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SYNTHESIS OF 9-SUBSTITUTED DERIVATIVES OF 6-(NITRO-IMIDAZOLYL)THIOPURINES

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The synthesis has been achieved of a series of 9-substituted derivatives of 6-(4-nitroimidazol-5-yl)- and 6-(5-nitroimidazol-4-yl)thiopurines by the reaction of 6-(nitroimidazolyl)thiopurines with alkyl and aralkyl halides, haloalcohols, haloacids and their esters, halo ketones, halo aldehyde acetals, and arylsulfonate esters using potassium carbonate in DMF.

Keywords: dimethylformamide, nitroimidazolylthiopurines, potassium carbonate, alkylation.

The alkylation reaction of 6-(1-methyl-4-nitroimidazol-5-yl)thiopurine (azathioprine, **1a**) at position 9 of the purine ring has been little studied [1, 2] and that of other 6-(nitromidazolyl)thiopurines not at all. At the same time, compounds of this series (e.g. 9-butylazathiopurine (butazothioprine)) have a high immunodepressive effect [1]. A high antitumor effect is also a feature of 9-alkyl substituted 6-thiopurine, thioguanine, and their S-alkyl (aralkyl, carboxyalkyl) derivatives. Thus by alkylation of 6-chloropurine in aprotic solvent (DMSO) in the presence of anhydrous potassium carbonate it was shown [3] that the reaction occurs principally at position 9 of the purine ring. It has also been found [4-7] that 6-alkyl(aralkyl)thiopurines are alkylated at position 9 under analogous conditions.

In continuation of reported work [2] and with the aim of searching for novel biologically active materials we have studied in more detail the alkylation of compound **1a** as well as 6-(1-butyl-4-nitro-2-propylimidazol-5-yl)thiopurine (**1b**), 6-(1-methyl-5-nitroimidazol-4-yl)thiopurine (**1c**), and 6-(2-ethyl-5-nitro-1-propylimidazol-4-yl)thiopurine (**1d**). The alkylating agents used were alkyl and aralkyl halides, haloalcohols, haloacids and their esters, halo ketones, halo aldehyde acetals, and arylsulfonic acids esters.

The reaction was carried out in anhydrous DMF in the presence of anhydrous potassium carbonate to avoid the formation of the difficult to separate mixtures of 7- and 9-alkyl-6-(nitromidazolyl)thiopurines [2]. As a result, the series of 9-substituted 6-(4-nitroimidazol-5-yl)thiopurines **2a-s** and the 6-(5-nitroimidazol-4-yl)thiopurines **2t,u** were obtained and their characteristics are given in Table 1. Aldehyde **2h** was prepared by the hydrolysis of the acetal **2g** and the acid **2n** (beside by direct synthesis from compound **1a** and bromoacetic acid in 41% yield) by the hydrolysis of its ethyl ester **2m** using an aqueous solution of sodium hydroxide (yield 70%).

