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NOVEL ALKYLATIONS OF CYCLIC THIOUREAS BY α-HALOCARBOXYLIC ACIDS AND THEIR ESTERS. 4*. ALKYLATION OF 1-METHYL-TETRAHYDROPYRIMIDINE-2(1H)-THIONE

P. M. Kushakova[1], Yu. V. Basan[1], A. I. Yulisova[1], V. V. Lifontova[1], S. M. Ramsh[1], A. V. Garabadgiu[1], and L. N. Belobrzeckaja Costa[2]

Alkylation of 1-methyltetrahydropyrimidine-2(1H)-thione (N-methylpropylenethiourea) with chloro- and bromoacetic acids and their esters have given the 8-methyl-3-oxo-2,3,6,7-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidin-8-ium chloride or bromide. The former is readily hydrolyzed in 95% ethanol to 3-[(3-methylamino)propyl]-1,3-thiazolidine-2,4-dione hydrochloride while the second is more stable towards hydrolysis such that the corresponding hydrobromide is not separated. A paradoxical trend in the extent of the hydrolysis decreasing with the content of the water in the alcoholic solution comes to a complete stop in water. A possible explanation of this phenomenon is given.

Keywords: 1-methyltetrahydropyrimidine-2(1H)-thione (N-methylpropylenethiourea), alkylation with chloro and bromoacetic acids and their esters.

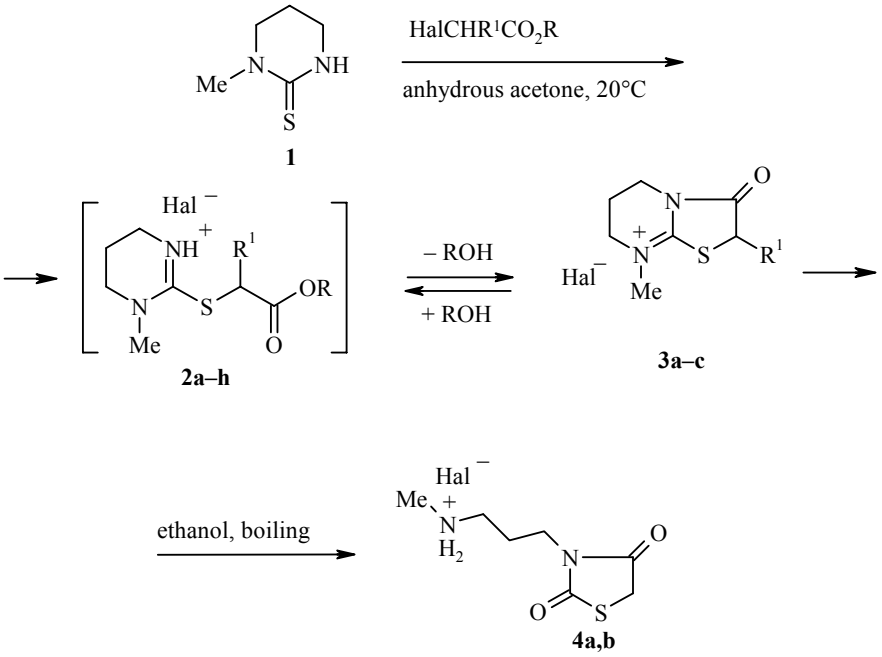
The reaction of tetrahydropyrimidine-2(1H)-thione (propylenethiourea) with α-halocarboxylic acids gives only the bicyclic thiazolo[3,2-*a*]pyrimidine hydrohalide structures [2-5]. As a result of alkylation with ethylbromo or ethylchloroacetate under "mild" conditions (room temperature in anhydrous acetone) it was possible to prepare "open" S-carbethoxymethyl propylenethiourea hydrohalide derivatives [5]. It was expected that the presence of an N-methyl substituent in the 1-methyltetrahydropyrimidine-2(1H)-thione molecule (**1**) would hinder the cyclization of the isothiouronium salts **2a-h** which were formed when alkylating with α-halocarboxylic acids and their esters. However, it was found that these salts are labile under the indicated "mild" conditions and are readily cyclized to the corresponding 6,5-bicyclic compounds **3a-c**.

Holding compound **1** with chloroacetic acid or its esters in anhydrous acetone at room temperature for from several hours to several days gave either a crystalline precipitate or an oil which crystallized on standing in vacuo over P_2O_5 or was self generating after several days (in the case of the butyl ester after 5 months). According to ^{1}H NMR and mass spectrometric data one and the same substance having the bicyclic structure 8-methyl-3-oxo-2,3,6,7-tetrahydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-8-ium chloride (**3a**) was formed in all

* For Communication 3 see [1].

