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SYNTHESIS OF 2-SUBSTITUTED 7-METHYL-6-(NITROIMIDAZOLYL)-THIOPURINES

E. V. Aleksandrova[1], P. M. Kochergin[2], L. V. Persanova[3], V. S. Korsunskii[2], and V. S. Shlikhunova[2]

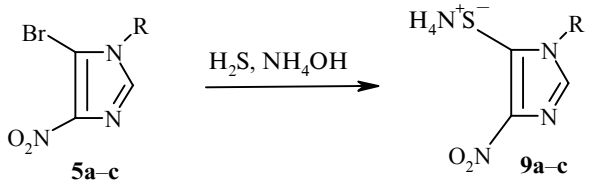
2-Substituted 7-methyl-6-(nitroimidazolyl)thiopurines have been synthesized by the reaction of 2-chloro(phenylamino, cycloalkylamino)-7-methyl-6-thiopurines with 5(4)-halo-4(5)-nitroimidazoles and the reaction of 2,6-dichloro-(6-chloro-2-dimethylamino)-7-methylpurines with sodium or ammonium salts of 5(4)-mercapto-4(5)-nitroimidazoles.

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

2-Substituted 7-alkyl-6-(nitroimidazolyl)thiopurines have not been described in the literature. In a continuation of our work [1] aimed at the search of new anticancer and immunosuppressant substances we have synthesized 2-substituted 7-methyl-6-(nitroimidazolyl)thiopurines containing chlorine atom, arylamino, dialkylamino, cyclohexylamino groups at position 2.

We used 2-chloro-, 2-phenylamino-, 2-piperidino-, and 2-morpholino-7-methyl-6-thiopurines **1a-d**, and 2,6-dichloro- and 6-chloro-2-dimethylamino-7-methylpurines **2** and **3** as starting purine derivatives. The following imidazoles were used: various derivatives of 5-chloro-4-nitroimidazole **4a-d**, 5-bromo-4-nitroimidazole **5a-c**, 4-chloro-5-nitroimidazole **6**, sodium salts of 5-mercapto-4-nitroimidazoles **7a,b**, ammonium salts of 4-mercapto-5-nitroimidazoles **8a,b** and 5-mercapto-4-nitroimidazoles **9a-c**.

Ammonium salts of 5-mercapto-1-methyl(β-hydroxyethyl, β,γ-dihydroxypropyl)-2-methyl-4-nitroimidazoles **9a-c**, which have not been described in the literature, were prepared by the reaction of bromoimidazoles **5a-c** with ammonium sulfide:



5a–c **9a–c**

5, 9 a R = Me, **b** R = CH_2CH_2OH, **c** R = $CH_2CH(OH)CH_2OH$

[1] Zaporozhe State University of Medicine, Zaporozhe 330074, Ukraine. [2] Center for The Chemistry of Medicinal Substances, All-Russia Scientific Research Institute for Pharmaceutical Chemistry, Moscow 119815, Russia. [3] State Institute for Blood Replacement and Medicinal Preparations, Moscow 109044, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, 538-543, April, 2001. Original paper submitted March 30, 1999.

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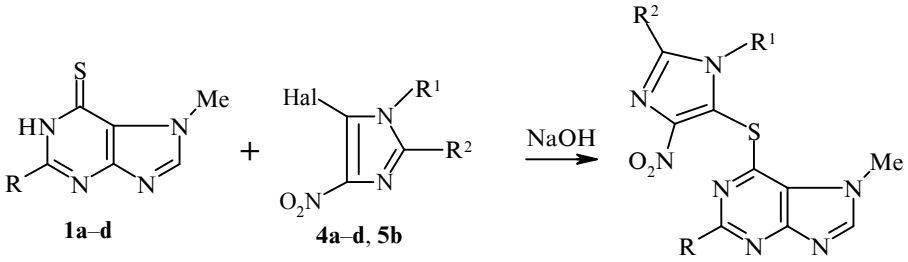
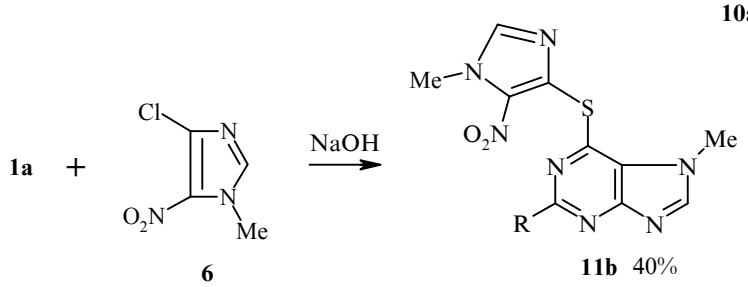
We used two methods for the synthesis of 2-substituted 7-methyl-6-(nitroimidazolyl)thiopurines: reaction of 6-thiopurines **1a-d** with nitrohaloimidazoles **4a-d**, **5a-c** (method A), and the reaction of 6-chloropurines **2,3** with sodium **7a,b** or ammonium **8a,b, 9a-c** salts of nitromercaptoimidazoles (method B).

