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# 2-AMINO-5,5-BIS(HYDROXYMETHYL)-1,3-THIAZOL-4(5H)-ONE AND ITS SPIRODIOXANE COMPOUNDS IN THE MANNICH REACTION

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*It was found that the aminomethylation of 2-amino-5,5-bis(hydroxymethyl)-1,3-thiazol-4(5H)-one and its spiro analogs using primary amines is accompanied by cyclization at the amidine fragment of the molecule with annelation of a tetrahydrotriazine ring. When using secondary amines the aminomethylation occurs at the exocyclic nitrogen atom.*

**Keywords:** 2-amino-5,5-bis(hydroxymethyl)-1,3-thiazol-4(5H)-one, 2-'amino-2-aryl(hetaryl)spiro-[1,3-dioxan-5,5'(4'H)-1',3'-thiazol]-4'-ones, 5-methyl- and 2-amino-5-ethyl-1,3-thiazol-4(5)-ones, aminomethylation.

We have previously been able to prepare a 5,5-bis(hydroxymethyl) derivative of 2-amino-1,3-thiazol-4(5H)-one (pseudothiohydantoin) (**1a**) [1] and synthesize a series of spiro-[1,3-dioxan-5,5'(4'H)-1',3'-thiazole] derivatives (**2a-e**) from it [2]. Compound **1a** is a "truncated" (fragmented) part of the compound **3a** molecule which shows high biological activity [3]. This encouraged us to develop a novel method for the preparation of active compound **3a** by the aminomethylation of the bis(hydroxymethyl) derivative **1a**. This was particularly in view of the fact that the preparation of compound **3a**, initially proposed *via* the direct aminomethylation of pseudothiohydantoin [3, 4] is accompanied by the formation of a side reaction product and the yield of the target compound **3a** does not exceed 30%. It also seemed suitable for developing a method of preparing homologs of compound **3a** through the variation of the amino component in the aminomethylation reaction of compound **1a**.

With the aim of subsequently studying the biological activity of the newly obtained compounds and revealing a structure-activity relationship we have also synthesized in the work the monohydroxymethyl and spiro analogs of compound **3a** using the **1b,c** or spiro compounds **2a-e** as substrates in the Mannich reaction and tert-butylamine or methylamine as the amino component. The aminomethylation of substrate **1a** with secondary cyclic amines also gave the Mannich bases **5a,b**, differing from compound **3a** in the acyclic structure of the aminomethyl fragment of the molecule. Finally, the hydroxymethylation of the thiazolo[3,2-*a*]pyrimidine derivative **6** gave compound **7** as the "desaminated" analog of compounds **3a**.

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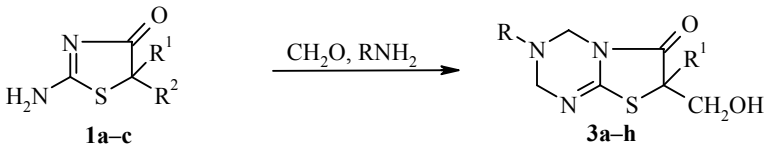
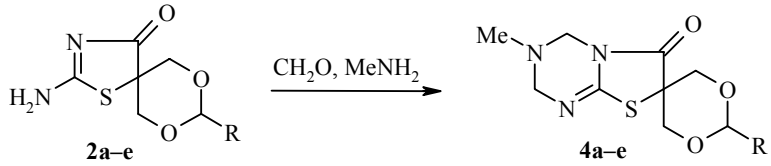


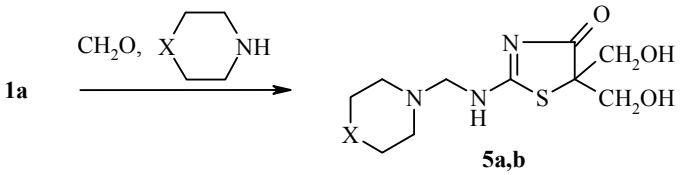

**1a–c** **3a–h**

**1 a** $R^1 = R^2 = CH_2OH$; **b** $R^1$ = Me, $R^2$ = H; **c** $R^1$ = Et, $R^2$ = H;
**3 a** R = *t*-Bu, **b** R = Me, **c** R = Et, **d** R = *c*-Hex, **e** R = Bn, **f** R = $Ph_2CH$;
**g**, **h** R = *t*-Bu; **a–f** $R^1 = CH_2OH$, **g** $R^1$ = Me, **h** $R^1$ = Et



