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CHEMICAL TRANSFORMATIONS OF 6-[(1-METHYL-4-NITRO-5-IMIDAZOLYL)-THIO]PURINE (AZATHIOPRINE)

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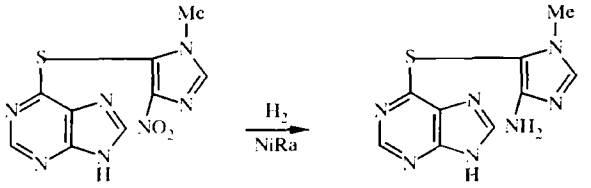
The chemical transformations of 6-[(1-methyl-4-nitro-5-imidazolyl)thio]purine (azathiopurine) – hydrogenation, acetylation, alkylation by lower alkyl halides at positions 7 and 9 of the purine ring, hydrolytic cleavage at the $C_{(6)}$–S and S–$C_{(5')}$ bonds – were studied.

Keywords: azathioprine, nitroimidazolylthiopurines, alkylation, acetylation, hydrogenation, hydrolysis.

6-[(1-Methyl-4-nitro-5-imidazolyl)thio]purine (azathioprine) (**1**) is used as an immunodepressant to suppress tissue incompatibility during organ transplantation [1], but the chemical characteristics of this compound have been studied little. Only the reaction of azathioprine with butyl iodide in DMSO in the presence of potassium carbonate has been investigated. Here 9-butylazathioprine (butazathioprine), which also has immunodepressant activity, was obtained [2-5].

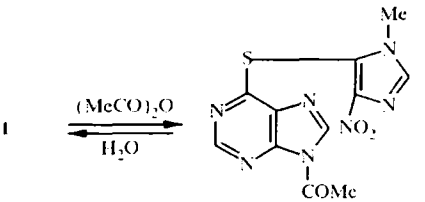
In view of the multifunctionality of the azathioprine molecule we studied the chemical characteristics of this compound (hydrogenation, acetylation, alkylation, hydrolytic cleavage in acidic media) in detail. The catalytic reduction of azathioprine to 6-[(4-amino-1-methyl-5-imidazolyl)thio]purine (**2**) takes place smoothly in DMFA in the presence of Raney nickel at room temperature at initial hydrogen pressure of 50 atm.



1 **2** (72%)

S-Purinyl-substituted 4-amino-5-mercaptoimidazoles have not been described in the literature.

Azathioprine is readily acetylated by acetic anhydride on heating with the formation of 9-acetyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purine (**3**). This compound is unstable to the action of moisture and is readily hydrolyzed to the initial compound **1** at standing in water at room temperature or after brief heating in commercial absolute methanol containing not more than 0.1% of water.



1 **3** (74%)

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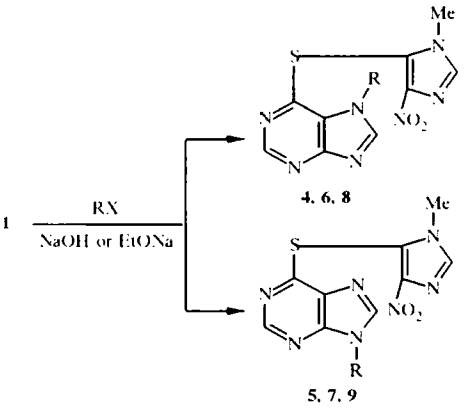
We adopted the structure of compound **3** by analogy with the structure of 9-acetyl-6-[(*p*-nitrobenzyl)thio]purine, which is formed at the acetylation of 6-(*p*-nitrobenzyl)thiopurine with acetic anhydride [6].

The alkylation of azathioprine, leading to the formation of 7- and 9-alkyl-substituted compounds, is considerably more complicated. We studied two methods for the alkylation of azathioprine by lower alkyl halides (methyl iodide, ethyl iodide, propyl bromide) in a protic solvent (methanol, ethanol) in the presence of sodium hydroxide or sodium alcoholate and in an aprotic solvent (DMFA) in the presence of potassium carbonate.

