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The *S,X*-Acetals in Nucleoside Chemistry. I. The Synthesis of 2'- and 5'-*O*-Methylthiomethylribonucleosides

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Abstract—Ribonucleoside 2'- and 5'-*O*-methylthiomethyl derivatives were synthesized from selectively protected nucleosides by the action of a dimethyl sulfoxide–acetic anhydride–acetic acid mixture.

Key words: ribonucleosides, methylthiomethylation, thioacetals, Pummerer's rearrangement

INTRODUCTION

The Pummerer rearrangement in its initial variant, which involves the use of a DMSO–acetic anhydride system, has been used for decades for the synthesis of α-substituted sulfides in satisfactory yields [1]. Its mechanism, studied by Johnson and Philips [2], is presented in Scheme 1. The sequence of reactions suggests that the addition of alcohols to the reaction mixture would be a convenient method for the synthesis of *O,S*-acetals.

It is known that thioacetals open wide synthetic possibilities such as a change in the sulfur valent state, a substitution of other substituents for the alkylthio group, or the introduction of some substituents in the α-position to the sulfur atom [2, 3]. This has prompted the development of methods for the introduction and removal of the *O*-methylthiomethyl group [4–7]. In the nucleoside series, 2'-*O*-methylthiomethyl derivatives of adenosine and guanosine were first described as by-products in the oxidation reaction of hydroxyl groups in selectively protected nucleosides by the DMSO–acetic anhydride mixture [8]. 3'-*O*-Methylthiomethyl-5'-deoxy-5'-methylthioadenosine was similarly obtained upon the oxidation of protected methylthioadenosine under the same conditions. The yield of this by-product changes from 2 to 23% depending on the quality of DMSO and the reaction time [9].

The DMSO–Ac_2O mixture provides good results in the synthesis of *O*-methylthiomethyl derivatives of acyclic nucleoside analogues, since the starting compounds are tertiary alcohols [10] stable under the conditions of oxidation. In the case of carbohydrates, the addition of acetic acid to the DMSO–Ac_2O mixture was shown to inhibit the oxidation of primary and secondary alcohols and, thus, makes the process of their *O*-methylthiomethylation predominant [5].

The DMSO–Ac_2O–AcOH system was first applied to the synthesis of nucleosides (including those of the riboside series) substituted with the methylthiomethyl group at their carbohydrate residue during work on the synthesis of α-substituted *O*-alkylnucleosides [11–13]. This system was then used successfully for the synthesis of 2'-*O*-methylthiomethyluridine: its yield was 55% [14].

The dimethyl sulfide–benzoyl peroxide system is an alternative agent for *O*-methylthiomethylation [7]. For the first time, it was used for the synthesis of 3'-*O*-methylthiomethylnucleosides of the deoxy series [15, 16]. 2'-*O*-Methylthiomethylnucleosides were recently obtained by using this reagent [17]. It was also shown that both of the reagents may be applied to the synthesis of 5'-*O*-methylthiomethyl-2'-deoxynucleosides [13, 16]. However, neither experimental details nor product characteristics are given in [11–13, 17].

We describe here the synthesis and characterization of 2'-*O*- and 5'-*O*-methylthiomethylribonucleosides, which are important for the following reasons. The polyribonucleotides bearing 2'-*O*-methylthiomethyl substituents have an enhanced stability toward nucleases [17]. Biologically active compounds with antiviral, antiarthritic, antiparasitic, and immunosuppressive activities have been found among the 5'-modified nucleosides. The majority of them are either analogues of *S*-adenosylmethionine, one of the key components of the biological transmethylation system (e.g., *S*-adenosyl-*L*-homocystein, 5'-deoxy-5'-isobutyladenosine, or 5'-deoxy-5'-methylthioadenosine), or are inhibitors of the enzymes of this system. In this group of compounds, an intensive search for biologically active substances is proceeding [9, 18–21]. The 5'-*O*-methylthiomethylribonucleosides, in particular, 5'-*O*-meth-

