Chemistry of Heterocyclic Compounds, Vol. 41, No. 7, 2005

HYDROLYSIS OF 7,7-SUBSTITUTED DERIVATIVES OF 3-*tert*-BUTYL-3,4-DIHYDRO-2H-THIAZOLO-[3,2-*a*][1,3,5]TRIAZIN-6(7H)-ONE

S. M. Ramsh[1], A. G. Ivanenko[2], V. A. Shpilevyi[1], N. L. Medvedskiy[1], and P. M. Kushakova[1]

Alkaline hydrolysis of 3-tert-butyl-7,7-bis(hydroxymethyl)-3,4-dihydro-2H-thiazolo[3,2-a][1,3,5]-triazin-6(7H)-one can occur in three directions: with cleavage of the tetrahydrotriazine ring, with cleavage of the thiazolidine ring, and also with opening of both rings. Depending on the process conditions, either the hydrolysis product corresponding to the first direction or the hydrolytic decomposition products corresponding to the second and third directions can be obtained in preparative quantities. Hydrolysis of 3,3'-di-tert-butyl-3',4'-dihydro-2'H-spiro[(perhydro-1,3-oxazine)-5,7'-thiazolo[3,2-a][1,3,5]triazin]-6'-one in $(NH_4)_2CO_3$ solution occurs in two steps: in the first step, cleavage of the tetrahydrotriazine ring occurs; and in the second step, opening of the perhydrooxazine ring occurs.

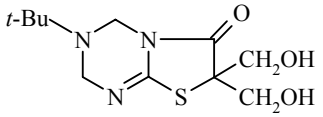
Keywords: 3,3'-di-*tert*-butyl-3',4'-dihydro-2'H-spiro[(perhydro-1,3-oxazine)-5,7'-thiazolo[3,2-*a*][1,3,5]-triazin]-6'-one, 3-*tert*-butyl-7,7-bis(hydroxymethyl)-3,4-dihydro-2H-thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-one, hydrolysis.

2-Amino-4-thiazolinone (pseudothiohydantoin), because of the presence of mobile hydrogen atoms at the position 5 of the heterocycle, can react with aldehydes: when it is treated with aromatic aldehydes, we see formation of 5-arylidene derivatives [1], while 5,5-disubstitution occurs when it is treated with formaldehyde in alkaline medium [2]. Such activity for the position 5 of the heterocycle is also observed in the reaction of pseudothiohydantoin with some primary amines and formaldehyde: along with the expected aminomethylation reaction involving the amidine moiety of the molecule, substitution also occurs at this position [3]. Here in the case of *tert*-butylamine, two such "anomalous" reaction products could be isolated from the reaction mixture: 3-*tert*-butyl-7,7-bis(hydroxymethyl)-3,4-dihydro-2H-thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-one (**1**, called thiazolo-triazine in the following) and 3,3'-di-*tert*-butyl-3',4'-dihydro-2'H-spiro[(perhydro-1,3-oxazine)-5,7'-thiazolo-[3,2-*a*][1,3,5]triazin]-6'-one (**2**, called spirane in the following).

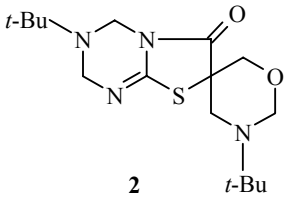
According to [3], compounds **1** and **2** which contain N-aminomethyl moieties are readily hydrolyzed, but the composition and structure of the hydrolysis products were not established. Considering that these compounds have biological activity [4], it was of interest to determine possible routes for their hydrolytic decomposition, especially since contradictory data are available in the literature on alkaline hydrolysis of pseudothiohydantoin itself [1, 5-7].

---

[1] St. Petersburg State Technical University, St. Petersburg 198013, Russia; e-mail: gsramsh@mail.wplus.net. [2] Institute of Toxicology, Ministry of Health, Russian Federation, St. Petersburg 193019; e-mail: drugs@mail.lanck.net. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 1089-1097, July, 2005. Original article submitted October 12, 2003.