Alkylation in protic solvents leads to the formation of a mixture of two isomers, i.e., 7-alkyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purines **4, 6, 8** and 9-alkyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purines **5, 7, 9**.



4, 5 R = Me; 6, 7 R = Et; 8, 9 R = Pr; X = Br, I

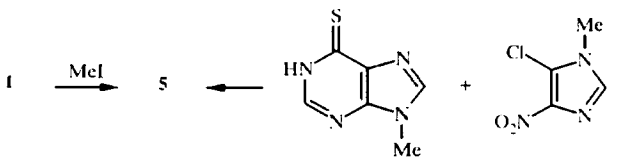
In spite of the 10-15% excess of alkyl halide, this reaction does not go to completion – the recovery of the unreacted azathioprine amounts to 27-29%.

Mixtures of the 7- and 9-isomers were isolated from azathioprine by treatment with an aqueous solution of sodium hydroxide and were then separated by fractional crystallization (compounds **4-8**) or isolated by preparative chromatography (compound **9**). The yield of the pure compounds was 2-11% for 7-alkyl isomers **4, 6, 8** and 6-46% for 9-alkyl isomers **5, 7, 9**. The alkylation of azathioprine by the same alkyl halides takes place in a more well-defined manner in anhydrous DMFA in the presence of potassium carbonate. In this solvent, as also in DMSO [2], 9-alkyl-substituted azathioprines **5, 7, 9** are mainly formed with yields of 70-76%. We were unable to isolate the 7-alkyl isomers **4, 6, 8** from the mother solutions.

The previously described [2] 9-butyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purine (**10**) was obtained under analogous conditions by the reaction of azathioprine with butyl bromide. The yield was 74%.

The individuality of the 7- and 9-alkyl-substituted azathioprines **4-10** was established by TLC, and their composition and structure were established on the basis of the data from elemental analysis and the IR, UV, and ^{1}H NMR spectra and also by alternative syntheses in the case of 7- and 9-methyl-substituted azathioprines **4, 5**. Thus, the high-melting isomer **4**, isolated from the products of the methylation of azathioprine with methyl iodide in methanol, occured to be identical with 7-methyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purine that we obtained earlier by the reaction of 7-methyl-6-thiopurine with 5-chloro-1-methyl-4-nitroimidazole [7].

The low-melting isomer **5** obtained by the methylation of azathioprine in methanol and DMFA was identical with 9-methyl-6-(1-methyl-4-nitro-5-imidazolyl)thiopurine obtained by the reaction of 9-methyl-6-thiopurine with the above-mentioned methylnitrochloroimidazole.



9-Alkyl-substituted azathioprines **5, 7, 9** are more readily soluble in organic solvents, have larger R_f values, and melt at lower temperatures than their 7-alkyl isomers **4, 6, 8**. The IR spectra of compounds **4-9**, unlike the IR spectrum of the initial compound **1**, do not contain the absorption band of the NH group.

The UV spectra of azathioprine and its 9-alkyl-substituted derivatives **5, 7, 9** have one absorption maximum (278-280 nm) of identical intensity (log ε 4.24-4.27). In the UV spectra of 7-alkyl isomers **4, 6, 8** the maximum is shifted toward the long-wave region by 8-9 nm. A similar pattern is observed in the UV spectra of 7- and 9-methyl-substituted 6-alkylthiopurines [8].

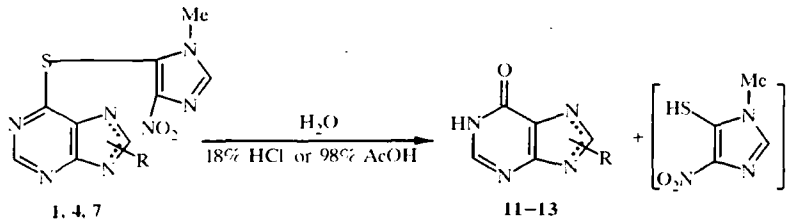
In the ^{1}H NMR spectrum of 7-ethyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purine (**6**) there are signals for the protons of the CH_3 group of the ethyl radical at position 7 of the purine ring (1.56), the CH_3 group at position 1 of the imidazole ring (4.55), and for the single protons at position 2 of the imidazole ring and at positions 2 and 8 of the purine ring in the regions of 8.22, 8.55, and 8.72 ppm respectively.

