Chemistry of Heterocyclic Compounds, Vol. 42, No. 4, 2006

NEW DATA ON THE ALKYLATION OF CYCLIC THIOUREAS WITH α-HALOCARBOXYLIC ACIDS AND THEIR ESTERS. 2*. ALKYLATION OF TETRAHYDROPYRIMIDINE-2(1H)-THIONE AND 5,5-DIMETHYLTETRAHYDROPYRIMIDINE-2(1H)-THIONE

P. M. Kushakova, A. I. Yulisova, S. M. Ramsh, and A. V. Garabadgiu

In the absence of bases all the attempted variations for the alkylation of tetrahydropyrimidine-2(1H)-thione with α-halocarboxylic acids gave only the bicyclic product – 2-R-6,7-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidin-3(2H)-one hydrohalide. However the hydrohalide of the "open" S-ethoxycarbonyl derivative of propyleneisothiourea can be obtained by treatment of tetrahydropyrimidine-2(1H)-thione with ethyl chloro- or bromoacetate in anhydrous acetone at room temperature. Alkylation of 5,5-dimethyltetrahydro-2(1H)-pyrimidinethione with chloro- or bromoacetic acid in anhydrous acetone at room temperature gave the hydrohalide of the "open" S-carboxymethyl derivative of dimethylpropyleneisothiourea. All remaining variations for the alkylation of this substrate with α-halocarboxylic acids or their esters gave only the corresponding bicyclic compounds – the hydrohalide of 2-R-6,6-dimethyl-6,7-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidin-3(2H)-one – independently of the reaction conditions.

Keywords: 5,5-dimethyltetrahydro-2(1H)-pyrimidinethione, tetrahydropyrimidine-2(1H)-thione (propylenethiourea), reactions with α-halocarboxylic acids and their esters.

Alkylation of tetrahydropyrimidine-2(1H)-thione (propylenethiourea) with α-halocarboxylic acids and their esters in boiling ethanol with a ratio of reagents propylenethiourea **1** – chloroacetic acid – sodium acetate 1:1.5:1.2 gave only the bicyclic compound 6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-3(2H)-one **2** in the form of the free base [2]. However according to an earlier paper [3], alkylation of propylenethiourea **1** with sodium chloroacetate gave "a product which was impossible to purify" (the solvent was not reported).

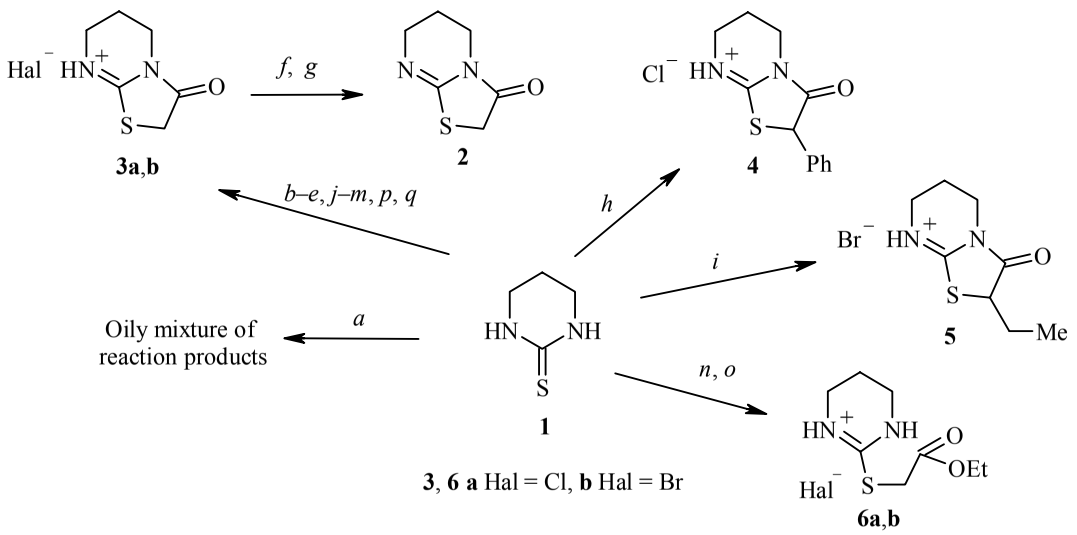
In an attempt to reproduce the method of paper [2] (route *a* in Scheme 1), we only isolated from the reaction mixture an uncrystallizable oil. TLC showed that the propylenethiourea **1** was absent, but there were two other compounds in comparable amounts apart from compound **2**. Separation of the oil into its components was unsuccessful. It is possible that under these alkylation conditions cyclization of the mercaptoacetic acid intermediate **A** does not occur completely because the medium is not sufficiently acidic [4] and a mixture of at least two reaction products, the amino acid **A** and the bicyclic compound **2** are formed as a mixture which is difficult to separate.

* For part 1 see [1].

