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# Unusual Reaction of 8-Bromo-3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-diones with Trisamine in Dimethylformamide

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**Abstract**—The reaction of 8-bromo-substituted 3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-diones with trisamine in DMF gave, instead of the expected 8-tris(hydroxymethyl)methylamino-substituted products, 8-dimethylamino-substituted 3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-diones. The formation of unusual reaction products was explained by the initial reaction of DMF with trisamine to form dimethylamine and subsequent nucleophilic substitution reaction of the latter with the bromine atom.

**Keywords:** 3,7-dihydro-1*H*-purine-2,6-diones, thietanes, trisamine, DMF, dimethylamine, nucleophilic substitution

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8-Substituted 3,7-dihydro-1*H*-purine-2,6-diones are of interest as potentially biologically active compounds [1–4]. 3,7-Dihydro-1*H*-purine-2,6-dione substituted in the 8-position are most commonly synthesized by the reaction of 8-halo-3,7-dihydro-1*H*-purine-2,6-diones with various nucleophilic reagents. We synthesized water-soluble 8-amino-substituted 3,7-dihydro-1*H*-purine-2,6-diones exhibiting hemorheological activity by the reaction of 8-bromo-substituted 3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-diones and hydrophilic amines (such as monoethanolamine) and piperazine, whose strongly basic amino groups allow facile salt formation [5–7].

Proceeding with the search for biologically active compounds among 3,7-dihydro-1*H*-purine-2,6-dione derivatives, we focused on the hydrophilic amine trisamine [2-amino-2-(hydroxymethyl)propane-1,3-diol]. The reaction of 8-bromo-substituted 3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-diones **1a–1h** with a 3-fold molar excess of trisamine in DMF under reflux for 1 h gave, instead of the expected 8-tris(hydroxymethyl)-methylamino-substituted products, 8-(dimethylamino)-substituted 3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-diones **2a–2h** (Scheme 1) in yields of 42–90%.

The composition and structure of compounds **2a–2h** were confirmed by elemental analysis and IR and NMR spectroscopy. The IR spectra show no stretching vibration bands of the O–H and N–H bonds of the trisamine residue, and the spectrum of compound **2a** displays the ν(N$^1$–H) band at 3230–3100 cm$^{-1}$.

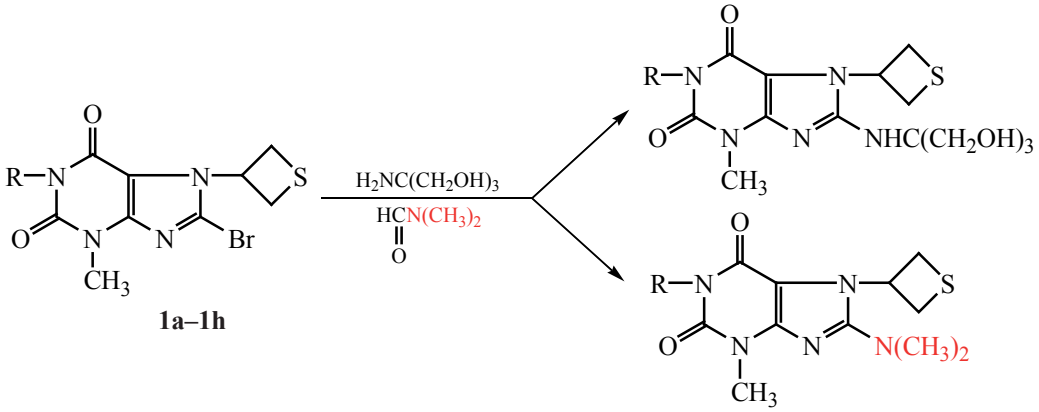
The $^1$H NMR spectra contain signals of the alkyl and methyl substituents on N$^1$ and N$^3$, characteristic multiplets of thietane ring protons, as well as a six-proton singlet at 2.9 ppm. The trisamine NH and OH protons do not appear in the $^1$H NMR spectra. The $^{13}$C NMR spectra contain, along with the carbon signals of the N$^1$ and N$^3$-substituents, thietane ring, and xanthine core, the 8-N$(CH_3)_2$ carbon signal at 42.9 ppm. The 8-NHC and $(CH_2OH)_3$ signals are lacking.

The mixed sample of compound **2b** with the sample obtained in a yield of 52% by the reaction of compound **1b** with dimethylamine in ethanol under reflux in an autoclave (Scheme 2), gave no melting point depression, and the spectral characteristics of the two samples coincided.

