9,9'-Thiobis-(1,2,3,4,7,8-hexahydro-7-methyl-6*H*-pyrimido[1,6-*a*]pyrimidine-6,8-dione)

Ondrej Šimo, Alfonz Rybár*, Juraj Alföldi, and Vladimír Pätoprstý

Institute of Chemistry, Slovak Academy of Sciences, Dubravska cesta 9,
SK-84238 Bratislava, Slovak Republik

Received September 9, 1998

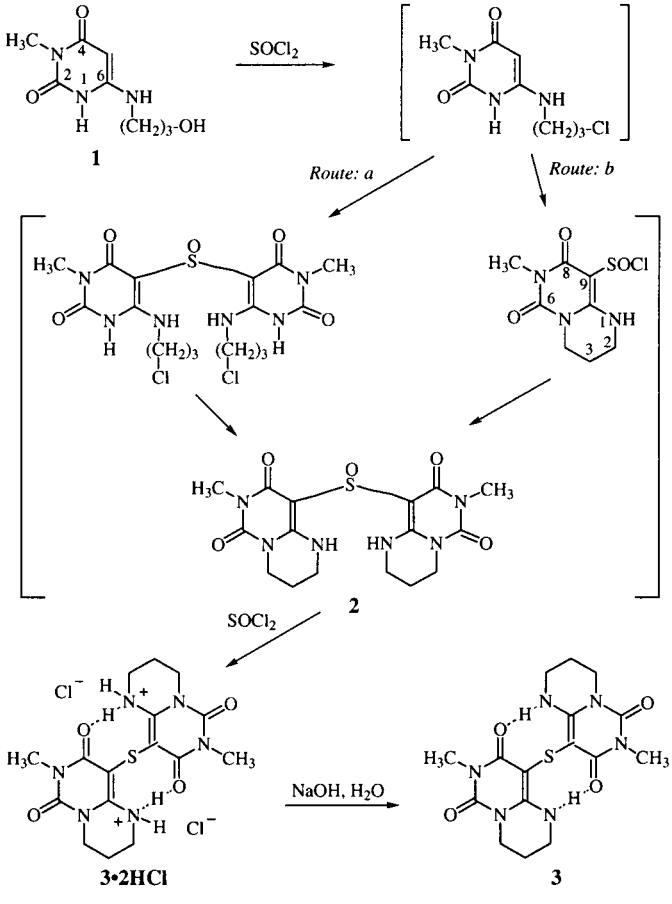
The 6-(3-hydroxypropylamino)-3-methylpyrimidine-2,4-dione (**1**) did not afford the expected 6-(3-chloropropylamino)- derivative on reaction with thionyl chloride, but, instead, the pyrimidine rings were joined *via* a sulfur bridge to give 9,9'-thiobis(1,2,3,4,7,8-hexahydro-7-methyl-6*H*-pyrimido[1,6-*a*]pyrimidine-6,8-dione) (**3**). An identical 9,9'-thiobis- derivative **3** was obtained when reacting thionyl chloride with 1,2,3,4,7,8-hexahydro-7-methyl-6*H*-pyrimido[1,6-*a*]pyrimidine-6,8-dione (**4**). We suppose the sulfoxide- derivative **2** to be the intermediate of both routes: it underwent reduction to the final sulfide **3** in excess thionyl chloride.

J. Heterocyclic Chem., **36**, 453 (1999).

Introduction.