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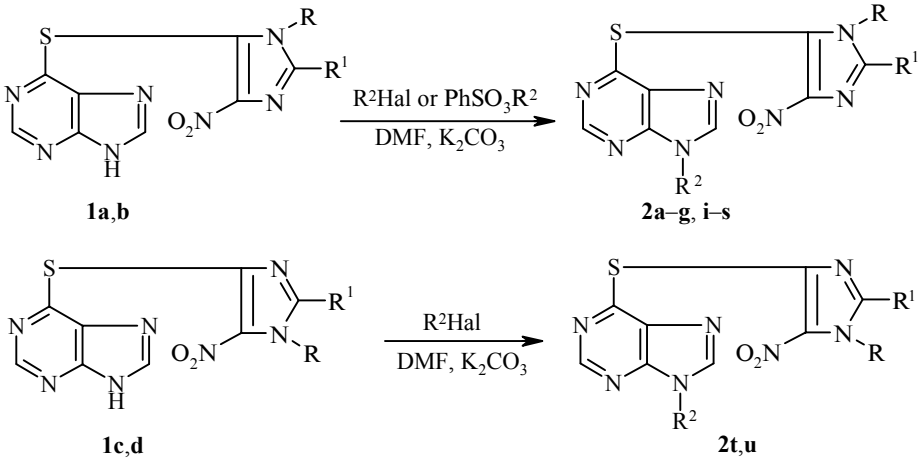
TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (decomp.) (solvent for crystallization)	IR spectrum*, cm^{-1}	Yield, %
		C	H	N	S			
2a	$C_{12}H_{13}N_7O_2S$	45.48 / 45.13	3.88 / 4.10	30.11 / 30.70	10.32 / 10.04	170-171 (methanol)		63
2b	$C_{13}H_{15}N_7O_2S$	46.66 / 46.83	4.62 / 4.54	29.23 / 29.41	9.60 / 9.62	95-96 (ethanol–water, 1 : 1)		78
2c	$C_{16}H_{13}N_7O_2S$	52.05 / 52.30	3.73 / 3.57	26.40 / 26.68	8.58 / 8.72	210-211 (DMF–water, 2 : 1)		89
2d	$C_{16}H_{12}ClN_4F_7O_2S$	48.13 / 47.82	2.92 / 3.01	24.76 / 24.40	7.97 / 7.97	213-214 (DMF–water, 1 : 1)		71
2e	$C_{17}H_{15}N_7O_2S$	53.58 / 53.53	4.04 / 3.96	25.82 / 25.71	8.38 / 8.40	175-176 (DMF–water, 1 : 1)		88
2f	$C_{11}H_{11}N_7O_3S$	40.82 / 41.11	3.17 / 3.45	30.59 / 30.52	10.16 / 9.93	190-191 (DMF–water, 1 : 2)	3520 (OH)	52
2g	$C_{15}H_{19}N_7O_4S$	45.83 / 45.79	5.03 / 4.86	25.41 / 24.92	8.17 / 8.15	151-152 (DMF–water, 1 : 3)	1065, 1120 (C–O–C)	41
2h	$C_{11}H_9N_7O_3S$	41.08 / 41.38	2.70 / 2.84	30.36 / 30.71	9.80 / 10.04	172-176 (precipitated from DMF using 2-propanol)		68
2i	$C_{12}H_{11}N_7O_3S$	42.85 / 43.23	3.37 / 3.32	29.01 / 29.41	9.59 / 9.61	204-205 (DMF-water, 1:1)		41
2j	$C_{17}H_{13}N_7O_3S$	51.80 / 51.64	3.21 / 3.31	24.74 / 24.79	7.97 / 8.10	223-224 (DMF–water, 1 : 1)	1680 (CO)	90
2k	$C_{18}H_{15}N_7O_4S$	50.96 / 50.82	3.54 / 3.55	22.75 / 23.04	7.63 / 7.54	194-195 (DMF–water, 1 : 1)	1680 (CO)	69
2l	$C_{17}H_{12}BrN_7O_3S$	42.89 / 43.04	2.72 / 2.55	20.62 / 20.67	6.60 / 6.76	224-225 (DMF–water, 1 : 1)	1700 (CO)	89
2n	$C_{11}H_9N_7O_4S$	39.81 / 39.40	3.13 / 2.70	28.60 / 29.24	9.46 / 9.56	225-226 (water)	1730 (CO), 3520 (OH)	41, 70
2o	$C_{11}H_8N_7O_4SNa \cdot 2H_2O$			25.05 / 24.95	8.04 / 8.16	192-193 (precipitated from water using acetone)		83
2p	$C_{16}H_{21}N_7O_2S$	51.55 / 51.18	5.57 / 5.64	25.97 / 26.12	8.75 / 8.54	145-146 (methanol–water, 1 : 1)		72
2q	$C_{17}H_{23}N_7O_2S$	52.40 / 52.42	6.03 / 5.95	24.94 / 25.18	8.33 / 8.23	127-128 (methanol)		84
2r	$C_{23}H_{25}N_7O_3S$	57.77 / 57.60	5.02 / 5.25	20.57 / 20.45	6.95 / 6.69	146-147 (80% 2-propanol)	1700 (CO)	82
2s	$C_{19}H_{25}N_7O_4S$	50.85 / 50.99	5.79 / 5.63	22.39 / 21.91	7.42 / 7.17	155-156 (anhydrous ethanol)	1750 (CO)	80
2t	$C_{11}H_{11}N_7O_2S$	43.34 / 43.27	3.67 / 3.63	31.68 / 32.11	10.64 / 10.52	181-182 (methanol)		48
2u	$C_{15}H_{19}N_7O_2S$			27.44 / 27.13	9.18 / 8.87	220-222 (80% 2-propanol)		27

* The absorption bands for the NO_2 groups are in the region 1330-1340 and 1540-1570 cm^{-1}.

