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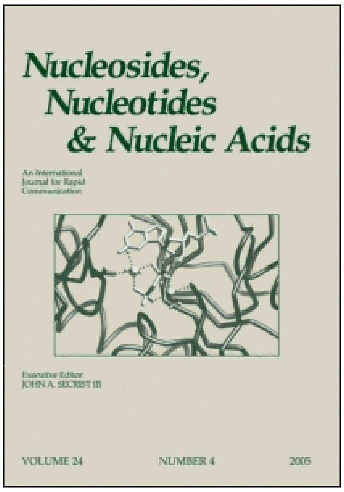

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Transglycosylation Reaction of 6-Thioguanosine

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TRANSGLYCOSYLATION REACTION OF 6-THIOGUANOSINE

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ABSTRACT: Peracetylated 6-thioguanosine (**2**) undergoes the so far unknown N→S transglycosylation reaction to form a stable $9,S^6$-bis(ribosyl) derivative (**3**) and N^2-acetyl-6-thioguanine (**4**). The reaction takes place at elevated temperatures with no catalyst, or in solution in the presence of acidic catalysts. The reversible 7⇄9 isomerization, characteristic for guanosine and its analogs, has not been observed in this case.

Introduction

The fully protected 6-oxopurine nucleosides, *i.e.* guanosine, inosine, $1,N^2$-ethenoguanosine and their acyclic analogs, readily undergo a reversible 7⇄9 transglycosylation in the presence of acidic catalysts.[1] The glycosyl migration process represents an intermolecular reaction and therefore, the 6-oxopurine nucleosides may serve as versatile substrates in the synthesis of new nucleoside analogs by applying the exchange methods: transpurination[2-4] or transglycosylation.[5] The fully reversible 7⇄9 transglycosylation of 6-oxopurine is a unique reaction in the nucleoside chemistry; glycosyl migration reactions of other purine and pyrimidine nucleosides are practically irreversible.[1,6]

In connection with our ongoing interest in the mechanism of transglycosylation, we have extended the study to 6-thioguanosine, a close structural analog of guanosine. A comparison of the 6-oxo and 6-thioxo series may give a plausible evidence, whether the presence of the C=O group in position 6 of the purine system is essential for the reversible 7⇄9 transglycosylation.

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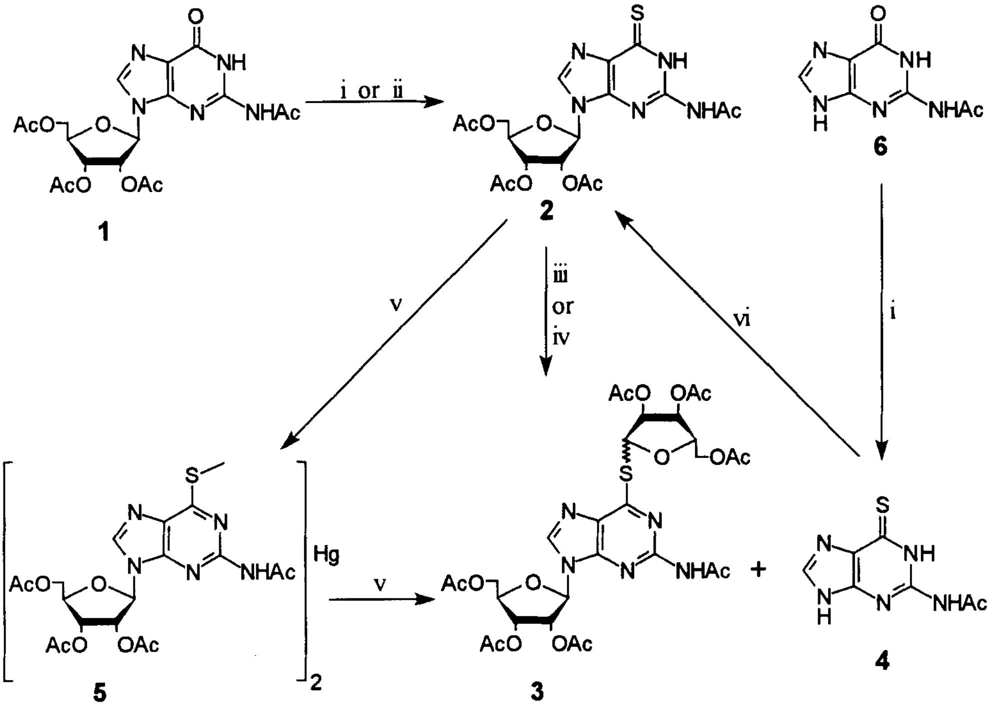
Little is known about transglycosylation of 6-mercaptopurine nucleosides. However, glycosyl migration reactions of the S→N type have been reported for other heterocycles possessing the thiocarbonyl group. It has been demonstrated that S^2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-mercaptopyrimidine undergoes rearrangement to a 1-substituted product in the presence of mercury bromide; the S→N transglycosylation, however, is considerably slower than the O→N migration for the respective O-glycoside.[7,8] This leads to the conclusion that S-nucleosides are more stable than the corresponding O-substituted compounds due to the stronger nucleophilicity of sulfur atom.