The 2-step synthesis of the important intermediate - 2-alkylpyrimido[*c*,*d*]purinediones - for the intended preparation of 1,2,3,4,7,8-hexahydro-7-methyl-6*H*-pyrimido[1,6-*a*]-pyrimidine-6,8-dione (**4**) from 6-(3-hydroxypropylamino)-3-methylpyrimidine-2,4-dione (**1**) and thionyl chloride failed. As found, the first step did not lead to the expected 6-(3-chloropropylamino)- derivative and consequently, the intermediate **4** could not be obtained by an intramolecular alkylation in this way. Surprisingly enough, two pyrimidinedione ring systems were joined together through a sulfur bridge. After the synthesis of 2-alkylpyrimido[*c*,*d*]purinediones was solved [1], we returned to the above-mentioned reaction of 6-(3-hydroxypropylamino)- derivative **1** with thionyl chloride and investigated it in more detail. It should be noted that reaction of thionyl chloride with pyrimidinediones in pyridine has already been studied [2], whereby a derivative of 6-benzylaminopyrimidine-2,4-dione gave rise

Scheme 1



to 4,6-dimethyl-2-phenyl-4,5,6,7-tetrahydro-5,7-dioxothiazolo[4,5-*d*]pyrimidine.

Results and Discussion.

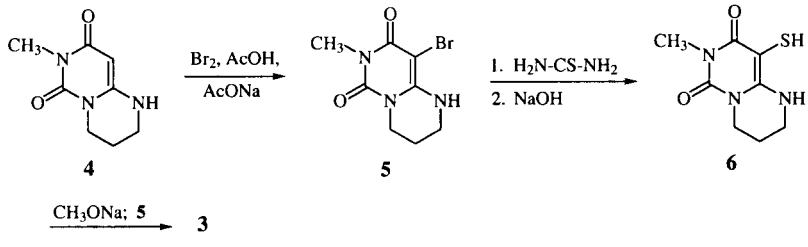
We found that the previously mentioned reaction of 6-(3-hydroxypropylamino)- derivative **1** occurred satisfactorily with thionyl chloride to provide 9,9'-thiobis-(1,2,3,4,7,8-hexahydro-7-methyl-6*H*-pyrimido[1,6-*a*]pyrimidine-6,8-dione) (**3**) in aromatic inert solvents (benzene or toluene) or in chlorinated hydrocarbons (chloroform or carbon tetrachloride) producing the required product as the dihydrochloride **3**. The latter compound was transformed into its base **3** with aqueous alkali hydroxide. We presume that the first step involved replacement of both of the active hydrogen atoms at position 5 of pyrimidinedione by an sulfinyl chloride group and the hydroxyl group in position 6 of the side chain by chlorine. Routes *a* or *b* (Scheme 1) led then to sulfoxide **2** in the second step. Both routes involved an intramolecular cyclization by elimination of hydrogen chloride from the chloropropylamine side chain and the acidic N-1 hydrogen due to the presence of sulfoxi- or sulfinyl chloride groups in position 5 of the pyrimidine ring system. Like cyclizations were reported with 6-(3-hydroxypropylamino)- and 6-(2-hydroxyethylamino)-5-nitropyrimidine-2,4-diones giving on heating in dimethylformamide [3] 9-nitro-1,2,3,4,7,8-hexahydro-7-methyl-6*H*-pyrimido[1,6-*a*]pyrimidine-6,8-dione and 8-nitro-1,2,3,4,6,7-hexahydro-6-methylimidazo[1,2-*c*]pyrimidine-5,7-dione, respectively, by removing a water molecule from the 6-hydroxypropylamino group and the N-1 hydrogen proton acidified by the nitro grouping in position 5 of the pyrimidine ring.

6*H*-pyrimido[1,6-*a*]pyrimidine-6,8-dione (**6**). The starting 9-bromo- derivative **5** was obtained by bromination of compound **4** in acetic acid and the intermediate **6** from the bromo- derivative *via* the corresponding thiuronium salt and subsequent decomposition in alkaline medium (Scheme 2).

An analogous substitution of the active hydrogen at position 5 of starting compound **1**, as known with the reaction with thionyl chloride, also took place with mesyl chloride where, in addition to mesylation of the hydroxypropylamino group at position 6. Concurrent intramolecular cyclization was observed yielding 9-methylsulfonylpyrimido[1,6-*a*]pyrimidinedione derivative **7**. This reaction required, however, the presence of triethylamine to neutralize hydrogen chloride produced (Scheme 3). Reduction of the sulfonyl group to sulfide and its desulfuration by Raney nikel afforded the pyrimido[1,6-*a*]pyrimidinedione derivative **4**.

