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# Synthesis of 5-(2-Hydroxyethyl)-1-thia-3,5,6,8-tetraaza- and 1,3,5,6,8-Pentaazaacenaphthylenes

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Synthesis of 5-(2-hydroxyethyl) derivatives of 1-thia-3,5,6,8-tetraaza- and 1,3,5,6,8-pentazaacenaphthylenes from 4,6-dichloro-2-methylthiopyrimidine-5-carbonitrile *via* the corresponding thieno- and pyrrolo[2,3-*d*]pyrimidines is described.

**Key words:** thieno[2,3-*d*]pyrimidine, pyrrolo[2,3-*d*]pyrimidine, cyclocondensation, 1,3,5,6,8-pentaazaacenaphthylene, 1-thia-3,5,6,8-tetraazaacenaphthylene

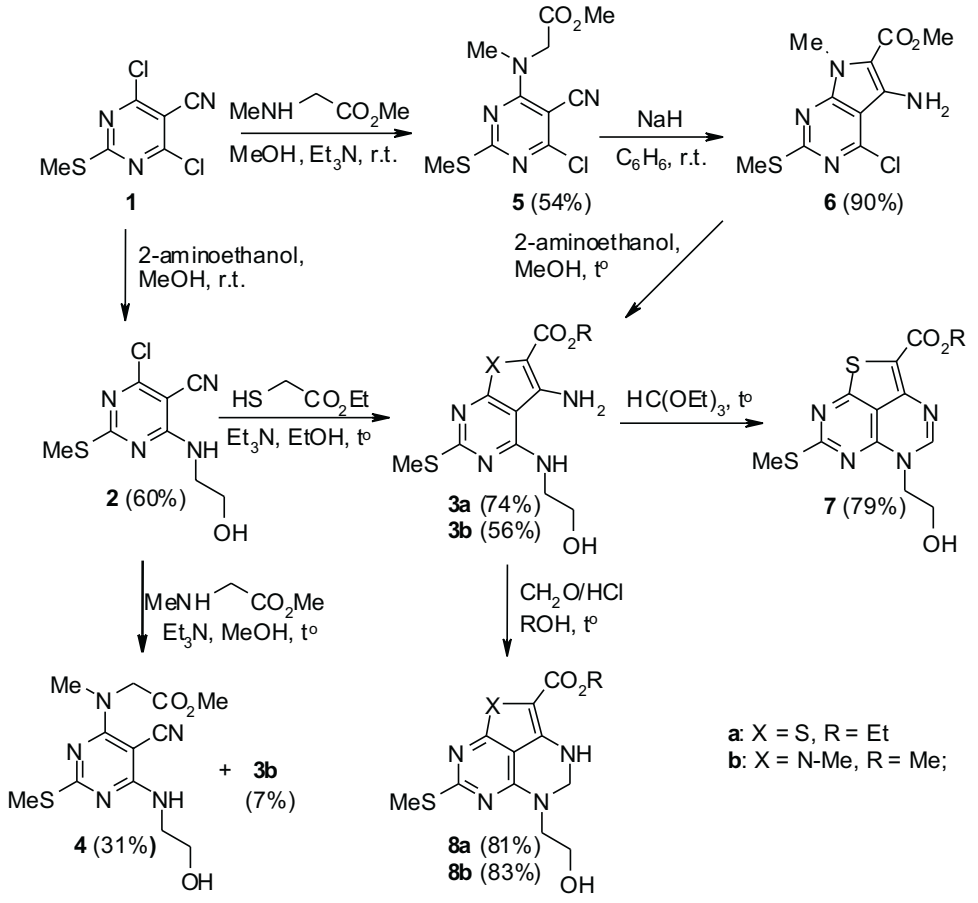
The importance of fused pyrimidines, which are common sources for the development of new potential therapeutic agents, is well known. Among them the thieno[2,3-*d*]- and pyrrolo[2,3-*d*]pyrimidine and their tri- and tetracyclic relatives are of considerable interest. They are reported to possess antihypertensive [1,2], antiinflammatory [3,4], anticancer [5–7], antiviral [8] activities and are potential antifolates [9,10]. Previously, we described the preparation of novel *peri*-fused heterocycles by the cyclocondensation of 4,5-diaminothieno[2,3-*d*]pyrimidines with nitrous acid or some one- and two-carbon C-electrophiles [11–14]. However, synthesis of the analogous heterocyclic systems, containing the pyrrolo[2,3-*d*]pyrimidine skeleton is still developed insufficiently. We now report on the preparation of 1,3,5,6,8-pentaaza- and 1-thia-3,5,6,8-tetraazaacenaphthylenes with 2-hydroxyethyl group, which can mimic the 2′-hydroxyl group of natural nucleosides [15,16]. This investigation was also stimulated by the reports that some nucleoside analogues of 1,4,5,6,8-pentaazaacenaphthylene, which is isomeric to the heterocycles described in this paper, possess potent antineoplastic activity [6,7].