1



2

From general considerations, in alkaline hydrolysis of thiazolotriazine **1** we may expect cleavage of both the tetrahydrotriazine ring and the thiazolidine ring. We have systematized many different pathways by which hydrolytic decomposition of compound **1** may occur by assigning them to one of the three possible hydrolysis routes (Scheme 1). The first route (1) is cleavage of the tetrahydrotriazine ring, to ultimately form 2-amino-5,5-bis(hydroxymethyl)-4-thiazolinone (**3**) (on the scheme, we show one of the possible pathways for this route). The second route (2) is cleavage of the thiazolidine ring, which in turn may be realized as four pathways occurring *via* intermediates **C** (pathway 2a), **F** (pathways 2b-2b' and 2b-2b") and **G** (pathway 2c); these two routes should ultimately lead to two sets of final hydrolysis products: 5-*tert*-butylperhydro-1,3,5-triazine-2-thione **(D**) and 2,3-dihydroxy-2-(hydroxymethyl)-2-propionic acid (**E**), 5-*tert*-butylperhydro-1,3,5-triazin-2-one (**4**) and 3-hydroxy-2-(hydroxymethyl)-2-mercaptopropionic acid (**H**) respectively. The third route (3) can be represented as a family of pathways corresponding to opening of both rings in one pathway (on Scheme 1, this route is represented by only some of the possible pathways of this type).

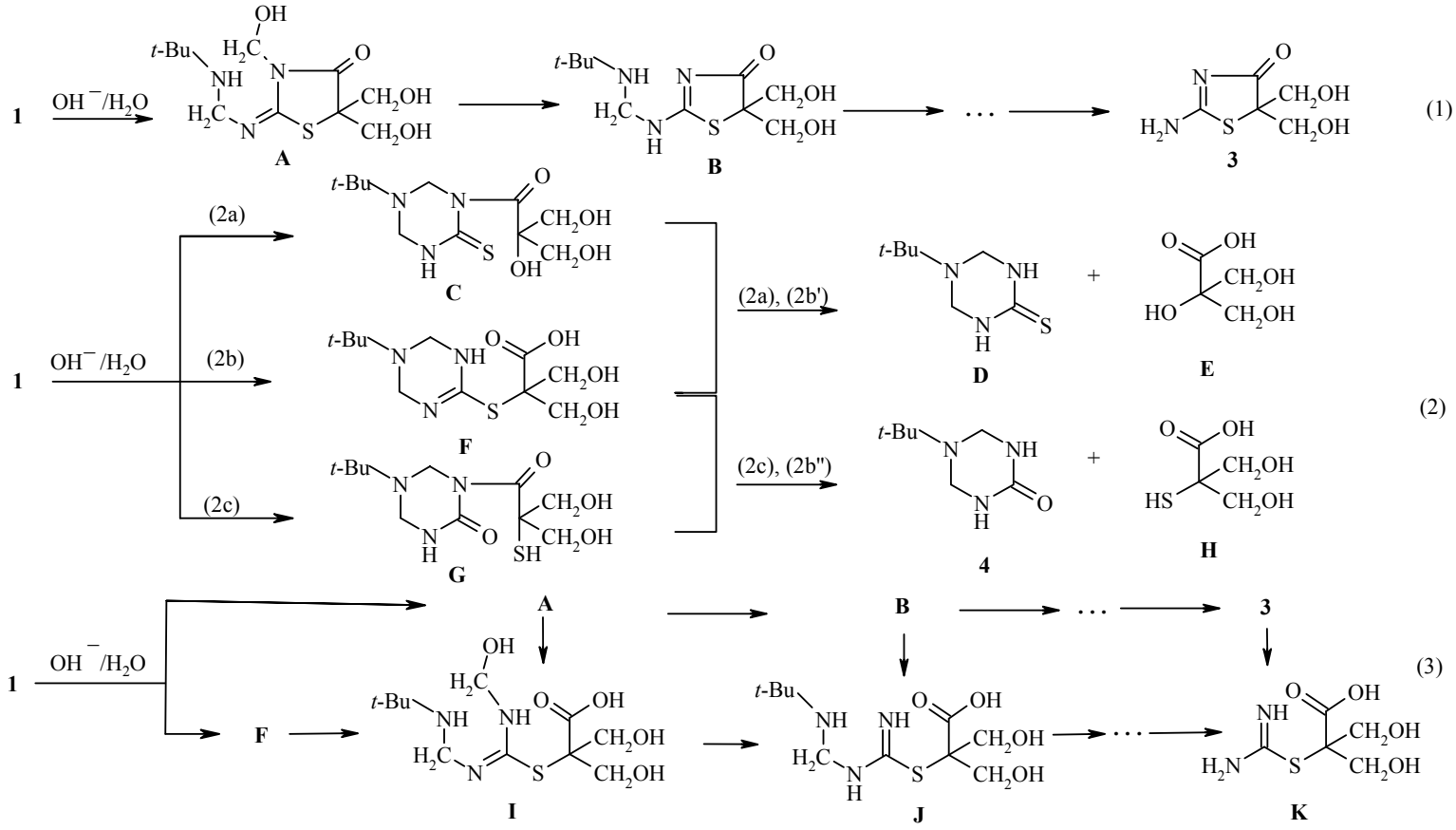
Our experiments showed that depending on the process conditions, we can isolate products corresponding to the different variants for hydrolytic decomposition of compound **1**; and judging from the observed yields, we can hypothesize a connection between the reaction conditions and the preferred routes for alkaline hydrolysis (or the extent to which they are realized). Thus as a result of hydrolysis of thiazolotriazine **1** in 25% aqueous ammonia at room temperature for 1 h, we were able to isolate 2-amino-5,5-bis(hydroxymethyl)-4-thiazolinone (**3**) in 70% yield (Scheme 1). Thus under the given conditions, route (1) is realized, corresponding to cleavage of the tetrahydrotriazine ring (not necessarily along the pathway shown in the Scheme). Such a way for the process to occur suggests that the thiazolidine ring withstands brief exposure to ammonium hydroxide at low temperatures, while cleavage of a tetrahydrotriazine ring containing N-aminomethyl moieties, occurring with separation of formaldehyde, is considerably accelerated in the presence of ammonia binding it.