[1] St. Petersburg State Technical University, St. Petersburg 198013, Russia; e-mail: gsramsh@mail.wplus.net. [2] Genoa State University, Genoa, Italy; e-mail: belobrzeckaja@libero.it. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1242-1251, August, 2006. Original article submitted August 2, 2005.

cases. In fact, the mass spectrum showed a "molecular ion" peak corresponding to the cation with *m/z* 171. The ^{1}H NMR spectrum in DMSO-d_6 also corresponded to structure **3a** and strongly recalled that of the desmethyl analog [5] with the exception of a small shift to lower field of the signal for the two H-2 protons (4.39 instead of 4.15 ppm) and this might be explained by the greater positive charge on the sulphur atom in the mesomeric cation **3a** when compared with its desmethyl analog.



2 a-d Hal = Cl, **e-h** Hal = Br; **a**,**e** R = R^1 = H, **b**,**f** R = Me, R^1 = H, **c**,**g** R = Et, R^1 = H, **d**,**h** R = Bu, R^1 = H; **3 a** Hal = Cl, R^1 = H; **b** Hal = Br, R^1 = H, **c** Hal = Br, R^1 = Et; **4 a** Hal = Cl, **b** Hal = Br

The initial formation of oily materials can be explained by the comparable rates of the alkylation and cyclization stages and the low solubility in acetone of the products of these stages (the hypothetical monocyclic intermediate compounds **2a-d** and the final bicycle **3a** which simultaneously fall out of the reaction mixture). In the subsequent step the oil containing the bicycle **3a** plus the intermediate compound **2** itself cyclizes and this aids the crystallization.

When bromoacetic acid, its methyl ester, or 2-bromobutanoic acid are used as alkylating agent there are rather rapidly produced in the reaction mixture well formed crystals of 8-methyl-3-oxo-2,3,6,7-tetrahydro-5H-[1,3]thiazolo[3,2-*a*][pyrimidin-8-ium bromide (**3b**) or its 2-ethyl derivative **3c**, i.e. the difficulty in crystallization of the initially produced oily precipitate did not arise (as was the case for the alkylation with chloroacetic acid and its derivatives). It can be proposed that the ease of separation of the bicyclic bromides **3b** and **3c** is due both to the greater rates of both process stages, i.e. the substrate **1** alkylation thanks to the greater rate constant for the alkylation with the bromo derivatives when compared with chloro derivatives and also the subsequent stage of cyclization of the intermediate compounds **2e,f,h** thanks to their greater concentration as a result of higher rate of build up and greater solubility when compared with the intermediate compounds **2a-d**. Also contributing is the greater time they exist in solutions of the first thanks to their higher solubility and longer time for cyclization in the solution state. Our data for the alkylation of homologous cyclic thioureas [1, 5, 6] also supports the greater solubility of the bromides than the analogous chlorides. In those cases where the

intermediate hydrobromides **2e** and **2g** still fall out of the reaction mixture (see below) they form well defined crystals and not "oil up" the precipitate formed from the reaction mixture thanks to their relatively high concentration in solution.

Crystals of the bicycle **3b** are very hygroscopic and upon standing in air they "deliquesce". The ^{1}H NMR spectrum in DMSO-d_6 points to the formation of a hydrate.

In one of the experiments the alkylation of substrate **1** by bromoethyl acetate at room temperature in acetone gave a mixture of crystal forms from which it was possible to separate mechanically the crystals of the bicyclic compound **3b** and of the intermediate monocyclic derivative **2g**. Refluxing the mixture of crystals in ethanol gave "complete" cyclization of derivative **2g** to bicycle **3b** but the separated material also contained 11% of the hydrobromide **4b** (see below).

The bicyclic derivative **3a** proved to be very sensitive to residual water in such solvents as DMSO-d_6* or rectified alcohol. Thus even with gentle and short heating in DMSO-d_6 in an NMR spectrometer ampule (with the aim of solubilizing the sample) it starts to undergo transformation to 3-[(3-methylamino)propyl]-1,3-thiazolidine-2,4-dione hydrochloride (**4a**), the content of which can reach 20%. When the oily compound **3a** crystallizes after some months the crystallized material contains up to 15-20% of compound **4a** admixture, either through increase in solvent water or *via* traces of moisture absorbed by the hygroscopic oil.