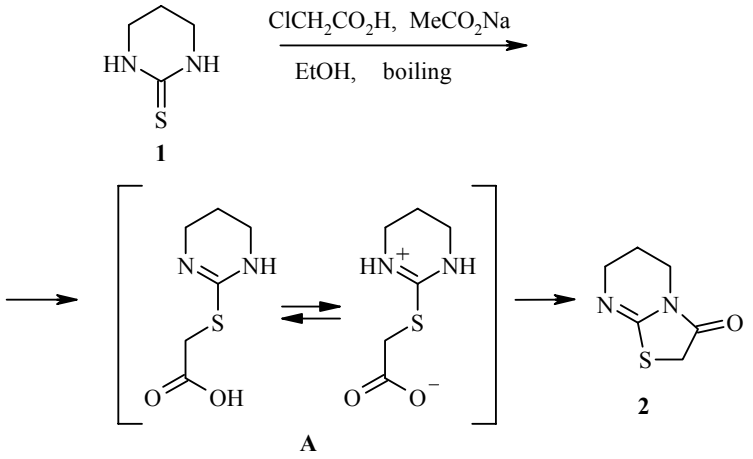
St. Petersburg State Technological University, St. Petersburg 198013, Russia; e-mail: gsramsh@mail.wplus.net. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, 593-604, April, 2006. Original article submitted December 12, 2004.

Scheme 1

Alkylation of tetrahydro-2(1H)-pyrimidinethione **1** with α-halocarboxylic acids and their esters



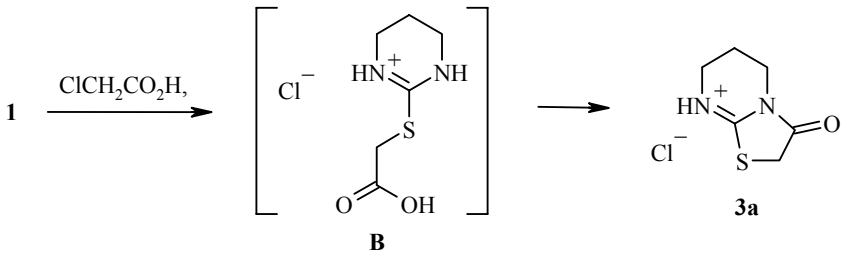
a – $ClCH_2CO_2H$, $MeCH_2CO_2Na$ / boiling ethanol; *b,c* – $HalCH_2CO_2H$ /boiling ethanol; *d,e* – $HalCH_2CO_2H$ / anhydrous acetone, 20°C; *f* – K_2CO_3/aqueous, extraction with chloroform (Hal = Cl); *g* – K_2CO_3/aqueous, extraction with benzene (Hal = Br); *h* – Cl(Ph)$CHCO_2H$ /boiling ethanol; *i* – Et(Br)$CHCO_2H$ / boiling ethanol; *j,l* – $HalCH_2CO_2Et$ / without solvent, boiling; *k,m* – $HalCH_2CO_2Et$ / boiling ethanol; *n,o* – $HalCH_2CO_2Et$ / anhydrous acetone, 20°C ; *p* – $ClCH_2CO_2Bu$ / boiling ethanol; *q* – $ClCH_2CO_2Bu$ / anhydrous acetone, 20°C // boiling ethanol



We believe that the authors [2] assumed some other substance to be **2** since the characteristics of the bicycle **2** differ from those cited [2] (see below).

It should be noted that similar difficulty in separating the reaction product did not occur when 2-imidazolidinethione (ethylenethiourea) was alkylated under the same conditions to give the five-membered analog of compound **A** [1], apparently because it has a much lower tendency to cyclize to the corresponding bicycle.

As a result of alkylating propylenethioures **1** with chloro- and bromoacetic acids in boiling ethanol in the absence of a base (routes *b* and *c* in Scheme 1) only bicyclic compounds were obtained – the hydrohalides of 6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-3(2H)-ne, **3a** and **3b** respectively. Cyclization of the hypothetical "open" intermediate **B** occurred so fast under these conditions that it was not detected in the reaction mixture by HPLC.



In fact only one new peak was detected, corresponding to the bicyclic hydrogen chloride **3a**, during alkylation with chloroacetic acid. The area of the peak for propylenethiourea starting material decreased as the area of the peak for **3a** increased, so that the sum of the areas of the two peaks was ~100%. This was quite unexpected because alkylation of 2-imidazolidinethione under the same conditions gave only a derivative of 2,4-thiazolidinedione, the product of the hydrolysis of the intermediately formed 5,5-bicyclic analog of compound **3a** [1]. Thus analytical data, which confirmed the results of the preparative experiment, also indicate the remarkable stability of the 6,5-bicycle **3a** to acid hydrolysis, which is completely different from its 5,5-bicyclic analog. These two circumstances – the tendency of the intermediate **B** to cyclization and the stability of compound **3a** to hydrolysis – may explain the greater stability of the 6,5-bicyclic system in comparison with the 5,5-bicyclic system.

Alkylation of propylenethiourea **1** with chloro- and bromoacetic acids in acetone in the cold (routes *d* and *e* in Scheme 1) also led to the bicyclic hydrogen halides **3a** and **3b** respectively, whereas 2-imidazolidinethione with chloroacetic acid under the same conditions gave only the five-membered analog of the "open" intermediate hydrochloride **B** [1].