Compound **3** was also obtained by an alternate synthesis to prove identity: hydroxylmethylation of pseudothiohydantoin according to the method in [2].

As a result of hydrolysis of thiazolotriazine **1** by 1.5 N aqueous NaOH at room temperature for 24 hours, we obtained 5-*tert*-butylperhydro-1,3,5-triazin-2-one (**4**) in 40% yield (Scheme 1), which we also synthesized from urea by a Mannich reaction. From the same reaction mixture, after it was neutralized to pH ~8 and an aqueous solution of $CaCl_2$ was added to it, we isolated one more compound as the calcium derivative. The patterns for the NMR spectrum for the 1H nuclei and the elemental analysis data for samples of this substance varied from run to run, remaining within a certain range, which allowed us to hypothesize its composition and average structure as formula **5**. This formula corresponds to a mixture of variable composition containing derivatives of oligomeric fractions (as basic Ca salts) corresponding to one of the possible hydrolysis intermediates: 3-hydroxy-2-(hydroxymethyl)-2-mercaptopropionic acid (**H**). The given derivatives differ in the structure of the terminal nitrogen-containing moiety R; and the length of the oligomeric chain (the number of units *n*), although it was not constant for different samples, varied within a relatively narrow range from 9 to 11.

The hypotheses concerning the composition and structure of the "mixed" compound **5** are based especially on analysis of the shape of the ^1H NMR spectra for the indicated samples in D_2O and the relative integrated intensity of the signals observed in the spectra that are located in the absorption region for methylene protons. In fact, the ratio of the intensities for the two broad signals at 3.9 ppm ($C\underline{H_2}OH$) and 3.0 ppm ($S–CH_2$) fluctuate within the range from 1.2:1 to 1.3:1, which corresponds to a number of units for the oligomeric chain *n*

Scheme 1

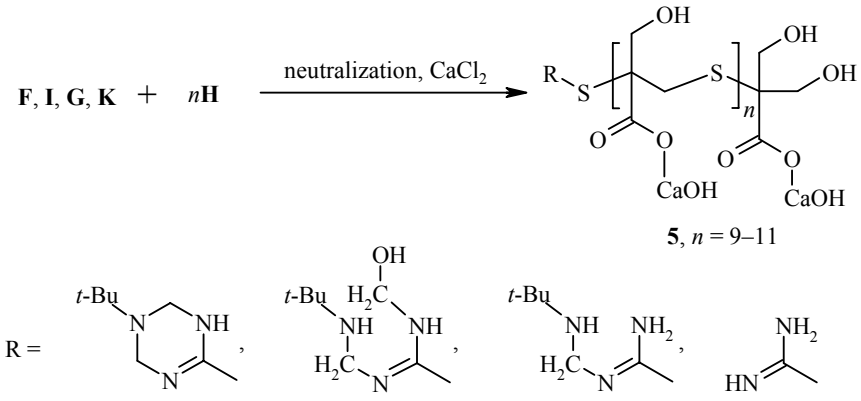


from 9 to 11. Besides these signals, in the ^{1}H NMR spectra of the samples we see from 1 to 3 signals for a *tert*-butyl group in the 1.2-1.4 ppm region with overall intensity 8-10% of the total intensity of the signals from methylene protons. Such a pattern in the absorption region for the *tert*-butyl group, combined with the definite variation in the elemental analysis data, suggests a "mixed" character for the hydrolysis product **5** (i.e., it generally contains several components differing in the terminal radical R) and variability of the composition of the mixture from run to run. We should note that the signals from the methylene protons of the terminal radicals probably overlap with the broad signal at 3.9 ppm.

