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SYNTHESIS OF 2-AMINO-6-(NITROIMIDAZOLYL)THIOPURINES

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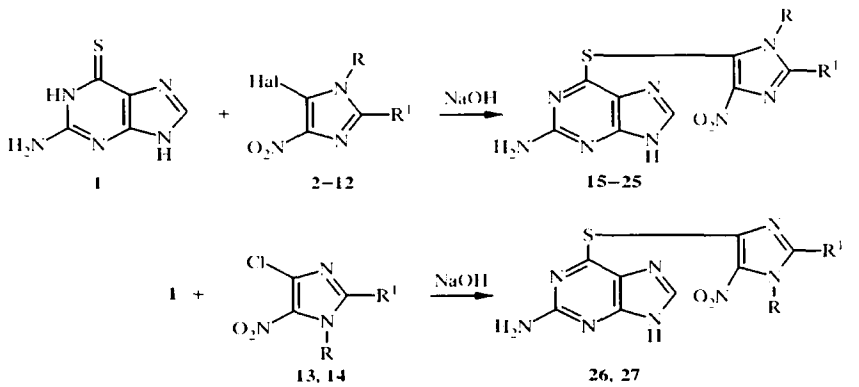
We have synthesized a series of novel 2-amino-6-(nitroimidazolyl)thiopurines by reaction of thioguanine with 1-alkyl(1,2-dialkyl)-5-chloro-4-nitro-, 2-alkyl(1,2-dialkyl)-5-bromo-4-nitro-, and 1-alkyl(1,2-dialkyl)-4-chloro-5-nitroimidazoles.

Keywords: halonitroimidazoles, nitroimidazolylthioguanines, thioguanine, immunodepressants.

The reaction of thioguanine [1] and its nucleoside [2] with 5-chloro(bromo)-4-nitroimidazoles has been insufficiently studied, while the reaction with 4-chloro-5-nitroimidazoles has not been studied at all. The compounds described in the patents [1, 2] exhibit antitumor and immunodepressant activity. The compound 2-amino-6-(1-methyl-4-nitro-5-imidazolyl)thiopurine (thiamiprine, guaneran) is especially interesting [3]: it has a stronger immunodepressant effect than azathioprine but is more toxic [4, 5].

With the objective of searching for less toxic compounds, we have studied the reaction of thioguanine (**1**) with various derivatives of imidazole: 1-alkyl(1,2-dialkyl)-5-chloro-4-nitro- (**2-8**), 2-alkyl-5(4)-bromo-4(5)-nitro- (**9**), 1-alkyl(hydroxyalkyl, carboxyalkyl)-2-alkyl-5-bromo-4-nitro- (**10**, **11**), and 1-alkyl(1,2-dialkyl)-4-chloro-5-nitroimidazoles (**13, 14**).

According to patent data [1], the reaction of thioguanine **1** with halonitroimidazoles is carried out in the presence of base with heating in water, aqueous alcohol, or DMSO for 4-48 h (usually 18-20 h).



2, **10**, **13**, **15**, **18**, **26** R = Me; **3**, **16** R = Bu; **4**, **14**, **19**, **27** R = Et; **5**, **20** R = Pr; **6**, **21** R = *i*-Bu; **7**, **22** R = Am; **8**, **23** R = *i*-Am; **9**, **17** R = H; **11**, **24** R = CH_2CH_2OH; **12**, **25** R = CH_2COOH; **2**, **3**, **13**, **15**, **16**, **26** R^1 = H; **4**, **9-12**, **14**, **17-19**, **24**, **25**, **27** R^1 = Me; **5**, **20** R^1 = Et; **6**, **21** R1 = *i*-Pr; **7**, **22** R^1 = Bu; **8**, **23** R^1 = *i*-Bu; **2-8** Hal = Cl; **9-12** Hal = Br

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TABLE 1. Characteristics of 2-amino-6-(nitroimidazolyl)thiopurines **15-27**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (with decomp.)	Yield, %
		C	H	N	S		
15*	$C_9H_5N_5O_2S$	36.80 / 36.98	3.00 / 2.76	38.30 / 38.34	10.97 / 10.97	>300	87
16	$C_{12}H_{11}N_5O_2S$	43.10 / 43.11	4.50 / 4.22		9.50 / 9.59	194-195	80
17	$C_9H_5N_5O_2S$	37.00 / 36.98	3.00 / 2.76	38.08 / 38.34	10.99 / 10.97	>350	86
18	$C_{10}H_{10}N_8O_2S$	39.47 / 39.21	3.15 / 3.29	36.15 / 36.58	10.20 / 10.47	>350	96
19	$C_{11}H_{12}N_8O_2S \cdot H_2O$	39.17 / 39.04	4.47 / 4.17	33.10 / 33.12	9.30 / 9.47	225-226	78
20	$C_{13}H_{16}N_8O_2S$	44.73 / 44.82	4.80 / 4.63	31.95 / 32.17	9.36 / 9.20	237-238	81
21	$C_{15}H_{20}N_8O_2S$	48.00 / 47.86	4.94 / 5.35	29.70 / 29.77	8.23 / 8.52	249-250	82
22	$C_{17}H_{24}N_8O_2S$	50.74 / 50.48	6.15 / 5.98	27.48 / 27.70	7.97 / 7.93	260-261	75
23	$C_{17}H_{24}N_8O_2S$	50.85 / 50.48	5.70 / 5.98	27.84 / 27.70	8.00 / 7.93	240-242	76
24	$C_{11}H_{11}N_5O_4S$	38.93 / 39.28	3.90 / 3.60	33.51 / 33.32	9.48 / 9.53	246-247	76
25	$C_{11}H_{10}N_6O_4S$	37.79 / 37.71	3.05 / 2.88	31.69 / 31.99	9.03 / 9.15	247-248	68
26	$C_9H_8O_2S \cdot H_2O$	34.40 / 34.84	3.07 / 3.25	35.66 / 36.11	10.07 / 10.33	264-265	58
27	$C_{12}H_{12}N_8O_2S$	41.30 / 41.24	3.75 / 3.78	34.77 / 34.98	9.76 / 10.00	265-266	78

* Obtained with the help of I. S. Mikhailova. According to data in [1], the decomposition temperature is 200°C.

