*Chemistry of Heterocyclic Compounds, Vol. 36, No. 1, 2000*

# PRODUCTS OF THE REACTION OF 2-CHLORO-6-THIO-7-METHYL-PURINE WITH AMINES

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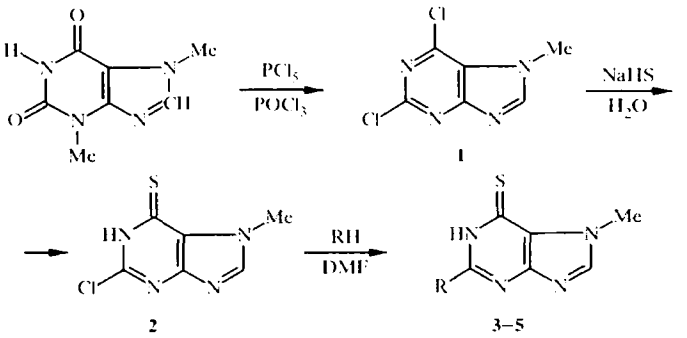
*Treatment of 2-chloro-6-thio-7-methylpurine with aniline, piperidine, or morpholine with heating in DMF gives 2-phenylamino(piperidino or morpholino)-6-thio-7-methylpurine. The scheme for the formation of the side products 2,6-dithio- and 2,6-dipiperidino-7-methylpurine is discussed.*

**Keywords:** chloropurine, thiopurines, chlorothiopurines, aminopurines, aniline, morpholine, piperidine.

6-Thiopurine, thioguanine and their derivatives show antileucosis and immunodepressant activity [1, 2]. With the aim of searching for novel biologically active compounds, it was of interest to synthesize some 2-amino-substituted 6-thio-7-methylpurines. The starting material was theobromine, from which we obtained 2,6-dichloro-7-methylpurine (**1**) by method [3] and 2-chloro-6-thio-7-methylpurine (**2**) from the latter by method [4].

Bearing in mind the low mobility of the chlorine atom in the position 2 of the purine ring, the reaction of chlorothiopurine **2** with aniline, piperidine, and morpholine was carried out under refluxing in DMF for 14-20 h using an excess of amine. The products were the previously unreported 2-phenylamino-, 2-piperidino-, and 2-morpholino-6-thio-7-methylpurines (**3-5**).




**3** R = PhNH; **4** R = piperidyl; **5** R = morpholyl

The low yields of compounds **3-5** (~25%) served to encourage a more detailed study of the reaction. The reaction turned out to be accompanied by side reactions. The formation of 2,6-dithio-7-methylpurine (**6**) was observed in about 30% yield in almost all cases.

Compound **6** has been reported in the literature and, for comparison, it was synthesized from compound **1** and sodium hydrosulfide according to the method [4]. Samples of this substance, prepared by the different methods, proved to be identical.

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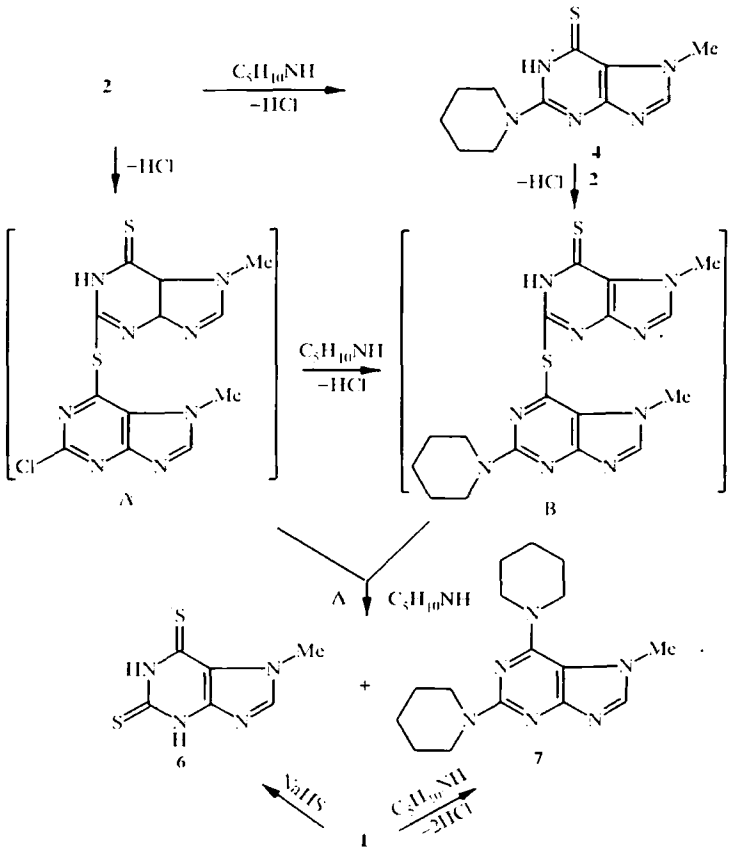
 0009-3122/00/3601-0074$25.00

The detailed study of the reaction of chlorothio compound **2** with piperidine allowed us to show the presence of a further side product (2,6-dipiperidino-7-methylpurine (**7**)). It could not be separated in the pure state but its presence in the reaction product was proved chromatographically. For comparison of compound **7**, it was synthesized from the dichloro compound **1** and piperidine by the method reported in study [5]. The $R_f$ values for samples of compound **7** proved to be identical.