Unfortunately, attempts to separate the mixture of salts **5** into individual components by recrystallization from different solvents were unsuccessful; we could only standardize it to some degree by reprecipitation with acetone from a formamide solution. We estimated the yield of the "mixed" product as ~60% based on one of the derivatives **5** with R = *t*-Bu–NH–CH_2–N=C(–NH_2)– and n = 10 (see Experimental).

Formation of cyclic urea **4** upon hydrolysis of thiazolotriazine **1** by 1.5 N NaOH suggests that one of the pathways for hydrolysis route (2) is realized under the given conditions, namely (2b)-(2b") or (2c). For simultaneous formation of the "mixed" compound **5** (Scheme 2), this reaction mixture should contain the intermediate monomer **H**, which is obtained along with compound **4** via one of the indicated pathways but can also be formed by a different way (not shown on Scheme 1), such as from intermediates **I**, **J**, or **K**. The intermediates **I**, **J**, or **K** needed (according to Scheme 2) to form the "acyclic" components of the "mixed" substance **5** can be formed only as a result of realization of the pathways included in the third hydrolysis route, such as shown in Scheme 1, while the intermediate **F** needed to form the "cyclic" component can be formed along pathway (2b). We should note that formation of the "mixed" compound **5** may be represented in ways different from that illustrated in Scheme 2, but for any of those ways the intermediates needed to form the "acyclic" components should be generated along pathways of type (3), i.e., with decomposition of both rings on one pathway.

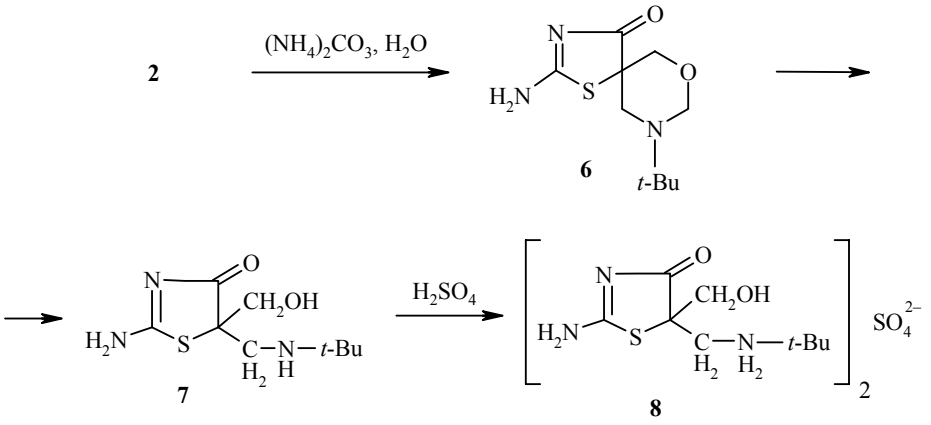
Scheme 2



The identified direction for hydrolytic decomposition of compound **1** in alkaline medium, leading to cyclic urea **4** and intermediate **H**, is different from the direction of decomposition of pseudothiohydantoin under comparable conditions, leading to thiourea and lactic acid [5]. A speculative explanation involves the different relative electrophilicity of the $C_{(2)}$, $C_{(4)}$, and $C_{(5)}$ positions of the thiazolidine ring of thiazolotriazine **1** and the thiazoline ring of pseudothiohydantoin: in the first case, the hydroxide ion preferentially attacks the $C_{(2)}$ and/or $C_{(4)}$ positions of the thiazolidine ring, which leads to realization of pathways (2c) and/or (2b), (2b"), while in the second case the $C_{(5)}$ position of the thiazoline ring is preferentially attacked with realization of a pathway of type (2a). This difference is possibly connected with the strong polarization of the pseudothiohydantoin molecule, which has a "nearly zwitterionic" structure [8].

