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NEW DATA ON THE ALKYLATION OF CYCLIC THIOUREAS WITH α-HALO-CARBOXYLIC ACIDS AND THEIR ESTERS. 3*. ALKYLATION OF BUTYLENETHIOUREAS

P. M. Kushakova[1], S. M. Ramsh[1], V. V. Lifontova[1], A. V. Garabadgiu[1], and L. N. Belobrzhetskaja Kosta[2]

The reactions of 1,3-diazepane-2-thione with α-halocarboxylic acids and their esters have been studied in detail. On alkylation of butylenethiourea with chloroacetic acid and ethyl chloro(bromo)acetate in anhydrous acetone at room temperature the hydrogen chloride of the S-carboxymethyl and the hydrogen halides of the S-ethoxycarbonylmethyl derivatives respectively of the cyclic substrate were formed initially. When butylenethiourea was alkylated with chloroacetic acid in boiling ethanol in the presence of sodium acetate the neutral (zwitterionic) form of its S-carboxymethyl derivative was also formed. Our results and the literature data on the alkylation of 5-, 6-, and 7-membered cyclic thioureas with α-halocarboxylic acids and their esters have been reviewed and interpreted.

Keywords: 1,3-diazepane-2-thione (butylenethiourea), reactions with α-halocarboxylic acids and their esters.

Only a single paper [2] has reported the alkylation of 1,3-diazepane-2-thione (**1**) with chloroacetic acid. The reaction of these components in water on boiling gave the hydrogen chloride of 3-(4-aminobutyl)-2,4-thiazolidinedione (**2**). There was no mention of the formation of any S-substituted derivatives of butylenethiourea **1** in this paper.

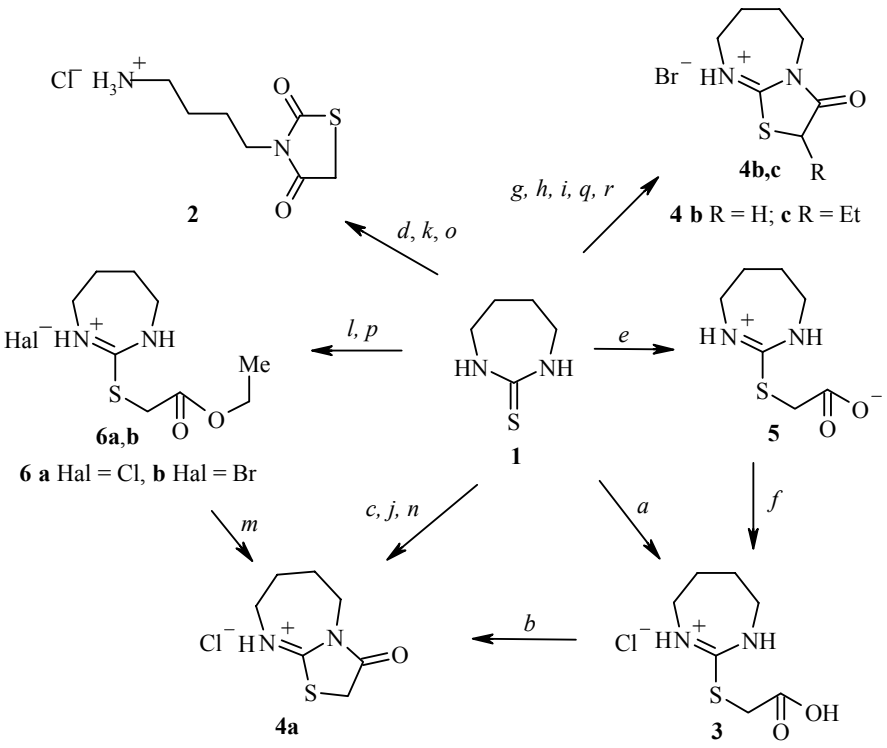
We have established that alkylation of butylenethiourea **1** with chloroacetic acid in anhydrous acetone at room temperature gave the S-substituted derivative – the hydrogen chloride of (4,5,6,7-tetrahydro-1H-1,3-diazepin-2-ylthio)acetic acid (**3**) (route *a*). Heating a solid sample of compound **3** at 100°C for 8 h in vacuum gave a bicyclic compound – the hydrogen chloride of 5,6,7,8-tetrahydro[1,3]thiazolo[3,2-*a*][1,3]diazepin-3(2H)-one (**4a**) (route *b*).