Therefore, heterocycles with a thiocarbonyl group partially undergo S-substitution under glycosylation conditions. For example, ribosylation of 6-methyl-2-thiouracil and 5,6-dimethyl-2-thiouracil gave S-ribosides as the main products, along with 3-substituted compounds.[9] The anticipated 1-riboside was not formed in this reaction. Other S-glycosylated derivatives were obtained during glycosylation of 5,6-dihydro-4-oxo-2-thiopyrolo-[2,3-*d*]pyrimidine,[10] 7-mercapto-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine,[11] 2-, 3-, and 4-mercaptoquinoline and 1-mercaptoisoquinoline.[12] In the chemistry of pteridines, glycosylation of 6,7-diphenyl-2-thiolumazine using the silyl method yielded S^2-riboside as the main product.[13] Similarly, S-ribosides were obtained in ribosylation of 2- and/or 4-mercaptopyridines and pyrimidines.[14,15] In most cases, the S-glycosylated products could be transformed to the respective N-glycosides. Mercury bromide was the most effective catalyst in the S→N transglycosylation,[16-19] however, the yield of the conversion was usually low.

Results and Discussion

The model compound for the study of transglycosylation, N^2-acetyl-6-thio-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)guanine (**2**), was synthesized in moderate yields (70% and 62%, respectively) by direct thiation of tetraacetylguanosine (**1**)[20] with Lawesson's reagent[21] or with phosphorus pentasulfide[22] in pyridine (Scheme 1). Compound **2** was then subjected to transglycosylation experiments. Under thermal conditions, *i.e.* heating at 210°C for 10 min without solvent and catalysts, the thioguanosine (**2**) was transformed into an equimolar mixture of 9,S^6-bis(ribosyl) product (**3**) and N^2-acetyl-6-thioguanine



SCHEME 1. *Reagents and conditions:* i, $[p\text{-}CH_3OC_6H_4P(S)S]_2$ in pyridine, reflux, 24-32 h; ii, P_2S_5 in pyridine/H_2O, 120°C, 6 h; iii, 210°C, 10 min; iv, $p\text{-}CH_3C_6H_4SO_3H$ in chlorobenzene, reflux, 1h; v, $HgBr_2$ in chlorobenzene, reflux, 7-60 min; vi, 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose, $p\text{-}CH_3C_6H_4SO_3H$ in chlorobenzene, reflux, 2 h.

(4). Quite similar results were obtained when nucleoside **2** was refluxed in chlorobenzene in the presence of *p*-toluenesulfonic acid.