As a result of hydrolysis of spirane **2** at room temperature in the presence of ammonium carbonate, we isolated two compounds: 2'-amino-3-*tert*-butylspiro[(perhydro-1,3-oxazine)-5,5'-thiazolin]-4'-one (**6**) corresponding to decomposition of the tetrahydrotriazine ring, and its analog with a cleaved perhydrooxazine ring, 2-amino-5-[(*tert*-butylamino)methyl]-5-(hydroxymethyl)-4-thiazolinone (**7**) (Scheme 3). Most likely, decomposition of the tetrahydrotriazine ring occurs first and only then is the perhydrooxazine ring opened, since compound **7** can also be obtained from its precursor **6** by treating the latter with hydroxylamine hydrochloride followed by neutralization of the reaction mixture with sodium methoxide. One more way to obtain compound **7** is to directly treat spirane **2** with hydroxylamine sulfate, followed by neutralization of the reaction mixture with aqueous base.

Scheme 3



Hydrolytic decomposition of the tetrahydrotriazine ring of spirane **2** in the presence of a formaldehyde-binding agent ($(NH_4)_2CO_3$ or an hydroxylamine salt) is quite expected, especially in light of data on hydrolysis of compound **1** in the presence of NH_3. The perhydrooxazine ring of compound **6** probably is cleaved in the presence of these agents at the most highly polarized bond $O_{(1)}$–$C_{(2)}$, where the bulky *tert*-butyl group in the $N_{(3)}$ position probably promotes the hydrolytic lability of this ring; after ring opening, cleavage of formaldehyde from the labile N-hydroxymethyl group occurs to form compound **7.**

When treated with sulfuric acid, compound **6** can be readily converted to the sulfate: bis{N-[2-amino-5-(hydroxymethyl)-4-oxo-5-thiazolinyl]methyl-N-*tert*-butylammonium} sulfate (**8**), which crystallizes from aqueous solutions as the trihydrate.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in KBr disks. The 1H NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) in DMSO-d_6 (compounds **6, 7**), D_2O (compound **4, 5, 8**), and in both solvents (compounds **3**), internal standard TMS. The ^{13}C NMR spectra of compounds **3, 4** were recorded in D_2O on the same spectrometer. TLC was carried out on Silufol UV-254 plates; eluent 5:1 benzene–2-propanol (unless otherwise indicated).

3-*tert*-Butyl-7,7-bis(hydroxymethyl)-3,4-dihydro-2H-thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-one (1) and **3,3'-di-*tert*-butyl-3',4'-dihydro-2'H-spiro[(perhydro-1,3-oxazine)-5,7'-thiazolo[3,2-*a*][1,3,5]triazin]-6'-one (2)** were obtained as described in [3], **2-amino-5,5-bis(hydroxymethyl)-4-thiazolinone (3)** was obtained according to the procedure in [2]. The characteristics of the synthesized compounds correspond to literature data.

5-*tert*-Butylperhydro-1,3,5-triazin-2-one (4). Urea (6.0 g, 100 mmol), *tert*-butylamine (7.3 g, 10.5 ml, 100 mmol), and formalin (16 ml, 0.2 mol) were boiled in ethanol (20 ml) for 5 h, then the reaction mixture was cooled down and the precipitate was filtered out. From the filtrate under atmospheric pressure, the liquid phase was distilled down to about 1/3 of the initial volume and another ~1 g of the precipitate formed was filtered out. The precipitates were combined, crystallized from ethanol, and dried for 4 h at 105°C. Yield 3.0 g (19%); mp 197-199°C. IR spectrum, ν, cm^{-1}: 3240 (N–H), 1680 (C=O). ^1H NMR spectrum, δ, ppm: 4.3 (4H, s, 4,6-CH_2); 1.2 (9H, s, $C(CH_3)_3$). ^{13}C NMR spectrum, δ, ppm: 158.5 (C=O); 57.0 (CH_2); 55.1 ($\underline{C}(CH_3)_3$); 27.7 ($C(\underline{C}H_3)_3$). Found, %: C 53.36; H 9.69; N 26.70. $C_7H_{15}N_3O$. Calculated, %: C 53.48; H 9.62; N 26.73. R_f 0.6 (Silufol UV-254, methanol, visualization in iodine vapor or an alcoholic solution of the universal indicator RKS 1-10).

Alkaline Hydrolysis of 3-*tert*-Butyl-7,7-bis(hydroxymethyl)-3,4-dihydro-2H-thiazolo[3,2-*a*][1,3,5]-triazin-6(7H)-one (1).