The assignment of the signals of the protons in the imidazole ring was made on the basis of [9] and in the purine bicycle on the basis of [10], in which it was indicated that the signal of the proton at position 2 is upfield from the signal of the proton at position 8 of the purine ring.

In [2, 11] 6-thiouric acid, 6-thiopurine, and 1-methyl-4-nitro-5-mercaptoimidazole were detected during investigation of the metabolism of azathioprine. In this connection it seemed of interest to investigate the behavior of azathioprine under the influence of acids and alkalies. Azathioprine was found to be comparatively stable when boiled in water for 3 h in the presence of equimolar amount of sodium hydroxide and was recovered unchanged with a yield of 83% after acidification of the solution to pH 6. When azathioprine was boiled in a 10-20% solution of sodium hydroxide, the molecule was completely destroyed as a result of instability of purine derivatives when heated in concentrated solutions of caustic alkalies [12].

The hydrolytic cleavage of azathioprine takes place in a less ambiguous manner when it is heated in hydrochloric and acetic acids. Thus, when the compound was boiled in 18% acetic acid for 40 min and in glacial acetic acid for 6 h, hypoxanthine **11** was isolated with yields of 36 and 81% respectively.

An analogous reaction path was observed when 7-methyl- and 9-ethyl-substituted azathioprines **4, 7** were boiled in 18% hydrochloric acid; 7-methylhypoxanthine **12** (yield 70%) and 9-ethylhypoxanthine **13** (yield 36%) were obtained.



1, 4, 7 **11–13**

1, 11 R = H; **4, 12** R = 7-Me; **7, 13** R = 9-Et

Our results agree with published data on the hydrolysis of 6-alkylthiopurines and 7-methyl-6-methylthiopurine on heating them in dilute hydrochloric and nitric acids, where hypoxanthine [13, 14] and 7-methylhypoxanthine [15] were isolated.

The second product from the hydrolysis of compounds **1, 4, 5**, i.e., 1-methyl-4-nitro-5-mercaptoimidazole, could not be isolated on account of its instability when heated in acids, but its presence in the reaction products was proved by its conversion into the more stable di(1-methyl-4-nitro-5-imidazolyl) disulfide (**14**). The disulfide **14** was isolated during the hydrolysis of 7-methyl-substituted azathioprine **4** in glacial acetic acid in the presence of hydrogen peroxide.

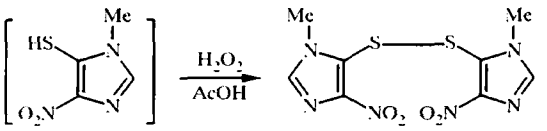


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TABLE 1. The Characteristics of the Synthesized Compounds **2-10, 12, 14**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (decomp.)	Yield, %
		C	H	N	S		
2	$C_9H_8N_4S$	43.99 / 43.71	3.99 / 3.67		12.75 / 13.02	201-202	82
3	$C_{11}H_9N_5O_3S$	41.40 / 41.38	3.00 / 2.84		10.03 / 10.04	205-207	74
4	$C_{10}H_9N_5O_2S$	41.15 / 41.23	3.32 / 3.11	33.68 / 33.66	11.18 / 11.01	254-255	3
5	$C_{10}H_9N_5O_2S \cdot H_2O$	38.90 / 38.83	3.69 / 3.56	31.61 / 31.71	10.64 / 10.36	168-169	24, 75.89
6	$C_{11}H_{11}N_5O_2S$	43.53 / 43.27	3.92 / 3.63	31.79 / 32.11	10.56 / 10.52	250-251	11
7	$C_{11}H_{11}N_5O_2S$	43.27 / 43.04	3.63 / 3.79	32.11 / 31.81	10.52 / 10.81	159-160	46, 76
8	$C_{12}H_{13}N_5O_2S$	45.22 / 45.13	4.16 / 4.10	30.86 / 30.70	10.30 / 10.04	234-236	2
9	$C_{12}H_{13}N_5O_2S$	45.52 / 45.13	4.32 / 4.10	30.19 / 30.70	10.10 / 10.04	125-127	6,70
10	$C_{13}H_{15}N_5O_2S$					126-127*	74
12	$C_6H_6N_4O \cdot HCl \cdot 1/2\ H_2O$*[2]	36.80 / 36.78	3.81 / 4.09				70
14	$C_8H_8N_6O_4S_2$	30.18 / 30.37	3.17 / 2.55		20.13 / 20.27	209-211	2

