PURINE NUCLEOSIDE ANALOGUES. 11.[+] AN ALTERNATIVE SYNTHESIS OF *N*- AND *O*-ALKYL DERIVATIVES OF 9- AND 7-[(2-ACETOXYETHOXY)METHYL]-N^2-ACETYLGUANINE[++]

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Alkylations of 9- and 7-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine with alkyl halogenides in the presence of base have been investigated affording a new route to the preparation of 1,N^2-dimethyl- as well as O^6-benzyl-9(7)-alkoxyalkylguanines. ^{1}H NMR spectra revealed that the 1,N^2-dimethyl derivatives exist as mixtures of two conformers at room temperature due to the restricted rotation about the C2–N2 bond. These findings agreed with conformational calculations.

Key words: Purines; Nucleosides; Acyclic nucleoside analogues; Acyclovir; Alkylation.

Since the discovery of antiviral properties of acyclovir, many of its analogues, modified both in the heterocycle and acyclic moiety, have been prepared and evaluated. The derivatives of acyclovir alkylated in the guanine ring have received relatively minor attention although it has been established that 1-methyl-9-[(2-acetoxyethoxy)methyl]guanine as well as some 9-(alkoxyalkyl)- and 9-(hydroxyalkyl)-1,7-dialkylguaninium salts exhibit marked antiherpetic activity and great selectivity[3,4]. The disadvantage of these compounds is their poor solubility which hinders the evaluation of their biological activity. Pharmacokinetic properties of alkyl derivatives of acyclovir as well as its 7-substituted isomer might be improved introducing an acetyl functionality at the exocyclic amino group of the guanine ring.

+ For the previous paper in this series see ref.[1]
++For the preliminary report see ref.[2]

Such compounds could be obtained by alkylation of 9-(or 7)-[(2-hydroxyethoxy)methyl]guanines with further acetylation[3–5]. On the other hand, 9-(or 7)-[(2-acetoxyethoxy)methyl]-N^2-acetylguanines are common intermediates in the preparation of acyclovir from guanine. Therefore, it seemed feasible to try to alkylate them to avoid the deacetylation–acetylation procedure.

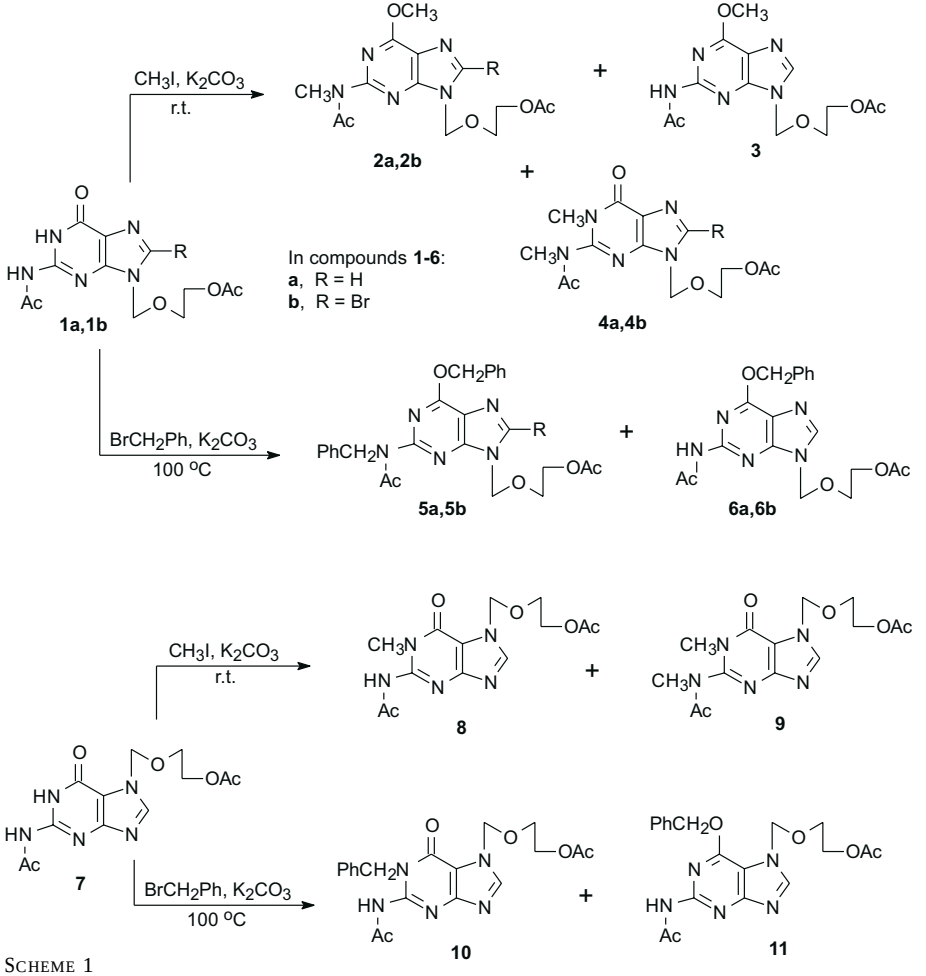
The objective of the present work was to investigate the alkylation of 9- and 7-[(2-acetoxyethoxy)methyl]-N^2-acetylguanines in order to obtain acyclovir derivatives alkylated in the guanine ring and acetylated at the exocyclic amino group.