A. Hydrolysis with Aqueous Ammonia.

2-Amino-5,5-bis(hydroxymethyl)-4-thiazolinone (3). Compound **1** (1.8 g, 6.6 mmol) was dissolved at ~20°C with rapid stirring in an aqueous solution of 25% NH_3; after 1 h, the solvent was distilled off under vacuum to dryness, raising the temperature at the end of the distillation to 60°C-70°C. The dry residue was dissolved in a minimal amount of methanol and an equal volume of chloroform was added to the solution obtained. The amorphous mass formed was vigorously shaken. After a few minutes, a crystalline, chromatographically homogeneous precipitate was formed which was filtered out, washed with ethanol, and dried in air until constant weight was achieved. Yield 0.81 g (70%); mp 188-191°C (ethanol), 190-191°C (water); according to the data in [2], mp 186-188°C. The spectral characteristics were identical to the characteristics of the sample obtained by the method in [2]. ^1H NMR spectrum, δ, ppm (DMSO-d_6): 8.8 (1H, s, NH_A); 8.7 (1H, s, NH_B); 5.2 (2H, broad, OH); 3.6 (4H, broad, CH_2). ^{13}C NMR spectrum, δ, ppm: 192.2 (C=O); 184.7 (C=N); 76.8 (C–S); 63.5 (C–O). Found, %: C 34.01; H 4.63; N 15.98. $C_5H_8N_2O_3S$. Calculated, %: C 34.08; H 4.58; N 15.90.

B. Hydrolysis with an Aqueous Sodium Hydroxide Solution.

5-*tert*-Butylperhydro-1,3,5-triazin-2-one (4). Compound **1** (2.0 g, 7.3 mmol) was dissolved with rapid stirring in a 1.5 N aqueous solution of NaOH (7 ml, 10.5 mmol). After 24 hours, the precipitate was filtered out.* If a precipitate was not formed, then the water was distilled off under vacuum until precipitation occurred. The precipitate was washed with water and dried first in air and then for 2 h at 105°C. Yield 0.46 g (40%); mp 198-199°C (ethanol). The spectral characteristics were identical to the characteristics of the sample obtained by the method described above. Found, %: C 53.21; H 9.78; N 27.20. $C_7H_{15}N_3O$. Calculated, %: C 53.48; H 9.62; N 26.73.

"Mixed" Compound 5 (giving one of the syntheses as an example). The filtrate obtained in the previous experiment was acidified with acetic acid to pH ~8, then an aqueous $CaCl_2$ solution of concentration 5 mol/l (1 ml) was added. The solution obtained was diluted with methanol (10 ml). The precipitate formed was filtered out and washed with methanol. Yield 0.85 g (57% based on structure **5**, R = *t*-Bu–NH–CH_2–N=C(–NH_2)–, *n* = 10); decomposes at 225-227°C (after reprecipitating from formamide by acetone). IR spectrum, ν, cm^{-1}: 1700 shoulder, 1590, 1395. ^1H NMR spectrum, δ, ppm: 3.9 (broad, $C\underline{H}_2OH$); 3.0 (broad, S–CH_2); 1.4 (*t*-Bu), relative signal intensities 1:0.87:0.18. Found, %: C 25.89; H 4.74; N 1.9; S 16.00. $C_{50}H_{81}Ca_{11}N_3O_{45}S_{11}$ (for **5**, R = *t*-Bu–NH–CH_2–N=C(–NH_2)–, *n* = 10, M = 2237.7520]. Calculated, %: C 26.84; H 3.65; N 1.88; S 15.76.

Hydrolysis of 3,3'-Di-*tert*-butyl-3',4'-dihydro-2'H-spiro[(perhydro-1,3-oxazine)-5,7'-thiazolo-[3,2-*a*][1,3,5]triazin]-6'-one (2).

* The filtrate was used later to obtain the "mixed" compound **5**.