An attempt to recrystallized compound **3a** from ethanol gave almost complete (~ 90% from NMR spectroscopic data) conversion to the hydrochloride **4a** which gave almost pure compound **4a** after a second "recrystallization". It was not surprising that refluxing compound **3a** for 1-2 h in ethanol also gave full conversion to the 2,4-thiazolidinedione derivative **4a**.

The formation of the thiazolidione derivative **4a** *via* hydrolysis of the 6,5-bicycle **3a** was quite unexpected because its N-desmethyl analog did not give a similar reaction [5], in contrast to the corresponding bicyclic seven (7,5-bicycle) and five (5,5-bicycle) cyclic thioureas for which this is typical [1, 6]. The structure of compound **4a** was confirmed by ^{1}H NMR and mass spectrometric data. The mass spectrum shows a molecular ion corresponding to the free base with *m/z* 188. The position of the signals in the ^{1}H NMR spectrum of compound **4a** are virtually the same as in the spectra of the thiazolidinedione derivatives prepared from 5,5- and 7,5-bicycles [1, 6]. The structure of the first of these has been proved in [2] by a counter synthesis.

The reasons for the relative hydrolytic lability of the tetrahydropyrimidine ring in the bicycle **3a** when compare with its N-desmethyl analog can be both steric hindrance of the first and also an alternative distribution of positive π-charge in the mesomeric bicyclic cation of compound **3a**, more favoring hydrolysis which likely occurs by a mechanism which is a reverse of the mechanism of the formation of a carbeneimmonium ion in the Mannich reaction [7].

The readiest transformation of **3a** to **4a** occurs upon refluxing for 1 h in rectified alcohol with an approximately 5% water content. Strange though it may seem, an increase in the water content (ethanol–water, 9:1 by volume) and at the same and even several times greater duration of hydrolysis caused a marked decrease in the degree of hydrolysis of the **3a** to **4a** conversion and this was supported by the NMR spectroscopic data of the samples separated from the hydrolysates*[2]. Additionally, acidification with dilute HCl did not affect the

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* The hydrolysis in DMSO-d_6 of compound **3a**, obtained by alkylation of substrate **1** with chloroacetic acid possible occurs because of the content in the sample of crystallization (hydrate) water. Even though the alkylation occurs in anhydrous acetone and the obtained oil crystallizes either under a layer of solvent or over P_2O_5 and only sometimes in air, water is formed in the reaction of **2a** to **3a**.

*[2] It is possible that these experiments on the composition of the samples separated from the hydrolysates (the **4a**/**3a** ratio) also relate to an increase in the solubility of the hydrolysis product **4a** in aqueous alcohol. If it falls out of rectified alcohol spontaneously then its separation from aqueous alcohol needs evaporation of the solvent to dryness and, in the dry state, it occurs in a mixture with unhydrolyzed hydrochloride **3a**.

degree of hydrolysis. Even more surprising is the fact that after refluxing compound **3a** in water for 3 h the oily sample obtained contained a mixture of compounds **3a** and **4a** with the former predominating. Hence the available data clearly do not tie up. The hydrolysis occurs in nonaqueous solvents containing a small amount of water but increasing the water content up to "pure" water for the same reaction time caused a decrease in the degree of hydrolysis. The reasons could be either a slow hydrolysis in "pure" water because of a decrease in the concentration of the hydrolysing structure **3a** or (if the transition between structures **3a** and **4a** is an equilibrium) a shift of the equilibrium to the hydrated bicycle form **3a**, differing from compound **4a**. In our opinion, independently of kinetic (rate) or thermodynamic (equilibrium) reasons the basis for the observed paradox occurring in water is an almost complete hydration of bicycle **3a** to the "open" monocyclic derivative **2a**. The available synthetic and spectroscopic facts confirm this proposal.