The so far unknown glycosyl migration reaction of the N→S type is not stereoselective, leading to the formation of S^6-α- and S^6-β-anomers (molar ratio 1:1, as judged from ^{1}H NMR spectra; Table 1), whereas 9-ribose maintains the β-configuration. The progress of reaction was monitored by the HPLC analysis (Fig. 1). The time-dependent distribution of products clearly indicates the following stoichiometry of the reaction: two molecules of substrate **2** give one molecule of diribosyl derivative **3** and one of free base **4**. Furthermore, tetraacetyl-6-thioguanosine remains in a dynamic equilibrium with products **3** and **4**. This means that migration of the ribofuranosyl group between S6 and N9 is reversible. In fact, even at the thermal conditions the yield of conversion never

TABLE 1. 300 MHz ^{1}H NMR Chemical shifts (ref. TMS, δ, ppm) in $(CD_3)_2SO$.[a]

Compd	1-H	N^2H	8-H	1'H	2'H	3'H	4'H	5'H	$NCOCH_3$	$OCOCH_3$
2	13.40	11.94	8.44	6.09	5.82	5.47	4.3-4.4		2.24	2.03, 2.06, 2.13
	bs,1	s,1	s,1	d,1	t,1	q,1	m,3		s,3	3s,9
				6.23	5.93	5.75				
$3^{b,c}$	-	10.66	8.53 8.54	d,2	t,2	q,2	4.0-4.5		2.21 2.23	2.02-2.13
		s,2	s,1 s,1	*6.62 7.24*	*5.57*	*5.38*	m,12		s,3 s,3	9s,36
				d,1 d.1	*m,2*	*m,2*				
4	13.39	11.85	8.32	-	-	-	-	-	2.22	-
	s,1	s,1	s,1						s,3	
5	-	10.65	8.52	6.15	5.90	5.77	4.29-4.44		2.15	1.96, 2.04, 2.11
		s,2	s,2	d,2	t,2	t,2	m, 6		s,6	3s, 18

TABLE 2. 75.43 MHz ^{13}C NMR Chemical shifts (ref. TMS, ppm) in $(CD_3)_2SO$.

Compd	C-6	NC=O	OC=O	C-2	C-4	C-8	C-5	C-1'	C-4'	C-2'	C-3'	C-5'	N-Ac	O-Ac
			169.1											20.1
2	174.2	173.8	169.3	147.5	145.0	140.3	131.8	84.6	79.9	72.1	70.2	62.9	23.9	20.3
			170.0											20.4
								86.0	79.8					
$3^{b,c}$	158.1	169.9	168.5-	151.9	149.4	143.0	127.5	86.1	79.9	72.2	70.3	63.2	24.5	20.3-
		170.1	-169.8		149.5	143.2	127.8	*82.5*	*79.0*	*70.6*	*70.4*	*62.6*	24.6	-20.5
								83.0	*79.1*	*74.2*	*70.5*	*62.8*		
4	169.2	173.7	-	144.6	150.9	146.9	125.8	-	-	-	-	-	23.7	-
			168.3											20.1
5	167.9	169.9	169.1	152.3	148.1	142.4	128.3	86.3	79.8	72.2	70.3	63.1	24.4	20.2
			169.2											20.3

[a] Figures following the observed multiplicities are numbers of protons estimated by integration; [b] an equimolar mixture of S^6-α and β-anomers; [c] data for S^6-ribose in italics.