RESULTS AND DISCUSSION

Methylation of 9-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine (**1a**) with methyl iodide in the presence of potassium carbonate in dimethylformamide resulted in a mixture of alkylated products (Scheme 1) from which compounds **2a**, **3** and **4a** were isolated by chromatography on silica gel in yields 8, 4 and 33%, respectively. The structures of compounds **2a**, **3** and **4a** were established on the basis of their ^{1}H NMR spectra (Table I). The chemical shift of the three-proton singlet in compounds **2a** (δ 4.10 ppm) and **3** (δ 4.12 ppm) supported *O*- rather than *N*-methylation[6] and therefore, this signal was assigned to OCH_3 group at position 6 of the purine system. The site of the second methyl substituent (δ 3.37 ppm) in **2a** was assumed to be the acetamido group. A downfield shift of N^2-acetyl singlet in **2a** was observed in comparison with the same signal in compound **3** (Table I). Taken together these data led us to propose the structures of 9-[(2-acetoxyethoxy)methyl]-6-methoxy-2-(*N*-methylacetamido)purine and 2-acetamido-9-[(2-acetoxyethoxy)methyl]-6-methoxypurine for **2a** and **3**, respectively. Chemical shifts of two methyl groups in the ^{1}H NMR spectrum of compound **4a** corresponded to those of NCH_3 functions[3], therefore, the structure of 9-[(2-acetoxyethoxy)methyl]-1-methyl-2-(*N*-methylacetamido)-6-oxopurine was assigned to this product. The chemical shifts of $NCOCH_3$ and $OCOCH_3$ for **4a** singlets were 2.27 and 1.96 ppm, but the ratio of the integral intensities of these signals was 1 : 5. On heating of **4a** to 130 °C, the signal of $NCOCH_3$ function was shifted up to 2.06 ppm and the intensity of both signals became equal corresponding to three protons each. Similar changes also occurred with NCH_3 signals. The four singlets at 3.11; 3.32; 3.37; 3.47 ppm transformed on heating into two signals at 3.23 and 3.47 ppm with the integral intensity of three protons each (Table I). On cooling to 27 °C, the starting spectrum was obtained. This indicated that,

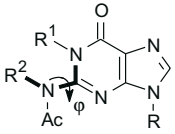
due to the restricted rotation about the C2–N2 bond at room temperature, compound **4a** exists as a mixture of two conformers. The ratio of both conformers was 1 : 2 and the signal of $NCOCH_3$ group protons in one of them overlapped with that of $OCOCH_3$ group.

Possible existence of these two conformers was also supported by conformational calculations performed using ECEPP/2 (ref.[7]) with dielectric constant ε = 2. It has been shown[8] that these potentials are applicable for such type of molecules and give qualitatively correct results. The energetic profile for torsion angle φ of **4a** was calculated with the step of 10 degrees. At each point of the profile, scanning of all other dihedral angles with the



SCHEME 1

step of 30 degrees and subsequent minimization were performed. The profile appeared to have two low-energy regions (the energy being within 5 kcal/mol gap above the lowest minimum found): $-110° < \varphi < -60°$ and $40° < \varphi < 120°$ separated by barriers, the lowest one being 40 kcal/mol above the lowest minimum. In comparison, the energetic profiles for torsion angle φ of model compound **I** contains three low-energy regions separated by barriers being only 10 kcal/mol above the lowest minimum found, and that of model compound **II** contains only one low-energy region at $140° < \varphi < 220°$. Qualitatively similar results were obtained using TRIPOS 5.2 force field[9].