We suggested that the reaction of compounds **1a–1h** with trisamine in boiling DMF involves initial reaction of trisamine with the solvent to form dimethylamine (Scheme 3), and the latter then enters nucleophilic substitution reaction with the bromine atom.

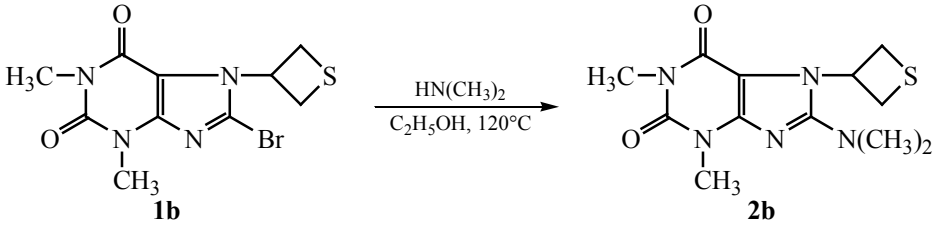
To obtaine evidence for this suggestion, we replaced DMF with methylformamide. As would be expected, the

**Scheme 1.**




R = H (**a**), Me (**b**), Et (**c**), Pr (**d**), Bu (**e**), $C_5H_{11}$ (**f**), $C_6H_{13}$ (**g**), Bn (**h**).

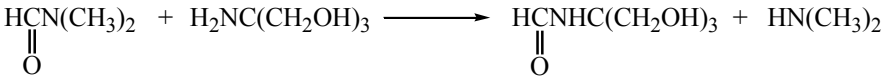
**Scheme 2.**



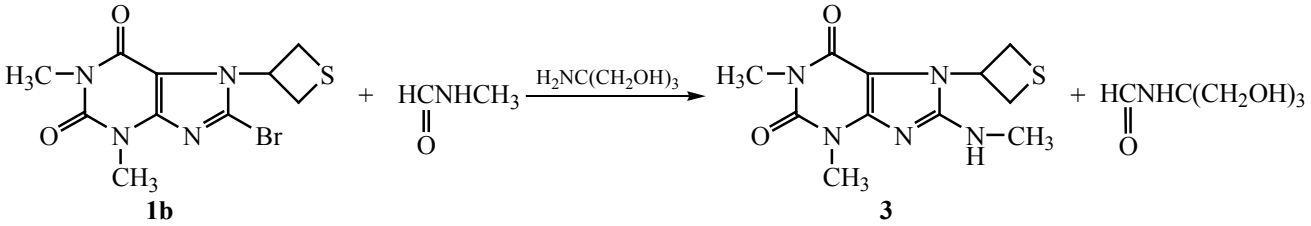

reaction of compound **1b** with trisamine in methylformamide gave 1,3-dimethyl-8-(methylamino)-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-dione **3** (Scheme 4) in a yield of 45%. The IR spectrum of compound **3** contains a stretching absorption band of the secondary N–H bond at 3364 $cm^{-1}$. In the $^1H$ NMR spectrum, the 8-NH proton appears as a quartet centered at 7.29 ppm, and the 8-$NCH_3$ proton appears as a doublet at 2.87 ppm (*J* 4.5 Hz). The $^{13}C$ NMR spectrum shows a 8-$NCH_3$ carbon signal at 29.26 ppm, and the 2D $^1H$–$^{15}N$ HMBC spectrum displays a methylamino nitrogen signal at 56.46 ppm.

Thus, the reaction of 8-bromo-substituted 3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-diones with trisamine in DMF forms, instead of the expected 8-tris(hydroxymethyl)methylamino-substituted products, 8-dimethylamino-substituted 3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-diones. This reaction opens up the way to the synthesis of 8-(dimethylamino)-3,7-dihydro-1*H*-purine-2,6-diones without using gaseous dimethylamine, thereby excluding the use of sealed tubes or an autoclave. The fact that the reaction with methylformamide occurs in a similar way suggests the

**Scheme 3.**




**Scheme 4.**



need to study this reaction with other formamides and heterocyclic derivatives.