The reaction of thiopurines **1a-d** with nitrohaloimidazoles occurred readily in the presence of sodium hydroxide on heating in water, 50-96% ethanol, or 80-100% isopropanol for 1-7 h.



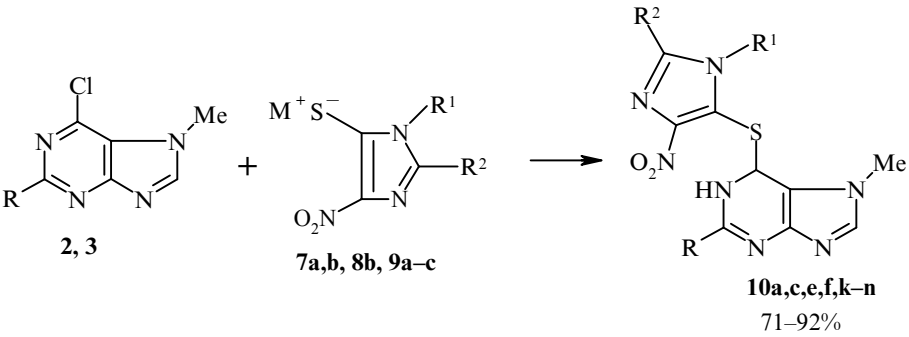
1a–d + **4a–d**, **5b** → **10a–j** 71–92%



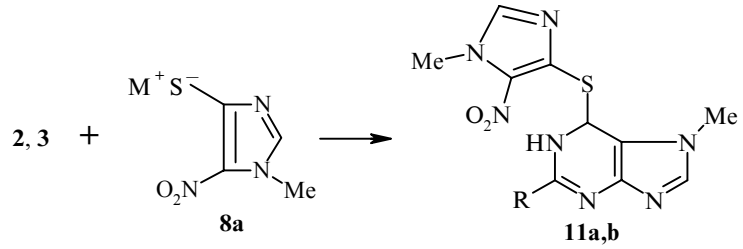
1a + **6** → **11b** 40%

1a, **10a-f** R = Cl; **10g** R = PhNH; **1c**, **10h,i** R = N-piperidyl; **1d**, **10j** R = N-morpholinyl;
4a, 5a, **10a,c,g,h,j** R^1 = Me; **4b,d, 10b,e,i** R^1 = Bu; **10f** R^1 = CH_2CH_2OH; **4c**, **10a,b,g-j** R^2 = H;
5a-c, **10c,f** R^2 = Me; **4c**, **10d** R^2 = Et; **1d**, **10e** R^2 = Pr; **4a-d** Hal = Cl; **5a,b** Hal = Br

The reaction of 6-chloropurines **2, 3** by method B with sodium salts **7a,b** or ammonium salts **8a, b, 9a-c** of nitromercaptoimidazoles was carried out in water, ethanol, or isopropanol with boiling for 1-5 h.



2, 3 + **7a,b, 8b, 9a–c** → **10a,c,e,f,k–n** 71–92%



2, 3 + **8a** → **11a,b**

2, **10a,c,e,f,k, 11b** R = Cl, **3**, **10l-n**, **11a** R = NMe_2; **8b**, **10n** R^1 = H; **7a**, **9a**, **10a,c,l,m** R^1 = Me;
7b, **10e** R = Bu; **9b**, **10f** R^1 = CH_2CH_2OH; **9c**, **10k** R^1 = $CH_2CH(OH)CH_2OH$; **7a**, **10a,l** R^2 = H;
9a-c, **10c,f,k,m,n** R^2 = Me; **7b**, **10e** R^2 = Pr; **7a,b** M = Na; **8a,b**, **9a-c** M = NH_4