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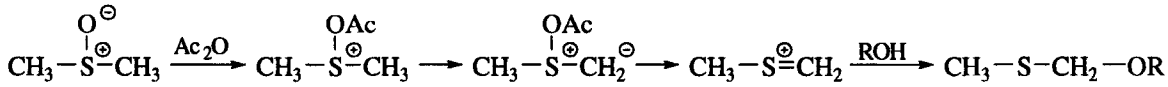
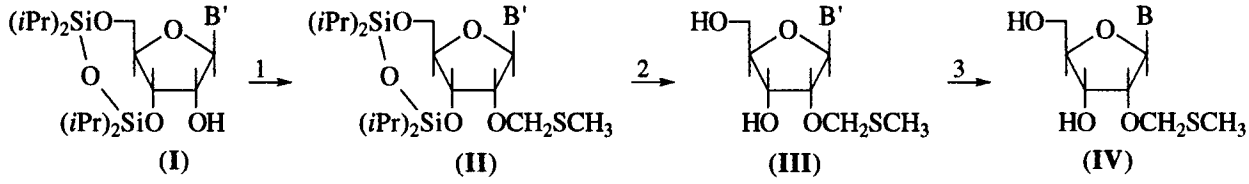


Scheme 1.



(a) B' = BzAde, B = Ade; (c) B' = BzCyt, B = Cyt;
(b) B' = IbGua, B = Gua; (d) B' = B = Ura.
1—DMSO/Ac_2O/AcOH (53 : 36 : 11 volume ratio); 2—$Bu_4N^+F^-$/THF; 3—NH_3/MeOH.
Ib, isobutyryl; 2. THF, tetrahydrofuran

Scheme 2.

ylthiomethyladenosine, may be considered to be precursors of a number of prospective biologically active substances due to their great synthetic possibilities.

RESULTS AND DISCUSSION

We synthesized 2'-*O*-methylthiomethylribonucleosides according to Scheme 2. Nucleosides (**Ia**)–(**Id**) [they had protected 3'- and 5'-hydroxyl groups [22] and the base amino group, except for uracyl in (**Id**)] were converted over a period of 60 h into the corresponding 2'-*O*-methylthiomethyl derivatives by the DMSO–Ac_2O–AcOH mixture at room temperature. The yields of the resulting (**IIa**)–(**IId**) were 60–70%; this means that the methylthiomethylation of hydroxyl functional groups in ribonucleosides by this reagent is as efficient as by the DMSO–benzoyl peroxide reagent, which ensures 55–70% yields [17]. The siloxadiyl protective groups from (**IIa**)–(**IId**) and the acyl protections of heterocyclic bases from (**IIIa**)–(**IIIc**) were successively removed by the action of tetrabutylammonium fluoride

Table 1. Yields and physicochemical characteristics of 2'-*O*-methylthiomethylnucleosides*

Compound	Starting compound	Load		Yield, %	Mp, °C (methanol)	UV spectrum***, λ_{max}, nm, (ε)	Mass spectrum
		mg	mmol				
(IIId)	**(IId)**	274	0.5	79	174.5–175.5	261.8(9800)	304.4 $(M)^+$
						261.8(9700)	327.2 $(M + Na)^+$
						261.2(7400)	343.2 $(M + K)^+$
(IVa)	**(IIIa)**	166	0.38	87	143–143.5	257.2(14600)	328.1 $(M + H)^+$
						259.6(14500)	330.2 $(M + 3H)^+$
						259.4(14800)	350.1 $(M + Na)^+$
(IVb)	**(IIIb)**	214	0.52	82	>220	257.0(11700)	344.1 $(M + H)^+$
						253.2(13400)	366.2 $(M + Na)^+$
						265.0(11300)	382.2 $(M + K)^+$
(IVc)	**(IIIc)**	105	0.26	83	151.5–152.5[2]*	279.8(12700)	304.1 $(M + H)^+$
						270.6(8900)	326.1 $(M + Na)^+$
						271.4(8900)	342.1 $(M + K)^+$