## EXPERIMENTAL

The IR spectra were measured on an Infralyum FT-02 spectrophotometer in KBr pellets. The $^1$H and $^{13}$C NMR spectra were registered on Bruker AM-300 (300 and 75 MHz, respectively) and Bruker AV-500 spectrometers (500 and 125 MHz, respectively), using residual proton signals of deuterated solvents as internal reference. The elemental analyses were obtained on a Euro3000 Hekatech analyzer. The melting points were measured on a Stuart SMP30 apparatus. The individuality of the synthesized compounds was confirmed by TLC on Sorbfil plates (eluent butanol–acetic acid–water, 4 : 1 : 2), the spots were visualized by exposure to iodine vapor.

Compounds **1** were synthesized as described in [8–10].

**Compounds 2a–2h** (*general procedure*). A solution of 4 mmol of 1-substituted 8-bromo-3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-dione **1a–1h** and 1.45 g (12 mmol) of trisamine in 30 mL of DMF was heated under reflux for 1 h. After cooling, the reaction mixture was diluted with 30 mL of water. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from ethanol.

**8-(Dimethylamino)-3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2a).** Yield 0.71 g (63%), white crystals, mp 223–225°C (decomp.). IR spectrum, ν, cm$^{-1}$: 3230–3100 (N–H), 1690, 1604 (C=O, C=N, C=C). $^1$H NMR spectrum (500 MHz, DMSO-$d_6$), δ, ppm: 2.87 s [6H, 8-N($CH_3$)$_2$], 3.24–3.27 m [2H, S($CH$)$_2$], 3.32 s (3H, 3-$CH_3$), 4.12–4.15 m [2H, S($CH$)$_2$], 5.32–5.40 m (1H, 7-CH), 10.98 s (1H, NH). $^{13}$C NMR spectrum (125 MHz, DMSO-$d_6$), δ, ppm: 29.02 (3-$CH_3$), 36.09 [S($CH_2$)$_2$], 42.81 [8-N($CH_3$)$_2$], 51.95 (7-CH), 104.60 (C$^5$), 150.72 (C$^4$), 151.26 (C$^2$), 154.56 (C$^6$), 158.07 (C$^8$). Found, %: C 46.67; H 5.57; N 24.64. $C_{11}H_{15}N_5O_2S$. Calculated, %: C 46.96; H 5.37; N 24.89.

**8-(Dimethylamino)-1,3-dimethyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2b).** Yield 0.50 g (42%), white crystals, mp 182–183°C. IR spectrum, ν, cm$^{-1}$: 1698, 1654, 1611 (C=O, C=N, C=C). $^1$H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 2.92 s [6H, 8-N($CH_3$)$_2$], 3.22–3.28 m [2H, S($CH$)$_2$], 3.45 s (3H, 1-$CH_3$), 3.52 s (3H, 3-$CH_3$), 4.33–4.39 m [2H, S($CH$)$_2$], 5.43–5.56 m (1H, 7-CH). Found, %: C 48.67; H 5.69; N 23.52. $C_{12}H_{17}N_5O_2S$. Calculated, %: C 48.80; H 5.80; N 23.71.

**8-(Dimethylamino)-1-ethyl-3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2c).** Yield 0.96 g (77%), white crystals, mp 186–188°C. IR spectrum, ν, cm$^{-1}$: 1686, 1658, 1651, 1608 (C=O, C=N, C=C). $^1$H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 1.26 t (3H, $CH_3$, *J* 7.0 Hz,), 2.92 s [6H, 8-N($CH_3$)$_2$], 3.21–3.30 m [2H, S($CH$)$_2$], 3.51 s (3H, 3-$CH_3$), 4.13 q (2H, 1-$CH_2$, *J* 7.0 Hz), 4.32–4.42 m [2H, S($CH$)$_2$], 5.42–5.56 m (1H, 7-CH). Found, %: C 50.24; H 6.31; N 22.36. $C_{13}H_{19}N_5O_2S$. Calculated, %: C 50.47; H 6.19; N 22.64.

**8-(Dimethylamino)-3-methyl-1-propyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2d).** Yield 0.87 g (67%), white crystals, mp 174–176°C. IR spectrum, ν, cm$^{-1}$: 1694, 1655, 1650, 1612 (C=O, C=N, C=C). $^1$H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 0.98 t (3H, $CH_3$, *J* 7.4 Hz), 1.64–1.78 m (2H, $CH_2$), 2.93 s [6H, 8-N($CH_3$)$_2$], 3.22–3.31 m [2H, S($CH$)$_2$], 3.53 s (3H, 3-$CH_3$), 4.00–4.08 m (2H, 1-$CH_2$), 4.34–4.43 m [2H, S($CH$)$_2$], 5.44–5.58 m (1H, 7-CH). Found, %: C 52.28; H 6.61; N 21.30. $C_{14}H_{21}N_5O_2S$. Calculated, %: C 51.99; H 6.54; N 21.65.