TABLE 1. The Characteristics of Compounds **9a-c, 10a-n, 11a,b**

Compound	Empirical formula	Found, % / Calculated, %					mp, °C (decomp.) (solvent for recrystallization)	Yield, % (method)
		C	H	Cl	N	S		
1	2	3	4	5	6	7	8	9
9a*	$C_5H_{10}N_4O_2S$	31.59 / 31.57	5.52 / 5.26		29.12 / 29.47	17.01 / 16.84	169-170	90 (A)
9b*	$C_6H_{12}N_4O_3S$	32.72 / 32.73	5.49 / 5.45		25.44 / 25.45	14.56 / 14.55	165-166	57 (A)
9c*	$C_7H_{15}N_4O_4S$	33.14 / 33.47	5.78 / 5.97		22.01 / 22.31	12.59 / 12.75	160-161	80 (A)
10a	$C_{10}H_8ClN_7O_2S$	36.99 / 36.87	2.54 / 2.48	10.77 / 10.88	30.17 / 30.10	9.89 / 9.84	254-255 (DMF–water, 1:1)	92 (A) 94 (B)
10b	$C_{13}H_{14}ClN_7O_2S$	42.46 / 42.45	3.82 / 3.84	9.61 / 9.64		8.77 / 8.72	164-165 (50% ethanol)	71 (A)
10c	$C_{11}H_{10}ClN_7O_2S$	38.62 / 38.88	3.05 / 2.97	10.17 / 40.43	29.35 / 28.86	9.96 / 9.44	253-254 (DMF)	75 (A) 80 (B)
10d	$C_{14}H_{16}ClN_7O_2S$	44.39 / 44.04	4.18 / 4.22	9.56 / 9.28	25.06 / 25.66	8.50 / 8.40	158-159 (50% methanol)	83 (A)
10e	$C_{16}H_{20}ClN_7O_2S$	46.53 / 48.88	4.80 / 4.91	8.71 / 8.65	23.80 / 23.92	7.93 / 7.82	131-132 (isopropanol)	81 (A) 90 (B)
10f*	$C_{12}H_{12}ClN_7O_3S$	39.08 / 38.97	3.30 / 3.27	9.69 / 9.59	26.42 / 26.52	8.82 / 8.67	209-210 (DMF–water, 1:2)	73 (A) 90 (B)

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
10g*	$C_{16}H_{14}N_8O_2S$	50.46 50.25	3.87 3.69		29.36 29.30	8.55 8.39	264-265 (DMF–water, 1:3)	76 (A)
10h	$C_{15}H_{18}N_8O_2S$	48.47 48.12	4.81 4.84		29.30 29.93	8.43 8.56	204-205 (DMF–water, 1:1)	88 (A)
10i	$C_{18}H_{24}N_8O_2S$	51.68 51.90	6.01 5.81			7.67 7.70	182-183 (isopropanol)	83 (A)
10j	$C_{14}H_{16}N_8O_3S$	44.78 44.67	4.48 4.28		29.57 29.77	8.89 8.52	270-271 (DMF–water, 1:1)	85 (A)
10k*	$C_{13}H_{13}ClN_7O_4$			8.57 8.39	24.59 24.53	8.06 8.04	203-204 (ethanol)	57 (B)
10l	$C_{12}H_{14}N_8O_2S$	43.29 43.11	4.47 4.22		33.19 33.52	9.57 9.62	234-236 (50% ethanol)	60 (B)
10m	$C_{13}H_{16}N_8O_2S$	44.50 44.82	4.42 4.65		32.16 32.17	9.50 9.20	253-255 (DMF–water, 1:1)	98 (B)
10n	$C_{12}H_{14}N_8O_2S$	43.19 43.11	4.43 4.22		33.42 33.52	9.43 9.59	236-237 (DMF)	90 (B)
11a	$C_{12}H_{14}N_8O_2S$	43.06 43.11	3.88 4.22		33.29 33.52	9.81 9.59	225-227 (DMF–water, 1:1)	50 (B)
11b	$C_{10}H_8ClN_7O_2S$	36.78 36.89	2.39 2.48		30.17 30.10	9.61 9.84	195-196 (water)	40 (A) 83 (B)

* IR spectra, ν, cm^{-1}: **9a** 1360, 1570 (NO_2); **9b** 1370, 1570 (NO_2), 3330 (OH); **9c** 1380, 1570 (NO_2), 3350 (OH); **10f** 1340, 1560 (NO_2), 3350 (OH); **10g** 1350, 1570 (NO_2), 3330 (OH); **10k** 1350, 1560 (NO_2), 3400 (OH).

Comparison of the two methods for the synthesis of 2-substituted 7-methyl-6-(nitroimidazolyl)-thiopurines shows that they are approximately equal in terms of yields and reaction time and the choice between them may be made on the basis of the availability of the purine and imidazole derivatives.

The purity of the compounds synthesized was established by TLC, and their structures and compositions – by IR spectra, elemental analysis, and independent syntheses. Thus compounds **10a,c,e,f** and **11b**, synthesized by both methods, were identical.