## RESULTS AND DISCUSSION

For the synthesis of the target compounds an easily available 4,6-dichloro-2-methylthiopyrimidine-5-carbonitrile (**1**) [17] was used as starting material. Previously, it has been established that nitrile **1** in the reaction with ethyl mercaptoacetate affords only the disubstituted product, *i.e.* 2,4-bis(ethoxycarbonylmethylthio)-2-methylthiopyrimidine-5-carbonitrile [18]. Therefore, in order to synthesise the thienopyrimidine derivative **3a** the nitrile **1** was allowed to react with ethanolamine firstly and then a tandem nucleophilic displacement/annulation reaction of the obtained compound **2** with ethyl mercaptoacetate was carried out to give thienopyrimidine **3a** in 74%

yield (Scheme). Reaction of **2** with sarcosine ester under the analogous conditions gave a mixture of methyl N-methyl-N-[5-cyano-4-(2-hydroxyethylamino)-2-methylthiopyrimidin-6-yl]aminoacetate (**4**) and pyrrolo[2,3-*d*]pyrimidine **3b** in 31% and 7% yields, respectively. Although in the latter process an excess of triethylamine was used and the reaction mixture was refluxed for 10 h, the desired compound **3b** was isolated only as a by-product. Stronger bases capable to promote the cyclization reaction of **4**, such as sodium methoxide or sodium hydride, did not give satisfactory results, probably, because of the acidic NH and OH groups present in the hydroxyethylamino substitutent. Thus, the reaction sequence, which was applied for the preparation of thienopyrimidine **3a,** appeared to be ineffective for the synthesis of **3b**. Therefore, we elaborated another route for the synthesis of pyrrolo[2,3-*d*]pyrimidine **3b**.

Scheme



The nitrile **1** reacted with sarcosine methyl ester to give compound **5**, which upon treatment with sodium hydride in benzene at room temperature afforded the corresponding pyrrolopyrimidine **6** in 90% yield [19]. Heating **6** with ethanolamine in methanol led to the desired pyrrolopyrimidine **3b**. In order to synthesise the title compounds, reactions of **3a,b** with ethyl orthoformate and formaldehyde were carried out. Heating **3a** with ethyl orthoformate in the presence of catalytic amount of sulfuric acid, led to the formation of 1-thia-3,5,6,8-tetraazaacenaphthylene **7** in 79% yield. Unfortunately, reaction of pyrrolopyrimidine **3b** with ethyl orthoformate proceeded with the formation of a complex mixture of several products inseparable by the column chromatography. In the reaction of compounds **3a,b** with 32% aqueous formaldehyde, the cyclocondensation occurred to give the corresponding 3,4-dihydroazaacenaphthylenes **8a,b** in good yields. It is important to point out that the latter reaction was successful only when catalytic amount of hydrochloric acid was used.

Structure of compounds **2–7** was assigned on the basis of their IR and $^1$H NMR spectra. For example, in the IR spectra of **2, 4** and **5** the absorption of the CN group in a region 2200–2218 cm$^{-1}$ is observed. The IR spectra of thieno- and pyrrolo-pyrimidines **3a,b** and **6** showed the absorption of the NH and $NH_2$ groups at 3300–3413 cm$^{-1}$. In the $^1$H NMR spectra of thieno- and pyrrolopyrimidines **3a,b**, along the signals of the particular groups a singlet, due to the $NH_2$ group is observed at 7.14 and 6.27 ppm, respectively. The $^1$H NMR spectra of tricyclic compounds **7**, **8a,b** disclosed the absence of signals for a primary amino group. Instead of it signals due the protons at C(4) of **7**, **8a,b** appeared.