**1-Butyl-8-(dimethylamino)-3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2e).** Yield 1.21 g (90%), white crystals, mp 135–138°C. IR spectrum, ν, cm$^{-1}$: 1693, 1648, 1616 (C=O, C=N, C=C). $^1$H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 0.93 t (3H, $CH_3$, *J* 7.2 Hz), 1.31–1.45 m (2H, $CH_2$), 1.57–1.69 m (2H, $CH_2$), 2.91 s [6H, 8-N($CH_3$)$_2$], 3.19–3.28 m [2H, S($CH$)$_2$], 3.50 s (3H, 3-$CH_3$), 3.99–4.07 m (2H, 1-$CH_2$), 4.31–4.39 m [2H, S($CH$)$_2$], 5.41–5.55 m (1H, 7-CH). Found, %: C 53.55; H 6.59; N 20.54. $C_{15}H_{23}N_5O_2S$. Calculated, %: C 53.39; H 6.87; N 20.75.

**8-(Dimethylamino)-3-methyl-1-pentyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2f).** Yield 1.25 g (89%), white crystals, mp 114–115°C. IR spectrum, ν, cm$^{-1}$: 1693, 1653, 1611 (C=O, C=N, C=C). $^1$H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 0.86 t (3H, $CH_3$, *J* 6.8 Hz), 1.30–1.33 m [4H, ($CH_2$)$_2$], 1.60–1.67 m (2H, $CH_2$), 2.90 s [6H, 8-N($CH_3$)$_2$], 3.19–3.24 m [2H, S($CH$)$_2$], 3.48 s (3H, 3-$CH_3$), 3.98–4.02 m (2H, 1-$CH_2$), 4.31–4.35 m [2H, S($CH$)$_2$], 5.42–5.50 m (1H, 7-CH). $^{13}$C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 14.06 ($CH_3$), 22.50 ($CH_2$), 27.85 ($CH_2$), 29.13 ($CH_2$), 29.71 (3-$CH_3$), 35.84 [S($CH_2$)$_2$], 41.72 (1-$CH_2$), 42.89 [8-N($CH_3$)$_2$], 51.80 (7-CH), 105.00 (C$^5$), 148.93 (C$^4$), 151.50 (C$^2$), 154.43 (C$^6$), 157.61 (C$^8$). Found, %: C 54.74; H 7.02; N 19.63. $C_{16}H_{25}N_5O_2S$. Calculated, %: C 54.68; H 7.17; N 19.93.

**8-(Dimethylamino)-1-hexyl-3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2g).** Yield 1.20 g (82%), white crystals, mp 108–110°C. IR spectrum, ν, cm$^{-1}$: 1691, 1657, 1650, 1611 (C=O, C=N, C=C). $^1$H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 0.88 t (3H, $CH_3$, *J* 7.0 Hz), 1.28–1.42 m [6H, $(CH_2)_3$], 1.63–1.70 m (2H, $CH_2$), 2.93 s [6H, 8-N$(CH_3)_2$], 3.24–3.28 m [2H, S$(CH)_2$], 3.52 s (3H, 3-$CH_3$), 4.03–4.07 m (2H, 1-$CH_2$), 4.36–4.40 m [2H, S$(CH)_2$], 5.46–5.54 m (1H, 7-CH). $^{13}$C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 14.08 ($CH_3$), 22.65 ($CH_2$), 26.71 ($CH_2$), 28.16 ($CH_2$), 29.74 (3-$CH_3$), 31.64 ($CH_2$), 35.86 [S$(CH_2)_2$], 41.80 (1-$CH_2$), 42.91 [8-N$(CH_3)_2$], 51.83 (7-CH), 105.04 (C$^5$), 148.95 (C$^4$), 151.53 (C$^2$), 154.47 (C$^6$), 157.61 (C$^8$). Found, %: C 55.49; H 7.20; N 19.01. $C_{17}H_{27}N_5O_2S$. Calculated, %: C 55.86; H 7.45; N 19.16.