In the same paper [2] another method was described for preparing the bicyclic compound **2** by neutralizing the hydrochloride **3a** with aqueous potassium carbonate. We did not succeed in reproducing this method – after neutralization of the hydrochloride **3a** nothing precipitated from solution. To isolate the bicycle **2**, after neutralization of the hydrochloride **3a** with either aqueous potassium or sodium carbonate we extracted it with chloroform (route *f*, Scheme 1) and then recrystallized the material from the chloroform extract from petroleum ether. The yield after recrystalization was 30%. Analogously neutralization of the hydrobromide **3b** with aqueous potassium carbonate, followed by extraction with benzene (route *g*, Scheme 1) gave the free base **2** in 12% yield (after recrystalization from isopropanol). The sample obtained was identical with that obtained from the hydrochloride **3a**. The melting point of our sample was 72-74°C (!). In contrast mp 201°C according to [2]. Data from mass spectrometry, ^{1}H NMR, and elemental analysis left no doubt that the compound we isolated has structure **2**. In particular the value of *m/z* for the molecular ion peak in the mass spectrum corresponds to the calculated value. In the ^{1}H NMR spectrum there is no signal for an NH proton and the signals of the protons of all the methylene groups are shifted to strong field in comparison with the hydrochloride **3a**. Taking all these points into consideration we believe that compound **2** was not isolated pure in work [2].

It should be noted that in the ^{1}H NMR spectrum taken in D_2O the methylene protons of the thiazolidine ring of the hydrochloride **3a** underwent deuterium exchange with the solvent, evidently as a result of acid catalyzed enolization of the CH_2–CO unit.

The presence of a bulky substituent in the α-position of the α-halocarboxylic acid did not prevent cyclization of the intermediate "open" compound of type **B** into the bicyclic structure. In fact the reaction of propylenethiourea with phenylchloroacetic acid and 2-bromobutanoic acids (routes *h* and *i*, Scheme 1) in boiling ethanol gave only the bicyclic compounds the hydrochloride of 2-phenyl-6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]-pyridimin-3(2H)-one (**4**) and the hydrobromide of 2-ethyl-6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyridimin-3(2H)-one (**5**) respectively. However in agreement with normal behavior [5], the reactions proceeded more slowly because of steric hindrance. For example. The time required for alkylation of propylenethiourea by 2-bromobutanoic acid to achieve an acceptable yield was about 10 times as long as with bromoacetic acid. As a result of this the conversion of substrate **1** into compounds **4** and **5** in a reasonable time was not large: their yields after recrystalization were only 10 and 40% respectively.

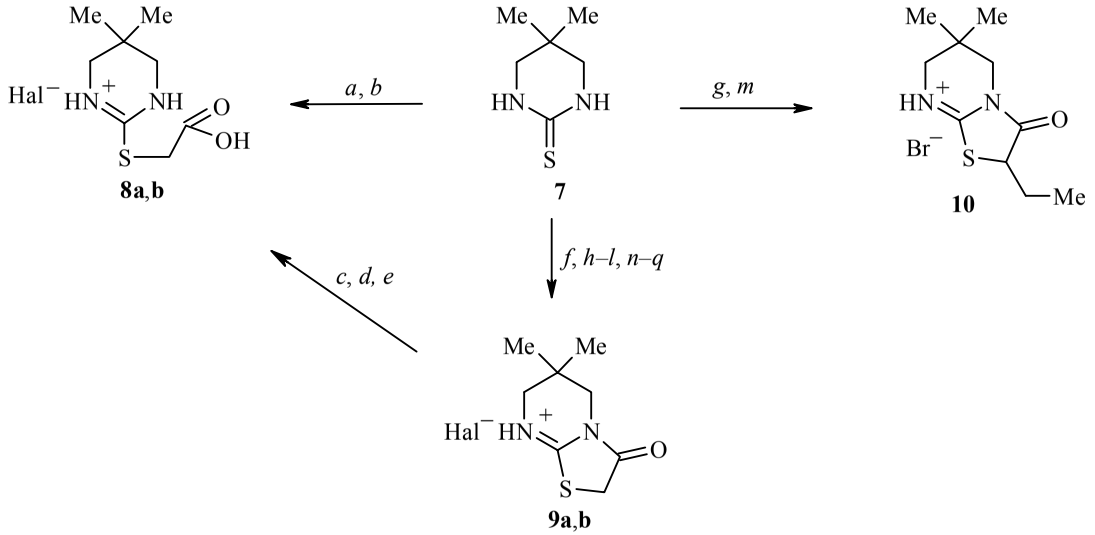
We also obtained hydrochloride **3a** from propylenethiourea **1** and ethyl chloroacetate: in a yield of 90% from 1:10 ratio of the reagents in boiling alkylating agent without solvent, following the published method [2] (route *j*, Scheme 1) and in a yield of 50% with a reactant ratio of 1:1.5 in boiling ethanol (route *k*, Scheme 1). Analogously, yields of the bicyclic hydrobromide **3b** of 68 and 50% respectively were obtained on alkylation of propylenethiourea **1** with ethyl bromoacetate in boiling alkylating agent without solvent and in boiling ethanol (routes *l* and *m*, Scheme 1).

Considering the slower rate of cyclization of the "open" intermediate compound with a bulky ester in comparison with the acid analog **B** (because of both the steric hindrance to cyclization and because such cyclizations should be acid catalyzed [4, 5]) we attempted to estimate the concentration of the intermediate in the reaction mixture from the alkylation of propylenethiourea **1** with ethyl chloroacetate in boiling ethanol using HPLC. The chromatograms obtained had the same form as those from alkylation with chloroacetic acid, i.e., they contained just two peaks which changed in intensity with time, the propylenethiourea **1** starting material and end product , the hydrochloride **3a**. The sum of their intensities was 97-98%. However three more signals with a total intensity of 2-3% were detected in the reaction mixture. This intensity remained practically unchanged during the reaction. It is possible that one of these minor peaks belonged to the ester analog of the "open" intermediate compound **B**.