Scheme 1



The formation of compounds **6** and **7** through reaction of chlorothio compound **2** with piperidine can probably be rationalized by initial reaction of starting compound **2** when heated in DMF with partial splitting off a molecule of hydrogen chloride to give sulfide (A). A second possible reaction route may be formation of sulfide B, which is obtained from chlorothiopurine **2** and 2-piperidino-6-thio-7-methylpurine (**4**). Under the reaction conditions sulfide A can be converted to sulfide B. Upon heating with piperidine, both sulfides can undergo a nucleophilic substitution reaction with cleavage of the $C_{(6)}$–S bond and formation of a mixture of compounds **6** and **7**.

When heated, 6-alkyl(carbalkoxy)thiopurines react with ammonia, and with primary and secondary amines with fission of the $C_{(6)}$–S bond to give the corresponding 6-aminopurine derivatives. 6-Carboxymethyl-7-methylpurine and ammonia gave 6-amino-7-methylpurine [6].

The reactions of compound **2** when heated with piperidine in DMF are given in Scheme 1. The reaction of **2** with morpholine also probably occurs similarly to that with piperidine.

The IR spectra of compounds **3-5** show bands in the regions of 3080-3600 and 1050-1200 $cm^{-1}$, typical for stretching vibrations of the NH and CS groups respectively.

## EXPERIMENTAL

IR spectra were taken on a UR-10 or a Perkin-Elmer 457 instrument using vaseline oil. TLC of the compounds was carried out on Silufol UV-254 plates using the system butanol–acetic acid–water (5:1:4) and visualized by iodine vapor or in UV light.

**2,6-Dichloro-7-methylpurine (1)** was prepared from theobromine by method [3]. Yield 95%; mp 194-195°C (water).

**2-Chloro-6-thio-7-methylpurine (2)** was obtained from compound **1** and NaSH using method [4]. It was purified by precipitation with acetic acid from an aqueous NaOH solution. Yield 94%; mp > 250°C (decomp.).

**2-Phenylamino-6-thio-7-methylpurine (3).** Mixture of compound **2** (4.0 g, 0.02 mol) and aniline (20.0 g, 0.45 mol) in anhydrous DMF (40 ml) was refluxed for 14 h, cooled, and the precipitate was filtered off, washed with water, and dried. Yield 1.3 g (25%); mp 264-265°C (with decomp., from DMF). IR spectrum: 3180, 3330 $cm^{-1}$ (NH). Found, %: C 56.30; H 4.63; N 26.97; S 12.12. $C_{11}H_{11}N_5O_2S$. Calculated, %: C 56.01; H 4.31; N 27.22; S 12.46.

**2-Piperidino-6-thio-7-methylpurine (4), 2,6-Dithio-7-methylpurine (6), and 2,6-Dipiperidino-7-methylpurine (7).** Mixture of compound **2** (3.0 g, 0.015 mol) and piperidine (11.0 g, 0.13 mol) was refluxed in anhydrous DMF (60 ml) for 14 h. The solution was evaporated in vacuo to volume of 10 ml, cooled, and the precipitate formed (mixture of compounds **4** and **6** according to TLC) was filtered off and crystallized from DMF. Compound **6** was obtained (0.46 g, 31%); mp > 300°C. IR spectrum: 3100 $cm^{-1}$ (NH). Found, %: C 36.15; H 3.37; N 28.10; S 32.35. $C_6H_6N_4S_2$. Calculated, %: C 36.35; H 3.05; N 28.26; S 32.34.

After removal of compounds **4** and **6** from 10 ml of the filtrate, water (10 ml) was added. The precipitate formed (1.1 g) was filtered (according to TLC it consisted of a mixture of compounds **4** and **7** with $R_f$ 0.57 and 0.33 respectively) and crystallized from water to give pure compound **4** (0.9 g, 24%) as yellow crystals; mp 210-212°C (decomp.). $R_f$ 0.57. IR spectrum: 3280, 3380, 3620 $cm^{-1}$ (NH). Found, %: C 53.24; H 5.75; N 27.76; S 13.25. $C_{11}H_{15}N_5S$. Calculated, %: C 52.99; H 6.06; N 28.09; S 12.86.

**2-Morpholino-6-thio-7-methylpurine (5) and 2,6-Dithio-7-methylpurine (6).** Mixture of compound **2** (6.0 g, 0.03 mol) and morpholine (12.0 g, 0.14 mol) was refluxed for 20 h in anhydrous DMF (60 ml). The solution was cooled, poured into water (140 ml), and neutralized by addition of acetic acid to pH 6. The precipitate formed (1.9 g, according to TLC a mixture of compounds **5** and **6**) was filtered off and crystallized from DMF to give pure compound **6** (0.8 g, 27%); mp > 300°C. IR spectrum: 3100 $cm^{-1}$.

After removal of precipitate of compounds **5** and **6** from the aqueous-DMF filtrate a precipitate (2.4 g) of impure compound **5** separated gradually on standing (over 16 h). It was crystallized from water to give pure compound **5** (1.9 g, 25%); mp 254-256°C (decomp.). IR spectrum: 3100, 3200, 3260 $cm^{-1}$ (NH). Found, %: C 47.65; H 5.42; N 27.87; S 12.97. $C_{10}H_{13}N_5OS$. Calculated, %: C 47.79; H 5.21; N 27.87; S 12.76.

**2,6-Dithio-7-methylpurine (6)** was prepared from compound **1** and NaSH in water with heating as described in method [4]; mp > 300°C (decomp.). IR spectrum: 3100 $cm^{-1}$ (NH).

**2,6-Dipiperidino-7-methylpurine (7)** was prepared from compound **1** and piperidine by method [5] with the difference that the reaction was carried out not in dioxane but in DMF (7 h reflux). Yield 63%; mp 177-178°C (benzene–petroleum ether), $R_f$ 0.33.

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