New Results on the Reactivity of 5,6-Diamino-4-hydroxy-2-mercaptopyrimidine

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The reaction of 5,6-diamino-4-hydroxy-2-mercaptopyrimidine with mono- and α,ω-dihalocompounds has been reinvestigated. Alkyl derivatives of 5-amino group, not previously described, have been obtained as reaction products. A comparison with the reactivity of 6-amino-4-hydroxy-2-mercaptopyrimidine has been also performed.

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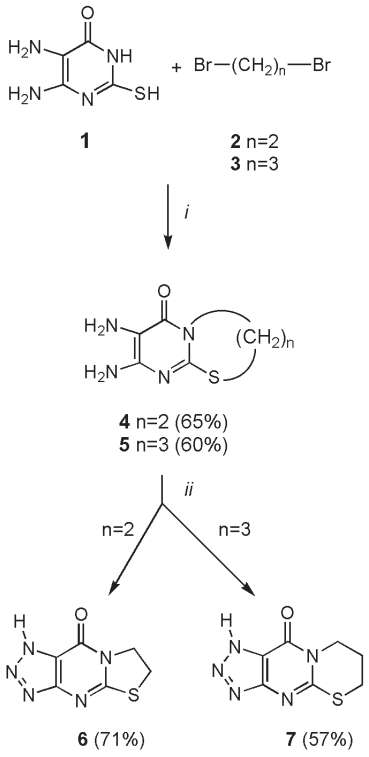
Introduction.

In the framework of our studies on polycyclic molecular structures suitable as adenosine receptor antagonists [1,2] we were interested to synthesize and to test 6,7-dihydro[1,3]thiazolo[3,2-*a*][1,2,3]triazolo[4,5-*d*]pyrimidin-9(1*H*)-one (**6**) and 7,8-dihydro-6*H*-[1,2,3]triazolo-[4',5':4,5]pyrimido[1,2-*b*][1,3]thiazin-10(1*H*)-one (**7**). A described procedure [3] gave the desired compounds starting from 5,6-diamino-4-hydroxy-2-mercaptopyrimidine (**1**) and α,ω-dihalogenoalkanes to give the pyrimidothiazoline or pyrimidothiazino moiety and then obtaining the triazole ring by using $NaNO_2$ and HCl (Scheme 1). We attempted to generalize the procedure employing α,ω-dihalogenoalkanes with increased chain length to obtain a thiazepine ring as well as monoalogenoalkanes with the aim to obtain alkylated at sulfur and at ring nitrogen structures.

Scheme 1

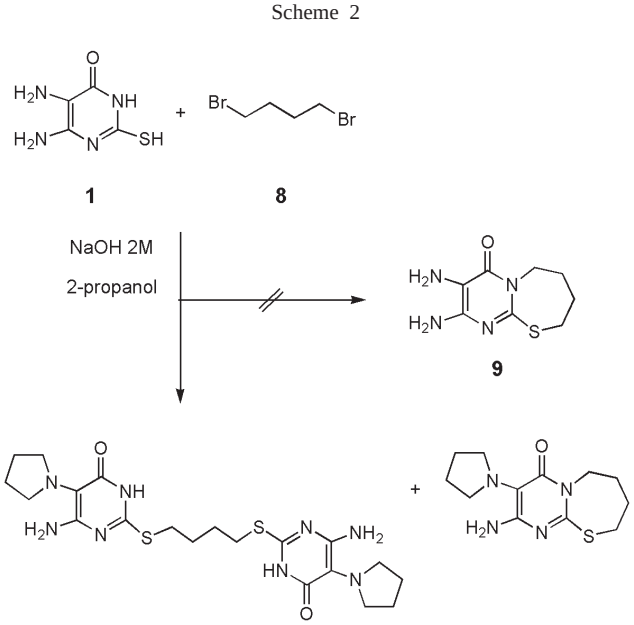


i) NaOH 2M, n-propanol. *ii*) $NaNO_2$, HCl

Results and Discussion.

First, we confirmed that **1** reacts with the dihaloderivative **2** (or **3**) to give **6** (or **7**) by the way of **4** (or **5**). Successively, we allowed **1** to react with 1,4-dibromobutane (**8**) to obtain the seven membered thiazepine ring. Marumoto and coworkers asserted [4] that the cyclization at S and N-3 of 2-mercaptopyrimidine moiety "decreases as the chain length of α,ω-dihalogenoalkanes increases" and on their substrates the 1,4-dibromobutane is a borderline reagent because they obtained the desired thiazepine derivative together with 1,4-bis(2-thioinosinyl)butane.