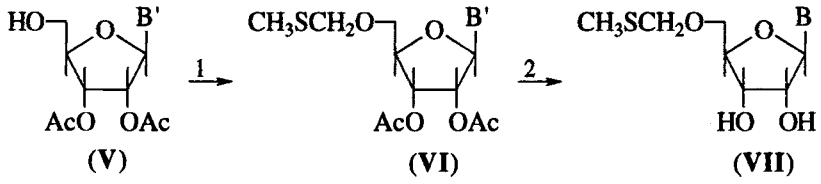
* (**IIId**) was isolated according to desilylation method A, whereas ammonolysis method A was applied for (**IVa**)–(**IVc**).
** Methanol–ether.
*** The parameters of the UV spectrum for each compound are given at pH 1, 7, and 13.

Table 2. ^{1}H NMR spectra of 2'-*O*-methylthiomethylribonucleosides*

Compound	H6 or H8 ($J_{6,5}$)	H5 or H2	OCH_2S ($J_{a,b}$)	SCH_3	H1' ($J_{1',2'}$)	H2' ($J_{2',3'}$)	H3' ($J_{3',4'}$)	H4'	H5' ($J_{H5'a,H5'b}$; $J_{4',5'a}$; $J_{4',5'b}$)	Other
(IIa)	8.78c	8.32s	5.08; 5.02dd (12.0)	2.21s	6.13s	4.70d (4.5)	4.73dd (8.0)	4.19m	4.26; 4.05ddd (12.5; 1.0; 2.5)	9.05 (NH); 7.50–8.10 (Ph); 1.20-0.90 (*i*Pr)
(IIb)	7.97s	–	5.03; 4.97dd (11.8)	2.15s	5.83s	4.50–4.42m		4.12m	4.24; 3.98ddd (13.0; 1.0; 2.2)	11.97, 8.31(2 × NH); 2.65, 1.26, 1.23 (H, CH_3 (Ib)); 1.20–0.90 (*i*Pr)
(IIc)	8.36d (7.5)	ç‡Î. Ph	5.15; 5.08dd (11.8)	2.21s	5.85s	4.40d (6.0)	4.27–4.18m		4.30; 4.02ddd (12.0)	8.70 (NH); 7.5–7.9 (Ph); 1.20–0.90 (*i*Pr)
(IId)	7.91d (8.3)	5.69d	5.0s	2.18s	5.75s	4.37d (4.5)	4.25dd (8.5)	4.16m	4.27; 4.0ddd (13.0; 1.0; 3.5)	8.60 (NH); 1.20–0.90 (*i*Pr)
(IIIa)	8.77s	8.75s	4.80; 4.69dd (11.6)	1.81s	6.20d (6.0)	4.87pt (5.0)	4.40m	4.05m	3.73; 3.62m (11.9)	11.25 (NH); 7.5–8.1 (Ph); 5.41 (3'-OH); 5.24 (5'-OH)
(IIIb)	8.28s	–	4.76; 4.66dd (11.6)	1.85s	5.96d (6.7)	4.67pt* (4.9)	4.33m	3.99m	3.65; 3.59dddd (11.9; 4.0; 4.0)	12.1, 11.65 (2 × NH); 5.32 (3'-OH); 5.15 (5'-OH); 2.78, 1.40 (Ib)
(IIIc)	8.54d (7.0)	7.36d	4.94; 4.84dd (11.5)	2.07s	5.90d (2.7)	4.22dd (5.0)	4.13m	3.95m	3.79; 3.63m (11.9)	11.25 (NH); 7.5–8.1 (Ph); 5.22 (3'-OH); 5.27 (5'-OH)
(IIId)	7.94d (8.1)	5.67d	4.81; 4.66dd (11.5)	1.99s	5.88d (5.5)	4.25pt (5.0)	4.13m	3.89m	3.64; 3.57m (12.3)	11.35 (NH); 5.25 (3'-OH); 5.18 (5'-OH)
(IVa)	8.38s	8.13s	4.73; 4.63dd (11.6)	1.76s	6.02d (6.3)	4.81dd (5.1)	4.33m	4.01m	3.68; 3.56dddd (11.9; 4.4; 6.5)	7.34 (NH_2); 5.52 (5'-OH); 5.33 (3'-OH)
(IVb)	7.97s	–	4.76; 4.66dd (11.5)	1.88s	5.85d (6.4)	4.61dd (4.9)	4.29m	3.95m	3.64; 3.57dddd (11.9; 3.4; 3.6)	10.59 (NH); 6.45 (NH_2); 5.25 (3'-OH); 5.13 (5'-OH)
(IVc)	7.92d (7.5)	5.73d	4.88; 4.76dd (11.3)	2.04s	5.87d (3.9)	4.15pt (5.2)	4.09m	3.86m	3.70; 3.59m (11.5)	7.16 (NH_2); 5.12 (3'-OH + 5'-OH)