Reaction of compound **4** with thionyl chloride gave the same 9,9'-thiobis- derivative **3**. This fact is in agreement with our presumption of the formation pathway from 6-(3-hydroxypropylamino)- derivative **1**. In contrast to the procedure illustrated in Scheme 1, the expected sulfoxide **2** could be detected in the mixture after reaction of pyrimido[1,6-*a*]pyrimidinedione **4** with thionyl chloride. Nevertheless, this compound is extraordinarily unstable and undergoes decomposition to the starting compound **4** in the presence of water and methanol even at room temperature. A substantially slower decomposition was observed in the presence of ethanol; this finding was exploited when effecting chromatographic separation in chloroform:ethanol 8:2. These experiments furnished

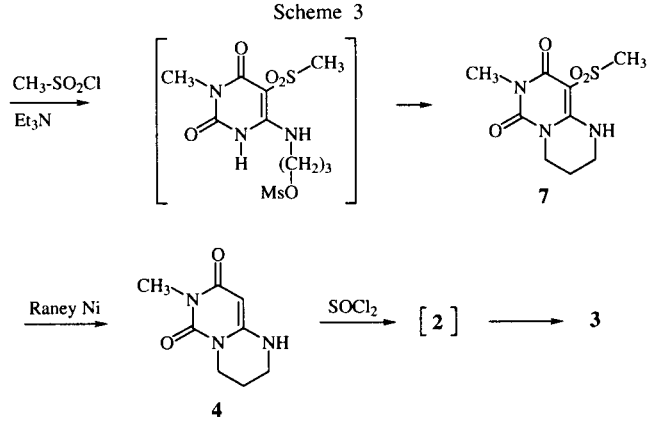
Scheme 2



By analogy with the use of thionyl chloride one can presume that 9,9'-thiobis- derivative **3** can only be formed *via* the corresponding sulfoxide intermediate **2**, which could not be, however, isolated and evidenced in the reaction of 6-(3-hydroxypropylamino)- derivative **1** with thionyl chloride. Since no common reduction agent capable to reduce sulfoxide **2** to sulfide **3** was present in the medium, we presumed that thionyl chloride had to be responsible for this reaction oxidizing itself to sulfuryl chloride. Reduction of sulfoxides by this agent have already been reported in the literature [4,5].

The structure of 9,9'-thiobis- derivative **3** was confirmed by synthesis from 9-bromo- **5** and 9-mercapto-3-methyl-

Scheme 3



only fractions enriched with sulfoxide **2** from which ir spectra were taken. The presence of the sulfoxide group was established by the appearence of a band at 1016 cm^{-1}. Fractions enriched with sulfoxide **2** reacted with thionyl chloride almost immediately to provide the 9,9'-thiobis- derivative **3**.

Attemps to obtain sulfoxide **2** also by oxidation of the 9,9'-thiobis- derivative **3** with various agents used commonly for oxidation of a sulfide to a sulfoxide (hydrogen peroxide, *m*-chloroperbenzoic acid, sodium periodate, nitrous acid, phenyltrimethylammonium tribromide, manganese dioxide) failed. Either oxidation of the sulfide did no occur, or destruction took place. Consequently, none of the products of all of these experiments showed the sulfoxide absorption band in its ir spectrum.

The structure of intermediates **4-7** and of the final product **3** were verified by elemental analysis, ^{1}H-nmr spectra and also by mass spectra. The nmr signal data were ascribed employing the standard procedures of the Bruker apparatus program: DEPT, single-frequency decoupling, 2D-COSY and 1D C-H correlations. The spatial arrangement of compound **3** was assigned early on in this project by an X-ray analysis [6].