Scheme 2



So we attempted, in our standard conditions (NaOH 2 *M*, 2-propanol), the reaction between **1** and **8**, but we obtained (Scheme 2) a complex mixture, in which we only recovered the unexpected derivatives **10** and **11** (6% and 2%, respectively), instead of the desired compound **9**. The nature of compounds **10** and **11** was determined on the basis of their ^{1}H, ^{13}C, and mass spectra.

Another procedure, described by Pecoraro and coworkers, [5] reported the synthesis of some thio- and 3-nitrogen-dialkyl derivatives of **1** by reaction with monohalogenoalkanes in NaOH 1 *M*.

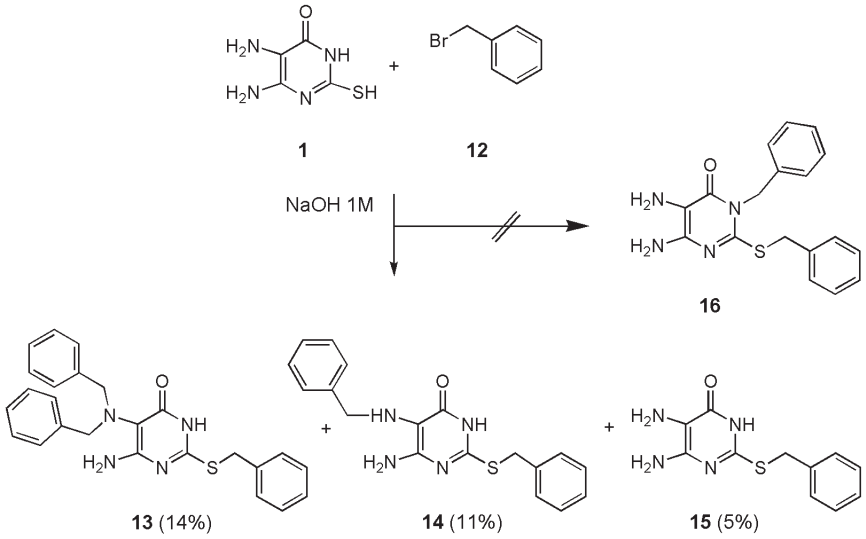
Following these reaction conditions, we obtained a complex mixture in which we recovered once again the compounds **10** (6%) and **11** (2%) in very small amount.

at different distances from the pyrimidinone ring.

We ascertained the structure of compound **14** on the basis of spectroscopic data and on the basis of a chemical proof. So, following the previously described procedure (NaOH 1 *M*) and starting from compound **14** we obtained **13** in 51% yield (see Experimental) by reaction with benzyl bromide (**12**). The alkylation site of compound **15** was also confirmed by reactivity. The reaction of **15** with 1,4-dibromobutane (**8**) gave compound **17** (Scheme 4) in 47% yield, thus confirming that the first alkylation has been on S atom.

The starting material **1**, is a polyfunctional compound and is very difficult to handle because it is insoluble in commonly used solvents for workup of reactions; its NMR

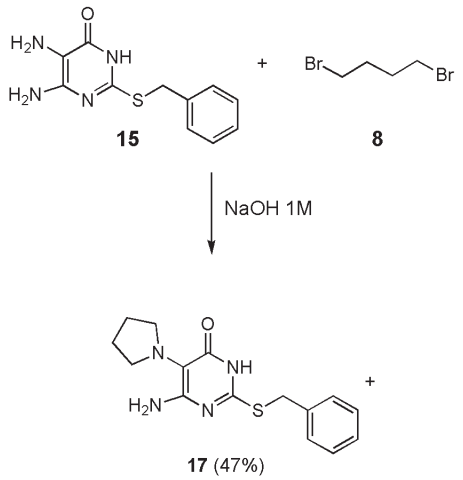
Scheme 3



This result although not unexpected, on the basis of the previous reaction, has been very intriguing for us, especially because the possibility of a different mechanism by using monohalogenoalkanes instead of 1,4-dibromobutane is not obvious. So, we repeated the reaction of **1** with benzyl bromide (**12**) as described by the Authors [5]. In our hands, the crude, after flash-chromatography, furnished compounds **13**, **14** and **15** in ratio 2.5:2:1, respectively (Scheme 3) in overall yield 30% and not the compound **16** in yield 60-80% as previously reported [5].

