3. A.-H. Abdel-Rahman, *Afinidad*, **54**, 135 (1997).
4. A. A.-H. Abdel-Rahman and M. T. Abdel-Aal, *Pharmazie*, **53**, 377 (1998).
5. A. Besada, N. B. Tadros, and Y. A. Gawargyious, *Egypt. J. Pharm. Sci.*, **30**, 251 (1989).
6. G. Adam, S. Kolczewski, V. Mutel, J. Wichmann, and T. J. Waltering, Eur. Pat. 98112915; *Ref. Zh. Khim.*, 23O136 (1999).
7. M. Imaidzumi, S. Sakada, and F. Kano, Jpn. Pat. 2-186688 (1992); *Ref. Zh. Khim.*, 14O59 (1995).
8. M. Macchia, G. Antonelli, A. Balsamo, S. Barontini, F. Calvani, D. Gentili, A. Martinelli, A. Rossello, O. Turrriziani, and R. Tesoro, *Farmaco*, **54**, 242 (1999).
9. J. S. Larson, A. M. T. Abdel, E. B. Pederson, and C. Nielsen, *J. Heterocycl. Chem.*, **38**, 679 (2001).
10. A. Mai, G. Sbardella, M. Artico, R. Ragno, S. Massa, E. Novellino, G. Greco, A. Lavfechia, C. Musiu, M. La Colla, M. E. Marongiu, P. La Colla, and R. J. Loddo, *J. Med. Chem.* **44**, 2544 (2001).
11. M. S. Novikov, A. A. Ozerov, A. K. Brel', M. B. Navrotskii, and O. G. Sim, in: *Chemistry and Technology of Heteroorganic Monomers and Polymeric Materials* [in Russian], Nauch. Trud. Volgograd Gosud. Techn. Univ. (2002), p. 53.
12. A. Mai, G. Sbardella, M. Artico, R. Ragno, S. Massa, E. Novellino, G. Greco, A. Lavfechia, C. Musiu, M. La Colla, M. E. Marongiu, P. La Colla, and R. Loddo, *J. Med. Chem.*, **42**, 619 (1999).
13. M. Quaglia, A. Mai, M. Artico, G. Sbardella, R. Ragno, S. Massa, D. del Piano, G. Setzu, S. Doratiotto, and V. Cotchini, *Chirality*, **13**, 75 (2001).
14. E. A. Sudbeck, C. Mao, T. K. Venkatachalam, L. Tuel-Angren, and F. M. Uckun, *Antimicrob. Agents Chemother.*, **42**, 3225 (1998).
15. D. R. Imam, A. A. El-Barbary, C. Nielsen, and E. B. Pedersen, *Monatsh. Chem.*, **133**, 723 (2002).

16. O. S. Pedersen, L. Petersen, M. Brandt, C. Nielsen, and E. B. Pedersen, *Monatsh. Chem.*, **130**, 1499 (1999).
17. H. Mitsuya and S. Broder, *Nature*, **325**, 773 (1987).
18. S. P. Goff, *J. Acquired Immune Defic. Syndr.*, **3**, 817 (1990).
19. H. Vorbruggen and B. A. Bennua, *Chem. Ber.*, **114**, 1279 (1995).
20. E. De Clercq, *J. Med. Chem.*, **38**, 2491 (1995).
21. M. Baba, H. Tanaka, T. Miysaka, Y. S. Ubasawa, R. T. Wolcer, and E. De Clercq, *Nucleosides Nucleotides*, **14**, 497 (1995).
22. M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon. J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis, and J. A. Montgomery, *J. Comput. Chem.*, **14**, 1347 (1993).