When butylenethiourea **1** was alkylated with chloroacetic acid in boiling 96% ethanol, the product of the reaction depended on the initial concentration of the cyclic substrate **1**. If the concentration was relatively large (~1 mol/l), the bicyclic compound **4a** was isolated (route *c*), whereas if it was relatively small (~0.15 mol/l) only thiazolidinedione **2** was isolated (route *d*). This is completely understandable since the latter is the product of the hydrolytic splitting of compound **1**.

* For part 2, see [1].

[1] St. Petersburg State Technological Institute, 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. 6, 940-948 , June, 2006.

Reactions occurring during the interactionof butylenethiourea
1 with α-halocarboxylic acids and their esters



a – $ClCH_2CO_2H$/anhydrous acetone, 20°C; *b* – heated at 100°C with no solvent; *c* – $ClCH_2CO_2H$ / ethanol, boiling; *d* – $ClCH_2CO_2H$ / ethanol, boiling; *e* – $ClCH_2CO_2H$, $MeCO_2Na$ / ethanol, boiling; *f* – HCl(aq) / ether, ethanol, 20°C; *g* – $BrCH_2CO_2H$ / anhydrous acetone, 20°C; *h* – $EtBrCH(Br)CO_2H$ / anhydrous acetone, 20°C; *i* – $BrCH_2CO_2H$ / ethanol, 20°C; *j* – $ClCH_2CO_2Et$ / without solvent, boiling; *k* --$ClCH_2CO_2Et$ / ethanol, boiling; *l* – $ClCH_2CO_2Et$ / anhydrous acetone, 20°C; *m* – **6a**, heated at 100°C without solvent; *n* – $ClCH_2CO_2Bu$ / anhydrous acetone, 20°C; *o* – $ClCH_2CO_2Bu$ / ethanol, boiling; *p* – $BrCH_2CO_2Et$ / anhydrous acetone, 20°C; *q* – $BrCH_2CO_2Et$ / without solvent, boiling; *r* – $BrCH_2CO_2Et$ / ethanol, boiling.

Using the method for alkylation of 2-imidazolidinethione (ethylenethiourea) [3], we treated butylenethiourea **1** with chloroacetic acid in ethanol in the presence of sodium acetate and obtained the zwitterionic (4,5,6,7-tetrahydro-1H-1,3-diazepin-3-yl-2-thio)acetate **5** (route *e*) which was then converted into the hydrochloride **3** by treatment with hydrochloric acid (route *f*). Apparently the isolation of individual S-substituted compounds of zwitterionic type on alkylation in weakly acidic media (chloroacetic acid and sodium acetate) is possible as a result of the difficulty of cyclizing it because of the strain in the bicyclic compound, since this cyclization is only possible for 5-membered ethylenethioureas [4] (5,5-bicycles) and 7-membered butylidenethioureas **1** (7,5-bicycles). Alkylation of 6-membered propylenethioureas with chloroacetic acid under similar conditions led to a mixture of compounds which was difficult to separate [1] apparently because of the relatively easy cyclization of the corresponding S-substituted monocyclic compound thanks to the great stability of the 6,5-bicycle.

Only the hydrobromide of 5,6,7,8-tetrahydro[1,3]thiazolo[3,2-*a*][1,3]diazepin-3(2H)-one (**4b**) was obtained from the reaction of butylidenethiourea **1** with bromoacetic acid in anhydrous acetone at room temperature (route *g*). Alkylation of substrate **1** with 2-bromobutanoic acid under the same conditions also gave only the hydrobromide of the bicyclic 2-ethyl-5,6,7,8-tetrahydro[1,3]thiazolo[3,2-*a*][1,3]diazepin-3(2H)-one (**4c**) (route *h*). Thus substitution of the halogen in the alkylating agent affects the nature of the compound produced: the monocyclic carboxymethyl derivative **3** was obtained in the case of chloroacetic acid, whereas the

bicyclic compounds **4b,c** were obtained in the case of α-bromocarboxylic acids. It is possible that two factors are involved here: the rate of alkylation and solubility. The rate of alkylation is much faster in the case of bromine than in the case of chlorine, and the *f* relatively more rapidly formed hydrobromide of the monocyclic product succeeds in cyclization (*via* the corresponding non-zwitterionic neutral form) leading to precipitation from the reaction mixture, whereas the more slowly formed and less soluble hydrochloride **3** precipitates immediately after its formation.