In fact, the spectrum of the bicycle **3a** in D_2O has nothing in common with the spectrum of compound **4a** in the same solvent. After heating a solution of the bicycle **3a** in D_2O for 30 min at 80-90°C in the NMR spectroscopy ampule the spectrum was virtually unchanged. No new signals appeared and the only loss was the signal for the methylene protons of the $SCH_2C(O)$ fragment at 4.30 ppm which is explained by proton exchange with the solvent (deuterium exchange) thanks to acid catalyzed enolization of this fragment [1, 5]. The spectrum of the bicycle **3a** recorded in D_2O differs from that in DMSO-d_6, remarkably recalling the spectrum of the N-desmethyl analog of the proposed derivative **2a** as do the spectra of the 5- and 7-membered homologs of the indicated analog [5, 6, 1]. In fact, the protons of the two methylene groups joined to the nitrogen atoms resonate in D_2O at a single frequency of 3.81 ppm while in DMSO-d_6 they absorb at different frequencies (3.80 for H-7 and 3.69 ppm for H-5). Evidently, despite the structural asymmetry, as a result of the presence of an N-methyl group, the positive π-charge in the mesomeric isothiouronium fragment of the proposed compound **2a** is distributed almost symmetrically across both nitrogen atoms such that the signals for both NCH_2 groups are close together.

The "open" hydrated form **2a**, however, cannot be separated from the solution in a pure state since it undergoes reversible dehydration to bicycle **3a** in the absence of an aqueous environment.

We attempted to develop a preparative, single stage method for the synthesis of compound **4a** by alkylation of substrate **1** with chloroacetic acid or its ethyl ester in refluxing ethanol. As a result of both experiments there are formed poorly crystallizing brown colored oils. According to their NMR spectroscopic data they contain mainly compound **4a** with a small amount of the bicycle **3a**. Crystallization of the oil, prepared by alkylation with the ester, from ethanol gave the crystalline hydrochloride **4a** with traces of the bicycle **3a**.

In contrast to the bicyclic hydrochloride **3a** the hydrobromide **3b** has a much lower tendency to further transformation to the corresponding thiazolidinedione derivative. In fact, it can not only be recrystallized from ethanol but it crystallized virtually unchanged from ethanol after being refluxed for up to 18 h in this solvent. After refluxing a mixture of compounds **2g** and **3b** (see above) for 2 h the content of the **4b** hydrobromide did not exceed 11%. The stability of the hydrobromide **3b** towards hydrolysis by "ethanolic" water is also shown by the possibility of preparing it *via* alkylation with bromoacetic acid in refluxing ethanol.

The appearance of the ^1H NMR spectrum of hydrobromide **3b** in DMSO-d_6 did not alter with moderate heating or when the sample was allowed to stand for two months. None the less, the dry residue obtained after refluxing compound **3b** in 90% ethanol for 4 h showed about 33% of the thiazolidinedione derivative **4b** along with the starting compound **3b** although the former could not be prepared in a pure state. Acidification of the reaction mixture with 1N HCl did not increase the degree of hydrolysis.

The lower tendency for the **3b** to **4b** transition when compared with **3a** to **4a** may be connected with a process kinetics, i.e. with a lower rate of this transition due to a decrease in the rate constant with exchange of chloride by bromide ion or to a lower concentration of the hydrolyzing structure **3b** (because of a greater shift of the **3b** to **2e** equilibrium towards the proposed hydrate form **2e**). It could also be related thermodynamically thanks to the already reported tendency of bicycle **3b** to hydration to the aminoacid derivative **2e** also under

conditions where the transition between **3b** and **4b** is an equilibrium. The possibility of recrystallizing compound **3b** from ethanol may be partially due to the marked solubility of the thiazolidinedione derivative in this solvent.

This proposal for the greater tendency of the bicyclic bromide **3b** when compared to the analogous chloride **3a** towards hydration to the corresponding carboxymethyl derivative i.e. the greater relative stability of **2e** when compared with **2a** is indirectly confirmed by the discovery in several "fresh" samples obtained by alkylation of substrate **1** with bromoacetic acid of 25-45% of the carboxymethyl derivative **2e*** along with the bicycle **3b**. In fact, the ^{1}H NMR spectra of such samples in DMSO-d_6 appear as the superposition of two sets of signals, the first of which is from the bicycle **3b** and the second can be assigned to the carboxymethyl derivative **2e** on the basis of the following observation. "Mixed" samples are converted to the pure compound **3b** either spontaneously on standing for several days or after heating at 77°C in vacuum for several hours. The spectrum of one of the "mixed" samples in D_2O, as is the spectrum of the other in DMSO-d_6 after the addition of D_2O to the ampule, is assigned not to a mixture of compounds but to a pure compound, most likely to the carboxymethyl derivative **2e** to which the bicycle **3b** is completely converted in water or in aqueous DMSO-d_6. These spectra are virtually coincident with the spectrum of bicycle **3a** in D_2O, where, as we have proposed, it occurs as the hydrated form **2a**, differing from compound **2e** only in its anion.