The ^{1}H NMR spectra (see Experimental) are consistent with the proposed structures. It can be noticed that in compound **13** the two CH_2 groups of the dibenzylamino substituent appear as isochronic AB systems. This finding is reasonable on the basis of both scale models and the results of MM calculations (program PCModel, Serena Software) showing that the dimethyleneamino moiety is perpendicular to the pyrimidinone ring and that, within each methylene group, the two protons are steadily located

Scheme 4

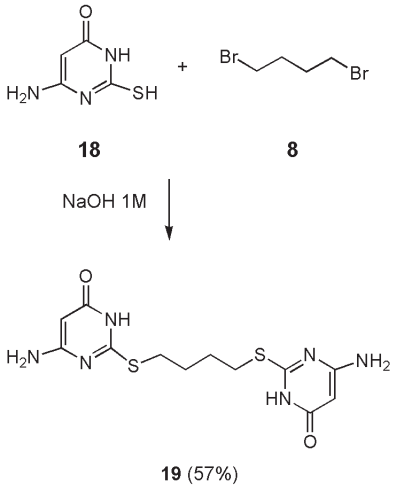


spectrum is not fully satisfactory because the molecule possess only exchangeable protons and, finally, the reactivity is probably strongly influenced by pH.

In the sodium hydroxide solution the reactive atoms are S>5-NH_2>>N-3 as summarized in Schemes 2 and 3. This is a new result, because previously the S and N-3 have been reported as the reactive atoms.

To confirm the high reactivity of the 5-NH_2 group we repeated the reaction starting from 6-amino-4-hydroxy-2-mercaptopyrimidine (**18**) and 1,4-dibromobutane (**8**) in NaOH 1 *M*. The reaction product was the bis(2-thio-6-aminouracyl)butane **19** (57%) without traces of a thiazepine derivative (Scheme 5). Finally, for sake of research, we repeated the reaction between **1** and **12** in NaOH 2M/2-propanol solvent obtaining compounds **13** and **14** in 5:1 ratio and overall yield 30%. The monobenzylderivative **15** was present only in TLC traces.

Scheme 5



19 (57%)

EXPERIMENTAL

Melting points were determined using a Büchi apparatus and are uncorrected. Ir spectra were obtained by a Perkin-Elmer FT-IR Spectrometer Spectrum 2000. NMR spectra were recorded on a Varian Mercury 400 Instrument in the Fourier transform mode at 21 ± 0.5 °C. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) chemical shifts (δ) are in ppm relative to TMS as secondary reference standard; coupling constants are in Hz. ESI-MS spectra were obtained on a micromass ZMD Waters instrument (3.2kV and 30V). Silica gel (Merck F254) and silica gel 60 (Merck 230-400 mesh) were used for analytical tlc and flash chromatography, respectively. Compounds **6** and **7** were obtained according to published procedures [3].

Reaction of 5,6-Diamino-4-hydroxy-2-mercaptopyrimidine with 1,4-Dibromobutane.

5,6-Diamino-4-hydroxy-2-mercaptopyrimidine (1 g, 6.3 mmol) was dissolved in NaOH 2 *M* (6.3 mL) and propan-2-ol (6.3 mL) was then added. 1,4-Dibromobutane (7.6 mmol) was then slowly added into the reaction mixture at room temperature, stirring continuing at the same temperature for 2 h and then at 60-70 °C for a further 5 h. The reaction mixture was extracted with $CHCl_3$ (3x20 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash-chromatography (eluant: $CHCl_3$/MeOH=97:3); the faster running band gave pure **11** (6%; mp: 176-178 °C), the slower one gave compound **10**, which was crystallized from water (2%; mp: 272-273 °C).

6-Amino-2-[(4-{[4-amino-6-oxo-5-(1-pyrrolidinyl)-1,6-dihydro-2-pyrimidinyl]thio}butyl)thio]-5-(1-pyrrolidinyl)-4(3*H*)-pyrimidinone (**10**).

Compound **10** has the following spectroscopic properties: ir (KBr): 3454, 3284, 3188, 3151, 2962, 1652, 1600, 783 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6) δ 11.40 (1H, bs exch., NH), 6.13 (2H, bs exch., NH_2), 3.06 (2H, m, SCH_2), 2.92 (4H, m, 2xNCH_2), 1.76 (4H, m, 2xCH_2), 1.68 (2H, m, CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6) δ 161.2 (C), 160.0 (C), 156.9 (C), 104.5 (C), 49.2 (2xCH_2N), 30.0 (CH_2S), 28.1 (CH_2), 25.1 (2xCH_2); ESI-MS (MeOH): 501 (**10**+Na^+).