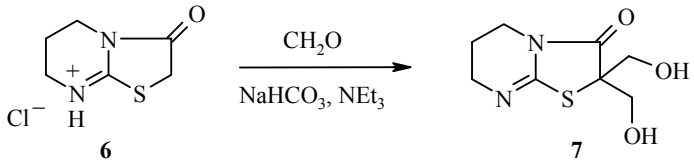

**2a–e** **4a–e**

**4 a** R = Ph, **b** R = *p*-$C_6H_4NO_2$, **c** R = *p*-$C_6H_4Me$, **d** R = 3-Py, **e** R = 4-Py




**5a,b**

**5 a** X = $CH_2$, **b** X = O




**6** **7**

As expected, the aminomethylation of compounds **1a-c** and **2a-e** gave the target Mannich bases [1,3]thiazolo[3,2-*a*][1,3,5]triazines **3a-h** and spiro[1,3-dioxan-5,7'(6'H)-[1,3]thiazolo[3,2-*a*][1,3,5]triazines **4a-e** respectively (Table 1).

A feature of the proposed method for aminomethylating compound **1a** (with the exclusion of the preparation of compound **3f**), which distinguishes it from the known method of aminomethylating a pseudothiohydantoin [4] is the absence of a specifically added solvent, water in this case being added in the reaction mixture as part of one of the reagents *viz*. formaldehyde (in the case of compound **3b** contained in the methylamine). Another feature distinguishing this method of preparing thiazolotriazines is the addition of potassium carbonate to the reaction mixture. Its role is in homogenization of the reaction mass and, possibly, in a base catalysis of the aminomethylation [5, 6]. A third difference for the proposed method is the use of an almost stoichiometric ratio of substrate to amine to formaldehyde since in the method for preparing thiazolotriazines by method [4] acceptable yields are achieved with a 1.5 to 2.5 fold excess of formaldehyde. For the preparation of compounds **3a,b** and **3d** the amine is added with cooling of the reaction mixture to 0-3°C.

Only in the preparation of compound **3f** is the reaction mixture heated to reflux and the product separated from it needs recrystallization. In the remaining examples the reaction takes place at room temperature and the reaction product is quite pure and does not need recrystallization. The yields of compounds **3a-f** varied from 46 to 98% (Table 1).

The yield of the thiazolotriazine **3a** by this new method reaches 70% which is more than twice the yield using the known method, i.e. by the direct aminomethylation of the pseudothiohydantoin [3, 4]. It should also be noted that the direct aminomethylation of the pseudothiohydantoin using methylamine as the amino component

TABLE 1. Characteristics of Compounds **3** and **4**

| Compound | Empirical formula | Found, % / Calculated, % | | | mp, °C | Yield, % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **3a** | $C_{11}H_{19}N_3O_3S$ | 48.41 / 48.33 | 6.97 / 7.01 | 15.38 / 15.37 | 159-60 (159 [4]) | 70 |
| **3b** | $C_8H_{13}N_3O_3S$ | 41.49 / 41.55 | 5.64 / 5.67 | 18.20 / 18.17 | 166-171 (dec.) | 71 |
| **3c** | $C_9H_{15}N_3O_3S$ | 44.09 / 44.07 | 6.09 / 6.16 | 17.19 / 17.13 | 131-133 | 40 |
| **3d** | $C_{13}H_{21}N_3O_3S$ | 52.18 / 52.15 | 7.01 / 7.07 | 13.94 / 14.04 | 135-137 | 76 |
| **3e** | $C_{14}H_{17}N_3O_3S$ | 54.78 / 54.71 | 5.54 / 5.57 | 13.63 / 13.67 | 146-147 (136-138 [4]) | 46 |
| **3f** | $C_{20}H_{21}N_3O_3S$ | 62.56 / 62.64 | 5.54 / 5.52 | 11.02 / 10.96 | 230-233 | 98 |
| **3g** | $C_{11}H_{19}N_3O_2S$ | 51.54 / 51.34 | 7.53 / 7.44 | 16.41 / 16.33 | 138-140 | 58 |
| **3h** | $C_{12}H_{21}N_3O_2S$ | 53.14 / 53.11 | 7.85 / 7.80 | 15.41 / 15.48 | 108-110 | 25 |
| **4a** | $C_{15}H_{17}N_3O_3S$ | 56.35 / 56.41 | 5.39 / 5.37 | 13.10 / 13.16 | 176-179 | 83 |
| **4b** | $C_{15}H_{16}N_4O_5S$ | 49.33 / 49.44 | 4.46 / 4.43 | 15.34 / 15.38 | 210-220 (dec.) | 77 |
| **4c** | $C_{16}H_{19}N_3O_3S$ | 57.71 / 57.64 | 5.70 / 5.74 | 12.64 / 12.60 | 220-227 (dec.) | 75 |
| **4d** | $C_{14}H_{16}N_4O_3S$ | 52.44 / 52.49 | 5.27 / 5.03 | 17.25 / 17.49 | 184-186 | 50 |
| **4e** | $C_{14}H_{16}N_4O_3S$ | 52.36 / 52.49 | 5.24 / 5.03 | 17.19 / 17.49 | 189-191 | 46 |

