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SYNTHESIS OF 7-METHYL-6-(NITROIMIDAZOLYL)THIOPURINES

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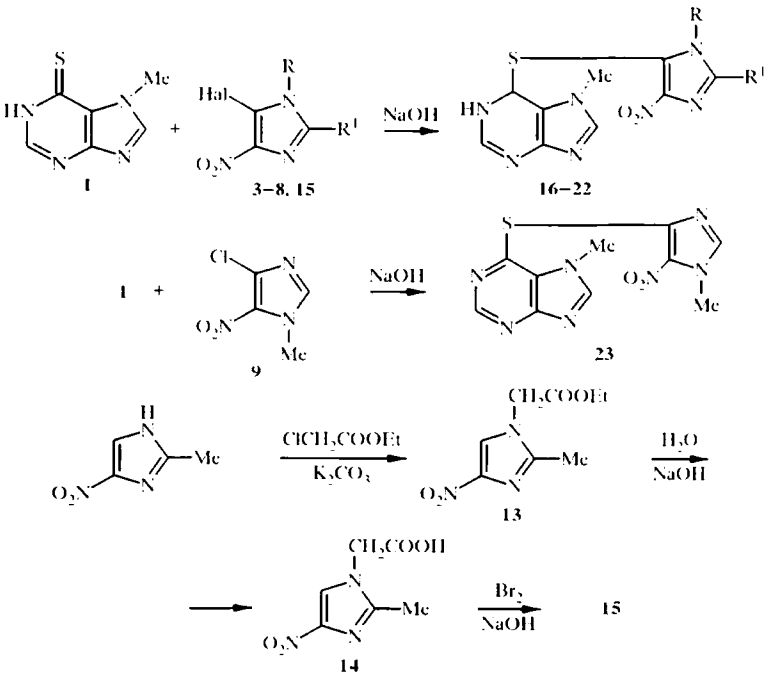
We have studied the reactions of 7-methyl-6-thiopurine with 5(4)-halo-4(5)-nitroimidazoles and 6-chloro-7-methylpurine with sodium and ammonium salts of 5-mercapto-4-nitroimidazoles. We have obtained a series of 7-methyl-6-(nitroimidazolyl)thiopurines not previously described in the literature.

Keywords: thiopurines, chloropurines, nitrohaloimidazoles, nitromercaptoimidazoles, nitroimidazolylthiopurines.

Extending work on synthesis of 5-(nitroimidazolyl)thiopurines [1-3] which exhibit immunodepressant action [4-6], we have synthesized a series of 7-methyl-6-(nitroimidazolyl)thiopurines not previously described in the literature. We have investigated two synthesis methods for these compounds, using 6-thio- (**1**) and 6-chloro-7-methylpurine (**2**) as the starting compounds.



3, **8**, **16**, **19** R = Me; **4**, **6**, **17**, **21** R = Bu; **7**, **18** R = H; **5**, **20** R = Pr; **22** R = CH_2COOH; **3**, **4**, **16**, **17** R^1 = H; **7**, **8**, **15**, **18**, **19**, **22** R^1 = Me; **5**, **20** R^1 = Et; **6**, **21** R^1 = Pr; **1-6**, **9** Hal = Cl; **7**, **8**, **15** Hal = Br

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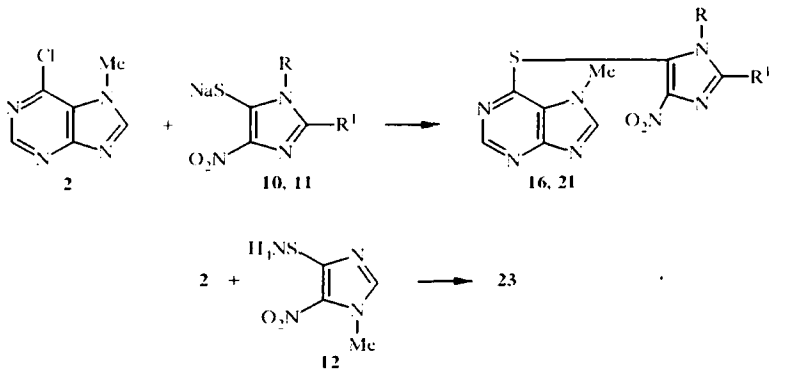
The first method involves reacting thiopurine **1** with 5(4)-halo-4(5)-nitroimidazoles (**3-9, 15**). 5-Bromo-1-carboxymethyl-2-methyl-4-nitroimidazole (**15**) was obtained from 2-methyl-4(5)-nitroimidazole *via* compounds **13** and **14** according to the scheme presented below. The reaction was carried out with boiling in water, 50-96% ethanol, or isopropanol in the presence of sodium hydroxide. The process was continued for 1-7 h. The yield of compounds **16-23** is 62% to 92%.