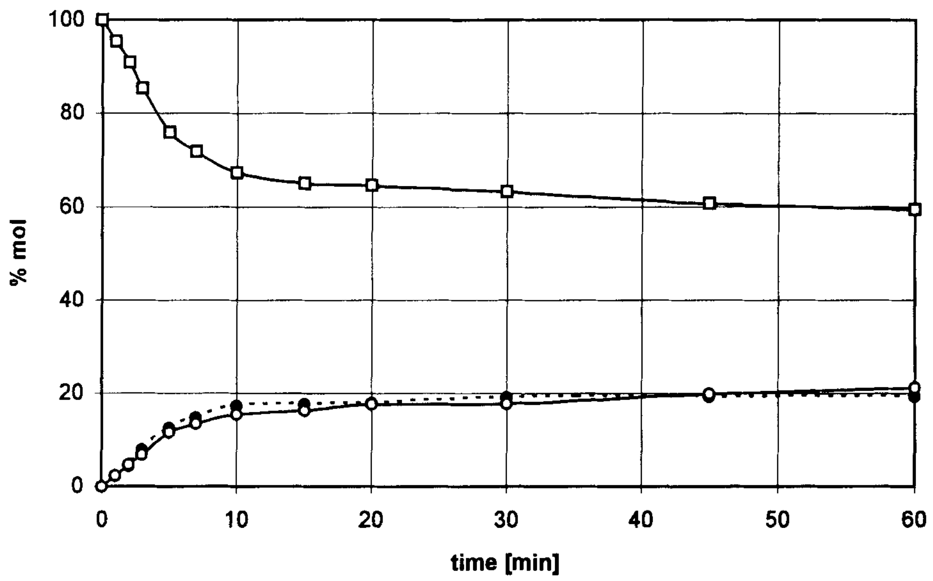


FIG. 1. Time-dependent product distribution for transglycosylation of tetraacetylthioguanosine (**2**) in the presence of *p*-toluenesulfonic acid (see Experimental): **2** □; **3** ●; **4** ○. The mole fractions are based on HPLC data.

exceeded 50%. However, isolated product **3** was rather stable when heated without catalysts and in the absence of N^2-acetyl-6-thioguanine (**4**). Any 7-ribosylated product, which could be anticipated by analogy with the 6-oxo series, was not detected in this study.

In another experiment, transglycosylation of **2** was catalyzed by mercury bromide. Surprisingly, after a short reaction period (7 min), the reaction mixture contained a new product not seen in the previous study (TLC). Structure of that compound was tentatively assigned as S^6-monoribosyl derivative of 6-thioguanine[23] on the basis of UV and ^{13}C NMR spectra (Table 2), which confirmed the S^6-substitution. Moreover, the integration of proton signals in the ^1H NMR suggests that sugar and aglycon portions were in the ratio 1:1. However, more precise study showed that the product contained mercury, determined either as mercury sulfide after treatment with thioacetamide, or by the polarographic method. Therefore, it may be assumed that this intermediate product has been formed in the initial interaction of nucleoside **2** with the catalyst. Finally, its structure has been solved on the basis of mass spectrometry, as a symmetrical dimer **5**: two molecules of the substrate are linked together with a mercury bridge attached to the sulfur atoms.

After a prolonged reaction time the dimer **5** undergoes rearrangement to the final product **3**. Interestingly, when mercury bromide was used as a catalyst, the S^6-β-anomer was formed predominantly at the early stages of transglycosylation. A prolonged heating (1-2 h) resulted in anomerization, which should be considered as a *post*-migration event.

Reversibility of the transglycosylation prompted us to further examine the ribosylation reaction of **4**. N^2-Acetyl-6-thioguanine (**4**) was synthesized from N^2-acetylguanine (**6**)[24] by thiation with Lawesson's reagent in pyridine. This product was identical to the compound isolated from reaction mixtures after transglycosylation experiments. Compound **4** may also be obtained by acetylation of 6-thioguanine.[25] Direct coupling reaction of **4** and 1,2,3,5-tetra-*O*-acetyl-l-β-D-ribofuranose performed in the presence of *p*-toluenesulfonic acid gave tetraacetyl-6-thioguanosine (**2**) as the first product formed. After a longer reaction time this compound was slowly converted to the final transglycosylation product **3**. It indicates that **4** is initially glycosylated at N9; no compound of the putative structure of S^6-monoribosyl derivative has been detected in this study. This result is in opposition to those reported for glycosylation of other heterocyclic bases (see Introduction), which initially undergo the S-substitution.