gave the des hydroxymethyl analog of compound **3b** [4] and use of ethyl- and cyclohexylamine did not generally give the Mannich bases.

The monohydroxymethylated analogs of compound **3a** (thiazolotriazines **3g** and **3h**) were prepared from the pseudothiohydantoin homologs **1b** or **1c** by direct aminomethylation using a known method for the aminomethylation of pseudothiohydantoin [4].

Due to the low solubility of the starting compounds **2a-e** the preparation of the spiro[1,3-dioxan-5,7'(6'H)-[1,3]thiazolo[3,2-*a*][1,3,5]triazines] **4a-e** is heterophasic even though, in the majority of cases (with the exclusion of the preparation of **4a**) ethanol was introduced as solvent and the reaction mixture was refluxed for several minutes. None the less, with an approximately 2-fold excess of formaldehyde and 2.5-fold excess of methylamine the reaction occurs quite readily and completely. The compounds obtained have acceptable quality and do not need recrystallization. Their yields were from 46-83% (Table 1).

The $^1$H NMR spectra of compounds **3a-h** and **4a-e** are given in Table 2.

In the reactions of polydentate nucleophilic substrates (to which compound **1a** can be assigned) with electrophilic reagents the central question is the regioselectivity of the process [7]. Through the aminomethylation of compound **1a** using aqueous formaldehyde and secondary amines using the method proposed in [8] for the aminomethylation of pseudothiohydantoin with aqueous formaldehyde and piperidine, we have separated pure monoaminomethyl derivatives and the indicated question reduces to the structure of the compounds produced. The $^1$H NMR spectroscopic analysis unambiguously shows that they are substituted at the exocyclic nitrogen atom as compounds **5a** and **5b**. The most characteristic spectroscopic indication for these compounds is the complex nature of the protons of the NH, $NCH_2N$, and hydroxyl protons, "sensitive" to both hindered rotation around the $C_{(2)}–N_{exo}$ bond and to an intramolecular association of one of the conformers via a hydroxymethyl group. A further confirmation of substitution at the exocyclic nitrogen atom is the relatively low frequency for the $C_{(2)}=N_{(3)}$ bond absorption (1590-1595 $cm^{-1}$) in the IR spectra [9, 10].

TABLE 2. Spectroscopic Characteristics of Compounds **3a-h**

| Com-pound | IR spectrum (in KBr), ν, $cm^{-1}$ | | $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm* | | | | |
|---|---|---|---|---|---|---|---|
| | C=O | C=N | $CH_2O\underline{H}$*2 | 2H-2 | 2H-4 | $C\underline{H}_2OH$*3 | R |
| **3a** | 1710 | 1630 | 5.64 (t) | 4.92 | 4.66 | 3.94, 3.88 | 1.34 |
| **3b** | 1700 | 1625 | 5.39 (t) | 4.50 | 4.22 | 3.67 | 2.38 |
| **3c** | 1720 | 1640 | 5.36 (br.) | 4.54 | 4.26 | 3.67 | 2.52 (m); 1.08 (m) |
| **3d** | 1720 | 1625 | 5.45 (br.) | 4.59 | 4.36 | 3.68 | 2.48 (m); 1.63 (m); 1.11 (m) |
| **3e** | 1690 | 1635 | 5.48 (t) | 4.42 | 4.36 | 3.68 | 7.35 (m, $C_6H_5$); 3.66 ($C_6H_5C\underline{H}_2$) |
| **3f** | 1715 | 1620 | 5.37 (br.) | 4.47 | 4.26 | 3.73 | 7.50-7.05 (m $C_6H_5$); 4.81 ($(C_6H_5)_2C\underline{H}$) |
| **3g***4,*5 | 1723 | 1650 | 5.31 (br.) | 4.69 | 4.40 | 3.66, 3.49 | 1.15 |
| **3h***6,*5 | 1730 | 1630 | 5.47 (br.) | 4.69 | 4.41 | 3.69, 3.55 | 1.09 |

* Multiplicities indicated for non singlet signals.