* According to published data [2], mp 126-127°C.

*[2] Found, %: Cl 18.07. Calculated, %: Cl 18.08.

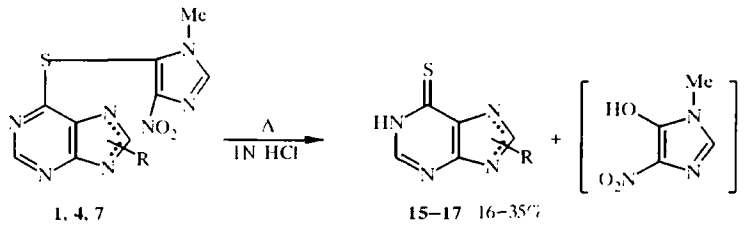
TABLE 2. The Spectral Characteristics of Compounds **1-12, 17**

Compound	Substituent at position 7 (9) of the purine ring	R_f*	UV spectrum		IR spectrum, cm^{-1}		
			λ_{max}, nm	log ε	NO_2	NH, NH_2	CO
1	H	1.00	280	4.24	1340, 1540	3120	
2	H					3100, 3230, 3500	
3	9-Ac				1380, 1570		1750
4	7-Me	0.65	288	4.23	1340, 1540		
5	9-Me	0.79	279	4.26	1340, 1550		
6*[2]	7-Et	0.80	288	4.18			
7	9-Et	1.04	279	4.27	1340, 1550		
8	7-Pr	0.85	288	4.15			
9	9-Pr	1.08	278	4.25	1340, 1550		
10	9-Bu				1340, 1540		
11	H					3080, 3140	1725
12	7-Me					3330, 3400	1730
17	9-Et					3120, 3180	

* The R_f values of compounds **4-9** are given with reference to R_f of azathioprine **1**, taken as 1.00. The absolute R_f value of azathioprine in the system is 0.48.

*[2] ^{1}H NMR spectrum (DMSO-d_6), ppm: 1.56 (3H, t, 7-CH_3); 3.70 (3H, s, 1-CH_3); 4.55 (2H, q, 7-CH_2); 8.22 (1H, 2-$H_{imidazole}$); 8.55 (1H, 2-H_{purine}); 8.72 (1H, 8-H_{purine}).

Azathioprine and its 7(9)-substituted derivatives are capable of being hydrolyzed at the S–$C_{(5)}$ bond when heated in weak hydrochloric acid. Thus, when azathioprine and its 7-methyl- and 9-ethyl-substituted derivatives **1, 4, 7** were boiled in 1N hydrochloric acid for 1.5-2 h, 6-thiopurine and its 7-methyl- and 9-ethyl-substituted derivatives **15-17** were isolated.



1, 4, 7 **15–17** 16–35%

1, 15 R = H; **4**, 16 R = 7-Me; **7**, 17 R = 9-Et

5-Hydroxy-1-methyl-4-nitroimidazole could not be isolated since it is extremely unstable and only survives in the form of the sodium salt [17].

The structure of the products from hydrolysis of azathioprine and its 7- and 9-alkyl-substituted derivatives **1, 4, 7** to 6-oxopurines **11-13** and 6-thiopurines **15-16** was confirmed by comparison with authentic samples of these compounds by the absence of melting point depressions and by the identity of the IR spectra.