The greater stability towards hydrolysis for the thiazolidinedione derivative of the bicyclic hydrobromide when compared with the hydrochloride was also supported by data obtained for the N-desmethyl 7,5- and 6,5-bicyclic homologs of compounds **3a** and **3b** [1, 5].

The alkylation of compound **1** by 2-bromobutanoic acid gave the 2-ethyl-8-methyl-3-oxo-2,3,6,7-tetrahydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-8-ium bromide (**3c**).

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker DPX-300 (300 MHz) and AM-200 (200 MHz) instruments with TMS as internal standard. IR spectra were taken on a UR-20 instrument for a thin layer. The mass spectra of compounds **3a** and **4a** were recorded on a Finnigan MAT Incos 50 instrument (EI, 70 eV). TLC was performed on Silufol UV-254 plates using butyl acetate–ethanol–chloroform (1:10:100) and ethanol–chloroform (1:10) systems. Anhydrous acetone was prepared by method [8].

1-Methyltetrahydropyrimidine-2(1H)-thione (1) was prepared by method [9] as proposed for the preparation of 2-imidazolidinethione. Yield 40%; mp 121-122°C (mp 123°C [10]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.70 (1H, s, NH); 3.33 (2H, *J* = 6, H-6); 3.25 (3H, s, CH_3); 3.15 (2H, m, H-4); 1.92 (2H, m, H-5).

8-Methyl-3-oxo-2,3,6,7-tetrahydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-8-ium Chloride (3a). A. Chloroacetic acid (0.614 g, 6.5 mmol) was added with vigorous stirring to a mixture of N-methylpropylenethiourea **1** (0.651 g, 5.0 mmol) in anhydrous acetone (20 ml) and the reaction mixture was left for 4 days at room temperature. The liquid phase was decanted from the oil formed with dispersed crystals which was placed in a vacuum desiccator over P_2O_5. After 1 week it had crystallized as a "solid like" mass. Yield 0.310 g (30%); mp 118-120°C. IR spectrum (thin layer), ν, cm^{-1}: 1750 (C=O), 1650 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.39 (2H, s, 2H-2); 3.71 (2H, t, *J* = 5, 2H-7)*[2]; 3.64 (2H, t, *J* = 5, 2H-5)*[2]; 3.36 (3H, s, NCH_3); 2.08 (2H, m, 2H-6). Mass spectrum, *m/z* (I_{rel}, %): 173 [M^++2] (2.0), 172 [M^++1] (1.5), 171 [M]$^+$ (4.0). Found %: C 40.63; H 5.42; N 13.54. $C_7H_{11}ClN_2OS$. Calculated, %: C 40.68; H 5.36; N 13.55.

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* The possible detection of compound **2e** may be connected with its build up in the reaction mixture thanks to the relatively high formation rate constant and rather low rate of subsequent cyclization.

*[2] The signals were sensitive to the presence of water in the sample and/or the DMSO-d_6.

B. Methyl chloroacetate (0.541 g, 0.44 ml, 5.0 mmol) was added with vigorous stirring to a mixture of compound **1** (0.495 g, 3.8 mmol) in anhydrous acetone (20 ml) and the reaction mixture was held for 4 days at room temperature. The liquid phase was decanted from the formed oil which was placed in a vacuum desiccator over P_2O_5 where it crystallized after 2 days. After 4 days a crystalline precipitate formed in the liquid phase and it was filtered off and washed on the filter with anhydrous acetone. Overall yield 0.453 g (58%). The ^{1}H NMR spectra of both samples were identical.

C1. Ethyl chloroacetate (0.614 g, 0.53 ml, 5 mmol) was added with vigorous stirring to a mixture of compound **1** (0.495 g, 3.8 mmol) in anhydrous acetone (15 ml) and the reaction mixture was held at room temperature for 1 day. The liquid phase was decanted from the oil which was placed in a vacuum desiccator over $CaCl_2$ where it crystallized after 2 months. The ^{1}H NMR spectrum of the freshly prepared oil corresponded to the structure proposed. Yield 0.403 g (51%).