The effect of the nature of the halogen on the rate of cyclization caused by ionic association, might also be expected if the cyclizing particle was the N-protonated form, but this is contrary to the known mechanism of amide formation[5]. Nevertheless ionic association may play a role in these reactions by affecting the solubility of the hydrohalides: the more associated hydrochlorides may be less soluble in comparison with the hydrobromides.

Alkylation of butylidenethiourea **1** with bromoacetic acid in ethanol at room temperature also gave only the bicyclic compound **4b** (route *i*), whereas on boiling in the same solvent for 2 h gave, according to the ^{1}H NMR spectrum, the hydrobromide of thiazolidinedione (not shown on the scheme) and the bicycle **4b** in a 2:1 ratio.

The alkylation of butylidenethiourea **1** with ethyl chloroacetate and ethyl 2-bromopropionate without solvent was reported [2] to give the bicyclic hydrochloride **4a** and the hydrobromide of its 2-methyl analog respectively. We repeated the first of these syntheses and indeed obtained the bicycle **4a** (route *j*). However, if the reaction with ethyl chloroacetate was carried out by boiling in 96% ethanol thiazolidinedione **2** was formed (route *k*), and in anhydrous acetone at room temperature the hydrochloride of the monocyclic ethyl (4,5,6,7-tetrahydro-1H-1,3-diazepin-2-ylthio)acetate (**6a**) was formed (route *l*). Heating a solid sample of compound **6a** at 100°C in vacuum gave, as in the case of the carboxyl analog **3**, the bicyclic derivative **4a** (route *m*), however the tendency to cyclize is much less: after 8h the conversion of **6a** to **4a** was about 25% according to the ^{1}H NMR data. When a sample was kept in DMSO-d_6 the extent of cyclization was only 30% after 3h at 80°C.

Only the bicyclic compound **4a** (route *n*) was isolated with butyl chloroacetate in anhydrous acetone at room temperature. When the reaction was carried out in boiling ethanol the product was thiazolidinedione **2** (route *o*).

Finally, butylidenethiourea **1** and ethyl bromoacetate in anhydrous acetone at room temperature formed the monocyclic hydrobromide of ethyl (4,5,6,7-tetrahydro-1H-1,3-diazepin-2-ylthio)acetate **6b** (route *p*), whereas on boiling without solvent or boiling in ethanol they gave the bicyclic hydrobromide of **4b** (routes *q* and *r* respectively). From a comparison of alkylation of compound **1** with chloro- (route *d*) and bromoacetic acid in boiling ethanol, and routes *r* and *k*, it can be concluded that the bicyclic hydrobromide **4b** is more stable to hydrolysis in comparison to the bicyclic hydrochloride **4a**.

In contrast to the analogous hydrochloride **6a**, the "open" hydrobromide **6b** showed practically no thermal conversion into the bicyclic derivative at 100°C in vacuum for a comparable time, which also indicates the important influence of the nature of the anion (chloride or bromide) on conversions of these compounds.