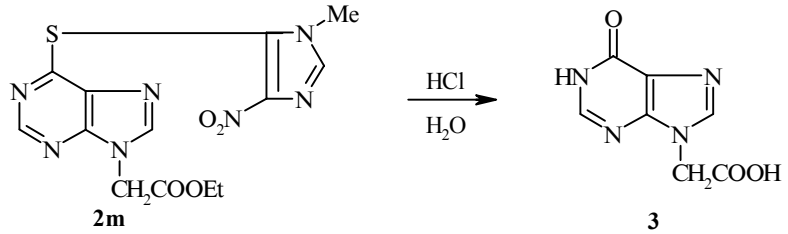


1a,**b** **2a–g**, **i–s**

1c,**d** **2t**,**u**

1a,c, **2a-o**,**t** R = Me; **1b**, **2p-s** R = Bu; **1d**, **2u** R = Pr; **1a,c**, **2a-p**,**t** R^1 = H; **1b**, **2p-s** R^1 = Pr; **1d**, **2u** R^1 = Et; **2a** R^2 = *i*-Pr; **2b** R^2 = *i*-Bu; **2c** R^2 = $PhCH_2$; **2d** R^2 = *p*-$ClC_6H_4CH_2$; **2e** R^2 = $PhCH_2CH_2$; **2f** R^2 = CH_2CH_2OH; **2g** R^2 = $CH_2CH(OEt)_2$; **2h** R^2 = CH_2CHO; **2i** R^2 = CH_2COMe; **2j,r** R^2 = CH_2COPh; **2k** R^2 = *p*-$MeOC_6H_4COCH_2$; **2l** R^2 = *p*-$BrC_6H_4COCH_2$; **2m,s** R^2 = CH_2COOEt; **2n** R^2 = CH_2COOH; **2o** R^2 = CH_2COONa; **2p** R^2 = Me; **2q,t,u** R^2 = Et; Hal = Cl, Br, I

The purity of compounds **2a-u** was confirmed using TLC and their composition and structure by reaction to the known 9-substituted hypoxanthine derivatives and from their IR spectra and elemental analytical data. Hence heating ester **2m** in 18% hydrochloric acid causes hydrolysis not only of the ester group but also fission of the $C_{(6)}$–S bond to give the 9-carboxymethylhypoxanthine **3** [3].



2m **3**

The IR spectra of the 9-substituted 6-(nitroimidazolyl)thiopurines **2a-u** show bands for the stretching vibrations of the NO_2 groups in the region 1330-1340 and 1540-1570 cm^{-1} (as in the IR spectra of the starting materials **1a-d**) but the purine ring NH bands are absent. In the IR spectra of the compounds which contain functional groups at the 9 position there are observed absorption bands for the corresponding OH groups in the region 3520 (compounds **2f,n**), the C–O–C bonds in the region 1065 and 1120 (acetal **2g**), and CO groups in the range 1650-1750 cm^{-1} (carbonyl compounds **2h-n,r,s**).

EXPERIMENTAL

IR spectra were obtained on UR-10 or Perkin-Elmer 457 instruments using vaseline oil. TLC was performed on Silufol-254 plates in the system butanol–acetic acid–water (5: 1: 4). The spots were visualized using iodine vapor or in UV light.

6-(1-Methyl-4-nitroimidazol-5-yl)thiopurine (1a, azathioprine) was a ready to use medicinal product of pharmaceutical grade.

6-(1-Butyl-4-nitro-2-propylimidazol-5-yl)thiopurine (1b) [8], 6-(1-Methyl-5-nitroimidazol-4-yl)-thiopurine (1c) [9], and 6-(2-Ethyl-5-nitro-1-propylimidazol-4-yl)thiopurine (1d) [9] were obtained using the methods referred to.