* Spectra of **(IIa)**–**(IId)** were measured in $CDCl_3$; those of **(IIIa)**–**(IIId)** and **(IVa)**–**(IVd)** were taken in DMSO-d_6. Chemical shifts (δ, ppm) and spin–spin coupling constants (*J*, Hz) are given. The coupling of signals was revealed on the basis of spin coupling constants. Integral intensities correspond to the indicated number of protons. Forms of resonances: s, singlet; d, doublet; dd, doublet of doublets; pt, pseudotriplet; ddd, doublet of doublets of doublets; dddd, doublet of doublets of doublets of doublets; and m, multiplet. Resonances from Ph, *i*Pr, and isobutyryl; from NH and NH_2; from 3'-OH and CH_3 of isobutyryl; and from 5'-OH are multiplets, broad singlets, doublets, and triplets, respectively.

** Superposition of OCH_2S.



(a) B' = BzAde, B = Ade; (c)B' = BzCyt, B = Cyt;
(b) B' = IbGua, B = Gua; (d) B' = B = Ura.
1—DMSO/Ac_2O/AcOH (53 : 36 : 11 volume ratio); 2—NH_3/MeOH.

Scheme 3.

in anhydrous tetrahydrofuran [8] and in methanolic ammonia, respectively.

The physicochemical characteristics of the resulting **(IIa)**–**(IId)**, **(IIIa)**–**(IIId)**, and **(IVa)**–**(IVc)** correspond to their structures (Tables 1, 2). Thus, the ^1H NMR spectra of all the 2'-*O*-methylthiomethyl derivatives (Table 2) exhibit resonances from CH_3S (singlet at 2.2–1.7 ppm) and OCH_2S groups [doublet of doublets (due to the diastereotopicity of these protons) or singlet at 5.1–4.6 ppm]. The 2'-proton resonates in the form of a doublet of doublets, a pseudotriplet, or a doublet when $J_{1',2'} = 0$. The form of these signals and the values of chemical shifts of protons in sugar residue and nucleic base vary depending on the protective groups in the nucleoside molecule.

5'-*O*-Methyltiomethylribonucleosides were synthesized as shown in Scheme 3. The starting **(Va)**–**(Vd)** with protected 2'- and 3'-hydroxyl groups and the exocyclic base amino group were converted into their 5'-*O*-methyltiomethyl derivatives **(VIa)**–**(VId)** with the DMSO–Ac_2O–AcOH mixture as described above in yields of 50–70% (see the Experimental section). The ammonolytic deprotection of these derivatives resulted in **(VIIa)**–**(VIId)**.

The physicochemical characteristics of **(VIa)**–**(VId)** and **(VIIa)**–**(VIId)** in Tables 3 and 4 convincingly confirm their structures. In particular, their ^1H NMR spectra (Table 4) exhibit resonances of protons from the CH_3S and OCH_2S groups. The resonances from other protons were found to coincide with or differ only insignificantly from the corresponding resonances in the starting nucleosides.