The 9,S^6-bis(ribosyl) derivative (**3**) is the most stable product in the transglycosylation of tetraacetyl-6-thioguanosine (**2**). Stability of **3** may be rationalized in the following way: the S^6-substitution imposes full aromacity of the pyrimidine ring and therefore, compound **3** does not belong to nucleosides of the "guanine type",[1] but rather to the "adenine type", in which category the 9-glycosyl derivatives are the most stable regioisomers.

Due to the strong nucleophilic character of sulfur, the pathway of transglycosylation of 6-thioguanosine is completely different than that of guanosine and its analogs. The mechanism of transglycosylation may be depicted as follows. Interaction of the substrate (**2**) with acidic catalysts facilitates the cleavage of the N-glycosylic bond, with generation of the acyloxonium sugar cation and liberation of free base (**4**). Another molecule of nucleoside **2** reacts with the sugar cation to form 9,S^6-*bis*-substituted product. In the 6-oxopurine series, the second sugar substituent attaches to N7 not to O6. This leads to the formation of very unstable 7,9-*bis*-glycosylpurine intermediates,[26,27] which undergo decomposition to a mixture of 7- and 9-regioisomers.

Experimental

Melting points were determined on a Laboratory Devices Mel-Temp II micromelting points apparatus and are uncorrected. UV spectra were measured in methanol on a Beckman DU-65 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 300 FT NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra were taken on an AMD-604 spectrometer using the LSIMS technique (Cs^+, 10 kV; in NBA). Elemental analyses were performed on a Perkin-Elmer 240 Elemental Analyzer. For determination of mercury, a CEM Microwave Sample Preparation System MDS-2000 and a Polaro-Sensors ECO-TRIBO Polarograph were used. TLC was conducted on Merck silica gel F_{254} 60 plates using the following solvent systems (measured by volume): A, chloroform - methanol (9:1); B, toluene - ethanol (4:1); C, dichloromethane - ethanol (95:5). For preparative short-column chromatography Merck TLC gel H 60 was used.

Analytical high performance liquid chromatography (HPLC) was performed using the following components from Waters Division of Millipore: Nova Pak C_{18} column (8 x 100 mm Radial-Pak Cartridge), 600E Multisolvent Delivery System with U6K Universal Liquid Chromatography Injector, 486 Tunable Absorbance Detector and 746 Data Module.

Tetraacetylguanosine (**1**) was prepared according to Reese and Saffhill[20] and then precipitated from chloroform to diethyl ether to give **1** as a white powder. N^2-Acetylguanine (**6**) was synthesized according to Shabarova *et al.*[24] and crystallized from 60% ethanol.

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-N^2-acetyl-6-thioguanine (2). *Method A.* Lawesson's reagent (2.7 g, 6.646 mmol) was added to a solution of **1** (3.0 g, 6.646 mmol) in freshly distilled pyridine (130 mL). The mixture was gently refluxed (oil bath temp. 130°C) with stirring for 32 h. The solvent was then evaporated and a resulting solid foam was chromatographed on a silica gel column (CH_2Cl_2 – EtOH gradient from 98:2 to 95:5). Evaporation of appropriate fractions gave 2.177 g (70%) of **2** as a solid foam. The product was identical in all respects (TLC, NMR) to that obtained in Method B.