*2 For all hydroxyl triplets the spin spin coupling $J$ = 5 Hz.

*3 The diastereotopic methylene protons of the hydroxymethyl group $CH_AH_BOH$ resonate as an AB-geminal quadruplet (dd) with $J^{gem}_{AB}$ = 12-13 Hz. In addition each signal of the quadruplet is split by the hydroxyl proton with $J$ = 5 Hz [4]. Because of overlap of signals the analysis of this part of the spectrum is difficult. For this reason the geometric mean of the signal chemical shifts are given.

*4 The 7-$CH_3$ protons absorb at 1.48 ppm.

*5 The diastereotopic methylene protons of the hydroxymethyl group $CH_AH_BOH$ resonate as an AB- quadruplet (dd) with $J^{gem}_{AB}$ = 11 Hz.

*6 The ethyl group signals are at 1.78 (2H, m, $C\underline{H}_2CH_3$) and 0.86 ppm (3H, t, $J$ = 7, $CH_2C\underline{H}_3$).

It should be noted that monosubstituted derivatives at an exocyclic nitrogen atom were also separated in the reactions of hydroxymethylation with aqueous formaldehyde and aminomethylation using aqueous formaldehyde and piperidine which are near in structure, i.e. a pseudothiohydantoin [11, 8] and its 5-aryl derivatives [12]. In the case of the aminomethylation of the pseudothiohydantoin there were separated a mixed hydroxymethylpiperidinomethyl derivative like **5a** but with two piperidinomethyls in positions $N_{exo}$ and $C_{(5)}$ and one hydroxymethyl in position 5. The compound thus separated had similar spectroscopic features to those noted above, even with the simplest pseudothiohydantoins monosubstituted at the exocyclic nitrogen atom, i.e. 2-methylamino-1,3-thiazol-4(5H)-one [14] and its 5-benzylidene analog [15].

A feature of carrying out the aminomethylation reaction of substrate **1a** by secondary amines is the selection of an unusual ratio of reagents and, in fact, a marked excess of the aminomethylating reagents. The ratio of substrate to formaldehyde to amine was 1:2.7:2.5 in the case of piperidine and 1:4.1:2 for morpholine. We associate this with the proposed stage of the process leading to the separation of **5a** and **5b**. Evidently during the process compound **1a** undergoes bisaminomethylation at both the cyclic and exocyclic nitrogen atoms. In fact a possible route of formation of compounds **3a-h, 4a-e** by aminomethylation of compounds **1a,**

TABLE 3. Spectroscopic Characteristics of Compounds **4a-e**

| Compound | IR spectrum (in KBr), ν, $cm^{-1}$ | | $^1$H NMR spectrum, δ, ppm* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | C=O | C=N | $C_6H_5$ (Py) | H-2 | 2H-2' | $H_AH_B$-4(6)*$^2$ | | 2H-4' | $NCH_3$ |
| | | | | | | $H_A$ | $H_B$ | | |
| **4a** | 1690 | 1620 | 7.42-7.34 (m) | 5.67 | 4.54 | 4.52 | 4.28 | 4.25 | 2.48 |
| **4b***$^3$ | 1685 | 1625 | 8.25 (d); 7.70 (d) | 5.94 | 4.55 | 4.54 | 4.35 | 4.25 | 2.45 |
| **4c***$^3$ | 1715 | 1630 | 7.30 (d); 7.17 (d) | 5.69 | 4.54 | 4.48 | 4.28 | 4.24 | 2.44 |
| **4d** | 1700 | 1640 | 8.59 (m); 7.79 (m); 7.42 (m) | 5.88 | 4.55 | 4.53 | 4.33 | 4.25 | 2.44 |
| **4e** | 1695 | 1615 | 8.61 (m); 7.40 (m) | 5.80 | 4.54 | 4.54 | 4.32 | 4.24 | 2.45 |

* Multiplicities indicated for non singlet signals.

*$^2$ The diastereotopic methylene group proton signals for $H_AH_B$-4(6) appear as a geminal AB-quadruplet with $J^{gem}_{AB}$ = 11-12 Hz.