2'-Amino-3-*tert*-butylspiro[(perhydro-1,3-oxazine)-5,5'-thiazolin]-4'-one (6). A solution of compound **2** (17.0 g, 50 mmol) in methanol (20 ml) was poured with stirring into a solution of $(NH_4)_2CO_3$ (9.6 g, 100 mmol) in water (50 ml). The initially formed droplets of oil gradually solidified and were converted to a white precipitate, and slight evolution of gas was observed. The large clumps of precipitate were mechanically broken up and stirring was continued for another 1 h 30 min to 2 h, the precipitate was filtered out,* washed with water, dried in air, and washed with benzene. Yield, 3.3 g (27%). *T*mp 200°C-201°C (from methanol). The substance was almost insoluble in water. It slowly went into solution when held at pH ~4.5 (dissolution time was about 40-60 min), obviously due to hydrolysis to form compound **7**. The basic nitrogen and formaldehyde formed were titrated with 0.1 N HCl or Na_2SO_3 solution respectively; the ratio of the titrated nitrogen and formaldehyde was 2:1. IR spectrum, ν, cm_{-1}: 1680 (C=O), 1640 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.0 (1H, s, $N\underline{H}_AH_B$); 8.9 (1H, s, $NH_A\underline{H}_B$); 4.7 (1H, d, $^{gem}J_{AB}$ = 9, 2-$\underline{H}_AH_B$); 3.9 (1H, d, $^{gem}J_{AB}$ = 9, 2-$H_A\underline{H}_B$); 3.9 (1H, d, $^{gem}J_{AB}$ = 13, 6-$\underline{H}_AH_B$); 3.7 (1H, d, $^{gem}J_{AB}$ = 13, 6-$H_A\underline{H}_B$); 3.1 (1H, d, $^{gem}J_{AB}$ = 13, 4-$\underline{H}_AH_B$); 2.9 (1H, d, $^{gem}J_{AB}$ = 13, 4-$H_A\underline{H}_B$); 1.0 (9H, s, $C(CH_3)_3$). Found, %: C 49.32; H 7.05; N 18.23. $C_{10}H_{17}N_3O_2S$. Calculated, %: C 49.36; H 7.04; N 17.27.

2-Amino-5-[(*tert*-butylamino)methyl]-5-(hydroxymethyl)-4-thiazolinone (7). 1. The filtrate obtained in the previous experiment was evaporated under vacuum down to 15 ml; the precipitate formed was filtered out, washed with water, and dried in air. Yield 1.6 g (14%). 1.3 g of the substance obtained was boiled in methanol (14 ml) and filtered to remove the insoluble residue, and then the filtrate was allowed to stand for a few days. The precipitated crystals were filtered out and dried under vacuum. The yield in the crystallization step was 0.6 g (46%); mp 183-186°C (Kofler bench), 170-171°C (in a sealed capillary, 2°C/min). The compound was sparsely soluble in water, pK_a ~8.1 (potentiometric titration). IR spectrum, ν, cm^{-1}: 1680 (C=O), 1640 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.8-8.7 (2H, NH_2); 5.2 (1H, OH); 3.7 (1H, d, $^{gem}J_{AB}$ = 8, 5-C$\underline{H}_AH_BO$); 3.6 (1H, d, $^{gem}J_{AB}$ = 8, 5-C$H_A\underline{H}_BO$); 2.9 (1H, d, $^{gem}J_{AB}$ = 9, 5-C$\underline{H}_AH_BN$); 2.8 (1H, d, $^{gem}J_{AB}$ = 9, 5-C$H_A\underline{H}_BN$); 1.0 (9H, s, $C(CH_3)_3$). Found, %: C 46.59; H 7.42; N 18.75. $C_9H_{17}N_3O_2S$. Calculated, %: C 46.73; H 7.41; N 18.17.

2. A solution of compound **2** (50 g, 147 mmol) in methanol (200 ml) was added dropwise with stirring over a period of 1 h 30 min to a solution of hydroxylamine sulfate (36 g, 220 mmol) in water (52 ml), and then another hydroxylamine sulfate (7 g, 43 mmol) was added to the reaction mixture and stirring was continued for 40 min. A mixture of a 25% aqueous solution of NH_3 (10 ml) was added to the reaction mixture (to pH ~5.5), the solution was cooled down to 15°C and filtered to remove the ammonium sulfate precipitate. The filtrate was diluted with a two-fold volume of acetonitrile and the sulfate precipitate formed **8** was filtered out (see below). Yield 22.0 g (49% based on the trihydrate).

The salt obtained **8** was dissolved in a minimal amount of water (~25 ml) and the solution was alkalinized by addition of 50% aqueous NaOH in portions, monitoring the pH of an aliquot (0.1 ml of the solution was diluted with water to make up a volume of 30 ml) on a pH meter. First at pH ~8 tarry substances fell out of solution, which were removed by decanting the solution. Addition of base to the solution was continued until a precipitate formed (at pH ~10). Yield of the air-dried substance 11.0 g (32%).

The mother liquor obtained after removing salt **8** was evaporated under vacuum (~40°C) down to a volume of ~70 ml and alkalinized similarly, and another 3.3 g (10%) of the compound was isolated.

Both precipitates were combined and recrystallized from methanol (140 ml).*[2] The substance was slowly crystallized (cooling down to 8°C). Yield 4.4 g (13%). The insoluble residue was crystallized from ethanol (60 ml). Yield 1.8 g (5.3%); mp 183-186°C (Kofler bench), 173°C (in a sealed capillary, 2°C/min). The spectral characteristics and elemental analysis data correspond to the values given above.