EXPERIMENTAL

All chemicals employed were of reagent grade and used without further purification. Melting points were determined on a hot-stage microscope (Boetius). The nmr measurements were run on a Bruker AM-300 spectrometer operating at 300.13 MHz for ^{1}H-nmr in 5 mm broadband or 5 mm ^{1}H-nmr probes. The spectra were recorded at 25° in deuteriochloroform or in dimethyl-d_6 sulfoxide, tetramethylsilane being the internal reference. Elemental analyses were carried out with a Carlo Erba model 1106 Elemental Analyser. Reactions were monitored by tlc on Silufol UV_{254} sheets (Kavalier, Votice, Czech Republic) in chloroform-methanol (9:1) and spots were located by uv light. Sodium sulfate was used to dry organic solutions.

9,9'-Thiobis-(1,2,3,4,7,8-hexahydro-7-methyl-6*H*-pyrimido-[1,6-*a*]pyrimidine-6,8-dione) Dihydrochloride (**3. 2 HCl**).

Thionyl chloride (2.28 ml, 3.72 g, 31.25 mmoles) was added to a stirred suspension of compound **1** (2.50 g, 12.5 mmoles) in toluene (18 ml), the mixture was heated slowly to 100° (*ca.* 1 hour) and this temperature was maintained constant for an additional 4 hours. Volatile components were distilled under reduced pressure and the residue treated with chloroform (70 ml) was refluxed for 15 minutes. The cooled suspension (30°) was filtered, the powdery beige product was washed with chloroform (30 ml, 50°) and dried under diminished pressure, yield 2.13 g (73%), mp >320°; ms: (m/z) 392 (M^+ - 2 HCl); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 2.11 (quintet, 4H, 2x H-3), 3.21 (s, 6H, 2x N-CH_3), 3.55 (t, 4H, 2x H-2), 3.82 (t, 2H, 2x H_A-4), 3.98 (t, 2H, 2x H_B-4), 8.47 (t, 2H, CH_2-N^+H···O=C), 11.17 (s, 2H, CH_2-N^+-H···O=C).

Anal. Calcd. for $C_{16}H_{22}Cl_2N_6O_4S$: C, 41.30; H, 4.77; Cl, 15.24; N, 18.06; S, 6.89. Found: C, 41.09; H, 4.66; Cl, 15.33; N, 17.77; S, 6.71.

9,9'-Thiobis-(1,2,3,4,7,8-hexahydro-7-methyl-6*H*-pyrimido-[1,6-*a*]pyrimidine-6,8-dione) **3**.

Method A.

Dihydrochloride **3•2HCl** (930 mg, 2.0 mmoles) was suspended in water (20 ml) and dissolved by addition of 1*M* sodium hydroxide (4.0 ml, 4.0 mmoles) with stirring at ambient temperature. Base **3** separated after *ca.* 10 minutes and was filtered, washed with water and air-dried, yield 675 mg (86%).

Method B.

Thionyl chloride (1.92 g. 1.18 ml, 16.14 mmoles) was added dropwise to a stirred suspension of pyrimido[1,6-*a*]pyrimidine-dione **4** (1.95 g, 10.76 mmoles) in toluene (25 ml) and the mixture was heated to 90° for 3 hours. The volatile portion was distilled under reduced pressure and the residue was crystallized from ethanol-water (1:1, 200 ml), yield 1.15 g (54%).

Method C.

Sodium methoxide in methanol (1*M*, 0.2 ml, 0.20 mmole) was added to a suspension of the 9-mercapto- derivative **6** (43 mg, 0.20 mmole) in ethanol-dioxane (1:1, 20 ml). The solution thus formed was treated with 9-bromo- derivative **5** (52 mg, 0.20 mmole) and refluxed for 5 hours. Solvents were removed under diminished pressure and the product was dissolved in hot chloroform (10 ml). The chloroform extract was concentrated to half volume and the title compound precipitated by addition of diethyl ether (8 ml), yield 69 mg (88%), mp 317-319° (ethanol-water, 1:1); ms: (m/z) 392 (M^+); ^{1}H-nmr (deuteriochloroform): 2.04 (quintet, 4H, 2x H-3), 3.32 (s, 6H, 2x N-CH_3), 3.53 (dt, 4H, 2x H-2), 3.84 (t, 2H, H_A-4), 3.99 (t, 2H, H_B-4), 9.12 (s, 2H, NH···O=C).