The IR spectra of compounds **10f,g,k** contained absorption bands for NO_2 group in the regions of 1340-1350 and 1560-1570 cm^{-1} and for the OH and NH_2 groups in the regions of 3350-3400 and 3330 cm^{-1} respectively.

EXPERIMENTAL

IR spectra of nujol mulls were recorded with UR-10 and Perkin-Elmer 457 spectrometers. TLC was carried out on Silufol UV-254 strips with a variety of solvents and with development by iodine vapor or UV light.

2-Chloro-, 2-phenylamino-, 2-piperidino-, and 2-morpholino-7-methyl-6-thiopurines **1a-d** were prepared by method [2], 2,6-dichloro-7-methylpurine (**2**) by method [3], and 6-chloro-2-dimethylamino-7-methylpurine (**3**) by method [4].

1-Methyl-, 1-butyl-, 1-propyl-2-ethyl-, and 1-butyl-5-chloro-4-nitro-2-propylimidazoles **4a-d** were prepared by method [5].

1,2-Dimethyl-, 1-(β-hydroxyethyl)-2-methyl-, and 6-bromo-1-(β,γ-dihydroxypropyl)-2-methyl-4-nitroimidazoles **5a-c** were prepared by method [6].

4-Chloro-1-methyl-5-nitroimidazole (**6**) was prepared by method [7].

Sodium salts of 1-methyl- and 1-butyl-5-mercapto-4-nitro-2-propylimidazoles **7a,b** and ammonium salts of 4-mercapto-1-methyl-5-nitro- and 5(4)-mercapto-2-methyl-4(5)-nitroimidazoles **8a,b** were prepared by method [8].

Ammonium Salts of 1,2-Dimethyl-, 1-(β-Hydroxyethyl)-2-methyl- and 1-(β,γ-Dihydroxypropyl)-5-mercapto-2-methyl-4-nitroimidazoles 9a-c. Hydrogen sulfide was passed through suspension of nitrobromoimidazoles **5a-c** (0.025 mol) in 8% aqueous ammonia (30 ml) for 15 min, during which the temperature of the reaction mixture rose to 40-45°C. The reaction mixture was stirred for 30 min at 20-25°C, cooled to 15-18°C, the precipitate was filtered off, washed twice with a small amount of cold water, then cold ethanol, and dried to give yellow crystals of **9a-c** readily soluble in water.

2-Substituted 7-Methyl-6-(4-nitroimidazolyl-5)thiopurines 10a-n and 6-(5-Nitroimidazol-4-yl)thiopurines 11a,b (Table). Method A. Mixture of 6-thiopurine **1a-d** (0.01 mol), NaOH (0.01 mol), and nitrohaloimidazole **4a-d**, **5a,b** (0.01 mol) in 70% ethanol (70 ml) (for preparation of compounds **10a**, **11b**), 50% ethanol (60 ml) (compound **10b**), water (70 ml) (for preparation of compound **10c**), 80% propanol-2 (50 ml) (for preparation of compound **10d**), anhydrous propanol-2 (80 ml) (for preparation of compounds **10a,i**) and ethanol (70 ml) (for preparation of compounds **10f-h,j**, **11b**) was boiled for 1 h (compounds **10a,c,e, 11b**), 2 h (compound **10d**), 3 h (compounds **10f, h, i**), 5 h (compound **10j**), 6 h (compound **10g**), and 7 h (compound **10b**). At the end of the heating period the reaction mixture was cooled to 15-20°C, the precipitate was filtered off, washed with water, and dried. The alcoholic mother liquor was evaporated to small volume to isolate more of the product. Compounds **10a-j** and **11b** were obtained.

Method B. Mixture of 6-chloropurine **2,3** (0.01 mol) and sodium **7a,b** or ammonium salt **8a,b, 9a-c** of nitromercaptoimidazole (0.01 mol) in water (100 ml) (for preparation of compounds **10a,c**), in 80% isopropanol (70 ml) (for compounds **10f,k-n,11a,b**) was boiled for 1 h (compounds **10a,c,e,k**), 2 h (compounds **10f,m,n**), 4 h (compounds **10l, 11a**), or 5 h (compound **11b**). The reaction mixture was cooled to 15-20°C, the precipitate

was filtered off, washed with water, and dried. The alcoholic solutions were evaporated in vacuum to small volume to isolate more of the required product. Compounds **10a,c,e,f,k-n, 11a,b** were obtained. Compounds **10a,c,e,f,** and **11b** did not give a depression of the melting point with samples prepared by method A.

Compounds **10a-n, 11a,b** are yellow or light yellow crystalline substances which are difficult to dissolve in cold water and most organic solvents.

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