*$^3$ Aromatic coupling constants $J_{arom}$ = 8 Hz, δ (H-4) = 2.34 ppm.

**2a-e** by primary amines is also formation of an intermediate bisaminomethylated derivative and its subsequent cyclization. Experimentally the choice of the ratio of reagents chosen for the non catalyzed course of similar reactions [4] is close to that used by us to prepared compounds **5a** and **5b**. In the case of the aminomethylation of compound **1a** by secondary amines these suggested bisaminomethylated derivatives, *via* gentle heating of the reaction mixture in ethanol, undergo solvolysis with fission of an aminomethyl group from the cyclic nitrogen atom and the formation of monoaminomethyl derivatives at the exocyclic nitrogen **5a** and **5b**.

In order to prepare 2,2-bis(hydroxymethyl)-6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-3(2H)-one (**7**) (the desaminated analog of compound **3**) the hydrochloride **6** was neutralized *in situ* with sodium bicarbonate in a minimal amount of water followed by treatment with aqueous formaldehyde in the presence of a catalytic amount of triethylamine according to method [1].

## EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer as a thin layer and $^1$H NMR spectra on Bruker AC-200 (200 MHz), AM-300 (300 MHz), and AM-500 (500 MHz) spectrometers using DMSO-$d_6$ and with TMS as internal standard. TLC was performed on Silufol UV-254 plates with acetone–hexane (1:1) or benzene-isopropyl alcohol (5:1) as eluent.

The bis(hydroxymethyl) derivative of pseudothiohydantoin **1a** was prepared as the monohydrate by method [1], compounds **1b,c** by [16], the spiro[1,3-dioxan-5,5'(4'H)-1',3'-thiazoles] **2a-e** by [2], and compound **6** by [17].

**3-*tert*-Butyl-7,7-bis(hydroxymethyl)-3,4-dihydro-2H-[1,3]thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-one (3a).** 37% Formalin (2.0 ml, 24.9 mmol) and potassium carbonate (1 g) were added to compound **1** monohydrate (2.0 g, 10.3 mmol). The mixture was stirred until full solution of compound **1** (1-1.5 h) and, with continued stirring, the solution was cooled in an ice bath to 0-3°C. *tert*-Butylamine (0.835 g, 1.2 ml, 11.5 mmol) was added. After some time a precipitate appeared in the bulk of the solution. After 2 h the mixture was again cooled and the precipitate was filtered off and washed three times with portions of iced water.

**7,7-Bis(hydroxymethyl)-3-methyl-3,4-dihydro-2H-[1,3]thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-one (3b)** was prepared similarly to compound **3a** from compound **1** monohydrate (3.0 g, 15.4 mmol), formalin (3.0 ml, 37.4 mmol), potassium carbonate (1 g), and 25% aqueous methylamine solution (2.1 ml, 17.1 mmol).

**3-ethyl-7,7-Bis(hydroxymethyl)- 3,4-dihydro-2H-[1,3]thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-one (3c).** 37% Formalin (3.0 g, 37.4 mmol) and potassium carbonate (1 g) were added to compound **1** monohydrate (3.00 g, 15.4 mmol). The mixture was stirred until full solution of compound **1** (1-1.5 h) and, with continued stirring, the solution was cooled and ethylamine hydrochloride (1.40 g, 17.2 mmol) and, portionwise, potassium carbonate (0.954 g, 9.0 mmol) were added. After 1 day the reaction mixture was cooled in an ice bath and the precipitate was filtered off, washed three times with portions of iced water, and dried in vacuo. The dried product was washed with benzene and twice with acetone.

**3-cyclohexyl-7,7-Bis(hydroxymethyl)- 3,4-dihydro-2H-[1,3]thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-one (3d)** was prepared similarly to compound **3a**. The dried material was washed with benzene.

**3-Benzyl-7,7-bis(hydroxymethyl)-3,4-dihydro-2H-[1,3]thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-one (3e).** Formalin (1 ml, 12.5 mmol) and potassium carbonate (1 g) were added to compound **1** monohydrate (0.999 g, 5.67 mmol). After 1 h benzylamine (0.608 g, 0.62 ml, 5.7 mmol) was added to the homogenous reaction mass. The reaction product was periodically agitated and the precipitate formed was triturated. After 3 h the precipitate was filtered off, washed three times with portions of water, and dried in vacuo. The dried product was washed twice with benzene.