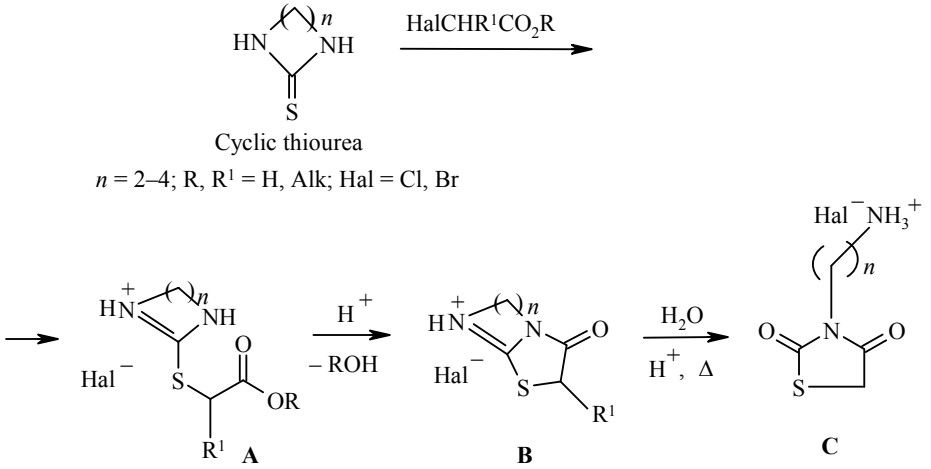
By comparing the results obtained with date on the alkylation of 2-imidazolidinethione (ethylenethiourea) [4] and tetrahydropyridimidin-2(1H)-thione (propylenethiourea) [1] with α-halocarboxylic acids and their esters, definite generalities in the behavior of 5-membered ethylenethioureas and 7-membered butylidenethioureas can be discerned, which differentiate them from the behavior of 6-membered propylenethioureas in these reactions. These generalities include the following:

– alkylation of 5- and 7-membered cyclic thioureas with chloroacetic acid in boiling ethanol in the presence of sodium acetate (weakly acidic conditions) leads to the formation of zwitterionic compounds of type **5**, which can be converted into the corresponding hydrochlorides of type **3** by treatment with HCl;

– hydrochlorides of monocyclic S-carboxymethyl derivatives of type **3** were isolated from both cases on alkylation with chloroacetic acid in anhydrous acetone at room temperature;

– alkylation with chloroacetic acid or its esters in boiling ethanol led in both cases to formation of the corresponding 2,4-thiazolidinediones of type **2**.

These generalizations and analysis of the results of this and our previous studies [1, 4], and also of the literature data, confirm the following sequence of conversions during the alkylation of cyclic thioureas with bifunctional alkylating agents – α-halocarboxylic acids and their esters:



1) In the first stage of the process a S-substituted monocyclic ("open") derivative **A** is formed, which can be isolated when the reaction is carried out in anhydrous acetone: in the cases of the 5-membered (2-imidazolidinethione) [4] and 7-membered (1,3-diazepane-2-thione) compounds on alkylation with either the halocarboxylic acids or their esters; in the case of C-substituted 6-membered thioureas (5,5-dimethyltetrahydro-2(1H)-pyrimidinethione) [1] – only on alkylation with acids, and in the case of unsubstituted 6-membered thioureas (tetrahydro-2(1H)-pyrimidinethione) [1] only on alkylation with esters.

2) Then the "open" derivative **A** can cyclize into the bicyclic compound **B** spontaneously (6-membered tetrahydro-2(1H)pyrimidinethione and 5,5-dimethyltetrahydro-2(1H)-pyrimidinethione [1]) or under the influence of thermal activation and a specially added acid catalyst (5-membered 2-imidazolyldithione [4]); monocyclic derivatives of 7-membered 1,3-diazepane-2-thione take an intermediate position in respect to their tendency to cyclize. In all cases with specially chosen conditions for carrying out the process, the bicyclic derivatives **B** may be isolated with varying degrees of difficulty from the reaction mixture: most readily in the case of tetrahydro-2(1H)-pyrmidinethione (6,5-bicycle) [1] and with the greatest difficulty in the case of 2-imidazolidinethione (5,5-bicycle) [4].

3) In the third stage of the process the bicyclic compound **B**, because it is a salt of a Schiff's base, may undergo hydrolysis if water is present in the reaction medium to give a derivative of 2,4-thiazolidinedione **C**, the final product in the chain in the reaction under discussion. The tendency to hydrolytic breakdown with formation of the 2,4-thiazolidinedione **C** is clearly expressed in the bicyclic derivatives of 2-imidazolinethione (5,5-bicycles) [4] and 1,3-diazepane-2-thione (7,5-bicycle), whereas for effective rupture of the azomethine unit C=N in the bicyclic compound **B** the medium must be acidic enough and vigorous conditions must be employed (boiling). The bicyclic derivatives of tetrahydro-2(1H)-pyrimidinethione and 5,5-dimethyltetrahydro-2(1H)-pyrimidinethione (6,5-bicycles) are sufficiently stable to hydrolysis that the 2,4-thiazolidinedione derivatives **C** corresponding to them were not obtained [1].