This observation prompted a study of the reaction in anhydrous acetone at room temperature. The completely unexpected crystalline residues isolated from the reaction mixture from the alkylation of propylenethiourea **1** with ethyl chloroacetate and ethyl bromoacetate in acetone at room temperature (routes *n* and *o*, Scheme 1) were the hydrohalides of the "open" S-ethoxycarbonylmethyl derivatives of propylenethiourea

Scheme 2

Alkylation of 5,5-dimethyltetrahydro-2(1H)-pyrimidinethione (**7**) with α-halocarboxylic acids and their esters.



8, **9** **a** Hal = Cl, **b** Hal = Br

a,b – $HalCH_2CO_2H$/ anhydrous acetone, 20°C; *c,d* – boiling ethanol; *e* – **8a**: heating at 100°C without solvent; *f* – $BrCH_2CO_2H$ / boiling anhydrous acetone; *g* – $CH_2CH_2CHCO_2H$ / anhydrous acetone, 20°C; *h,i* – $HalCH_2CO_2H$ / boiling ethanol; *k* – $HalCH_2CO_2Et$ / boiling ethanol; *l* – $ClCH_2CO_2Bu$ / boiling ethanol; *m* – $MeCH_2CHBrCO_2H$ / boiling ethanol; *n,o* – $HalCH_2CO_2Et$ / anhydrous acetone, 20°C; *p* – $ClCH_2CO_2Bu$ / anhydrous acetone, 20°C; *q* – $BrCH_2CO_2Bu$ / boiling anhydrous acetone.

– the hydrochloride of ethyl (1,4,5,6-tetrahydro-2-pyrimidinylthio)acetate (**6a**) and its hydrobromide **6b** respectively, with traces of the bicyclic forms **3a** and **3b** (8 and 20% respectively from ^{1}H NMR data). It was not possible to obtain compounds **6a** and **6b** in greater purity because of their lability.

Only the bicyclic hydrochloride **3a** was isolated when ethyl chloroacetate was replaced as alkylating agent by butyl chloroacetate with a longer alkyl group either in boiling ethanol or in anhydrous acetone at room temperature (routes *p* and *q*, Scheme 1).

The analog of the "open" S-carboxymethyl intermediate compound **B** was successfully obtained by modifying the tetrahydropyrimidine unit and creating steric hindrance to spontaneous cyclization into the 6,5-bicycle. In fact when 5,5-dimethyltetrahydro-2(1H)pyrimidinethione (**7**) reacted with chloro- and bromoacetic acids in anhydrous acetone at room temperature the pure hydrohalides of [(5,5-dimethyl-1,4,5,6-tetrahydro-2-pyrimidinyl)thio]acetic acids **8a** and **8b** respectively (routes *a* and *b,* Scheme 2). These compounds are deactivated in comparison with the intermediate compound **B**. When bromoacetic acid was used as the alkylating agent, the reaction mixture contained along with the "open" compound **8b** about 9% of the bicycle **9b** to judge from the ^{1}H NMR spectrum. It is possible that this is connected with the very low solubility of the hydrobromide **9b** which dissolves only poorly even in DMSO-d_6. After storing this sample in a closed box in the air for 20 months the content of the bicycle **9b** reached 35%.

It is known that six-membered heterocyclic compounds exist predominantly in the *chair* conformation, but the influence of substituents in the heterocycle on the geometry of the molecule overcome this regularity, as in the cyclohexane series [6]. In particular, the *gem*-dimethyl group "compresses" the six-membered ring [6] which evidently makes it more difficult to cyclize the "open" S-carboxymethyl compound **8** into bicyclic derivative *9* because of overlap of fragments of the molecules in the transition state, for example, because of the unsuitable orientation of the unshared pair of electrons on the cyclic nitrogen atom relative to the carbonyl groups.

Cyclization of the "open" hydrochloride **8a** did not occur even on boiling for 2 hours in anhydrous acetone, possibly because of its low solubility in the solvent and also because of the very low concentration of the non-zwitterionic of the amino acid – it is this form which should undergo acid catalyzed cyclization [5]. The "open" hydrobromide **8b** is converted under these conditions into the bicyclic hydrobromide of 6,6-dimethyl-6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimnidin-3(2H)-one (**9b**) in 9-10% yield.

Boiling the "open" hydrohalides **8a** or **8b** in ethanol led to the formation of the bicyclic hydrochloride **9a** or the hydrobromide **9b** respectively (routes *c* and *d*, Scheme 2). The "open" hydrobromide **8b** spontaneously cyclized in D_2O solution directly in the ampul in the NMR spectrometer; to judge from the spectrum after keeping for two weeks in solution at room temperature the content of the hydrobromide **9b** reached 98%. Like compound **3a**, the methylene protons of the thiazolidine ring of the hydrobromide **9b** underwent deuterium exchange with the solvent.

The behavior of the compounds **8a** and **8b** on keeping in vacuum for 6 h without solvent at 100°C differed. The hydrochloride **8a** was converted into the bicycle **9a** (route *e*, Scheme 2) whereas the hydrobromide **8b** remained unchanged. It is possible that the bromide ion creates steric hindrance to cyclization in the solid phase.

Boiling compound **7** with bromoacetic acid in anhydrous acetone gave the bicyclic hydrobromide **9b** (route *f*, Scheme 2): the product contained about 7% of the "open" form **8b** according to ^{1}H NMR data.