Method B. Phosphorus pentasulfide (778 mg, 3.5 mmol) was added to a solution of tetraacetylguanosine (**1**; 451.4 mg, 1.0 mmol) in pyridine (5 mL) containing 40 μL of water. The reaction mixture was stirred at 120°C (oil bath) for 6 h; further portions of water (10 μL each) were added after 1, 2, 3 and 4 h of heating. Pyridine was then evaporated and a resulting brown oil was treated with water (25 mL) and chloroform (25 mL). The aqueous layer was washed with chloroform (2 x 20 mL); the combined chloroform extracts were dried with Na_2SO_4 and evaporated to an oil, which was chromatographed on a silica gel short column (3.5 x 9 cm) in $CHCl_3$ – MeOH, 98:2. Fractions containing the main product **2** were evaporated to a solid foam. Yield 290 mg (62%). Attempted crystallization from alcohols and 60% aq. ethanol failed. R_F 0.58(A); 0.43(B), 0.45(C) (substrate **1**: 0.41, 0.30, 0.32, respectively). λ_{max} 332 nm (ε 22,600). Anal. Calcd. for $C_{18}H_{21}N_5O_8S$ (467.45) C, 46.25; H, 4.53; N, 14.98, S, 6.87. Found: C, 46.35; H, 4.67; N, 14.69; S, 6.77. LSIMS HR: Calcd. for MH^+ $C_{18}H_{22}N_5O_8S$: 468.11891. Found: 468.11893.

Transglycosylation reaction of 2. 9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-S^6-(2,3,5-tri-*O*-acetyl-α,β-D-ribofuranosyl)-N^2-acetyl-6-thioguanine (3). *Thermal conditions.* A sample of **2** (160 mg, 0.34 mmol) was heated without solvents in an open flask at 210°C for 10 min. The resulting melt was dissolved in chloroform and products were separated by short-column chromatography in $CHCl_3$ – MeOH, 98:2. First fractions contained a 1:1 anomeric mixture of 9,S^6-diribosyl derivative **3** as a solid foam after evaporation of solvents. Yield 62 mg (50%). R_F 0.71(A); 0.54(B), 0.50(C). λ_{max} 244 nm (ε 25,200), 293 (15,400), 298 (sh; 14,800). LSIMS HR: Calcd. for MH^+ $C_{29}H_{36}N_5O_{15}S$: 726.19286. Found: 726.19272. Evaporation of further fractions yielded compound **4** (18.0 mg, 50%), identical to the authentic sample of N^2-acetyl-6-thioguanine (TLC, ^{1}H NMR).

In the presence of p-toluenesulfonic acid. A solution of nucleoside **2** (100 mg, 0.214 mmol) and *p*-toluenesulfonic acid monohydrate (4.1 mg, 0.0214 mmol) in chlorobenzene (10 mL) was refluxed (oil bath temp. 150°C) with stirring for 1 h. The solvent was then removed by evaporation. Short-column separation as described above allowed 22.2 mg (29%) of **3** and 6.9 mg (31%) of **4**. The progress of reaction was monitored by HPLC. Elution with a MeOH – H_2O reversed gradient (from 35% to 100% MeOH; flow rate 1 mL min^{-1}) gave a good separation for compounds **2**, **3** and **4**. The assignment of the peaks was performed by comparing the retention times and UV spectra with those of the original samples. UV-absorption was measured at 300 nm and the following ε_{300} values [L mol^{-1} cm^{-1}] were taken for calculation of mole fractions: 11,200 for **2**; 14,750 for **3**; 7,200 for **4**. The results are presented in Fig. 1.