Thus as a result of alkylation of 5-membered ethylenethioreas [4] and 7-membered butylidenethioureas under corresponding reaction conditions one may obtain any of the products of the reaction chain – "open" monocyclic derivatives of **A**, bicyclic derivatives of **B**, or derivatives of 2,4-thiazoledione **C**. As a result of alkylation of 6-membered propylenethioureas – tetrahydro-2(1H)-pyrimidinethione and 5,5-dimethyltetrahydro-2(1H)-pyrimidinethione – only two products, **A** or **B**, can be isolated [1].

The characteristics noted in the behavior of the cyclic thioureas under the reaction conditions studied which depend on the size of the rings may be explained in terms of the relative stability of one of the possible reaction products, namely the corresponding bicyclic compound **B**:

– the similarity in the behavior under the reaction conditions of ethylenethiourea [4] and butylidenethiourea, consisting in the possibility of isolating any of the three possible reaction products **A**, **B**, or **C** (n = 2,4), is a consequence of the stress in 5,5- and 5,7-bicyclic systems of type **B** which makes them difficult to form and easy to undergo acid catalysed hydrolysis;

– the impossibility of isolation of the S-carboxymethyl derivatives **A** (R = H, n = 3) in the case of tetrahydro-2(1H)-pyrimidinethione and S-alkoxycarbonylmethyl derivatives **A** (R = Alk, n = 3) in the case of 5,5-dimethyltetrahydro-2(1H)-pyrimidinethione, as equally for the corresponding derivatives of 2,4-thiazolidinedione **C** (n = 3) [1], is in complete accord with the relatively high stability of the 6,5-bicyclic systems **B** (n = 3) in comparison with the 5,5- and 7,5-bicyclic systems **B** (n = 2,4), which leads to a high rate of cyclization of the "open" monocyclic derivative **A** (n = 3) to give the 6,5-bicyclic systems **B** (n =3) and the stability of the latter to hydrolysis to derivatives of 2,4-thiazolidinedione **C** (n = 3).

The difference in behavior between 5,5-dimethyltetrahydro-2(1H)-pyrimidinethione and tetrahydro-2(1H)-pyrimidinethione with respect to the possibility of isolating the S-substituted monocyclic derivative **A** (R = H, Alk, n = 3) [1] may be explained by two basic factors: 1) the slower rate of cyclization of derivative **A** into bicyclic **B** because of steric hindrance in the transition state caused by the bulky substituents in the 6-membered ring in the case of derivatives of 5,5-dimethyltetrahydro-2(1H)-pyrimidinethione; 2) differences in solubility of the monocyclic derivatives **A** in the six-membered thioureas in the reaction medium, which affects both the time the monocyclic derivative stays in solution and the concentration of the molecular form corresponding to its spontaneous cyclization into the bicycle **B**, and hence on the degree of conversion of **A** into **B**.

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions (solvent as internal standard) were recorded with Bruker DPX-300 (300 MHz) and Bruker AM-200 (200 MHz) machines. TLC was carried out on Silufol UV-254 strips 1:10:100 butyl acetate-ethanol-chloroform eluant. Anhydrous acetone was prepared as in [6].

1,3-Diazepane-2-thione (Butylenethiourea, 1) [7]. Carbon disulfide (12.6 g, 10.0 ml, 165 mmol) was added slowly dropwise and with vigorous stirring to a mixture of butanediamine (13.2 g, 150 mmol) in ethanol (25 ml) and water (25 ml). After the initial formation of a precipitate the flask was placed on a water bath and heated to 60°C. On completion of the addition of the carbon disulfide, the temperature was raised to 100°C, the reaction mixture was boiled for 1 h, hydrochloric acid (1.2 ml) was then added and boiling continued until the precipitate had dissolved completely. The reaction mixture was then cooled, the precipitate formed was filtered off, washed with cold acetone (2 × 10 ml), and recrystallized from ethanol. Yield 6.0 g (31%); mp 180-181°C (180°C [2]). ^{1}H NMR spectrum, δ, ppm: 7.65 (2H, s, NH_2); 3.10 (4H, m, 2H-4,7); 1.60 (4H, m, 2H-5,6).