We also attempted to obtain the ethyl analog of the "open" compound **8a** by the reaction of the substrate **7** with 2-bromobutanoic acid in anhydrous acetone at room temperature, however in this case only the corresponding bicyclic compound was isolated – the hydrobromide of 2-ethyl-6,6-dimethyl-6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-3[2H]-one (**10**) (route *g*, Scheme 2). It is possible that this is connected with the slow rate of alkylation with 2-bromobutanoic acid in comparison with bromoacetic acid and/or the greater solubility of the first formed ethyl analog in comparison with compound **8a**, consequently it is able to cyclize into the bicycle **10** before separating from the reaction mixture.

Reaction of substrate **7** with chloroacetic or bromoacetic acids, their ethyl esters or butyl chloroacetate in boiling ethanol gave the hydrohalides of the bicyclic compounds **9a** or **9b** (routes *h*, and *i-l* respectively, Scheme 2), but with 2-bromobutanoic acid it gave the hydrobromide of the bicycle **10** (route *m*, Scheme 2).

It is remarkable that interaction substrate **7** with ethyl chloroacetate, ethyl bromoacetate, or butyl bromoacetate in anhydrous acetone at room temperature gave only hydrohalides of the bicycles **9a** and **9b** (routes *n*, *o*, and *p*, Scheme 2, respectively), but not corresponding "open" S-alkoxycarbonylmethyl derivatives, as happened in the case of alkylation of propylenethiourea **1** with ethyl chloroacetate or ethyl bromoacetate in analogous conditions (Scheme 1). A possible reason for this difference may be the greater solubility in acetone of the "open" S-alkoxycarbonylmethyl derivatives of **7** in comparison with their analogs – the S-ethoxycarbonylmethyl derivatives **6a** and **6b** or the S-carboxymethyl derivatives **8a** and **8b**: these analogs fall out of the reaction mixture practically as soon as they are formed, whereas the hypothetical S-alkoxycarboxymethyl derivatives of compound **7** remain in solution for some tens of hours (see experimental) nd are able to cyclize with formation of the 6,-bicycles **9a** and **9b**. It is possible the existence of different concentrations of the spontaneously cyclizing form, namely the free base of the intermediate "open" S-alkoxycarbonylmethyl during the alkylation of compound **7** with esters of haloacetic acids in comparison with the concentration of the neutral zwitterionic forms of the corresponding amino acids hydrohalides **8a** and **8b** during the alkylation of this compound with haloacetic acids – because of the greater solubility of the "open" intermediate of the ester type and lower acidity of the reaction medium in the case of alkylation with an ester (under conditions when this "concentration effect" is not compensated for by acceleration of cyclization on going from the ester to the acid).

As expected, boiling substrate **7** with ethyl bromoacetate in anhydrous acetone also gave the bicyclic hydrobromide **9b** (route *q*, Scheme 2)

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions (compounds **3a**, **8b**, and **9b** in DMSO-d_6 and D_2O) were recorded with Bruker DPV-300 (300 MHz) and Bruker AM-200 (200 MHz) spectrometers with the solvent as internal standard. IR spectra of compounds **8b** and **9b** were recorded with Shimadzu FTIR-8400S Fourier spectrometer and the mass spectrum of compound **2** with a Finnigan MAT INCOS 50 (EI, 70eV) machine. HPLC analysis with spectrophotometric detection was carried out on a Varian 9065 chromatograph with a reverse phase column – Phenyl (250 × 4.6 mm), liquid phase 50% MeCN–50% 0.5 mol/l $NaClO_4$, wavelength 254 nm, rate of flow of eluent 1 ml/min, data treated with the Polychrom suite of programs. TLC was carried out on Silufol UV-254 strips with a 1:10:100 butyl acetate-ethanol-chloroform system. Anhydrous acetone was prepared by a known method [7].

Tetrahydropyrimidine-2(1H)-thione (1) was prepared according to [8]; mp 209-210°C (mp 209°C [9]). ^{1}H NMR spectrum, δ, ppm: 7.78 (2H, s, NH_2); 3.13 (4H,m, 2H-4,6); 1.77 (2H, m,2H-5).

6,7-Dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-3(2H)-one (2). A (route f, Scheme 1). Compound **3a** (2.45 g, 12.7 mmol) was dissolved in aqueous K_2CO_3 (15 ml, *c* 125 g/l), the solution was extracted with chloroform (3 × 50 ml), the extracts were combined, dried with $MgSO_4$ overnight, the solvent was evaporated in air, and the residue was recrystallized from petroleum ether. Yield 1.09 g (55%); mp 72-74°C (mp 201°C [2]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.85 (2H, s, 2H-2); 3.60 (2H, t, *J* = 6.2, 2H-7); 3.35 (2H, t, *J* = 6, 2H-5); 1.80 (2H, m, 2H-6). Mass spectrum: *m/z* (I_{rel}, %): 158 [M^+ + 2] (5), 157 [M^+ + 1] (9), 156 [M^+] (100). Found, %: C 46.57; H 5.23; N 17.83. $C_6H_8N_2OS$ (M 156.2). Calculated, %: C 46.15; H 5.16; N 17.94.

B (route g, Scheme 1). Prepared from compound **3b** analogously to method A with the following differences: the extractant was benzene and the recrystalization solvent was propanol-2. Yield 12%; mp 72-74°C.