Products **(IIId)**, **(IVa)**–**(IVc)**, and **(VIIa)**–**(VIId)** were characterized by mass spectrometry and UV spec-

Table 3. Yields and physicochemical characteristics of 5'-*O*-methylthiomethylnucleosides

Compound	Starting compound	Load		Isolation method*	Yield, %	Mp, °C (methanol)	UV spectrum***, λ_{max}, nm, (ε)	Mass spectrum
		mg	mmol					
(VIIa)	**(VIa)**	361	0.7	B	81	137–138	257.4 (14600) 259.4 (14800) 259.6 (15000)	328.2 $(M + H)^+$ 350.2 $(M + Na)^+$
(VIIb)	**(VIb)**	200	0.402	**** A	75	223–225**	256.6 (12100) 253.6 (13200) 265.2 (11300)	344.2 $(M + H)^+$ 366.1 $(M + Na)^+$
(VIIc)	**(VIc)**	290	0.586	B	80	98–99***	279.4 (12900) 270.8 (8800) 272.0 (8800)	304.2 $(M + H)^+$ 326.2 $(M + Na)^+$ 342.1 $(M + K)^+$
(VIId)	**(VId)**	210	0.54	B	77	147–148	261.6 (10000) 261.8 (9700) 262.2 (7500)	304.4 $(M)^+$ 327.2 $(M + Na)^+$ 343.2 $(M + K)^+$

* After ammonolysis (see the Experimental section).
** Methanol–water.
*** Methanol–ether.
**** The parameters of the UV spectra for each compound are given at pH 1, 7, and 13.

Table 4. ^{1}H NMR spectra of 5'-*O*-methylthiomethylribonucleosides*

Compound	H6 or H8 ($J_{6,5}$)	H5 or H2	OCH_2S ($J_{a,b}$)	SCH_3	H1' ($J_{1',2'}$)	H2' ($J_{2',3'}$)	H3' ($J_{3',4'}$)	H4'	H5' ($J_{H5'a,H5'b}$; $J_{4',5'a}$; $J_{4',5'b}$)	Other
(VIa)	8.79s	8.49s	4.81; 4.70dd (11.6)	2.06s	6.45d (6.5)	5.83dd (5.2)	5.59dd (2.6)	4.47m	3.88; 3.85ddd (10.8; 2.7; 2.6)	9.62 (NH); 2.21, 2.19 (2 × CH_3CO); 7.5–8.1 (Ph)
(VIb)	7.93s	–	4.73; 4.69dd (11.6)	2.08s	6.01d (5.8)	5.95pt (5.2)	5.70dd (3.8)	4.39m	3.87; 3.76ddd (10.7; 3.2; 3.7)	12.1, 8.8 (2 × NH); 2.64, 1.28 (Ib); 2.19, 2.17 (2 × CH_3CO)
(VIc)	8.24d (6.0)	superposition Ph	4.77; 4.71dd (11.5)	2.08s	6.36d (4.6)	5.45–5.37m		4.37m	3.88; 3.79ddd (10.8; 2.1; 2.1)	8.6 (NH); 7.5–7.9 (Ph); 2.2, 2.1 (2 × CH_3CO)
(VId)	7.71d (8.1)	5.75d	4.74; 4.68dd (11.5)	2.05s	6.24d (7.0)	5.30dd (5.4)	5.37dd (2.2)	4.30m	3.79; 3.77ddd (10.8; 2.2; 2.2)	8.53 (NH); 2.18, 2.12 (2 × CH_3CO)
(VIIa)	8.30s	8.15s	4.70; 4.69dd (11.3)	2.06s	5.90d (5.3)	4.60m* (5.0)	4.16m* (4.2)	4.06m	3.75; 3.63ddd (10.5; 3.8; 5.0)	7.28 (NH_2); 5.52 (2'-OH); 5.30 (3'-OH)
(VIIb)	7.85s	–	4.70s	2.07s	5.70d (5.5)	4.41m	4.07m	4.00m	3.69; 3.60ddd (10.7; 3.7; 4.9)	6.48 (NH_2); 5.47 (2'-OH); 5.24 (3'-OH) 10.64 (NH)
(VIIc)	7.69d (7.4)	5.74d	4.72; 4.71dd (11.5)	2.10s	5.78d (3.8)	3.96–3.85m (2.9; 4.2)			3.74; 3.6ddd (10.6; 2.3; 4.2)	7.14 (NH_2); 5.35 (2'-OH); 5.11 (3'-OH)
(VIId)	7.71d (8.5)	5.64d	4.72s	2.09s	5.77d (5.5)	4.03m	3.93m	3.97m	3.71; 3.60ddd (11.0; 3.5; 4.0)	11.35 (NH); 5.40 (2'-OH); 5.11 (3'-OH)