Hydrochloride of 3-(4-Aminobutyl)-1,3-thiazolidine-2,4-dione (2). A (route *o*). Butylenethiourea **1** (1.30 g, 10 mmol) dissolved in ethanol (10 ml) on heating, butyl chloroacetate (1.70 g, 1.54 ml, 11 mol) was added and the mixture was boiled for 2h 30 min. The solvent was removed in vacuum, the oil obtained was triturated with acetone, and the solid was then recrystallized from ethanol. Yield 0.536 g (24%); mp 154-155°C (155°C [2]). ^{1}H NMR spectrum, δ, ppm: 8.30 (3H, s, NH_3); 4.15 (2H, s, 2H-5); 3.60 (2H, m, $C\underline{H}_2NH_3$); 2.80 (2H, m, NCH_2); 1.60 (4H, m, $NCH_2(C\underline{H}_2)_2CH_2NH_3$). Found, %: C 37.44; H 5.67; N 12.51. $C_7H_{12}N_2O_2S{\cdot}HCl$. Calculated, %: C 37.41; H 5.83; N 12.47.

B (route *k*). Butylenethiourea **1** (2.43 g, 21 mmol) dissolved in ethanol (50 ml) on heating, ethyl chloroacetate (2.57 g, 2.2 ml, 21 mmol) was added and the reation mixture was boiled for 1 h. The solvent was removed in vacuum, and the precipitate was recrystallized from ethanol. Yield 2.80 g (66%).

C (route *d*). Butylenethiourea **1** (0.979 g, 7.5 mmol) dissolved in ethanol (25 ml) on heating, chloroacetic acid (1.06 g, 11 mmol) was added, and the mixture was boiled for 2 h. The solvent was removed in vacuum, the oil obtained was triturated with acetone, and the solid formed was recrystallized from ethanol. Yield 0.738 g (44%).

Hydrochloride of (4,5,6,7-Tetrahydro-1H-1,3-diazepin-2-ylthio)acetic Acid (3). A (route *a*). Chloroacetic acid (0.709 g, 75 mmol) was added with vigorous stirring to a solution butylenethiourea **1** (0.716 g, 5.5 mmol) in anhydrous acetone (20 ml) at room temperature and kept at that temperature for 3 d. The hydrochloride formed was filtered off and washed with anhydrous acetone (2 × 5 ml). Yield 1.04 g (84%); mp 146-148°C. ^{1}H NMR spectrum: 10.34 (2H, s, NH); 4.33 (2H, s, SCH_2); 3.42 (4H, m, 2H-4,7); 1.85 (4H, m, 2H-5,6). Found, %: C 37.19; H 5.89; N 12.27. $C_7H_{12}N_2O_2S$·HCl. Calculated, %: C 37.41; H 5.83; N 12.47.

B (route *k*). Hydrochloric acid (1 ml) was added dropwise with vigorous stirring to a mixture of (4,5,6,7-tetrahydro-1H-1,3-diazepin-3-yl-2-thio)acetate (**5**) in ether (25 ml) at room temperature . The colorless oil formed on the bottom of the flask crystallized after trituration with ethanol (25 ml). The solid obtained was recrystallized from 70% ethanol. Yield 0.350 g (52%).

Hydrochloride of 5,6,7,8-Tetrahydro[1,3-thiazolo[3,2-*a*][1,3]diazepin-3(2H)-one (4a). A (route *b*). A sample of compound **3** (0,225 g, 1.0 mmol) was kept in vacumm (10-15 mm Hg) at 100°C for 7 h. Yield 0.206 g (100%); mp 235-236°C (mp 236°C [2]). ^{1}H NMR spectrum, δ, ppm: 13.2 (1H, br. s, NH); 4.21 (2H, s, 2H-2); 4.05 (2H, m, 2H-8); 3.82 (2H, m, 2H-5); 2.07 (4H, m, 2H-6,7). Found, %: C 40.70; H 5.31; N 13.60. $C_7H_{10}N_2OS$·HCl. Calculated, %: C 40.68; H 5.36; N 13.55.