---

* The filtrate was used later to obtain Compound **7**.

*[2] The mother liquors were used later to obtain salt **8**.

3. Hydroxylamine hydrochloride (0.55 g, 7.9 mmol) was added to a suspension of compound **6** (2.05 g, 8.4 mmol) in methanol (40 ml). The reaction mixture was stirred until the components were almost completely dissolved (the cloudy solution had pH ~6-7 according to indicator paper) for 30 min, and then was allowed to stand overnight. Then it was alkalinized with 3 N sodium methoxide to pH ~10-11, the NaCl precipitate was filtered out, and the filtrate was evaporated under atmospheric pressure down to 1/3 volume and filtered again hot. After about 15 min, precipitation began. After 3 days, it was filtered out, washed with water, and dried in air. Yield 0.73 g (38%); mp 184-186°C (Kofler bench); 174°C (in a sealed capillary, 2°C/min). The spectral characteristics and elemental analysis data correspond to the values given above.

Bis{N-[2-amino-5-(hydroxymethyl)-4-oxo-5-thiazolinyl]methyl-N-*tert*-butylammonium} Sulfate (8). 1. Sulfuric acid (0.607 g, 0.33 ml, 5.9 mmol) was added with stirring to the combined mother liquors left over from recrystallization of compound **7** (see above), total volume of ~150 mL (methanol–ethanol, ~2:1, estimated content of compound **7** from potentiometric titration data was 12 mmol). The precipitate was filtered out, washed with methanol, recrystallized from 70% ethanol (20 ml), and dried in air until constant weight was achieved. Holding a weighed sample at 105°C for 24 hours led to weight loss corresponding to three water molecules per molecule of the salt. Yield of the trihydrate 1.2 g (32%); decomposes at 260-263°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 1640 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.9 (1H, d, $^{gem}J_{AB}$ = 12.5, C$\underline{H}_A$H$_B$O); 3.8 (1H, d, $^{gem}J_{AB}$ = 12.5, CH$_A\underline{H}_B$O); 3.6 (1H, d, $^{gem}J_{AB}$ = 15, C$\underline{H}_A$H$_B$N); 3.5 (1H, d, $^{gem}J_{AB}$ = 15, CH$_A\underline{H}_B$N) 1.4 (9H, s, C(CH$_3$)$_3$). Found, %: C 34.95; H 6.17; N 13.12. $C_{18}H_{36}N_6O_8S_3\cdot 3H_2O$. Calculated, %: C 35.17; H 6.89; N 13.67.

2. Ethanol (6 ml), water (2.2 ml), and sulfuric acid (0.184 g, 0.10 ml, 1.8 mmol) were added with stirring to compound **7** (0.60 g, 2.6 mmol). The reaction mixture was brought to the boiling point, the insoluble precipitate was filtered out, the filtrate was cooled down, the precipitated salt was filtered out and washed twice with 70% ethanol and dried under vacuum. Yield of the trihydrate 0.32 g (40%); decomposes at 254-259°C. The spectral characteristics and elemental analysis data correspond to the values given above.

We would like to thank D. B. Lazarev for help in preparation of this paper.

REFERENCES

1. F. C. Brown, *Chem. Rev.*, **61**, 463 (1961).
2. S. M. Ramsh and A. G. Ivanenko, *Khim. Geterotsikl. Soedin.*, 1743 (2003).
3. S. Yu. Solov'eva, S. M. Ramsh, and A. I. Ginak, *Khim. Geterotsikl. Soedin.*, 1204 (1983)
4. S. M. Ramsh, T. S. Basieva, O. Yu. Uryupov, S. Yu. Solov'eva, V. M. Vinogradov, A. I. Ginak, B. I. Krivoruchko, I. A. Shelkovnikov, and Yu. N. Shanin, USSR Inventor's Certificate 1095612; *B. I.* , No. 20, 197 (1984).
5. V. M. Fedoseev, A. A. Mandrugin, and M. N. Semenenko, *Khim. Geterotsikl. Soedin.*, 44 (1984).
6. H. Aspelund, *Acta Acad. Aboensis (Math. Phys.)*, No. 1, 1 (1964).
7. H. Aspelund, *Acta Acad. Aboensis (Math. Phys.)*, No. 2, 1 (1964).
8. S. M. Ramsh, N. A. Smorygo, and A. I. Ginak, *Khim. Geterotsikl. Soedin.*, 1066 (1984).