EXPERIMENTAL

The IR spectra were obtained on UR-1 or Perkin-Elmer 457 instruments for suspensions in Vaseline oil. The UV spectra were obtained on a ESPS-3 recording spectrometer in ethanol. The ^{1}H NMR spectra were recorded on an INM 4H-100 instrument in DMSO with TMS as internal standard. Thin-layer chromatography was carried out on Silufol UV-254 plates in the 5:4:1 butanol–acetic acid–water system with development in iodine vapor or UV light.

6-[(1-Methyl-4-nitro-5-imidazolyl)thio]purine (Azathioprine). The commercial product of pharmacopoeia purity, obtained by the method in [18], was employed.

6-[(4-Amino-1-methyl-5-imidazolyl)thio]purine (2). Solution of azathioprine (5.54 g, 0.02 mol) in DMF (300 ml) was placed in a revolving 0.5-liter stainless-steel autoclave. Raney nickel paste (5.0 g) was added, and the solution was hydrogenated at room temperature and initial hydrogen pressure of 50 atm. The absorption of hydrogen stopped after 1 h 30 min. The catalyst was filtered off and washed with a small amount of DMF. The filtrate was evaporated to dryness under vacuum, and the solid residue was triturated with acetone. The precipitate was filtered off, washed with ether, and dried. Yield 4.0 g (82%); mp 201-202°C (from 2-propanol, decomp.); R_f 0.23.

9-Acetyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purine (3). Mixture of azathioprine (2.77 g, 0.01 mol) and acetic anhydride (30 ml) was boiled for 30 min and cooled. The precipitate that separated was filtered off, washed with ether, and dried. Yield 2.35 g (74%); mp 204-206°C. The product was a yellow crystalline powder (mp 205-207°C, from acetic anhydride), poorly soluble in the majority of organic solvents. It was hydrolyzed to compound **1** when heated in 99.9% methanol for 10 min or allowed to stand in water at 20-22°C for 4-6 h.

7- and 9-Methyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purines (4, 5). To solution of azathioprine (5.54 g, 0.02 mol) in 1N aqueous solution of sodium hydroxide (20 ml) solution of methyl iodide (4.26 g, 0.03 mol) in 30 ml of methanol was added. The mixture was stirred for 20 h at 20-25°C. The precipitate was filtered off and added to 1N solution of sodium hydroxide (20 ml). The suspension was stirred, and the undissolved precipitate was filtered off, washed with water, and dried. Mixture of compounds **4** and **5** (R_f 0.65 and 0.79) was obtained. Yield 1.6 g. The water–methanol mother liquor was evaporated, and the residue was washed with 1N sodium hydroxide solution and with water and dried. Further 0.5 g of the mixture of compounds **4** and **5** were obtained. The mixture of compounds **4** and **5** (2.1 g) was boiled with acetone (20 ml), the hot solution was

filtered from the undissolved residue, and the residue was washed with acetone and dried. Compound **4** was obtained. Yield 0.17 g (3%); mp 254-255°C (R_f 0.65). Mixed melting test with 7-methyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purine [7] did not give melting point depression. The IR spectra of the samples were identical. Precipitate separated from the acetone mother liquor after cooling and standing for 12 h. It was filtered off and dried to give 1.4 g (24%) of compound **5**; mp 168-169°C (water) (R_f 0.79). Mixed melting test with 9-methyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purine **5** obtained as described above did not give melting point depression. The IR spectra of the samples were identical. From the combined alkaline mother liquor after acidification with acetic acid 1.6 g (29%) of the initial compound **1** (mp 242-244°C) were isolated, which did not give melting point depression with an authentic sample of azathioprine.