6,7-Dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-3(2H)-one Hydrochloride (3a). A (route b, Scheme 1). Propylenethiourea (0.58 g, 5.0 mmol) was dissolved ethanol (10 ml) on heating, a solution of chloroacetic acid (0.71 g, 7.5 mmol) in ethanol (10 ml) was added and the reaction mixture was boiled for 2h. The precipitate was filtered off and recrystallized from ethanol. Yield 0.42 g (44%); mp 260-261°C (mp 261°C [2]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.15 (2H, s, 2H-2); 3.70 (2H, t, *J* = 6, 2H-7); 3.57 (2H, t, *J* = 6, 2H-5); 2.04 (2H, 2H-6). The signal of the NH proton was detected in the 13.3-13.5 ppm field as a broad peak with an intensity of 0.5-0.8 H. ^{1}H NMR spectrum (D_2O), δ, ppm: 4.22 (2H, s, 2H-2); 3.81 (2H, s, 2H-7); 3.65 (2H, 2H-5 – the multiplicity of this signal was not detected); 2.13 (2H, m, 2H-6). Found, %: C 37.79; H 4.76; N 14.79. $C_6H_8N_2OS$·HCl. Calculated, %: C 37.40; H 4.71; N 14.54.

Compound **3a** was made by an analogous method from propylenethiourea **1** and ethyl chloroacetate (route *k*, Scheme 1) or butyl chloroacetate (route *p*, Scheme 1) in ethanol. The yields after recrystalization were 50 and 62% respectively.

B (route *j*, Scheme 1). Obtained from propylenethiourea **1** and ethyl chloroacetate without solvent as described in [2]. Yield 90%.

C (route *q*, Scheme 1). Butyl chloroacetate (1.95 g, 1.77 ml, 12.9 mmol) was added with intense stirring to propyenelthiourea **1** (1.16 g, 10.0 mmol) in anhydrous acetone (30 ml) and the reaction mixture was kept at room temperature for 7 h. The solvent was removed in vacuum. The oily residue was treated with petroleum ether and the precipitate was recrystallized from ethanol. Yield 1.70 g (93%).

D (route *d*, Scheme 1). Chloroacetic acid (0.62 g, 6.6 mmol) was added with stirring to propylenethiourea **1** (0.58 g, 5.0 mmol) in anhydrous acetone (15 ml) at room temperature and the reaction mixture was kept at room temperature for a week. The precipitate was filtered off and washed with anhydrous acetone (2 × 5 ml). Yield 0.82 g (85%).

6,7-Dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-3(2H)-one Hydrobromide (3b). A (routes *c* and *m*, Scheme 1). Obtained from propylenethiourea **1** and bromoacetic acid or its ethyl ester in ethanol, by a method analogous to method **A** for compound **3a**. Yield 70 % (route *c*) or 50% (route *m*); mp 278-281°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.90 (NH); 4.18 (2H, s, 2H-2); 3.73 (2H, t, *J* = 6, 2H-7); 3.62 (2H, t, *J* = 6, 2H-5); 2.07 (2H, m, 2H-6). Found, %: C 29.95; H 3.73; N 11.76. $C_6H_8N_2OS$·HBr. Calculated, %: C 30.39; H 3.83; N 11.81.

B (route *e*, Scheme 1). A mixture of propylenethiourea **1** (1.16 g, 10.0 mmol) and bromoacetic acid (1.74 g, 12.5 mmol) in anhydrous acetone (30 ml) was stirred vigorously for 5 h at room temperature. The precipitate was filtered off and washed with anhydrous acetone (2 × 5ml). Yield 0.92 g (39%) .

C (route *l*, Scheme 1). A mixture of propylenethiourea **1** (2.32 g, 20 mmol) and ethyl bromoacetate (33.4 g, 22.1 ml, 200 mmol) was boiled for 2 h. The precipitate which formed on cooling the reaction mixture was filtered off and recrystallized from ethanol. Yield 3.24 g (68%).

2-Phenyl-6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-3(2H)-one Hydrochloride (4) (route *h*, Scheme 1) was obtained from propylenethiourea **1** and phenylchloroacetic acid in ethanol by a method analogous to method **A** for compound **3a**. Yield 10%; mp 215-217°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.40 (1H, NH); 7.20-7.70, (5H, m, C_6H_5); 5.70 (1H, s, H-2); 4.10 (2H, t, *J* = 6, 2H-7); 3.90 (2h, t, *J* = 6, 2H-5); 2.10 (2H, m, 2H-6). Found, %: C 53.65; H 4.75; N 10.40. $C_{12}H_{12}N_2OS$·HCl. Calculated, %: C 53.64; H 4.88; N 10.42.

2-Ethyl--6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-3(2H)-one Hydrobromide (5) (route *l*, Scheme 1). Propylenethiourea **1** (0.58 g, 5.0 mmol) was dissolved on heating in ethanol (20 ml), 2-bromobutanoic acid (1.25 g, 0.80 ml, 7.5 mmol) was added and the mixture was boiled for 10 h. The solvent was removed in vacuum, the oily residue was treated with ethyl acetate and the precipitate formed was recrystallized from ethanol. Yield 0.5 g (38%); mp 205-207°C.

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.40 (1H, NH); 4.55 (1H, t, *J* = 7, H-2); 3.80 (2H, t, *J* = 6, 2H-7); 3.68 (2H, *J* = 6, 2H-5); 2.15 (2H, m, 2H-6); 2.04 (2H, m, $C\underline{H}_2CH_3$); 1.05 (3H, *J* = 8, $CH_2C\underline{H}_3$). Found, %: C 36.25; H 4.95; 10.55. $C_8H_{12}N_2OS$·HBr, %: C 36.24; H 5.94; N 10.56.