The second method involves reaction of chloropurine **2** with sodium or ammonium salts of 5-mercapto-4-nitro- and 4-mercapto-5-nitroimidazoles (**10-12**). The reaction proceeds with heating in ethanol, aqueous ethanol, or water over a 3-5 h period. The yield of compounds **16, 21, 23** is 61% to 90%.



10, 16 R = Me, R^1 = H; **11, 21** R = Bu, R^1 = Pr

The structure of the compounds **16-23** obtained was established based on elemental analysis data, IR spectra, and also alternate synthesis routes for compounds **16**, **21**, and **23**. These compounds, obtained by two methods, proved to be identical.

In the IR spectra of compounds **16-23**, there are absorption bands from the NO_2 group in the 1320-1370 cm^{-1} and 1530-1560 cm^{-1} region. In the IR spectrum of compound **22**, there is also a band in the 1710 cm^{-1} region, assigned to CO stretching vibrations.

TABLE 1. Characteristics of Synthesized Compounds **16-23**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, % (method)
		C	H	N	S		
16	$C_{10}H_9N_5O_2S$	41.15 / 41.23	3.32 / 3.11	33.68 / 33.66	11.18 / 11.01	254-255	92 (A) 83 (B)
17	$C_{15}H_{15}N_5O_2S$	46.62 / 46.84	4.71 / 4.54	29.23 / 29.41		184-185	81 (A)
18	$C_{10}H_9N_5O_2S$	41.00 / 41.23	3.06 / 3.11	33.30 / 33.66	10.91 / 11.01	224-225	62 (A)
19	$C_{11}H_{11}N_5O_2S$	43.47 / 43.27	3.88 / 3.63	31.69 / 32.11	10.59 / 10.50	238-239	81 (A)
20	$C_{11}H_9N_5O_2S$	48.32 / 48.40	5.09 / 4.93		9.33 / 9.23	179-181	83 (A)
21	$C_{16}H_{21}N_5O_2S$	51.35 / 51.18	5.68 / 5.64	25.54 / 26.12	8.82 / 8.54	178-179	80 (A) 90 (B)
22	$C_{12}H_{11}N_5O_3S$	41.43 / 41.26	3.20 / 3.17	28.07 / 28.07	9.18 / 9.18	207-208	68 (A)
23	$C_{10}H_9N_5O_2S$	41.33 / 41.23	3.14 / 3.11	33.87 / 33.66	10.91 / 11.01	182-183	69 (A) 61 (B)

EXPERIMENTAL

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

7-Methyl-6-thiopurine (1) was obtained according to the method [7]. Yield 70%; mp 306-307°C (dec., from water).

6-Chloro-7-methylpurine (2) was obtained according to the method [8]. Yield 82%; mp 198-199°C (toluene).

1-Methyl-, 1-Butyl-, 2-Ethyl-1-propyl- and 1-Butyl-5-chloro-4-nitro-2-propylimidazoles (3-6) were obtained according to the methods [9, 10].

5(4)-Bromo-2-methyl-4(5)-nitro- (7) and 5-Bromo-1,2-dimethyl-4-nitro- (8) imidazoles were obtained according to the method [11].

4-Chloro-1-methyl-5-nitroimidazole (9) was obtained according to the method [9].

Sodium Salt of 5-Mercapto-1-methyl-4-nitroimidazole (10), Sodium Salt of 1-Butyl-5-mercapto-4-nitro-2-propylimidazole (11) and Ammonium Salt of 4-Mercapto-1-methyl-5-nitroimidazole (12) were obtained according to the method [12].