7- and 9-Ethyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purines (6, 7). To solution of sodium ethoxide, prepared from anhydrous ethanol and sodium (0.46 g, 0.02 mol), azathioprine (5.54 g, 0.02 mol) and ethyl iodide (3.43 g, 0.02 mol) were added. The mixture was boiled for 8 h and cooled. The precipitate was filtered off, washed with 1N solution of sodium hydroxide and with water, and dried to give 0.65 g (11%) of compound **6**; mp 250-251°C (from 50% ethanol, decomp.) (R_f 0.80). The alcohol mother liquor after the isolation of compound **6** was evaporated to dryness. The residue was triturated with 1N solution of sodium hydroxide, filtered, washed with water until the washing water had a neutral reaction, and dried. Compound **7** was obtained. Yield 2.8 g (46%); mp 158-159°C (water) (R_f 0.44).

By acidifying the combined alkaline mother liquors from washing of compounds **6** and **7** 1.5 g (27%) of the unreacted azathioprine were isolated; mp 242-243°C (water).

7- and 9-Propyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purines (8, 9). Mixture of azathioprine (5.54 g, 0.02 mol), sodium hydroxide (0.8 g, 0.02 mol), and propyl bromide (2.96 g, 0.024 mol) in ethanol (150 ml) was boiled for 20 h. The reaction mass was filtered, the filtrate was evaporated, and water (50 ml) and 1N solution of sodium hydroxide (10 ml) were added to the residue. The mixture was extracted with chloroform (4 × 50 ml), and the extract was washed with water and dried with magnesium sulfate. The solvent was distilled off under vacuum, and the residue was triturated with ether. The precipitate was filtered off, washed with ether, and dried. A mixture of compounds **8** and **9** (1.8 g) was obtained (R_f 0.85 and 1.08). The mixture was crystallized from methanol and then from ethyl acetate. Compound **8** was obtained. Yield 0.14 g (2%); mp 234-236°C (decomp.) (R_f 0.85). The combined mother liquors after the isolation of compound **8** were evaporated to dryness under vacuum. The residue was chromatographed on a column of silica gel with ethyl acetate as eluent. The residue after distillation of the solvent was crystallized three times from methanol. Compound **9** was obtained. Yield 0.37 g (6%); mp 125-127°C (R_f 1.08).

9-Alkyl-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purines (5, 7, 9, 10). A. Mixture of 9-methyl-6-thiopurine (1.66 g, 0.01 mol) [19], 5-chloro-1-methyl-4-nitroimidazole (1.62 g, 0.01 mol), and sodium hydroxide (0.4 g, 0.01 mol) in water (160 ml) was boiled for 3 h and cooled. The precipitate was filtered off, washed with water, and dried. 9-Methyl-6-(1-methyl-4-nitro-5-imidazolyl)thiopurine **5** was obtained. Yield 2.50 g (89%); mp 164-166°C. After recrystallization from water mp 168-169°C.

B. To solution of azathioprine (2.77 g, 0.01 mol) in anhydrous DMF (50 ml) we added finely ground anhydrous potassium carbonate (1.4 g, 0.01 mol) and methyl iodide, ethyl iodide, propyl bromide, or butyl bromide (0.015 mol). The mixture was stirred at 40°C for 12 h (for preparation of compound **5**), at 70-72°C for 11 h (for preparation of compound **7**), at 70°C for 15 h (for preparation of compound **9**), and at 90°C for 12 h (for preparation of compound **10**). The reaction mixture was cooled and poured into water (150 ml). The precipitate was filtered off, washed on the filter with 30-40 ml of 1N solution of sodium hydroxide and then to neutral reaction with water, and dried. Compounds **5, 7, 9, 10** were obtained. Mixed melting tests with samples of the respective substances isolated during the alkylation of azathioprine by alkyl halides in alkaline media did not give a melting point depression. The IR spectra and R_f values of the samples were identical.

Hypoxanthine (11). A. Suspension of azathioprine (2.77 g, 0.01 mol) in 18% hydrochloric acid (20 ml) was boiled for 40 min. Solution from which brown vapor (nitrogen oxides) was emitted was quickly formed. The solution was heated with charcoal, filtered, cooled, and neutralized to pH 6.5 with aqueous ammonia. The precipitate was filtered off, washed with water and with acetone, and dried. Compound **11** was obtained. Yield 0.5 g (36%); decomposition temperature >330°C. The IR spectrum was identical with the spectrum of an authentic sample of hypoxanthine.