C2. Compound **1** (2.84 g, 0.022 mol) was dissolved in anhydrous acetone (75 ml) at room temperature and ethyl chloroacetate (3.43 g, 2.96 ml, 0.028 mmol) was added with vigorous stirring. After 4 week the yellowish crystalline aggregate formed at the bottom of the reaction vessel was filtered off and washed with acetone (3 × 10 ml). At the end of the washing the crystals began to "settle out" directly on the filter. The oily mass was dried in vacuo over P_2O_5 for several days until it "solidified". ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.30 (2H, s, 2H-2); 3.81 (2H, t, *J* = 5, 2H-7)*; 3.70 (2H, t, *J* = 5, 2H-5)*; 3.40 (3H, s, NCH_3); 2.14 (2H, m, 2H-6). ^{1}H NMR spectrum (D_2O), δ, ppm (*J*, Hz): 4.40 (2H, s, 2H-2); 3.79 (4H, t, *J* = 5, 2H-7,5); 3.42 (3H, s, NCH_3); 2.23 (2H, m, 2H-6). The spectrum in D_2O is apparently corresponding the "open" form **2e**.

Both spectra showed the presence of signals for about 4% of the thiazolidinedione **4a** as an admixture. It did not increase in D_2O upon heating the ampule for 30 min at 80°C. The signal for the SCH_2 group protons of the major component after heating was present at trace levels. Yield 3.09 g (68%).

8-Methyl-3-oxo-2,3,6,7-tetrahydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-8-ium Bromide (3b). A1. Bromoacetic acid (1.04 g, 7.5 mmol) was added with vigorous stirring to a mixture of compound **1** (0.599 g, 4.6 mmol) in anhydrous acetone (10 ml) after which the reaction mixture was stirred at room temperature for a further 20 min. The precipitate formed was filtered off and washed with anhydrous acetone (2 × 5 ml). Yield 0.97 g (84%); mp 95-97°C. IR spectrum (thin layer), ν, cm^{-1}: 1750 (C=O); 1650 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.37 (2H, s, 2H-2); 3.78 (2H, t, *J* = 5, 2H-7); 3.68 (2H, t, *J* = 5, 2H-5); 3.39 (3H, s, NCH_3); 2.14 (2H, m, 2H-6). Found, %: C 33.53, H 4.41; N 11.08. $C_7H_{11}BrN_2OS$. Calculated, %: C 33.48; H 4.41; N 11.15.

A2. Prepared similarly to method A1 from compound **1** (1.0 g, 7.7 mmol) and bromoacetic acid (1.39 g, 10 mmol) in anhydrous acetone (46 ml). The ^{1}H NMR spectrum of the precipitate in DMSO-d_6 showed superposition of the signals of two substances, *viz*. the bicyclic bromide **3b** and a substance which was assigned the "open" structure **2e**. The set of ^{1}H NMR signals for compound **2e** in DMSO-d_6 solvent were, δ, ppm (*J*, Hz): 9.58 (1H, NH)*[2]; 4.27 (2H, s, SCH_2); 3.58 (2H, t, *J* = 6, 2H-6); 3.39 (2H-4 proton signal obscured by the signal for the NCH_3 group protons, bicycle **3b**); 3.31 (3H, s, NCH_3); 2.00 (2H, m, 2H-5). The "mixed" precipitate was heated for 3 h in a vacuum pistol at 77°C (CCl_4), after which its ^{1}H NMR spectrum in DMSO-d_6 corresponded to compound **3b**. Yield 1.70 g (88%). The ^{1}H NMR spectrum (DMSO-d_6) of the "mixed" precipitate recorded after several days following its preparation also corresponded to compound **3b**. The ^{1}H NMR spectrum (D_2O) of the "mixed" precipitate (evidently corresponding to compound **2e** showed, δ, ppm (*J*, Hz): 4.31 (2H, s, SCH_2); 3.80 (4H, m, 2H-4,6); 3.43 (3H, s, NCH_3); 2.23 (2H, m, 2H-5). ^{1}H NMR spectrum (DMSO-d_6 + D_2O) of the "mixed" precipitate (evidently compound **2e**) showed, δ, ppm (*J*, Hz): 4.12 (2H, s, SCH_2); 3.62 (4H, t, *J* = 5, 2H-4,6); 3.27 (3H, s, NCH_3); 2.06 (2H, m, 2H-5).