In the presence of $HgBr_2$. A mixture of **2** (200 mg, 0.428 mmol) and $HgBr_2$ (77.2 mg, 0.214 mmol) was refluxed in chlorobenzene (10 mL) for 7 min. The solvent was then removed by evaporation, and a resulting solid foam was chromatographed on a silica gel short column (3 x 10 cm) in dichloromethane - ethanol 98:2. First UV-absorbing fractions contained the 9,S^6-diribosyl derivative **3** (33.4 mg, 21%), as a 1:3.5 mixture of S^6-α- and β-anomers, respectively (^{1}H NMR). Evaporation of further fractions gave the main product **5** as a white solid. Yield 151.3 mg (62%). An analytical sample was crystallized from 60% aq. ethanol, mp 158-160°C. R_F 0.63(A); 0.47(B); 0.40(C). λ_{max} 252, 304 nm. Determination of mercury: Calcd. for $C_{36}H_{40}N_{10}O_{16}S_2Hg$ (1134.48) %Hg, 17.70. Found: %Hg, 17.26 (determined as HgS after hydrolysis in 1N HCl, 100°C, and precipitation with thioacetamide); 18.20 (polarographic method). LSIMS LR: m/z 1135 (MH^+), 877 (MH^+-Rac_3), 669, 619 (MH^+-2Rac_3), 468, 411, 260, 210 (for mercury-containing fragments presented only peaks of isotope ^{202}Hg). A similar reaction of a prolonged heating time (2 h) gave an equimolar mixture of **3** and **5**, in which **3** was a 1:1.2 anomeric mixture of S^6-α and β compounds as determined by ^{1}H NMR (signals of 1'H at δ 7.24 and 6.62 ppm, respectively).

Stability of 3 under transglycosylation conditions. Three samples of 9,S^6-diribosylguanine derivative (**3**; 10 mg, 13.8 μmol) were heated without solvents at 200°C for 10 min; at 210°C for 5 min, and at 220°C for 10 min. The resulting melts were dissolved in chloroform and analyzed by TLC and HPLC; the reaction mixtures contained mainly unreacted **3** and traces of N^2-acetyl-6-thioguanine (**4**) in the amounts not exceeding 5%. Another sample of **3** (13.8 μmol) was refluxed in chlorobenzene (5 mL) in the presence of *p*-toluenesulfonic acid monohydrate (1.38 μmol; added as a solution in 100 μL of acetonitrile) for 45 min. HPLC analysis showed the presence of **3** (35%), **2** (47%), and **4** (12%).

N^2-Acetyl-6-thioguanine (4). A suspension of N^2-acetylguanine (**6**, 1.0 g, 5.176 mmol) and Lawesson's reagent (2.30 g, 5.693 mmol) in dry pyridine (100 mL) was vigorously stirred under reflux for 24 h. After this time the reaction mixture was adsorbed on a portion of silica gel (70-230 mesh, *ca* 5 g) by evaporation of pyridine. The gel was coevaporated with toluene (2 x 50 mL) and applied into a silica gel column (3.7 x 10 cm). Elution with chloroform - methanol 9:1 gave **4** as a chromatographically homogenous product, 498 mg (46%) as a pale-yellow solid. An analytical sample was recrystallized from boiling water,[25] mp > 250°C. R_F 0.35(A) (0.26 for substrate **6**). λ_{max} 292 nm (sh; ε 6,300), 333 (16,800). Anal. Calcd. for $C_7H_7N_5OS.H_2O$ (227.24) C, 37.28; H, 3.99; N, 30.82, S, 14.11. Found: C, 37.28; H, 4.18; N, 30.56; S, 14.26.

Direct ribosylation of N^2-acetyl-6-thioguanine (4). A mixture of N^2-acetyl-6-thioguanine (**4**; 100 mg, 0.478 mmol), 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (304 mg, 0.956 mmol) and *p*-toluenesulfonic acid monohydrate (9.1 mg, 0.048 mmol) was refluxed in dry chlorobenzene (10 mL). The progress of reaction was monitored by TLC in solvent A. Tetracetyl derivative **2** was the only reaction product after 15 min of heating, whereas after a prolonged reaction time (30-120 min) both **2** and **3** (in increasing amounts) were detected in the reaction mixture. After 2 h of refluxing, chlorobenzene was removed by evaporation, and the products were separated as in the case of transglycosylation of **2** in the presence of *p*-TsOH. The first UV-absorbing fractions contained diribosyl derivative **3**; yield 29.2 mg (8.4%). Evaporation of further fractions gave 56.6 mg (25%) of peracetylated 6-thioguanosine (**2**).

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