Anal. Calcd for $C_{20}H_{30}N_8O_2S_2$: C, 50.19; H, 6.32; N, 23.41. Found: C, 50.20; H, 6.33; N, 23.38.

2-Amino-3-(1-pyrrolidinyl)-6,7,8,9-tetrahydro-4*H*-pyrimido-[2,1-*b*][1,3]thiazepin-4-one (**11**).

Compound **11** has the following spectroscopic properties: ir (KBr): 3417, 3275, 3144, 2952, 1642, 1594, 775 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6) δ 6.23 (2H, bs exch., NH_2), 4.19 (2H, m, NCH_2), 3.04 (2H, m, SCH_2), 2.95 (4H, m, 2xNCH_2), 1.92 (2H, m, CH_2), 1.80 (4H, m, 2xCH_2), 1.79 (2H, m, CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6) δ 159.4 (C), 159.0 (C), 158.0 (C), 106.0 (C), 48.9 (2xCH_2N), 43.7 (CH_2N), 31.5 (CH_2S), 27.6 (CH_2), 26.2 (CH_2), 25.1 (2xCH_2); ESI-MS (MeOH): 289 (**11**+Na^+).

Anal. Calcd for $C_{12}H_{18}N_4OS$: C, 54.11; H, 6.81; N, 21.03. Found: C, 54.13; H, 6.81; N, 21.03.

Reaction of 5,6-Diamino-4-hydroxy-2-mercaptopyrimidine with Benzyl Bromide.

Benzyl bromide (62 mmol) was added dropwise into a solution of 5,6-diamino-4-hydroxy-2-mercaptopyrimidine (5 g, 31 mmol) in NaOH 1 *M* (62 mL). The reaction mixture was kept, under stirring, for 7 h at 50-55 °C and then left overnight at room temperature. The precipitate, collected by filtration and dried on KOH was purified by flash chromatography (eluant: $CHCl_3$/MeOH=97:3) to give, in order of elution, the following three pure compounds: **13** (14%; mp: 189-190 °C); **14** (11%; mp: 172-175 °C); **15** (5%; mp: 148-151 °C).

6-Amino-2-(benzylthio)-5-(dibenzylamino)-4(*3H*)-pyrimidinone (**13**).

Compound **13** has the following spectroscopic properties: ir (KBr): 3497, 3382, 3254, 3187, 3028, 2929, 1626, 1580, 786 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6) δ 11.67 (1H, bs exch., NH), 7.38-7.19 (15H, m, H-Ar), 6.16 (2H, bs exch., NH_2), 4.23 (2H, s, CH_2S), 4.03 (4H, 2 AB systems, 2xCH_2N); ^{13}C nmr (dimethyl sulfoxide-d_6) δ 160.8 (C), 160.7 (C), 157.0 (C), 139.5 (2xC), 137.3 (C), 130.0 (2xCH), 128.7 (4xCH), 128.3 (2xCH), 127.9 (4xCH), 127.1 (CH), 126.7 (2xCH), 104.7 (C), 55.3 (2xCH_2N), 33.4 (CH_2S); ESI-MS (MeOH): 451 (**13**+Na^+).

Anal. Calcd for $C_{25}H_{24}N_4OS$: C, 70.07; H, 5.64; N, 13.07. Found: C, 70.09; H, 5.65; N, 13.05.

5,6-Diamino-3-benzyl-2-(benzylthio)-4(*3H*)-pyrimidinone (**14**).

Compound **14** has the following spectroscopic properties: ir (KBr): 3440, 3366, 3326, 3172, 3025, 2862, 1608, 1577, 781 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6) δ 11.75 (1H, bs exch., NH), 7.44-7.17 (10H, m, H-Ar), 6.12 (2H, bs exch., NH_2), 4.30 (2H, s, CH_2S), 3.96 (2H, s, CH_2N), 3.60 (1H, bs exch., NH); ^{13}C nmr (dimethyl sulfoxide-d_6) δ 160.2 (C), 155.4 (C), 153.2 (C), 140.9 (C), 137.8 (C), 129.0 (2xCH), 128.3 (2xCH), 127.9 (4xCH), 127.1 (CH), 126.5 (CH), 105.6 (C), 49.8 (CH_2N), 33.4 (CH_2S); ESI-MS (MeOH): 361 (**14**+Na^+).

Anal. Calcd for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.55. Found: C, 63.83; H, 5.35; N, 16.52.

5,6-Diamino-2-(benzylthio)-4(*3H*)-pyrimidinone (**15**).