B. Solution of azathioprine (2.77 g, 0.01 mol) in glacial acetic acid (80 ml) was boiled for 6 h. The dark-brown solution was treated with charcoal and filtered. The solvent was distilled off under vacuum, and the solid residue was washed with acetone and with ether and dried. Yield 1.1 g (81%); decomposition temperature >330°C. The IR spectrum was identical with the IR spectrum of an authentic sample of hypoxanthine.

7-Methylhypoxanthine (12). Suspension of compound **4** (2.5 g, 0.0086 mol) in 18% hydrochloric acid (25 ml) was boiled for 1 h. The solution was heated with charcoal and filtered. The filtrate was evaporated to dryness under vacuum. The solid residue was triturated with acetone, and the precipitate was filtered off, washed with acetone, and dried. 7-Methylhypoxanthine hydrochloride was obtained. Yield 1.14 g (70%); mp 242-244°C (methanol). The base **12**, decomposing at >300°C, was isolated from hydrochloride by the action of the calculated amount of sodium ethoxide in ethanol, filtration from the sodium chloride precipitate, and evaporation of the filtrate to dryness. The IR spectrum of the compound was identical with the spectrum of 7-methylhypoxanthine obtained by the method [20].

9-Ethylhypoxanthine (13). Suspension of compound **7** (5.5 g, 0.018 mol) in 18% hydrochloric acid (55 ml) was boiled for 2 h. The brown solution was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in ethanol, and alcohol solution of ammonia was added to pH 7.5. The solution was evaporated to half the volume and filtered from the ammonium chloride precipitate. From the filtrate by precipitation with ether 1.06 g (36%) of a substance melting at 261-263°C (darkens at 200°C) were isolated. By repeated reprecipitatation from ethanol with ether the pure substance **13** was obtained; mp 263-265°C (decomp.). Published data [21]: mp 263-265°C.

Di(1-methyl-4-nitro-5-imidazolyl) Disulfide (14). To solution of compound **4** (2.91 g, 0.01 mol) in glacial acetic acid (50 ml) 27.3% hydrogen peroxide (2.5 g, 0.02 mol) was added. The mixture was stirred at 75-80°C for 14 h. The transparent solution was evaporated under vacuum to a third of the volume and cooled, and water (40 ml) was added. The yellow precipitate was filtered off, washed with water, and dried. Yield 0.3 g, (2%); mp 209-211°C (decomp., from 50% ethanol).

6-Thiopurine (15). Suspension of azathioprine (2.77 g, 0.01 mol) in 1N hydrochloric acid (25 ml) was boiled for 1.5 h. The solution was purified with charcoal, filtered, and neutralized to pH 4 with aqueous ammonia. The precipitate was filtered off, washed with water and with acetone, and dried. 6-Thiopurine hydrate was obtained. Yield 0.6 g (35%); mp 310-312°C (decomp.). Mixed melting test with an authentic sample did not give melting point depression. The IR spectra of the samples were identical.

6-Thio-7-methylpurine (16). Suspension of compound **4** (2.5 g, 0.0086 mol) in of 1N hydrochloric acid (25 ml) was boiled for 2 h and treated as described for the production of compound **15** with the exception that the precipitate was washed additionally with alcohol and ether and crystallized from water. Yield 0.27 (18%); mp 305-306°C (decomp.). Mixed melting test with a sample obtained by the method in [15] did not give melting point depression. The IR spectra were identical.

6-Thio-9-ethylpurine (17). Suspension of compound **7** (5.0 g, 0.0172 mol) in 1N hydrochloric acid (50 ml) was boiled for 1.5 h. The solution was cooled and neutralized to pH 6 with sodium bicarbonate. The precipitate was filtered off, washed with water and with acetone, and dried. Yield 0.86 g (29%); mp 333-336°C (decomp., from water). Published data [21]: mp 334-337°C (decomp.).

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