B (route *m*). A sample of ethyl (4,5,6,7-tetrahydro-1H-1,3-diazepin-3-ylthio)acetate (**6a**) (0.100 g, 0.39 mmol) was kept in a vacuum (10-15 mm Hg) at 100°C for 8 h. The extent of conversion of **6a** to **4a** was 25% according to ^{1}H NMR data.

C (route *c*). Butylenethiourea **1** (1.30 g, 10 mmol) was dissolved on heating in ethanol (10 ml), chloroacetic acid (1.42 g, 15 mmol) was added to the solution which was then boiled for 3 h 30 min. The solvent was removed in vacuum and the residue was recrystallized from ethanol. Yield 0.810 g (39%).

D (route *j*). Obtained from butylenethiourea **1** and ethyl chloroacetate, as described in [2], and recrystallized from ethanol. Yield 75%.

E (route *n*). Butyl chloroacetate (1.66 g, 1.50 ml, 11 mmol) was added with vigorous stirring to a mixture butylenethiourea **1** (1.30 g, 10 mmol) in anhydrous acetone (30 ml). The reaction mixture was kept at room temperature for 2 d. The precipitate produced was filtered off and washed with acetone. Yield 0.623 g (30%).

Hydrogen Bromide of 5,6,7,8-Tetrahydro[1,3]thiazolo[3,2-*a*][1,3]diazepin-3(2H)-one (4b). A. Bromoacetic acid (0.35 g, 2.5 mmol) was added with vigorous stirring to a mixture of butylenethiourea **1** (0.30 g, 2.3 mmol) in anhydrous acetone (15 ml). The reaction mixture was kept at room temperature for 30 min after which a colorless oily precipitate formed on the walls of the flask. The precipitate which solidified over 1 day was filtered off, washed with anhydrous acetone (2 × 5 ml) and dried for 3 h in vacuum over P_2O_5. Yield 0.350 g (60%); mp 226-227°C. ^{1}H NMR spectrum, δ, ppm: 11.95 (1H, s, NH); 4.27 (2H, s, 2H-2)*; 4.07 (2H, m 2H-8); 3.84 (2H, m, 2H-5); 2.07 (4H, m 2H-6,7). Found, %: C 33.45; H 4.46; N 11.17. $C_7H_{10}N_2OS$·HBr. Calculated, %: C 33.48; H 4.41; N 11.15.

B (route *i*). Bromoacetic acid (1.20 g, 8.6 mmol) in ethanol (5 ml) was added with vigorus stirring to a mixture of butylenethiourea **1** (0.60 g, 4.6 mmol) in ethanol (5 ml). The mixture was kept at room temperature for 20 min, after which the solvent was allowed to evaporate. The oil formed crystallized over a day. The crystals were washed with anhydrous acetone (2 × 5 ml) and filtered off. Yield 0.558 g (48%).

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* To judge from the ^{1}H NMR spectrum in D_2O the methylene protons 2H-2 of the thiazolidine of hydrobromide **4b** (4.21 ppm) underwent hydrogen exchange with the solvent (deuterium exchange) apparently as a result of acid catalyzed enolization of the $CH_2C(O)$ unit.

C (route *q*). Butylenethiourea **1** (0.60 g, 4.6 mmol) dissolved on heating in ethanol (10 ml). Ethyl bromoacetate (1.15 g, 0.76 ml, 6.9 mmol) was added to this solution which was boiled for 30 min. The solvent was then allowed to evaporate and the precipitate was recrystallized from ethanol. Yield 0.349 g (30%).

D (route *r*). A mixture of butylenethiourea (1.30 g, 10 mmol) and ethyl bromoacetate (16.7 g, 11.0 ml, 100 mmol) was boiled for 15 min, the precipitate formed was filtered off and recrystallized from ethanol. Yield 1.10 g (44%).