In conclusion, the present investigation provides simple synthetic methods for the preparation of 1-thia-3,5,6,8-tetraaza- and 1,3,5,6,8-pentaazaacenaphthylenes bearing hydroxyethyl group, obtainable only with difficulty otherwise.

## EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were run in Nujol mulls on a Perkin-Elmer FT-IR spectrophotometer Spectrum BX II. $^1$H NMR spectra were recorded on a Tesla BS 587A spectrometer (80 MHz) using tetramethylsilane as internal standard. All reactions and purity of the synthesised compounds were monitored by TLC using Silica gel 60 $F_{254}$ aluminum plates (Merck). Visualization was accomplished by UV light. All reagents and solvents were purchased from Aldrich. Microanalyses were performed by the Microanalysis Laboratory of the Department of Organic Chemistry of Vilnius University.

**6-Chloro-4-(2-hydroxyethylamino)-2-methylthiopyrimidine-5-carbonitrile (2).** To a suspension of nitrile **1** (1.5 g, 6.8 mmol) in methanol (20 mL) 2-aminoethanol (0.83 g, 13.6 mmol) was added dropwise. After 5 min the precipitate was filtered off, washed with water and recrystallized to give 1.0 g (60%) of compound **2**, m.p. 179–181°C (from 2-propanol). IR: 3403 (NH), 3331 (OH); 2218 cm$^{-1}$ (CN). $^1$H NMR ($CDCl_3$): 1.87 (1 H, t, *J*= 4.6 Hz, OH), 2.53 (3H, s, $SCH_3$), 3.72–3.92 (4H, m, $NCH_2$, $OCH_2$), 6.01 (2H, br. s, NH). Anal. Calcd. for $C_8H_9ClN_4OS$ (244.70): C, 39.3; H, 3.7; N 22.9. Found: C, 39.5; H, 3.9; N, 22.7.

**Ethyl 5-amino-4-(2-hydroxyethylamino)-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylate (3a).** A mixture of **2** (0.83 g, 3.4 mmol), ethyl mercaptoacetate (0.42 g, 3.6 mmol) and triethylamine (0.7 g, 7.0 mmol) in ethanol (15 ml) was refluxed for 4.5 h. The precipitate was filtered off, washed with 2-propanol and recrystallized to give 0.83 g (74%) of compound **3a**, m.p. 188.5–190.5°C (from

acetonitrile). IR: 3400, 3347, 3300 (NH, $NH_2$); 3157 (OH); 1672 $cm^{-1}$ (CO). $^1H$ NMR (DMSO-$d_6$): 1.29 (3 H, t, J = 7.2 Hz, $CH_3$) 2.50 (3H, s, $SCH_3$), 3.62 (4H, m, $CH_2CH_2$), 4.25 (2H, q, J = 7.2 Hz, $OCH_2$), 4.87 (1H, t, J = 4.2 Hz, OH), 7.14 (2H, br.s, $NH_2$), 7.47 (1H, br.s, NH). Anal. Calcd. for $C_{12}H_{16}N_4O_3S_2$ (328.41): C, 43.9; H, 4.9; N, 17.1. Found: C, 44.2; H, 4.6; N, 17.3.

**Methyl 5-amino-4-(2-hydroxyethylamino)-7-methyl-2-methylthio-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (3b).** To a solution of compound **6** (0.15 g, 0.5 mmol) in methanol (10 ml) 2-aminoethanol (0.06 g, 1.04 mmol) was added dropwise. The mixture was stirred at room temperature for 15 min and then refluxed for 8 h. After cooling to room temperature the precipitate was filtered off and recrystallized to give 0.09 g (56%) of compound **3b**, m. p. 234–235°C (from acetonitrile). IR: 3413, 3390, 3297 (NH, $NH_2$); 3130 (OH); 1688 $cm^{-1}$ (CO). $^1H$ NMR (DMSO-$d_6$): 2.48 (3H, s, $SCH_3$), 3.4–3.6 (4H, m, $CH_2CH_2$), 3.69 (3H, s, $NCH_3$), 3.80 (3H, s, $OCH_3$), 4.83 (1H, t, $J$ = 5.5 Hz, OH), 6.27 (2H, br. s, $NH_2$), 7.36 (1H, br. s, NH). Anal. Calcd. for $C_{12}H_{17}N_5O_3S$ (311.36): C, 46.3; H, 5.5; N, 22.5. Found: C, 46.5; H, 5.8; N, 22.7.