* Spectra of **(VIa)**–**(VId)** were measured in $CDCl_3$; those of **(VIIa)**–**(VIId)** were taken in DMSO-d_6. Chemical shifts (δ, ppm) and spin–spin coupling constants (*J*, Hz) are given. The coupling of signals was revealed on the basis of spin coupling constants and forms of signals. Integral intensities correspond to the indicated number of protons.

** Spin–spin coupling constants were determined in the experiment according to deuteroexchange with ^2H_2O. Forms of resonances: s, singlet; d, doublet; dd, doublet of doublets; pt, pseudotriplet; ddd, doublet of doublets of doublets; and m, multiplet. Resonances from Ph; from NH and NH_2; from 2'-OH, 3'-OH and CH_3 of isobutyryl; and from CH_3CO are multiplets, broad singlets, doublets, and singlets, respectively.

troscopy methods (see Tables 1 and 3, respectively). The UV spectra of these derivatives suggest that no modification or destruction of nucleic bases occurs during their synthesis.

In this way, we established that methylthiomethylation with the DMSO–Ac_2O–AcOH mixture is a sufficiently good method for the synthesis of 2'- and 5'-*O*-methylthiomethyl derivatives of ribonucleosides.

EXPERIMENTAL

Melting points were not corrected. For TLC, Silufol UV 254 (Kavalier, Czech Republic) and Kieselgel 60 F_{254} precoated plates (Merck, Germany) were used. Silica gel L 40/100 (Kavalier, Czech Republic) was used for column chromatography. Nucleosides, chlorotrimethylsilane, and Dowex 50W × 8-200 were from Sigma (United States); 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane and tetrabutylammonium fluoride trihydrate were from Fluka (Switzerland); and dimethyl sulfoxide (DMSO) was from Merck (Germany). Other reagents and solvents were of domestic production.

UV, ^{1}H NMR, and MALDI TOF mass spectra were measured on a Shimadzu UV-160 spectrophotometer (Japan), Bruker DRX-500 spectrometer (Germany), and Vision 2000 spectrometer (Thermo Bioanalysis Corp., UK), respectively.

Yields and physicochemical characteristics of all the compounds synthesized are given in Tables 1–4.

Nucleosides (**Ia**)–(**Id**) were synthesized as described in [22]. (**Va**)–(**Vd**) were obtained using a dimethoxytrityl protective group for 5'-hydroxyl according to a procedure similar to that used in [23, 24].

Methylthiomethylation of hydroxyl groups in ribonucleosides (general procedure). Acetic anhydride (2.15 ml), acetic acid (0.65 ml), and DMSO (3.15 ml) were added to a nucleoside (**Ia**), (**Ib**), (**Ic**), (**Id**), (**Va**), (**Vb**), (**Vc**), or (**Vd**) (1 mmol). The mixture was kept for 3 days at 20°C, with TLC-monitoring in a 9.5 : 1 chloroform–methanol system. After the reaction was completed, the mixture was poured into a cooled 10% Na_2CO_3 solution (30 ml) under stirring. After cessation of the carbon dioxide evolvement, the aqueous layer was extracted with chloroform (3 × 20 ml), and the extract was dried with anhydrous Na_2SO_4 and evaporated in the vacuum of a water-jet and, then, an oil for-vacuum pump. The residue was purified by chromatography on a silica gel column eluted by a gradient of methanol in chloroform from 0 to 2%. The following substances were thus obtained:

***N*^{6}-Benzoyl-2'-*O*-methylthiomethyl-5',3'-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl)adenosine (IIa):** a glass-like foamy mass, yield 1.27 g (70.9%) from 1.63 g (2.66 mmol) of (**Ia**).