Anal. Calcd. for $C_{16}H_{20}N_6O_4S$: C, 48.97; H, 5.14; N, 21.42; S, 8.17. Found: C, 48.91; H, 5.15; N, 21.21; S, 8.32.

9-Bromo-1,2,3,4,7,8-hexahydro-7-methyl-6*H*-pyrimido[1,6-*a*]-pyrimidine-6,8-dione **5**.

Sodium acetate trihydrate (708 mg, 5.2 mmoles) was first added to a stirred solution of compound **4** (724 mg, 4.0 mmoles); bromine (780 mg, 0.23 ml, 4.5 mmoles) in acetic acid (2.5 ml) was then added droppwise to the mixture at room temperature during 5 minutes. Stirring was continued for 2 hours, then acetic acid was removed under diminished pressure and the residue was extracted with chloroform (3 x 30 ml) at reflux temperature. The combined extracts were evaporated to dryness under reduced pressure and the crude bromo- derivative was crystallized from ethanol-water (1:1, 60 ml), yield 790 mg (76%), mp 240-244° dec (ethanol-water, 1:1); ms: (m/z) 261, 259 (M^+); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 2.01 (quintet, 2H, H-3), 3.25 (s, 3H, N-CH_3), 3.39 (t, 2H, H-2), 3.89 (t, 2H, H-4), 7.41 (bs, 1H, NH).

Anal. Calcd. for $C_8H_{10}BrN_3O_2$: C, 36.94; H, 3.88; N, 16.16; Br, 30.72. Found: C, 37.06; H, 3.79; N, 15.93; Br, 30.61.

9-Mercapto-1,2,3,4,7,8-hexahydro-7-methyl-6*H*-pyrimido-[1,6-*a*]pyrimidine-6,8-dione **6**.

Compound **5** (260 mg, 1.0 mmole) and thiourea (77 mg, 1.0 mmole) in ethanol (10 ml) were refluxed with stirring for 1.5 hours. Ethanol was removed under reduced pressure and the remaining residue was refluxed in chloroform-dioxane (1:1, 10 ml, 30 minutes) to remove the unreacted components. The required thiuronium bromide, separating after cooling, was filtered and dried under reduced pressure at room temperature, yield 311 mg (93%).

The product (310 mg, 0.92 mmole) dissolved in water was treated with a mixture of 1*M* sodium hydroxide (2.03 ml, 2.03 mmoles) and water (3.7 ml) with stirring at 70° for 10 minutes. The 9-mercapto- derivative **6** separated successively after addition of alkali and conversion of the thiuronium bromide was completed during 30 minutes. The crystals which separated were filtered and dried *in vacuo*, yield 129 mg (66%), mp 241-243° (water); ms: (m/z) 213 (M^+); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 2.02 (quintet, 2H, H-3), 3.21 (s, 3H, N-CH_3), 3.39 (t, 2H, H-2), 3.42 (s, 1H, SH), 3.89 (t, 2H, H-4), 7.88 (bs, 1H, NH).

Anal. Calcd. for $C_8H_{11}N_3O_2S$: C, 45.06; H, 5.20; N, 19.70; S, 15.03. Found: C, 44.82; H, 5.04; N, 19.54; S, 14.97.

9-(Methylsulfonyl)-1,2,3,4,7,8-hexahydro-7-methyl-6*H*-pyrimido-[1,6-*a*]-pyrimidine-6,8-dione **7**.