1-Ethoxycarbonylmethyl-2-methyl-4-nitroimidazole (13). A mixture of 2-methyl-4(5)-nitroimidazole (12.7 g, 0.1 mol), chloroacetic acid ethyl ester (24.4 g, 0.2 mol), and anhydrous K_2CO_3 (14.0 g, 0.1 mol) in anhydrous DMF (100 ml) was stirred for 7 h at 80-82°C. Water (250 ml) was added to the reaction mass; the precipitate was filtered off, washed with water, and dried. Yield 15.0 g (70%); mp 105-106°C (water). IR spectrum, cm^{-1}: 1340, 1550 (NO_2); 1740 (CO). Found, %: C 44.61; H 4.96; N 19.83. $C_8H_{11}N_3O_4$. Calculated, %: C 45.07; H 5.20; N 19.71.

1-Carboxymethyl-2-methyl-4-nitroimidazole (14). A mixture of compound **13** (15.0 g, 0.07 mol) and 40% NaOH solution (7 ml, 0.07 mol) in water (100 ml) was boiled for 30 min (for the last 5 min, with charcoal). The solution was filtered, cooled, and acidified with HCl to pH 2; the precipitate was filtered off and reprecipitated with HCl from an aqueous solution of $NaHCO_3$. Yield 7.2 g (55%); mp 210-212°C (dec.). Found, %: C 38.73; H 3.81; N 22.78. $C_6H_7N_3O_4$. Calculated, %: 38.92; H 3.81; N 22.70.

5-Bromo-1-carboxymethyl-2-methyl-4-nitroimidazole (15). Water (80 ml) was added to a solution of compound **14** (3.7 g, 0.02 mol) in 1N NaOH solution (20 ml, 0.02 mol), and then bromine (3.5 g, 0.021 mol) was added dropwise. The mixture was stirred for 2 h at 45-50°C, cooled, and acidified with HCl to pH 2; the precipitate was filtered off, washed with water, and dried. Yield 4.1 g (77%); mp 233-236°C (dec., from water). Found, %: C 27.56; H 2.51; Br 29.89; N 16.02. $C_6H_6BrN_3O_4$. Calculated, %: C 27.29; H 2.29; Br 30.27; N 15.91.

7-methyl-6-(nitroimidazolyl)thiopurines (16-23). A. A mixture of thiopurine **1** (0.01 mol), NaOH (0.01 mol), and nitrochloro(bromo)imidazole (**3-9, 15**) (0.01 mol) in 50% ethanol (70 ml) (in synthesis of compounds **16, 19, 21**), in 70% ethanol (70 ml) (for compounds **17, 20**), or in ethanol (70 ml) (compound **23**), anhydrous isopropanol (80 ml) (compound **18**), or water (70 ml) (compound **22**) was boiled for 1 h (for synthesis of compound **22**), 2 h (compounds **18, 20**), 3 h (compounds **16, 21**), 4 h (compound **19**), 6 h (compound **23**), and 7 h (compound **17**). The reaction mass was cooled; the precipitate was filtered out, washed with water, and dried. An additional amount of the compound was obtained by evaporation of the mother liquors down to a small volume. Compound **22** was obtained similarly, except that NaOH (0.02 mol) was used and the compound was isolated from the reaction aqueous solution by acidification with HCl to pH 2.

B. A mixture of chloropurine **2** (0.01 mol) and sodium or ammonium salt of nitromercaptoimidazole (**10-12**) (0.01 mol) in 70% ethanol (70 ml) (in synthesis of compounds **16, 21**) or in water (100 ml) (in synthesis of **23**) was boiled for 3 h (in synthesis of **16, 21**) or 5 h (in synthesis of **23**). Then the reaction mixtures were treated as described in experiment **A**. Mixed samples with the compounds obtained according to method **A** did not give a depression of the melting point. The IR spectra of the samples were identical.

Compounds **16-23**: yellow or light yellow crystalline materials, difficultly soluble in cold water and moderately soluble in most organic solvents.

For analysis, the compounds were purified by crystallization from water (**16, 18, 22, 23**), 50% ethanol (**17**), DMF–water 1:2 (**19**), DMF–water 1:1 (**20, 21**).

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