***N*^{2}-Isobutyryl-2'-*O*-methylthiomethyl-5',3'-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl)guanosine (IIb):** mp 129–130°C (from methanol), yield 1.25 g (61%) from 1.86 g (3.12 mmol) of (**Ib**).

***N*^{4}-Benzoyl-2'-*O*-methylthiomethyl-5',3'-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl)cytidine (IIc):** a glass-like foamy mass, yield 1.08 g (68.6%) from 1.43 g (2.42 mmol) of (**Ic**).

2'-*O*-Methylthiomethyl-5',3'-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl)uridine (IId): mp 146–146.5°C (from methanol), yield 1.23 g (60.1%) from 1.82 g (3.74 mmol) of (**Id**).

***N*^{6}-Benzoyl-2',3'-di-*O*-acetyl-5'-*O*-methylthiomethyladenosine (VIa):** a glass-like yellowish mass, yield 1.98 g (52.2%) from 3.356 g (7.37 mmol) of (**Va**).

2',3'-Di-*O*-acetyl-*N*^{2}-isobutyryl-5'-*O*-methylthiomethylguanosine (VIb): a glass-like yellowish mass, yield 805 mg (54.5%) from 1.31 g (2.97 mmol) of (**Vb**).

***N*^{6}-Benzoyl-2',3'-di-*O*-acetyl-5'-*O*-methylthiomethylcytidine (VIc):** mp 160–161°C (from methanol), yield 735 mg (70.4%) from 917 mg (2.13 mmol) of (**Vc**).

2',3'-Di-*O*-acetyl-5'-*O*-methylthiomethyluridine (VId): a glass-like yellowish mass, yield 0.66 g (50.3%) from 1.11 g (3.384 mmol) of (**Vd**).

Desilylation of methylthiomethyl derivatives of nucleosides. Tetrabutylammonium fluoride (2.2 ml of 1 M solution in tetrahydrofuran) was added to a solution of nucleoside (**IIa**), (**IIb**), (**IIc**), or (**IId**) (1 mmol in 5 ml of dry tetrahydrofuran), the mixture was kept for 1 day at 20°C, and evaporated. The residue was separated by column chromatography on silica gel, the corresponding fraction was evaporated, and the product was recrystallized (method A). When the recrystallization failed, the mixture after the desilylation was evaporated, and the residue was dissolved in aqueous methanol and filtered through a layer of Dowex 50W in NH_4^+-form. The filtrate was evaporated, and the product was purified by column chromatography on silica gel (method B). The following derivatives were thus obtained:

***N*^{6}-Benzoyl-2'-*O*-methylthiomethyladenosine (IIIa):** mp 151–152°C (from 1% methanol in chloroform), yield 180 mg (83.4%) from 337 mg (0.5 mmol) of (**IIa**).

***N*^{2}-Isobutyryl-2'-*O*-methylthiomethylguanosine (IIIb):** light amorphous mass, yield 232 mg (92.1%) from 400 mg (0.61 mmol) of (**IIb**).

***N*^{4}-Benzoyl-2'-*O*-methylthiomethylcytidine (IIIc):** mp 159–160°C (from chloroform–hexane), yield 162 mg (79.5%) from 325 mg (0.5 mmol) of (**IIc**).

2'-*O*-Methylthiomethyluridine (IIId): yield 120 mg (78.9%) from 274 mg (0.5 mmol) of (**IId**) (method A), see Table 1 for mp.

Removal of acyl protective groups. A solution of nucleoside (**IIIa**), (**IIIb**), (**IIIc**), (**VIa**), (**VIb**), (**VIc**), or (**VId**) in semisaturated methanolic ammonia (methanol saturated with gaseous ammonia at 0°C was diluted

twice with methanol) was kept at 20°C for 1 day [2 days in the case of (**IIIb**) and (**VIb**)] and evaporated. The product was recrystallized (method A) or purified by chromatography on silica gel while eluting with a gradient of methanol in chloroform from 5 to 10% (method B). The details of these experiments are given in Tables 1 and 3.

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