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* The signals were sensitive to the presence of water in the sample and/or the DMSO-d_6

*[2] The hydroxyl proton did not appear due to rapid exchange with residual solvent water

A3. Prepared similarly to method A1 from compound **1** (0.833 g, 6.4 mmol) and bromoacetic acid (1.45 g, 10.4 mmol) in anhydrous acetone (15 ml) with the only difference that the precipitate was filtered off after 1 day and was dried in vacuo over P_2O_5. Yield 1.53 g (95%).^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.35 (2H, s, 2H-2); 3.81 (2H, t, *J* = 5, 2H-7); 3.71 (2H, t, *J* = 6, 2H-5); 3.41 (3H, s, NCH_3); 2.18 (2H, m, 2H-6). After one day the crystals "deliquesced" and the ^{1}H NMR spectrum (DMSO-d_6) showed a signal for water of hydration at 3.36 ppm as well as the signal for residual water at 3.26 ppm.

B. Prepared similarly to method A1 from compound **1** (0.651 g, 5.0 mmol) and methyl bromoacetate (0.994 g, 0.62 ml, 6.5 mmol) in anhydrous acetone (30 ml) with the difference that the reaction mixture was held at room temperature for 1 day. Yield 0.75 g (60%).

C1. Prepared similarly to method B from compound **1** (0.495 g, 3.8 mmol) and methyl bromoacetate (0.833 g, 0.55 ml, 5.0 mmol) in anhydrous acetone (23 ml). Yield 0.102 g (11%).

C2. Prepared similarly to method C1 from compound **1** (0.651 g, 5.0 mmol) and ethyl bromoacetate (1.10 g, 0.73 ml, 6.6 mmol) in anhydrous acetone (30 ml) with the difference that the precipitate was filtered off after 1 week. Two types of crystal were observed: a course, colorless, transparent precipitate (1) and a fine, yellowish precipitate (2). ^{1}H NMR spectrum (DMSO-d_6) of precipitate 1 (corresponded with compound **2g**), δ, ppm (*J*, Hz): 9.90 (1H, NH); 4.48 (2H, s, SCH_2); 4.16 (2H, q, *J* = 7, $C\underline{H}_2CH_3$); 3.64 (2H, t, *J* = 5, 2H-6); 3.41 (2H, t, *J* = 5, 2H-4); 3.37 (3H, s, NCH_3); 2.02 (2H, m, 2H-5); 1.26 (3H, t, *J* = 7, $CH_2C\underline{H}_3$). Because of the small amount of the available crystals the melting point of precipitate 1 was not determined and the elemental analysis was not carried out. The ^{1}H NMR spectrum (DMSO-d_6) of precipitate 2 corresponded with compound **3b**. The overall yield was 0.510 g (41% based on compound **3b**).

D. Bromoacetic acid (1.28 g, 9.2 mmol) was added to a mixture of compound **1** (1.0 g, 7.7 mmol) in ethanol (10 ml) and the reaction product was refluxed for 2 h and cooled. The precipitate formed was filtered off and recrystallized from ethanol. Yield 0.343 g (18%).

2-Ethyl-8-methyl-3-oxo-2,3,6,7-tetrahydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-8-ium Bromide (3c) was prepared similarly to compound **3b** by method A1 from compound **1** (0.378 g, 2.9 mmol) and 2-bromobutanoic acid (0.627 g, 0.40 ml, 3.8 mmol) in anhydrous acetone (10 ml) with the difference that the reaction product was held at room temperature for 3 days. Yield 0.429 g (53%); mp 178-180°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.15 (1H, 2H-2); 3.90 (2H, m, 2H-7); 3.65 (2H, m, 2H-5); 3.30 (3H, s, NCH_3); 2.25 (2H, m, 2H-6); 2.00 (2H, m, $C\underline{H}_2CH_3$); 1.10 (3H, m, $CH_2C\underline{H}_3$). Found, %: C 38.38; H 5.78; N 9.57. $C_9H_{15}BrN_2OS$. Calculated, %: C 38.72; H 5.42; N 10.03.