**3-Benzhydryl-7,7-bis(hydroxymethyl)-3,4-dihydro-2H-[1,3]thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-one (3f).** 37% Formalin (2.0 ml, 24.9 mmol) and benzhydrylamine (2.09 g, 11.4 mmol) were added to compound **1** monohydrate (2.00 g, 10.3 mmol). The thickening mixture was stirred for 2 h and then periodically heated to reflux for a further 1 h. The precipitate formed on cooling was twice washed with methanol and recrystallized from butanol.

**3-*tert*-Butyl-7-(hydroxymethyl)-7-methyl-3,4-dihydro-2H-[1,3]thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-one (3g)** was prepared from compound **1b** similarly to compound **3a** from pseudothiohydantoin [4]. It was recrystallized from benzene.

**3-*tert*-Butyl-7-ethyl-7-(hydroxymethyl)-3,4-dihydro-2H-[1,3]thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-one (3h).** *tert*-Butylamine (1.53 g, 2.2 ml, 21.0 mmol) was added with stirring to compound **1c** (2.0 g, 13.9 mmol) in formalin (4.9 ml, 61 mmol) and stirred for 2.5 h. It was diluted with benzene (10 ml) and stirring was continued for a further 2 h and then left at room temperature for 2 days. The benzene layer was separated and the aqueous layer was stirred and extracted with more benzene (10 ml). The benzene extracts were combined and dried over sodium sulfate after which solvent was distilled off in vacuo with a bath temperature of 40-50°C. The oily residue crystallized with vigorous and prolonged grinding in hexane and the precipitate formed was filtered off and recrystallized from a mixture of benzene and hexane (1:10).

**3'-Methyl-2-phenyl-3',4'-dihydro-2'H-spiro[1,3-dioxan-5,7'(6H')-[1,3]thiazolo[3,2-*a*][1,3,5]triazin-6'-one] (4a).** 37% Formalin (0.55 ml, 6.85 mmol) and 25% aqueous methylamine (0.55 ml, 4.47 mmol) were added with vigorous stirring to compound **2a** (0.45 g, 1.7 mmol) in water (2 ml). The reaction product was held at room temperature for 1 day. The precipitate was filtered off and washed with water.

**3'-Methyl-2-(4-nitrophenyl)-3',4'-dihydro-2'H-spiro[1,3-dioxan-5,7'(6H')-[1,3]thiazolo[3,2-*a*][1,3,5]-triazin-6'-one] (4b)** Formalin (1.0 ml, 12.4 mmol) and an aqueous solution of methylamine (1.0 ml, 8.13 mmol) were added to compound **2b** (1.0 gm 3.23 mmol) in ethanol (15 ml) and refluxed for 5 min. After 2 h the precipitate formed on cooling the reaction product was filtered and washed twice with ethanol.

**3'-Methyl-2-(4-methylphenyl)-3',4'-dihydro-2'H-spiro[1,3-dioxan-5,7'(6H')-[1,3]thiazolo[3,2-*a*]-[1,3,5]-triazin-6'-one] (4c)** was prepared similarly to compound **4b** from compound **2c**.

**3'-Methyl-2-pyridin-3-yl-3',4'-dihydro-2'H-spiro[1,3-dioxan-5,7'(6H')-[1,3]thiazolo[3,2-*a*][1,3,5]-triazin-6'-one] (4d).** Formalin (1.2 ml, 14.9 mmol) and an aqueous solution of methylamine (1.2 ml, 9.8 mmol)

were added to compound **2d** (1.0 g, 3.77 mmol) in ethanol (4 ml) and refluxed for 3 min. The product was cooled to room temperature and left for 1 day in the fridge. The precipitate was filtered off and washed with water.

**3'-Methyl-2-pyridin-4-yl-3',4'-dihydro-2'H-spiro[1,3-dioxan-5,7'(6H')-[1,3]thiazolo[3,2-*a*][1,3,5]-triazin-6'-one] (4e).** Formalin (1.2 ml, 14.9 mmol) and an aqueous solution of methylamine (1.2 ml, 9.8 mmol) were added to compound **2e** (1.0 g, 3.77 mmol) in ethanol (3 ml) and refluxed for 3 min. The product was cooled to room temperature and poured into a Petri dish. The precipitate formed after 1 h was washed out with water, filtered, and twice washed with water.