**Reaction of 6-chloro-4-(2-hydroxyethylamino)-2-methylthiopyrimidine-5-carbonitrile (2) with methyl ester of sarcosine.** A mixture of compound **2** (0.57 g, 2.3 mmol), methyl ester of sarcosine hydrochloride (0.35 g, 2.5 mmol) and triethylamine (0.73 g, 7.1 mmol) in methanol (15 ml) was refluxed for 10 h. After cooling to room temperature the precipitate was filtered off, washed with water and purified by column chromatography using silica gel 60 (0.063–0.200 mm) (ethyl acetate/chloroform 1:4 and then ethyl acetate). Fraction with $R_f$ 0.35 was collected. The solvent was evaporated to dryness, the solid was recrystallized to give 0.03 g (7%) of compound **3b**, m.p. 234–235°C (from acetonitrile).

The mother liquor was concentrated to dryness. The obtained solid was washed with water and recrystallized to give 0.22 g (31 %) of compound **4**, m.p. 134–135°C (from 2-propanol). IR: 3346 (NH,OH), 2200 (CN), 1742 (CO). $^1H$ NMR ($CD_2Cl_2$): 1.70 (1H, br.s, OH), 2.4 (3H, s, $SCH_3$), 3.43 (3H, s, $NCH_3$), 3.73 (3H, s, $OCH_3$), 3.6–3.86 (4H, m, $CH_2CH_2$), 4.34 (2H, s, $NCH_2$), 5.87 (1H, br.s, NH). Anal. Calcd. for $C_{12}H_{17}N_5O_3S$ (311.36): C, 46.3; H, 5.5; N, 22.5. Found: C, 46.4; H, 5.3; N, 22.3.

**Methyl 6-chloro-4-[N-(methoxycarbonylmethyl)-N-methylamino]-2-methylthio-pyrimidine-5-carbonitrile (5).** To a mixture of compound **1** (1 g, 4.5 mmol), methyl ester of sarcosine hydrochloride (1.08 g, 7.8 mmol) in methanol (15 ml) triethylamine (1.46 g, 14.4 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1.5 h, the precipitate was filtered off, washed with water and recrystallized to give 0.7 g (54%) of compound **5**, m.p. 108–109°C (from 2-propanol). IR: 2216 (CN), 1756 $cm^{-1}$ (CO). $^1H$ NMR (DMSO-$d_6$): 2.45 (s, 3 H, $SCH_3$), 3.48 (s, 3 H, $NCH_3$), 3.75 (s, 3 H, $OCH_3$), 4.5 (s, 2 H, $NCH_2$). $^{13}C$ NMR (20.082 MHz, $CDCl_3$): 14.13, 40.01, 52.5, 53.48, 84.98, 115.55, 160.87, 163.93, 168.61, 174.55. Anal. Calcd. for $C_{10}H_{11}ClN_4O_2S$ (286.74): C, 41.9; H, 3.9; N, 19.5. Found: C, 42.2; H, 3.99; N, 19.3.

**Methyl 5-amino-4-chloro-7-methyl-2-methylthio-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-carboxylate (6).** To a solution of compound **5** (2 g, 6.97 mmol) in benzene (20 ml) under argon atmosphere suspension of sodium hydride in mineral oil (60%) (1.14 g, 28.5 mmol) was added portionwise under stirring at room temperature. The reaction mixture was stirred 30 h at room temperature and then quenched with water. The benzene layer was separated and aqueous layer was extracted with benzene (2x50 ml). Organic layers were combined, washed with water several times, dried over $MgSO_4$ and evaporated under reduced pressure to dryness. The obtained residue was recrystallized to give 1.8 g (90%) of compound **6**, m.p. 149–151°C (from methanol). IR: 3502, 3385 ($NH_2$), 1684 $cm^{-1}$ (CO). $^1H$ NMR ($CDCl_3$): 2.62 (s, 3 H, $SCH_3$), 3.9 (s, 3 H, $NCH_3$), 3.94 (s, 3 H, $OCH_3$), 5.56 (br s, 2 H, $NH_2$). Anal. Calcd. for $C_{10}H_{11}ClN_4O_2S$ (286.74): C, 41.9; H, 3.9; N, 19.5. Found: C, 41.7; H, 4.1; N, 19.7.