Using TLC to monitor the course of the process, we established that the reaction of the thio compound **1** with 5-chloro(bromo)-4-nitroimidazoles **2-12** occurs over a period of 1-6 h at boiling of equimolar amounts of the indicated reagents and sodium hydroxide in water, aqueous alcohol, or alcohol (ethanol, isopropanol) solutions. The yield of compounds **15-25** is 68% to 96%. The use of 4-chloro-5-nitroimidazoles **13**, **14** in this reaction requires an increase in the process time up to 5-6 h when carrying out the reaction in boiling ethanol, and the yields of compounds **26**, **27** are reduced to 58-78%.

The structure of compounds **16-27**, which have not been described previously in the literature, was established based on elemental analysis data (Table 1) and their IR spectra. In the IR spectra of the investigated

TABLE 2. IR Spectra of 2-Amino-6-(nitroimidazolyl)thiopurines **17-21**, **24**, **25**

Compound	ν, cm^{-1}	
	NO_2	NH and NH_2
17	1340, 1530	3080, 3380, 3490
18	1350, 1560	3070, 3220, 3350, 3470
19	1340, 1550	3150, 3210, 3320, 3420
20	1360, 1550	3170, 3220, 3330, 3400
21	1370, 1550	3120, 3220, 3350, 3440
24	1320, 1560	3210, 3330, 3400, 3500
25*	1320, 1540	3150, 3230, 3340

* 1650 cm^{-1} (CO).

compounds (Table 2), we observe absorption bands of the NO_2 group in the region 1320-1370 cm^{-1} and 1530-1570 cm^{-1}, of the NH and NH_2 groups of the purine ring in the region 3070-3500 cm^{-1}. In the IR spectrum of acid **25**, in addition there is a band for the stretching vibrations of the CO group at 1650 cm^{-1}.

EXPERIMENTAL

The IR spectra of the compounds were taken on UR-10 or Perkin Elmer 457 instruments in the solid state as suspensions in vaseline oil. The purity of the compounds was determined by TLC on Silufol UV-254 plates in the system butanol–acetic acid–water, 5:1:4. Visualization was by iodine vapor or in UV light.

2-Amino-6-thiopurine (Thioguanine, 1) was obtained by the method [6]. Decomposition temperature 350°C (DMF–water). IR spectrum: 3120, 3280 cm^{-1} (NH, NH_2).

1-Methyl, 1-Butyl-, 1-Ethyl-2-methyl-, 2-Ethyl-1-propyl-, 1-Isobutyl-2-isopropyl-, 1-Amyl-2-butyl-, and 5-Chloro-1-isoamyl-2-isobutyl-4-nitroimidazoles (2-8) were obtained by the methods [7, 8].

5(4)-Bromo-2-methyl-4(5)-nitro-, 5-Bromo-1,2-dimethyl-4-nitro-, and 5-Bromo-1-(β-hydroxyethyl)-2-methyl-4-nitroimidazoles (9-11) were obtained by the method [9].

5-Bromo-1-carboxymethyl-2-methyl-4-nitroimidazole (12) was obtained by the method in [10].

4-Chloro-1-methyl- and 4-Chloro-1-ethyl-2-methyl-5-nitroimidiazoles (13, 14) were obtained by the method [7].

2-Amino-6-(nitroimidazolyl)thiopurines (15-27). A mixture of thioguanine **1** (0.01 mol), NaOH (40% aqueous solution, 0.01 mol) and (0.01 mol) chloro(bromo)nitroimidazole **2-14** in water (100 ml) (for synthesis of compounds **15, 17-21, 25**), isopropanol (50 ml) (for synthesis of **16**), 50% ethanol (130 ml) (for synthesis of **22, 23**), ethanol (65 ml) (for synthesis of **24, 26, 27**) was boiled for 1 h (for synthesis of **17, 19-21**), 4 h (for synthesis of **15, 22, 23**), or 6 h (for synthesis of **24, 26, 27**). The course of the reaction was monitored by TLC. At the end of the reaction, the mixture was cooled; the precipitate was filtered off, washed with water, and dried. An additional amount of compound **27** was isolated by evaporation of the alcoholic mother liquor down to a small volume.

In synthesis of acid **25**, we used NaOH (0.02 mol per 0.01 mol of the starting bromonitroimidazole **12**). The reaction mixture was neutralized by acetic acid to pH 5; the precipitate was filtered off, washed with water, and dried.

For analysis, the compounds were purified by crystallization from DMF (**15, 17, 18**), aqueous ethanol (**16**), water (**19, 24, 26**), methanol (**20**), DMF–water 1:1 (**21, 23**), DMF–water 2:1 (**22**), DMF–water 3:1 (**27**) and reprecipitation by acetic acid from an aqueous sodium bicarbonate solution (**25**).

Compounds **15-27**: pale yellow or yellow crystalline materials, difficultly soluble in water and most organic solvents. Soluble in solutions of alkali hydroxides; in mineral acid solutions, they form unstable salts which are hydrolyzed to the free bases when these solutions are diluted with water.

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