3-[(3-Methylamino)propyl]-1,3-thiazolidine-2,4-dione Hydrochloride (4a). A. Butyl chloroacetate (1.96 g, 1.78 ml, 13 mmol) was added with vigorous stirring to a mixture of compound **1** (1.30 g, 10 mmol) in anhydrous acetone (20 ml), the reaction mixture was left at room temperature for 20 days, and then the solvent was allowed to evaporate by itself. The oily residue crystallized after 5 months. The crystalline mass obtained was twice recrystallized from ethanol. Yield 0.339 g (15%); mp 198-200°C. IR spectrum (thin layer), ν, cm^{-1}: 1700 (C=O), 2790 (N–CH_3). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.13 (2H, NH_2); 4.14 (2H, s, 2H-5); 3.58 (2H, t, *J* = 7, 2H-1'); 2.87 (2H, t, *J* = 8, 2H-3'); 2.50* (3H, NCH_3); 1.90 (2H, m, 2H-2'). ^{1}H NMR spectrum (D_2O), δ, ppm (*J*, Hz): 4.14 (2H, s, 2H-5); 3.70 (2H, t, *J* = 7, 2H-1'); 3.05 (2H, t, *J* = 8, 2H-3'), 2.70 (3H, s, NCH_3); 1.97 (2H, m, 2H-2'). Mass spectrum, *m/z* (I_{rel}, %): 190 $[M^+ + 2]$ (0.7), 189 $[M^+ + 1]$ (0.7), 188 $[M]^+$ (8.3). Found, %: C 37.40; H 5.75; N 12.40. $C_7H_{13}ClN_2O_2S$. Calculated, %: C 37.41; H 5.83; N 12.47.

B. Compound **1** (0.495 g, 3.8 mmol) was dissolved in anhydrous acetone (15 ml) at room temperature and ethyl chloroacetate (0.613 g, 0.53 ml, 5 mmol) was added with vigorous stirring. After 2 weeks the crystalline plates formed on the bottom of the reaction vessel were filtered off, washed with anhydrous acetone

* Superimposed on the signal for the residual solvent protons. The sample was poorly soluble in DMSO-d_6.

(10 ml), and dried in a vacuum for 2 h over $CaCl_2$. A yellow oil had formed after standing in a vacuum desiccator for 2 weeks and after a further 2 weeks this had turned red-orange. The oil began to crystallize after a further 2 weeks but full crystallization was not observed. Yield 0.681 g.

The obtained oil and crystal mixture was refluxed in ethanol (10 ml) for 2.5 h and after 2 days pink, needle shaped crystals were filtered off, washed with ethanol (2 × 10 ml), and dried in vacuo. Yield 0.11 g (13%).

C. Compound **3a** (0.248 g, 0.0012 mol) was refluxed in ethanol (5 ml) for 45 min, the solvent was evaporated in a stream of warm air at atmospheric pressure, and the solid residue was recrystallized from ethanol. Yield 0.138 g (51%).

D. N-methylpropylenethiourea (**5**, 2.6 g, 20 mmol) was dissolved with heating in ethanol (50 ml), ethyl chloroacetate (3.19 g, 2.75 ml, 26 mmol) was added, and the product was refluxed for 1 h. After 5 days the solvent was evaporated in a stream of warm air to give a yellow oil (5.23 g) containing dispersed crystals. After 6 weeks the oil was refluxed in ethanol (10 ml) for 30 min and the needle-like, yellowish crystals formed on cooling were filtered off, washed with ethanol (5 ml), and dried for 1 h in vacuo over P_2O_5. Yield 0.370 g (8%).

3-[(3-Methylamino)propyl]-1,3-thiazolidine-2,4-dione Hydrobromide (4b) (Attempted Preparation). A. A solution of compound **3b** (0.141 g, 0.56 mmol) in ethanol (9 ml) and water (0.5 ml) was refluxed for 4 h and the solvent was then allowed to evaporate by itself. The oil formed was placed in a vacuum desiccator over P_2O_5 where it crystallized after 2 months. Yield 0.134 g. The ^{1}H NMR spectrum of the sample obtained was a superposition of the signals for compound **3b** and the proposed **4b**. The content of **4b** in the sample was 33%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.73 (2H, NH_2); 4.14 (2H, s, 2H-5); 3.60 (2H, t, *J* = 7, 2H-1'); 2.91 (2H, t, *J* = 7, 2H-3'); 2.54 (3H, t, *J* = 7, NCH_3); 1.92 (2H, m, 2H-2).

B. The experiment was carried out similarly but acidifying the reaction mixture with one drop of 1N HCl. Yield 0.133 g. The content of compound **4b** in the obtained "mixed" sample was 28%.

C. The crystalline mass from experiment C2 (0.3 g) for preparing compound **3b** in ethanol (10 ml) was refluxed for 2 h after which the solvent was evaporated in a stream of warm air. The dark-brown oily residue changed to a hardened mass after 3 weeks and was crystallized from ethanol (3.5 ml). The solid red-brown residue formed 2 days after self evaporation of solvent was dried in vacuo. Yield 0.29 g. The ^{1}H NMR spectrum of the obtained sample was a superposition of signals for compound **3b** and the proposed **4b**. The content of **4b** in the sample was 11%.

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