**1-Benzyl-8-(dimethylamino)-3-methyl-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2h).** Yield 1.10 g (74%), yellowish white crystals, mp 165–167°C. IR spectrum, ν, cm$^{-1}$: 1696, 1654, 1642, 1618 (C=O, C=N, C=C). $^1$H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 2.92 s [6H, 8-N$(CH_3)_2$], 3.24–3.28 m [2H, S$(CH)_2$], 3.50 s (3H, 3-$CH_3$), 4.37–4.42 m [2H, S$(CH)_2$], 5.26 s (2H, 1-$CH_2$), 5.45–5.54 m [1H, 7-CH], 7.21–7.53 m (5H, $C_6H_5$). $^{13}$C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 29.80 (3-$CH_3$), 35.90 [S$(CH_2)_2$], 42.86 [8-N$(CH_3)_2$], 44.49 (1-$CH_2$), 51.89 (7-CH), 104.94 (C$^5$), 127.31 (CH-*p*), 128.29 (2CH-*m*), 128.83 (2CH-*o*), 137.73 (C$^1_{arom}$), 149.19 (C$^4$), 151.58 (C$^2$), 154.43 (C$^6$), 157.82 (C$^8$). Found, %: C 58.52; H 5.62; N 18.49. $C_{18}H_{21}N_5O_2S$. Calculated, %: C 58.20; H 5.70; N 18.85.

**Independent synthesis of compound 2b.** A steel autoclave was charged with 1.32 g (4 mmol) of compound **1b**, 50 mL of ethanol, and 12.03 g of 30% aqueous dimethylamine (80 mmol). The autoclave was closed and heated at 120°C for 5 h. After completion of the reaction and cooling, the autoclave was opened (no excess pressure was found) and unloaded, the reaction mixture was evaporated to dryness, the residue was poured with 25 mL of water, and the solid material was filtered off, washed with water, and dried. Yield 0.61 g (52%), white crystals, mp 183–184°C (EtOH). IR spectrum, ν, cm$^{-1}$: 1698, 1653, 1611 (C=O, C=N, C=C). $^1$H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 2.93 s [6H, 8-N$(CH_3)_2$], 3.22–3.28 m [2H, S$(CH)_2$], 3.45 s (3H, 1-$CH_3$), 3.52 s (3H, 3-$CH_3$), 4.33–4.39 m [2H, S$(CH)_2$], 5.43–5.56 m (1H, 7-CH). Found, %: C 48.55; H 5.68; N 23.49. $C_{12}H_{17}N_5O_2S$. Calculated, %: C 48.80; H 5.80; N 23.71.

**1,3-Dimethyl-8-(methylamino)-7-(thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3).** A solution of 0.66 g (2 mmol) of compound **1b** and 0.73 g (6 mmol) of trisamine in 15 mL of methylformamide was heated under reflux for 1 h. The reaction mixture was cooled down, and the precipitate that formed was filtered off, washed with water, and dried. Yield 0.25 g (45%), white crystals, mp 279°C (decomp., EtOH). IR spectrum, ν, cm$^{-1}$: 3364 (N–H), 1689, 1648, 1609 (C=O, C=N, C=C). $^1$H NMR spectrum (500 MHz, DMSO-$d_6$), δ, ppm: 2.87 d (3H, 8-N$CH_3$, *J* 4.5 Hz), 3.17–3.21 m [2H, S$(CH)_2$], 3.25 s (3H, 1-$CH_3$), 3.36 s (3H, 3-$CH_3$), 4.15–4.19 m [2H, S$(CH)_2$], 5.49–5.58 m (1H, 7-CH), 7.29 q (1H, 8-NH, *J* 4.5 Hz). $^{13}$C NMR spectrum (125 MHz, DMSO-$d_6$), δ, ppm: 27.74 (1-$CH_3$), 29.26 (8-N$CH_3$), 29.40 (3-$CH_3$), 35.83 [S$(CH_2)_2$], 48.79 (7-CH), 102.02 (C$^5$), 149.89 (C$^4$), 150.91 (C$^2$), 152.84 (C$^6$), 153.31 (C$^8$).$^{15}$N NMR spectrum (50 MHz, DMSO-$d_6$), δ, ppm: 56.457 (8-N), 114.523 (N$^3$), 139.487 (N$^7$), 145.159 (N$^1$), 190.600 (N$^9$). Found, %: C 46.59; H 5.77; N 24.61. $C_{11}H_{15}N_5O_2S$. Calculated, %: C 46.96; H 5.37; N 24.89.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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