**5,5-Bis(hydroxymethyl)-2-[(piperidinomethyl)amino]-1,3-thiazol-4(5H)-one (5a).** A mixture of compound **1b** (2.0 g,11.4 mmol), formalin (2.3 ml, 28.6 mmol), and piperidine (2.24 g, 2.6 ml, 26.3 mmol) was stirred at room temperature for 2.5 h and then left overnight. The liquid phase was distilled to dryness in vacuo at 40-50°C and the residual glassy mass was dissolved in ethanol with moderate heating and stirring. The solution obtained was left at room temperature for 2 days. The precipitate was filtered off and dried in vacuo over $CaCl_2$. Yield 2.65 g (85%); mp 158-159°C (acetonitrile). IR spectrum, ν, $cm^{-1}$: 1685 (C=O), 1595 (C=N). $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 9.15 (0.7H, s, $NH_E$); 8.56 (0.3H, s, $NH_Z$); 5.05 (0.35H, t, $J$ = 5, $OH_{ass}$); 4.86 (1.65H, m, $OH_{E+Z}$); 4.52 (0.29H, s, $C\underline{H}_2NH_{ass}$); 4.24 (1.1H, s, $C\underline{H}_2NH_E$); 3.98 (0.61H, d, $J$ = 17, $C\underline{H}_2NH_Z$); 3.72-3.62 (8H, m, $C\underline{H}_2OH$, piperidino H-2,6); 1.56-1.33 (6H, m, piperidino H-3,4,5). Found, %: C 48.44; H 6.97, N 15.39. $C_{11}H_{19}N_3O_3S$. Calculated, %: C 48.33; H 7.01; N 15.37.

**5,5-Bis(hydroxymethyl)-2-[(morpholinomethyl)amino]-1,3-thiazol-4(5H)-one (5b)** was prepared similarly to compound **5a** from compound **1a** (4.0 g, 22.7 mmol), formalin (7.4 ml, 92.1 mmol), and morpholine (4.0 g, 4 ml, 45.9 mmol). Yield 6.05 g (97%); mp 162-163°C with decomp. (from acetonitrile or a 1:10 mixture of ethanol and benzene). IR spectrum, ν, $cm^{-1}$: 1705 (C=O), 1590 (C=N). $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 9.40 (0.58H, s, $NH_E$); 8.82 (0.19H, s, $NH_{ass}$); 8.70 (0.23H, s, $NH_Z$); 5.41 (0.21H, t, $J$ = 5, $OH_{ass}$); 5.16 (1.79H, m, $OH_{E+Z}$); 4.52 (0.24H, s, $C\underline{H}_2NH_{ass}$); 4.24 (1.19H, d, $J$ = 4, $C\underline{H}_2NH_E$); 4.00 (0.57H, s, $CH_2NH_Z$); 3.70-3.37 (12H, m, $C\underline{H}_2OH$, morpholino H-2,3,5,6). Found, %: C 43.74; H 6.29; N 15.43. $C_{10}H_{17}N_3O_4S$. Calculated, %: C 43.62; H 6.22; N 15.26.

**2,2-Bis(hydroxymethyl)-6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidin-3(2H)-one (7).** Compound **6** (5.2 g, 27.0 mmol) was added portionwise to a mixture of sodium bicarbonate (2.27 g, 27.0 mmol) in water (2 ml) using a magnetic follower as stirrer. Stirring was continued and formalin (10.0 ml, 125 mmol) and triethylamine (0.335 g, 0.46 ml, 3.3 mmol) were added to the homogeneous solution obtained. Stirring was continued at room temperature for a further 3 h. The finely crystalline precipitate was filtered off and recrystallized from a mixture of *i*-PrOH and $CCl_4$ (1:4). Yield 3.72 g (64%); mp 157-159°C. IR spectrum, ν, $cm^{-1}$: 1725 (C=O), 1641 (C=N). $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 5.33 (2H, s, OH); 3.70 (2H, d, $J^{gem}_{AB}$ = 13, $C\underline{H}_AH_B$); 3.63 (2H, d, $J^{gem}_{AB}$ = 13, $CH_AC\underline{H}_B$); 3.52 (2H, t, $J$ = 7, H-7); 3.40 (2H, t, $J$ = 7, H-5); 1.70 (2H, m, H-6). Found, %: C 44.38; H 5.63; N 13.04. $C_8H_{12}N_2O_3S$. Calculated, %: C 44.43; H 5.59; N 12.95.

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