Torsion angle φ is shown in bold line

Compound	R^1	R^2
4a	CH_3	CH_3
I	CH_3	H
II	H	CH_3

R = $CH_2OCH_2CH_2OAc$

Treatment of **1a** with benzyl bromide in the presence of potassium carbonate resulted in a formation of two alkylation products, **5a** and **6a**. Both the products exhibited a two-proton singlet, at 5.59 ppm for **5a** and 5.60 ppm for **6a**, in their ^{1}H NMR spectra (Table II) assigned to the benzylic methylene group attached to the oxygen at position 6 of the purine system. The singlet at 5.22 ppm in compound **5a** was attributed to the second benzylic methylene group attached to the exocyclic acetamido function at position 2. An additional support for the benzylation sites in **5a** and **6a** was provided by their ^{13}C NMR spectra (Table III). It has generally been established that the chemical shifts of carbons attached to oxygen usually occur at substantially lower fields than those of carbons attached to nitrogen[10]. This regularity allowed us to attribute the peaks at 72.47 ppm for **5a** and 72.29 ppm for **6a** to OCH_2Ph function, but the signal at 48.85 ppm for **5a** to NCH_2Ph group. Taking into account all these data, the structures of 9-[(2-acetoxyethoxy)methyl]-2-(*N*-benzylacetamido)-6-benzyloxypurine and 2-acetamido-9-[(2-acetoxyethoxy)methyl]-6-benzyloxypurine were proposed for compounds **5a** and **6a**, respectively.

The investigation of the influence of 8-bromo substituent on the course of the reaction showed that alkylation of 9-[(2-acetoxyethoxy)methyl]-N^2-acetyl-8-bromoguanine (**1b**) followed the route similar to that of **1a**. When substrate **1b** reacted with methyl iodide in the presence of potassium carbonate 9-[(2-acetoxyethoxy)methyl]-8-bromo-6-methoxy-2-(*N*-methylacetamido)purine (**2b**) and 9-[(2-acetoxyethoxy)methyl]-8-bromo-1-methyl-2-(*N*-methyl-

acetamido)-6-oxopurine (**4b**) were obtained in yields 34 and 37%, respectively. 6-Methoxy derivative was not isolated in this case. The analogous reaction of **1b** with benzyl bromide afforded 9-[(2-acetoxyethoxy)methyl]-2-(*N*-benzylacetamido)-6-benzyloxy-8-bromopurine (**5b**) as well as 2-acetamido-9-[(2-acetoxyethoxy)methyl]-6-benzyloxy-8-bromopurine (**6b**). The structures of compounds **2b**, **4b**, **5b** and **6b** were confirmed by their ^{1}H NMR spectra (Tables I and II) the patterns of which were fully consistent with those observed in the corresponding 8-unsubstituted analogues **2a**, **4a**, **5a** and **6a**.

Alkylation of 7-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine (**7**) with methyl iodide in the presence of potassium carbonate afforded **8** and **9** in poor overall yields. The three-proton singlet at 3.60 ppm in ^{1}H NMR spectrum of **8** (Table I) could be attributed to the methyl group attached to the ring nitrogen[3] the structure of this product beeing 2-acetamido-7-[(2-acetoxyethoxy)methyl]-1-methyl-6-oxopurine. ^{1}H NMR spectrum of compound **9** was similar to that of **4a** (Table I). The presence of two methyl

TABLE I
^{1}H NMR chemical shifts (δ, ppm) of *N*- and/or *O*-methyl derivatives of 9-(or 7)-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine

Compound	NH (s, 1 H)	8-H (s, 1 H)	NCH_2 (s, 2 H)	NCH_3 or OCH_3 (s, 3 H)	CH_2CH_2 2 × (m, 2 H)	$COCH_3$ (s, 3 H)
2a	–	8.38	5.58	4.10; 3.37	4.04; 3.71	2.38; 1.91
2b	–	–	5.56	4.09; 3.39	4.07; 3.72	2.43; 1.92
3	10.31	8.29	5.53	4.12	3.72 (m, 4 H)	2.23; 1.92
4a	–	8.32	5.57	3.47 (s, 2 H) 3.37 (s, 1 H) 3.32 (s, 1 H) 3.11 (s, 2 H)	4.09; 3.72	2.27 (s, 1 H) 1.96 (s, 5 H)
4a[a]	–	8.30	5.57	3.47; 3.23	4.07; 3.72	2.06; 1.92
4b	–	–	5.49	3.42 (s, 2 H) 3.27 (s, 2 H) 3.19 (s, 2 H)	4.06; 3.70	2.27 (s, 1 H) 1.93 (s, 5 H)
8	13.41	8.38	5.67	3.60	4.00; 3.70	2.11; 1.94
9	–	8.52	5.78	3.47 (s, 2 H) 3.39 (s, 1 H) 3.32 (s, 1 H) 3.10 (s, 2 H)	4.10; 3.77	2.26 (s, 1 H) 1.97 (s, 3 H) 1.92 (s, 2 H)

[a] At 130 °C.

groups at the ring nitrogen 1 and the exocyclic acetamido function were supported by the corresponding peaks in the region 3.10–3.47 ppm. The protons of $NCOCH_3$ group in compound **9** exhibited two signals (2.26 and 1.92 ppm) in the ratio of 2 : 3 and total intensity of three protons. The signal of $OCOCH_3$ function protons was at 1.97 ppm. This spectral evidence proved the restricted rotation about the C2–N2 bond at room temperature in product **9** similar as in compound **4a**. Two products, **10** and **11**, have also been obtained in benzylation of compound **7**. According to the ^{1}H NMR spectra (Table II) and elemental analysis, both of them were monobenzylated derivatives. The benzylation sites in products **10** and **11** were established using the ^{13}C NMR spectra (Table III). The peak of the benzylic methylene carbon in **11** appeared at 75.67 ppm supporting its attachment to the exocyclic oxygen. In **10**, the corresponding peak was shifted upfield (51.35 ppm) and therefore it could be assigned to NCH_2Ph function. Benzylation of the exocyclic acetamido group at position 2 of guanine was excluded in this case since no changes were observed in the chemical shift of the $NCOCH_3$ singlet in the ^{1}H NMR spectrum of **10** in comparison with the same signal of compound **7** (ref.[11]). Taking into account these data the structures of **10** and **11** were ultimately established as 2-acetamido-7-[(2-acetoxyethoxy)methyl]-1-benzyl-6-oxopurine and 2-acetamido-7-[(2-acetoxyethoxy)methyl]-6-benzyloxypurine, respectively.

From the results discussed above, it can be concluded that methylation and benzylation of 9-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine differed

TABLE II

^{1}H NMR chemical shifts (δ, ppm) of *N*- and *O*-benzyl derivatives of 9-(or 7)-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine

Compound	NH (s, 1 H)	8-H (s, 1 H)	C_6H_5 (m, 5 H)	NCH_2 or OCH_2 (s, 2 H)	CH_2CH_2 2 × (s, 2 H)	$COCH_3$ (s, 3 H)
5a	–	8.42	7.38; 7.18	5.59; 5.54; 5.22	3.99; 3.64	2.44; 1.88
5b	–	–	7.32; 7.16	5.53; 5.30	4.08; 3.60	2.50; 1.98
6a	10.38	8.31	7.53; 7.36	5.60; 5.56	4.04; 3.76	2.27; 1.91
6b	10.53	–	7.50	5.61; 5.52	4.07; 3.76	2.28; 1.92
10	13.59	8.42	7.33	5.68; 5.41	4.04; 3.74	2.11; 1.91
11	10.40	8.61	7.40	5.66; 5.64	3.97; 3.59	2.21; 1.86

TABLE III
^{13}C NMR chemical shifts (δ, ppm) of *N*- and/or *O*-benzyl derivatives of 9-(or 7)-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine

Compound	$NCOCH_3$ $OCOCH_3$	C-6	C-4	C-2	C-8	C-5	Phenyl	(2-Acetoxyethoxy)methyl	OCH_2Ph NCH_2Ph	$NCOCH_3$ $OCOCH_3$
5a	171.27	159.53	154.54	153.00	144.03	117.58	138.06; 136.06; 128.40	68.27	72.47	25.30
	170.09						128.05; 128.01; 127.93 127.06; 126.56; 126.35	67.14 62.70	48.85	20.34
6a	170.12	159.76	153.29	152.36	143.02	116.86	136.15; 128.67; 128.55	67.78	72.29	24.74
	169.18						128.37; 128.17; 128.02 127.22	67.04 62.67	–	20.40
10	189.09	156.73	156.65	153.70	149.27	113.31	141.02; 133.36; 133.04	80.12	–	33.30
	175.15						132.56	71.74 67.62	51.35	25.47
11	170.04	162.93	156.14	152.12	147.21	108.53	136.02; 128.35; 128.06	67.75	75.67	24.58
	169.01							66.15 62.60	–	20.36

from the same reactions with N^2-unsubstituted substrate, as the acetyl group of N^2 favoured the alkylation at exocyclic sites, affording 1-methyl-2-(*N*-methylacetamido)- and 6-benzyloxy-9-[(2-acetoxyethoxy)methyl]purines as principle products. The introduction of bromine at position 8 of the purine did not substantially influence the alkylation. Methylation and benzylation of 7-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine proceeded with lower yields and with some preference for N^1-monoalkylation, although N^2-methylation and O^6-benzylation were also essential. Thus, the alkylation of 9-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine and its 7-substituted isomer in the presence of base could be used to synthesize a series of mono- and dialkyl-9-(or 7)-[(2-acetoxyethoxy)methyl]-N^2-acetylguanines, otherwise available only in complicated multi-step processes. Antiviral and immunomodulating properties of the synthesized compounds are under evaluation.

EXPERIMENTAL

All reagents were of commercial grade. Reagent grade solvents were used without further purification. Melting points were determined on a Boetius hot-stage microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 400 (400 MHz) spectrometer in DMSO-d_6 with tetramethylsilane as an internal standard. UV spectra were measured on a Hitachi U-3200 spectrometer in ethanolic solutions in quartz cells with optical length 1 cm. Column chromatography was performed on silica gel L 100/400 (Czech Republic). Analytical and UV spectral data are given in Table IV.

9-[(2-Acetoxyethoxy)methyl]-6-methoxy-2-(*N*-methylacetamido)purine (**2a**);
2-Acetamido-9-[(2-acetoxyethoxy)methyl]-6-methoxypurine (**3**);
9-[(2-Acetoxyethoxy)methyl]-1-methyl-2-(*N*-methylacetamido)-6-oxopurine (**4a**)

A mixture of **1a** (2.48 g, 8 mmol), methyl iodide (2.27 g, 16 mmol) and K_2CO_3 (2.21 g, 16 mmol) in dimethylformamide (80 ml) was stirred at 50 °C for 16 h. After cooling to room temperature, the insoluable material was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in chloroform and applied onto a silica gel column. Eluting with chloroform and recrystallization from ethanol yielded 0.21 g of compound **2a**. Compounds **3** and **4a** were eluted with chloroform–ethanol (40 : 1) and recrystallized from ethanol affording 0.11 g of **3** and 0.90 g of **4a**.

9-[(2-Acetoxyethoxy)methyl]-8-bromo-6-methoxy-2-(*N*-methylacetamido)purine (**2b**);
9-[(2-Acetoxyethoxy)methyl]-8-bromo-1-methyl-2-(*N*-methylacetamido)-6-oxopurine (**4b**)

A mixture of **1b** (0.31 g, 0.8 mmol), methyl iodide (0.23 g, 1.6 mmol) and K_2CO_3 (0.2 g, 1.6 mmol) in dimethylformamide (25 ml) was stirred at room temperature for 24 h. The isolation and purification of alkylation products **2b** and **4b** were carried out in the same way as for compounds **2a** and **4a** affording 0.11 g of **2b** and 0.12 g of **4b**.