Hydrogen Bromide of 2-Ethyl-5,6,7,8-tetrahydro[1,3]thiazolo[3,2-*a*][1,3]diazepin-3(2H)-one (4c, route *h*) was obtained from butylenethiourea **1** (0.70 g, 5.4 mmol) and 2-bromobutanoic acid (1.35 g, 0.86 ml, 8.1 mmol) in anhydrous acetone (30 ml) by a method analogous to method A for preparing compound **3**, the sole difference being that the reaction mixture was kept at room temperature for 2 d. Yield 0.30 g (20%); mp 178-180°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.30 (1H, s, NH); 4.59 (1H, t, *J* = 7, H-2); 4.14 (2H, m, 2H-8); 3.89 (2H, m, 2H-5); 2.12 (6H, m, 2H-6,7, $C\underline{H}_2CH_3$); 1.05 (3H, t, *J* = 7, $CH_2C\underline{H}_3$). Found, %: C 38.86; H 5.04; N 10.02. $C_9H_{14}N_2OS\cdot HBr$. Calculated, % C 38.72; H 5.42; N 10.03.

(4,5,6,7-Tetrahydro-1H-1,3-diazepin-3-yl-2-thio)acetate (5, route *e*). Butylenethiourea **1** (1.30 g, 10.0 mmol) dissolved on heating in ethanol (20 ml). Chloroacetic acid (0.945 g, 10.0 mmol) and sodium acetate (0.820 g, 10.0 mmol) were added to the solution which was then boiled for 6 h. The precipitate which formed on cooling the reaction mixture was filtered off and recrystallized twice from ethanol. Yield 1.05 g (56%); mp 112-114°C. ^{1}H NMR spectrum, δ, ppm: 11.80 (2H, s, NH); 4.50 (2H, m, SCH_2); 3.60 (4H, m, 2H-4,7); 2.00 (4H, m 2H-5,6). Found, %: C 44.66; H 6.48; N 14.86. $C_7H_{12}N_2O_2S$. Calculated, %: C 44.66; H 6.43; N 14.88.

Hydrochloride of Ethyl (4,5,6,7-Tetrahydro-1H-1,3-diazepin-2-ylthio)acetate (6a, route *l*) was obtained from butylenethiourea **1** (0.60 g, 4.6 mmol) and ethyl chloroacetate (0.84 g, 0.72 ml, 6.8 mmol) in anhydrous acetone (10 ml) analogously to method A for the preparation of compound **3** except that the mixture was kept at room temperature for 2 h. Yield 0.111 g (9%); mp 176-178°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.54 (2H, s, NH); 4.48 (2H, s, SCH_2); 4.16 (2H, q, *J* = 7, $C\underline{H}_2CH_3$); 3.45 (4H, m, 2H-4,7); 1.82 (4H, m, 2H-5,6); 1.30 (3H, t, *J* = 7, $CH_2C\underline{H}_3$). Found, %: C 42.78; H 6.81; N 11.09. $C_9H_{16}N_2O_2S\cdot HCl$. Calculated, %: C 42.77; H 6.78; N 11.08.

Hydrobromide of Ethyl (4,5,6,7-Tetrahydro-1H-1,3-diazepin-2-ylthio)acetate (6b, route *p*) was obtained from butylenthioourea **1** (0.39 g, 3.0 mmol) and ethyl bromoacetate (0.752 g, 0.49 ml, 4.5 mmol) by a method analogous for preparing compound **6a**, except that the mixture was kept for 20 min. Yield 0.592 g (66%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.03 (2H, s, NH); 4.35 (2H, s, SCH_2); 4.18 (2H, q, *J* = 7, $C\underline{H}_2CH_3$); 3.44 (4H, m, 2H-4,7); 1.82 (4H, m, 2H-5,6); 1.29 (3H, t, *J* = 7, $CH_2C\underline{H}_3$). Found, %: C 36.36; H 5.66; N 9.61. $C_9H_{16}N_2O_2S\cdot HBr$. Calculated, %: C 36.37; H 5.77; N 9.43.

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