Ethyl (1,4,5,6-Tetrahydro-2-pyrimidinylthio)acetate Hydrochloride (6a) (route *n*, Scheme 1). Ethyl chloroacetate (1.59 g, 1.37 ml, 13.0 mmol) was added with stirring to propylenethiourea **1** (1.16 g, 10 mmol) in anhydrous acetone (30 ml). The precipitate which formed over a week was filtered off and washed with anhydrous acetone (2 × 5 ml). Yield 1.65 g (69%); mp 132-134°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.41 (2H, 2NH); 4.38 (2H, s, SCH_2); 4.16 (2H, q, *J* = 7, $C\underline{H}_2CH_3$); 3.38 (4H, t, *J* = 5, 2H-4,6); 1.91 (2H, m, 2H-5); 1.26 (3H, t, *J* = 7, $CH_2C\underline{H}_3$). Found, %: C 40.43; H 6.41; N 11.38. $C_8H_{14}N_2O_2S{\cdot}HCl$. Calculated, %: C 40.25; H 6.33; N 11.73.

Ethyl (1,4,5,6-Tetrahydro-2-pyrimidinylthio)acetate Hydrobromide (6b) was obtained analogously from propylenethiourea **1** and ethyl bromoacetate (route *o*, Scheme 1). Yield 1.07 g, (38%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.03 (2H, 2NH); 4.29 (2H, s, SCH_2); 4.17 (2H, q, *J* = 7, $C\underline{H}_2CH_3$); 3.42 (4H, t, *J* = 5, 2H-4,6); 1.95 (2H, m, 2H-5); 1.27 (3H, t, *J* = 7, $CH_2C\underline{H}_3$). Found, %: C 34.12; H 5.29; N 9.59. $C_8H_{14}N_2O_2S{\cdot}HBr$. Calculated, %: C 33.93; H 5.34; N 9.89.

5,5-Dimethyltetrahydro-2(1H)-pyrimidinethione (7) was prepared by method [8]; mp 186-188°C (ethanol). ^{1}H NMR spectrum, δ, ppm : 7.76 (2H, 2NH); 2.81-2.82 (4H, 2H-4,6); 0.97 (6H, 2 CH_3). Found, %: C 49.75; H 8.21; N 19.52. $C_6H_{12}N_2S$. Calculated, %: C 49.96; H 8.39; N 19.42.

[(5,5-Dimethyl-1,4,5,6-tetrahydro-2-pyrimidinyl)thio]acetic Acid Hydrochloride (8a) (route *a*, Scheme 2). Chloroacetic acid (0.71 g, 7.5 mmol) was added with intense stirring to compound **7** (0.72 g, 5.0 mmol) in anhydrous acetone (20 ml) and the mixture was kept at room temperature for 3 days. The precipitate was filtered off and washed with anhydrous acetone (2 × 5 ml). Yield 1.02 g (85%); mp 216-218°C. ^{1}H NMR spectrum, δ, ppm: 10.40 (2H, 2NH); 4.35 (2H, s, SCH_2); 3.10 (4H, s, 2H-4,6); 1.05 (6H, s, 2 CH_3). Found, %: C 40.23; H 6.35; N 11.65. $C_8H_{14}N_2O_2S{\cdot}HCl$. Calculated, %: C 40.25; H 6.33; N 11.73.

[(5,5-Dimethyl-1,4,5,6-tetrahydro-2-pyrimidinyl)thio]acetic Acid Hydrobromide (8b) was prepared analogously from compound **7** and bromoacetic acid (route *b*, Scheme 2), but the reaction mixture was kept for 7 days. Yield 0.64 g (64%); mp 245-246°C. IR spectrum (KBr), ν, cm^{-1}: 3327 (NH), 2895-3166 (CH), 1742 (C=O), 1724 (C=O), 1620 (C=N), 1568 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 10.03 (2H, 2NH); 4.21 (2H, s, SCH_2); 3.10 (4H, s, 2H-4,6); 1.04 (6H, s, 2 CH_3). ^{1}H NMR spectrum (D_2O), δ, ppm: 3.97 (2H, s, SCH_2); 3.15 (4H, s, 2H-4,6); 1.01 (6H, s, 2 CH_3). Found, %: C 34.21; H 5.58; N 9.73. $C_8H_{14}N_2O_2S{\cdot}HBr$. Calculated, %: C 33.93; H 5.34; N 9.89.

6,6-Dimethyl-6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidine-3(2H)-thione Hydrochloride (9a). A (route *c*, Scheme 2). Compound **8a** (0.25 g, 1.05 mmol) was boiled in ethanol (10 ml) for 50 min, the solvent was removed at atmospheric pressure, and the residue was recrystallized from ethanol. Yield 0.10 g (43%), m.p.225-227°C. ^{1}H NMR Spectrum, δ, ppm: 10.95 (1H, NH); 4.20 (2H, s, 2H-2); 3.45 (2H, s, 2H-7); 3.30 (2H, s, 2H-5); 1.05 (6H, s, 2 CH_3). Found, %: C 43.56; H 5.98; N 12.72. $C_8H_{12}N_2OS{\cdot}HCl$. Calculated, %: C 43.53; H 5.94; N 12.69.

B (route *e*, Scheme 2). A sample of compound **8a** (0.101 g, 0.42 mmol) was maintained in vacuum at 100°C for 6 h. Yield 0.093 g (100%).