**Ethyl 5-(2-hydroxyethyl)-7-methylthio-5*H*-1-thia-3,5,6,8-tetraazaacenaphthylene-2-carboxylate (7).** A solution of compound **3a** (0.38 g, 1.2 mmol) in triethyl orthoformate (5 ml) was heated at 100°C for 6 h. Then a drop of sulfuric acid was added. After 15 min the reaction mixture was cooled to room temperature. The precipitate was filtered off, washed with 2-propanol and recrystallized to give 0.29 g (79%) of compound **7**, m.p. 224–225°C (from ethanol). IR: 3406 (OH), 1691 $cm^{-1}$ (CO). $^1H$ NMR (DMSO-$d_6$): 1.32 (3H, t, $J$ = 8 Hz, $CH_3$), 2.55 (3H, s, $SCH_3$), 3.58–3.8 (2H, m, $OCH_2$), 4.06 (2H, t, $J$ = 6 Hz,

$NCH_2$), 4.30 (2H, q, $J$ = 8 Hz, $OCH_2$), 5.04 (1H, t, $J$ = 6 Hz, OH), 8.15 (1H, s, $C_4$-H). Anal. Calcd. for $C_{13}H_{14}N_4O_3S_2$ (338.41): C, 46.1; H, 4.2; N, 16.6. Found: 46.3; H, 3.9; N, 16.8.

**Ethyl 5-(2-hydroxyethyl)-7-methylthio-3,4-dihydro-5*H*-1-thia-3,5,6,8-tetraazaacenaphthylene-2-carboxylate (8a).** To a mixture of **3a** (0.1 g, 0.304 mmol), ethanol (8 ml) and 32% aq. formaldehyde (0.02 g, 0.67 mmol) one drop of concentrated HCl acid was added. The mixture was stirred at reflux for 24 h. After cooling to room temperature the precipitate was filtered off, washed with ethanol and recrystallized to give 0.084 g (81%) of compound **8a**, m.p. 222–223°C (from ethanol). IR: 3392 (NH), 3312 (OH), 1657 $cm^{-1}$ (CO). $^1$H NMR (DMSO-$d_6$): 1.30 (3H, t, $J$ = 7.3 Hz, $CH_3$), 2.51 (3H, s, $SCH_3$), 3.5–3.65 (4H, m, $CH_2CH_2$), 4.25 (2H, q, $J$ = 7.3 Hz, $OCH_2$), 4.82 (2H, s, $C_4$-H), 4.92 (1H, s, OH), 7.44 (1H, s, NH). Anal. Calcd. for $C_{13}H_{16}N_4O_3S_2$ (340.43): C, 45.9; H, 4.7; N, 16.5. Found: C, 45.9; H, 4.6; N, 16.7.

**Methyl 5-(2-hydroxyethyl)-1-methyl-7-methylthio-1,3,4,5-tetrahydro-1,3,5,6,8-pentaazaacenaphthylene-2-carboxylate (8b).** Compound **8b** was synthesized according to the procedure described for **8a**. Methanol was used as a solvent. Yield 83%, m.p. 228–230°C (from 2-propanol). IR: 3392 (NH), 3146 (OH); 1687 $cm^{-1}$ (CO). $^1$H NMR (DMSO-$d_6$): 2.49 (3H, s, $SCH_3$), 3.52–3.65 (4H, m, $CH_2CH_2$), 4.81 (2H, s, $C_4$-H), 4.84 (1H, br.s, OH), 7.36 (1H, br.s, NH). Anal. Calcd. for $C_{13}H_{17}N_5O_3S$ (323.38): C, 48.3; H, 5.3; N, 21.7. Found: C, 48.1; H, 5.4; N, 21.8.

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