9-Substituted Derivatives of 6-(4-Nitroimidazol-5-yl)thiopurines (2a-s) and 6-(5-Nitroimidazol-4-yl)thiopurines (2t,u). (General Method). A. Finely ground anhydrous potassium carbonate (0.011 mol) was added to a solution of the 6-(nitroimidazolyl)thiopurine **1a-d** (0.01 mol) in anhydrous DMF (40-50 ml), and this was followed by the alkyl halide (methyl iodide, ethyl iodide, isopropyl bromide, isobutyl bromide) (0.02 mol) or the aralkyl halide (benzyl chloride, 4-chlorobenzyl chloride, phenethyl bromide), ethylenechlorohydrin, bromoacetaldehyde diethyl acetal, α-bromo ketone (bromoacetone, phenacyl bromide, 4-methoxyphenacyl bromide, 4-bromophenacyl bromide), or bromoacetic acid (or its ethyl ester) (0.011-0.015 mol). The reaction mixture was stirred: at 40°C for 9 h (for preparation of compound **2p**), at 70°C for 7 h (**2r**), 9 h (**2t,u**), 10 h (**2i,m**), 15 h (**2a**), or 17 h (**2k**), or at 80°C for 10 h (**2c,d,g,j,l,n,s**), 15 h (**2e,f**), or 17 h (**2b**). At the end of the heating period the reaction product was poured into water (150-200 ml) and the precipitated solid was filtered off, washed on the filter with sodium hydroxide solution (1 N, 3-4 times, each 10-15 ml), with water to neutral reaction of the water wash, and then dried to give compounds **2a-g,i-m,p,r-u**. Compounds **2a,b,e-g,i,j,s** were separated by distillation of the DMF in vacuo and subsequent treatment of the residue as described above. Acid **2n** was separated after distillation of DMF in vacuo. The residue was dissolved in water, the solution treated with activated carbon, filtered, acidified, and then treated with formic acid to pH 5. The precipitated solid (according to TLC containing an admixture of the starting compound **1a**) was filtered, suspended in water, sodium bicarbonate (1.43 g) added, the solution filtered from the residual **1a**, acidified with formic acid to pH 5, and the residue was filtered off, washed with water, and dried to give the acid **2n** in 41% yield.

B. A mixture of compound **1a, b** (0.01 mol), finely ground anhydrous potassium carbonate (0.01 mol), and the methyl or ethyl benzenesulfonate (0.011 mol) in anhydrous DMF (40 ml) was stirred at 80-82°C for 10 h, cooled, poured into water (200 ml), and treated as above as reported in method A to give compounds **2p,q**. The yield of compound **2p** was 77%. A sample, mixed with a sample prepared as in method A (yield 72%), did not show a depressed melting point and their IR spectra were identical.

Compounds **2a-u** are high melting yellow, light yellow, or colorless (compound **2l**) crystalline materials which are insoluble in water (except **2n, o**) and difficultly soluble in the majority of organic solvents.

9-Formylmethyl-6-(1-methyl-4-nitroimidazol-5-yl)thiopurine (2h). A suspension of the acetal **2g** (1.46 g, 0.005 mol) in 36% HCl (10 ml) was stirred for 2 h at 18-20°C, during which time the starting material dissolved fully. The solution was diluted with water (20 ml) and 25% aqueous ammonia was added with ice cooling and stirring to pH 5. The separate solid was filtered, washed with water, and dried to give the aldehyde **2h** (0.8 g).

9-Carboxymethyl-6-(1-methyl-4-nitroimidazol-5-yl)thiopurine (2n). A suspension of the ester **2m** (3.36 g, 0.01 mol) and NaOH solution (1N, 10 ml, 0.01 mol) was refluxed for 30 min, during which time the starting material dissolved fully. The solution was heated with activated carbon, filtered, the filtrate acidified with formic acid to pH 4, and the precipitate was filtered, washed with water, and dried to give compound **2n** (2.3 g, 70%); mp 225-226°C (water). A sample, mixed with a sample prepared as in method A, did not show a depressed melting point and their IR spectra were identical.

Sodium Salt of 9-Carboxymethyl-6-(1-methyl-4-nitroimidazol-5-yl)thiopurine (2o). Obtained by reaction of equimolar amounts of the acid **2n** and $NaHCO_3$ in water with subsequent precipitation from the aqueous solution using acetone.

9-Carboxymethylhypoxanthine (3). A suspension of compound **2p** (9.07 g, 0.025 mol) in 18% HCl (90 ml) was refluxed for 2 h. The solution formed was treated by heating with activated carbon and then filtered. The filtrate was carefully neutralized with a 20% solution of NaOH with cooling and stirring to pH 2-3. The precipitated solid was filtered off, washed with water and then acetone, and dried to give compound **3** (2.7 g, 56%); mp 263-266°C (decomp., precipitated with HCl from the basic solution). IR spectrum, ν, cm^{-1}: 1680,

1730 (CO), 3070, 3130 (NH, OH). According to the work in [3] the melting point is 264°C (decomp.). The sodium salt of the acid was prepared similarly to the analogous salt **2o**. Yield 97% as colorless crystals; mp > 350°C (decomp., precipitated from water using acetone). Found, %: N 23.70. $C_7H_5N_4NaO_3$. Calculated, %: N 23.93.

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