C (route *h*, Scheme 2). Obtained from compound **7** and chloroacetic acid in ethanol analogously to method **A** for compound **3a**, except that the solvent was removed in vacuum to obtain the precipitate. Yield 55%.

D (route *j*, Scheme 2). Obtained from compound **7** and ethyl chloroacetate in ethanol analogously to method **B** for compound **9a**, except that the ethyl chloroacetate all at once without preliminary solution in ethanol and that the reaction time was 5 h. Yield 50%.

E (route *l*, Scheme 2). Obtained from compound **7** and butyl chloroacetate in ethanol analogously to method **D** for the preparation of compound **3a**, but the reaction time was 7.5 h. Yield 47%.

F (route *n*, Scheme 2). Obtained from compound **7** and ethyl chloroacetate in anhydrous acetone analogously to method **D** for the preparation of compound **3a** except that the reaction mixture was kept for 3 d. Yield 50%.

G (route *p*, Scheme 2). Obtained from compound **7** and butyl chloroacetate in anhydrous acetone analogously to method **F** for the preparation of compound **9a**, except that the reaction mixture was kept for 2 days. Yield 50%.

6,6-dimethyl-6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidine-3(2H)-thione Hydrobromide (9b). A (route *f*, Scheme 2). Obtained from compound **7** and bromoacetic acid in acetone analogously to method **C** to obtain compound **9a**, except that the precipitate was not recrystallized but was washed on the filter with anhydrous acetone (2 × 5 ml). Yield 55%; mp 259-260°C. IR spectrum (KBr), ν, cm^{-1}: 3450 (NH), 2760-2970 (CH), 1761 (C=O), 1629 (C=N), 1522 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.25 (2H, s, 2H-2); 3.46 (2H, s, 2H-7); 3.36 (2H, s, 2H-5); 1.09 (6H, s, 2 CH_3), the signal of the NH proton was not detected.

^{1}H NMR spectrum (D_2O), δ, ppm: 4.27 (2H, s, 2H-2); 3.55 (2H, s, 2H-7); 3.40 (2H, s, 2H-5); 1.09 (6H, s, 2 CH_3). Found, %: C 36.32; H 4.71; N 10.80. $C_8H_{12}N_2OS\cdot HBr$. Calculated, %: C 36.24; H 4.94; N 10.56.

B (route *i*, Scheme 2). Obtained from compound **7** and bromoacetic acid in ethanol analogously to method **A** for compound **9a** except that the boiling time was 1 h. Yield 36%.

C (route *k*, Scheme 2). Obtained from compound **7** and ethyl bromoacetate in ethanol analogously to method **A** for compound **9a**, except that the boiling time was 1.5 h. Yield 66%.

D (route *o*, Scheme 2). Obtained from compound **7** and ethyl bromoacetate in acetone analogously to the method for preparing compound **8b**. Yield 58%.

E (route *q*, Scheme 2). Obtained from compound **7** and ethyl bromoacetate in acetone analogously to method **A** for the preparation of compound **9b**. Yield 45%.

F (route *d*. Scheme 2). Obtained from compound **8b** by boiling for 2 h in ethanol analogously to method **A** for compound **9a**. The precipitate was not recrystallized but was immediately analyzed by ^{1}H NMR spectroscopy. The sample contained 82% hydrobromide **9b**, wile the rest consisted of compound **8b** and an unidentified mixture.

6,6-Dimethyl-6,7dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-3(2H)-one Hydrobromide (10). A (route *g*, Scheme 2). Obtained from compound **7** and 2-bromobutanoic acid in anhydrous acetone analogously to method **G** for the preparation of compound **9a**, except that the solvent was removed in vacuum to obtain the precipitate. Yield 45%; mp 214-216°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.90 (1H, NH); 4.60 (1H, t, *J* = 7, H-2); 3.65 (2H, s, 2H-7); 3.40 (2H, s, 2H-5); 2.10 (2H, m, $C\underline{H}_2CH_3$); 1.09 (9H, $(CH_3)_2$, $CH_2C\underline{H}_3$).

B (route *m*, Scheme 2). Obtained from compound **7** and 2-bromobutanoic acid in ethanol analogously to the method for compound **3a** with these differences: the 2-bromobutanoic acid was immediately with out dissolving in ethanol, the reaction time was 8.5 h, and the solvent was removed in vacuo to obtain the precipitate. Yield 60%.

REFERENCES

1. P. M. Kushakova, S. M. Ramsh, and A. V. Garabadgiu, *Khim. Geterotsikl. Soedin.,* 250 (2006).
2. S. N. Dehuri and A. Nayak, *J. Indian Chem. Soc.,* **60**, 970 (1983).
3. J. A. VanAllan, *J. Org. Chem.,* **21**, 24 (1956).
4. J. Kavalek, S.-E. Bahaie, and B. Sterba, *Coll. Czech. Chem. Commun.,* **45,**263 (1980).
5. J. March, *Organic Chemistry* [Russian translation], Vol. 2,pp. 369, 340 (1988).
6. V. M. Potapov, *Stereochemistry* [in Russian], Khimiya, Moscow, pp. 533, 333 (1976).
7. V. M. Potapov (editor), *Organicum*, [in Russian], Mir, Moscow, Vol. 2, 335 (1979).
8. A. F. McKay and W. G. Hatton. *J. Am. Chem. Soc.,* **78**, 1618 (1956).