Compound **15** has the following spectroscopic properties: ir (KBr): 3462, 3351, 3292, 3027, 2920, 1636, 1535, 751 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6) δ 11.80 (1H, bs exch., NH), 7.43-7.20 (5H, m, H-Ar), 5.81 (2H, bs exch., NH_2), 4.29 (2H, s, CH_2S), 3.58 (2H, bs exch., NH_2); ^{13}C nmr (dimethyl sulfoxide-d_6) δ 157.2 (C), 148.7 (C), 148.0 (C), 138.1 (C), 129.0 (2xCH), 128.3 (2xCH), 127.0 (CH), 106.4 (C), 33.5 (CH_2S); ESI-MS (MeOH): 271 (**15**+Na^+).

Anal. Calcd for $C_{11}H_{12}N_4OS$: C, 53.21; H, 4.87; N, 22.56. Found: C, 53.18; H, 4.89; N, 22.54.

Reaction of **14** with Benzyl Bromide.

Operating as above, but starting from compound **14** (1 g, 3 mmol) and benzyl bromide (3 mmol) we obtained the derivative **13** (51%; mp: 189-190 °C).

Reaction of **15** with 1,4-Dibromobutane.

1,4-Dibromobutane (4 mmol) was added dropwise into a solution of **15** (1 g, 4 mmol) in NaOH 1 *M* (8 mL). The reaction mixture was kept, under stirring, for 2 h and then at 60-70 °C for a further 5 h. The reaction mixture was then kept, under stirring, for 7 h at 50-55 °C and finally left overnight at room temperature. The precipitate, collected by filtration and dried on KOH, was purified by flash-chromatography (eluant: $CHCl_3$/MeOH=98:2) to yield compound **17** (47%; mp: 184-186 °C).

6-Amino-2-(benzylthio)-5-(1-pyrrolidinyl)-4(3*H*)-pyrimidinone (**17**).

Compound **17** has the following spectroscopic properties: ir (KBr): 3440, 3272, 3183, 3125, 2962, 2912, 1605, 1557, 783 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6) δ 11.65 (1H, bs exch., NH), 7.46-7.26 (5H, m, H-Ar); 6.29 (2H, bs exch., NH_2), 4.34 (2H, s, SCH_2), 2.97 (4H, m, 2xNCH_2), 1.81 (4H, m, 2xCH_2); ^{13}C nmr (dimethyl sulfoxide-d_6) δ 161.2 (C), 160.2 (C), 156.7 (C), 137.9 (C), 129.2 (2xCH), 128.4 (2xCH), 127.1 (CH), 104.6 (C), 49.2 (2xCH_2N); 33.4 (CH_2S), 25.1 (2xCH_2); ESI-MS (MeOH): 325.0 (**17**+Na^+).

Anal. Calcd for $C_{15}H_{18}N_4OS$: C, 59.58; H, 6.00; N, 18.53. Found: C, 59.61; H, 6.00; N, 18.51.

Reaction of 6-Amino-4-hydroxy-2-mercaptopyrimidine with 1,4-Dibromobutane.

1,4-Dibromobutane (7.44 mmol) was added dropwise into a solution of 6-amino-4-hydroxy-2-mercaptopyrimidine monohydrate **18** (1 g, 6.2 mmol) in NaOH 1 *M* (12.4 mL). The reaction mixture was kept, under stirring, for 3 h at 50-55 °C. After cooling, the resultant precipitate was collected by filtration. The solution was cooled to 0 °C and acidified to pH=3 with AcOH; the solid was then collected by filtration. The combined precipitates were purified by flash chromatography ($CHCl_3$/MeOH=95:5) to yield compound **19** (57%; mp: 176-178 °C).

6-Amino-2-({4-[4-amino-6-oxo-1,6-dihydro-2-pyrimidinyl]-thio}butyl)thio)-4(3*H*)-pyrimidinone (**19**)

Compound **19** has the following spectroscopic properties: ir (KBr): 3468, 3410, 3326, 3202, 3018, 2922, 1617, 1576, 803 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6) δ 11.40 (1H, bs exch., NH), 6.41 (2H, bs exch., NH_2), 4.90 (1H, s, H-5), 3.10 (2H, m, CH_2S), 1.72 (2H, m, CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6) δ 164.2 (C), 163.5 (C), 162.1 (C), 81.3 (C), 28.8 (CH_2S), 28.1 (CH_2); ESI-MS (MeOH): 363 (**19**+Na^+).

Anal. Calcd for $C_{12}H_{16}N_6O_2S_2$: C, 42.34; H, 4.74; N, 24.69. Found: C, 42.31; H, 4.75; N, 24.67.

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