TABLE IV
Analytical and UV spectral data of *N*- and *O*-alkyl derivatives of 9-(or 7)-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine

Compound	M.p., °C	Yield, %	Calculated/Found			λ_{max}, nm (ε)
			% C	% H	% N	
2a	99–100	8	49.85	5.68	20.76	268.1 (6 724)
			49.80	5.71	20.68	
2b	99–100	34	40.40	4.36	16.83	275.6 (11 820)
			40.36	4.23	16.81	
3	177–179	4	48.29	5.30	21.66	268.0 (6 436)
			48.54	5.27	21.30	
4a	128–131	33	49.85	5.68	20.76	253.3 (2 852)
			49.94	5.80	20.52	276.0 (2 166)
4b	165–166	37	40.40	4.36	16.83	258.7 (4 644)
			40.37	4.20	16.77	276.5 (3 750)
5a	oil	13	63.79	5.56	14.31	267.1 (5 433)
			63.71	5.43	14.68	
5b	oil	9	54.94	4.61	12.32	
			55.29	4.45	12.00	
6a	136–138	50	57.14	5.30	17.54	268.6 (6 084)
			56.93	5.36	17.80	
6b	106–107	43	47.71	4.21	14.64	276.0 (9 006)
			47.72	4.13	14.62	
8	131–133	16	48.29	5.30	21.66	275.5 (8 484)
			48.00	5.11	22.01	
9	126–128	21	49.85	5.68	20.76	261.4 (5 646)
			49.97	5.85	20.49	
10	101–102	14	57.14	5.30	17.54	278.6 (9 712)
			57.43	5.14	17.28	
11	188–189	30	57.14	5.30	17.54	
			57.51	5.24	17.29	

9-[(2-Acetoxyethoxy)methyl]-2-(*N*-benzylacetamido)-6-benzyloxypurine (**5a**);
2-Acetamido-9-[(2-acetoxyethoxy)methyl]-6-benzyloxypurine (**6a**)

A mixture of **1a** (1.24 g, 4 mmol), benzyl bromide (0.72 g, 4.2 mmol) and K_2CO_3 (0.58 g, 4.2 mmol) in dimethylformamide (40 ml) was stirred at 100 °C for 16 h. After cooling to room temperature, the insoluble material was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was suspended in chloroform (100 ml), the solid was filtered off, the filtrate was concentrated *in vacuo* and applied onto a silica gel column. Elution was performed with chloroform–ethanol (40 : 1). Fractions, containing the chromatographically more mobile product, were pooled, concentrated to a minimal volume and repeatedly purified on a silica gel column to give 0.25 g of compound **5a**.

Fractions, containing the other product, were evaporated, the residue was recrystallized from ethanol to afford 0.82 g of **6a**.

9-[(2-Acetoxyethoxy)methyl]-2-(*N*-benzylacetamido)-6-benzyloxy-8-bromopurine (**5b**);
2-Acetamido-9-[(2-acetoxyethoxy)methyl]-6-benzyloxypurine (**6b**)

A mixture of **1b** (1.0 g, 2.6 mmol), benzyl bromide (0.56 g, 3.3 mmol) and K_2CO_3 (0.46 g, 3.3 mmol) in dimethylformamide (30 ml) was stirred at 100 °C for 8 h. The isolation and purification of products **5b** and **6b** were carried out as described for **5a** and **6a** affording 0.13 g of **5b** and 0.53 g of **6b**.

2-Acetamido-7-[(2-acetoxyethoxy)methyl]-1-methyl-6-oxopurine (**8**);
7-[(2-Acetoxyethoxy)methyl]-1-methyl-2-(*N*-methylacetamido)-6-oxopurine (**9**)

A mixture of **7** (0.62 g, 2.0 mmol), methyl iodide (0.48 g, 4.0 mmol) and K_2CO_3 (0.56 g, 4.0 mmol) in dimethylformamide (25 ml) was stirred at 50 °C for 3 days. The work-up of the reaction mixture was the same as described above for compounds **2a** and **4a**. Elution with chloroform–ethanol (40 : 1) and recrystallization from ethanol afforded 0.10 g of product **8** and 0.14 g of product **9**.

2-Acetamido-7-[(2-acetoxyethoxy)methyl]-1-benzyl-6-oxopurine (**10**);
2-Acetamido-7-[(2-acetoxyethoxy)methyl]-6-benzyloxypurine (**11**)

A mixture of **7** (0.62 g, 2 mmol), benzyl bromide (0.43 g, 2.5 mmol) and K_2CO_3 (0.35 g, 2.5 mmol) in dimethylformamide (25 ml) was stirred at 100 °C for 16 h. The work-up of the reaction mixture was the same as described above for compounds **2a** and **4a**. Elution with chloroform and recrystallization from ethanol afforded 0.11 g of compound **10**. Compound **11** (0.24 g) was eluted with chloroform–ethanol (40 : 1) and recrystallized from ethanol.

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