Mesyl chloride (13.9 ml, 0.18 mole) in dichloromethane (20 ml) was added dropwise to a stirred solution of compound **1** (11.95 g, 60 mmoles) and triethylamine (41.8 ml, 0.30 mole) in dichloromethane (450 ml) during 15 minutes at room temperature. The stirred mixture was allowed to react for 5 hours at the same temperature. The volatile portion was distilled under reduced pressure and the residue was crystallized from ethanol-water (12:5, 170 ml), yield 11.5 g (74%), mp 210-212° (ethanol-water, 12:5); ms: (m/z) 259 (M^+); ^{1}H-nmr (deuteriochloroform): δ 2.09 (quintet, 2H, H-3), 3.30 (s, 3H, N-CH_3), 3.34 (s, 3H, SO_2-CH_3), 3.46 (dt, 2H, H-2), 3.99 (t, 2H, H-4), 9.04 (bs, 1H, NH).

Anal. Calcd. for $C_9H_{13}N_3O_4S$: C, 41.69; H, 5.05; N, 16.21; S, 12.37. Found: C, 41.78; H, 5.10; N, 15.91; S, 12.47.

7-Methyl-1,2,3,4,7,8-hexahydro-6*H*-pyrimido[1,6-*a*]pyrimidine-6,8-dione **4**.

Method A.

Powdered zinc (10 g) was added successively to solution of compound **7** (5.19 g, 20 mmoles) in concentrated hydrochloric acid (40 ml) during 2 hours. The starting material was fully consumed after *ca.* 5 hours (tlc). The mixture was then concentrated to a thick sirup under diminished pressure and diluted with water (400 ml). The *p*H value was adjusted to 8 and the solution was vacuum-evaporated to dryness. The residue was extracted with chloroform (3 x 150 ml) at reflux temperature, the organic layer was dried (sodium sulfate), concentrated to drynes under diminished pressure and the residue was crystallized from ethanol-diethyl ether (2:1, 75 ml), yield 0.90 g (25%).

Method B.

A mixture composed of compound **7** (1.4 g, 5.4 mmoles), water (120 ml) and Raney nickel T4 (freshly prepared, 8.0 g, moist) was refluxed with stirring for 1.5 hours. The catalyst was filtered off, the filtrate was extracted with chloroform (4 x 40 ml), the combined extracts were dried (sodium sulfate), vacuum-evaporated to drynes and the residue was crystallized from acetone (150 ml), yield 0.76 g (78%), mp 274-277° (ethanol); ms: (m/z) 181 (M^+); ^{1}H-nmr (deuteriochloroform): δ 2.08 (quintet, 2H, H-3), 3.31 (s, 3H, N-CH_3), 3.38 (t, 2H, H-4), 3.42 (t, 2H, H-2), 4.81 (s, 1H, H-9), 5.19 (bs, 1H, NH).

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.87; H, 6.30; N, 22.97.

Acknowledgement.

This work was partially suported by a grant from the Slovak Grant Agency (project No. 2/4144/97) and partially by pharmaceutical corporation SLOVAKOFARMA, Hlohovec, Slovak Republic.

REFERENCES AND NOTES

[1] O. Šimo, A. Rybár, J. Alföldi, *Synthesis*, 837 (1995).

[2] J. W. Daly, O. Hong, W. L. Padgett, M. T. Shamim, K. A. Jacobson, and D. Ukena, *Biochem. Pharmacol.*, **37**, 655 (1988).

[3] E. Uhlmann and W. Pfleiderer, *Heterocycles*, **15**, 437 (1981).

[4] N. P. Volinskii, G. D. Gal'pern, and V. V. Smolzaninov, *Neftekhimiya*, **4**, 371 (1964); *Chem. Abstr.*, **61**, 8245f (1964).

[5] R. Tanikaga, K. Nakayama, K. Tanaka, and A. Kaji, *Chem. Letters*, 395 (1977).

[6] V. Kettmann, A. Bozóová, and A. Rybár, *Acta Cryst.*, **C51**, 1861 (1995).