A New Synthesis of Acyclovir Prodrugs. N^2-Acetylacyclovir and 6-Deoxyacyclovir

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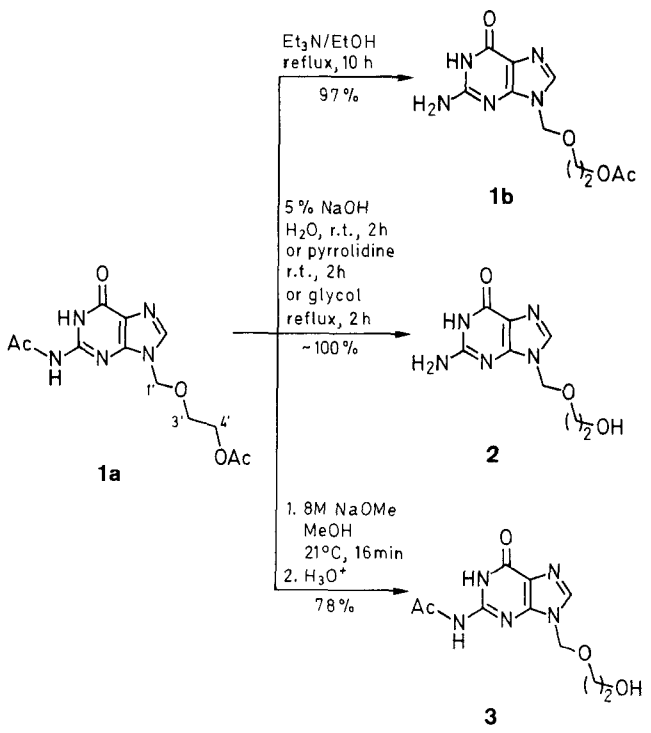
9-(2-Acetoxyethoxy)-2-amino-1,9-dihydro-6*H*-purin-6-one **(1b)** and 2-acetylamino-9-(2-hydroxyethoxy)methyl-1,9-dihydro-6*H*-purin-6-one (N^2-acetylacyclovir **3**) were prepared from 9-[(2-acetoxyethoxy)methyl]-2-acetylamino-1,9-dihydro-6*H*-purin-6-one **(1a)** using regioselective deacetylation procedures. Compounds **1a** and **1b** were chlorinated with phosphoryl chloride to give 9-[(2-acetoxyethoxy)methyl]-2-acetylamino-6-chloro-9*H*-purine **(4a)** and its N^2-deacetylated counterpart **(4b)**, respectively. Subsequent reductive dechlorination of **4a** and **4b** under conditions of catalytic transfer hydrogenolysis followed by deprotection afforded 6-deoxyacyclovir **(7)** in a good overall yield.

2-Amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one (acyclovir, Zovirax, **2**) is a highly specific inhibitor of herpes virus replication with a much higher efficacy and much lower host cell toxicity than previously available compounds.[1,2] Various forms of this drug have been in the clinical use since 1982. The oral form is highly effective in the treatment of herpes simplex infections, but its degree of gastrointestinal absorption is insufficient to give plasma acyclovir concentrations effective against more resistant viruses such as varicella-zoster virus, Epstein Barr virus and others.[3] This stimulated the search for prodrugs that are well absorbed after oral administration and then converted to acyclovir. Among many compounds tested, 2-amino-9-[2-hydroxyethoxy)methyl]-9*H*-purine (**7**, 6-deoxyacyclovir) was shown to be such a prodrug that might be clinically applicable.[4] It has much greater solubility in water than **2** and is readily oxidized intracellularly to acyclovir by xanthine oxidase.[5]

Two syntheses of **7** have appeared to date, both starting from rather expensive 2-amino-6-chloropurine,[5,6] which is prepared from guanine. The original synthesis[5] is based on the alkylation of 2-amino-6-chloropurine with the appropriately protected acyclic fragment. The alkylation step is not a regioselective condensation and afforded a mixture of N-9 and N-7 substituted intermediates, which required a thorough purification before subsequent removal of the 6-chloro substituent by catalytic reduction. The second procedure took advantage of electrochemical reduction of 2-amino-6-chloropurine, followed by the similar sequence of reactions as above.[6]

In this paper, we wish to report the new and efficient synthesis of N^2-acetylacyclovir **(3)** and 6-deoxyacyclovir **(7)** using 9-[(2-acetoxyethoxy)methyl]-2-acetylamino-1,9-dihydro-6*H*-purin-6-one (N^2,*O*-diacetylacyclovir, **1a**) as a starting material. This compound was obtained before as an intermediate in the synthesis of acyclovir directly from guanine.[7-10]

At first, selective *N*- and *O*-deacetylation of **1a** were studied and efficient methods were designed for this particular case (Scheme **A**). The former is required since the *N*-deacetylated compound 9-(2-acetoxyethoxy)-2-amino-1,9-dihydro-6*H*-purin-6-one **(1b)** is halogenated in the subsequent step more readily than the parent compound **1a** (see below).

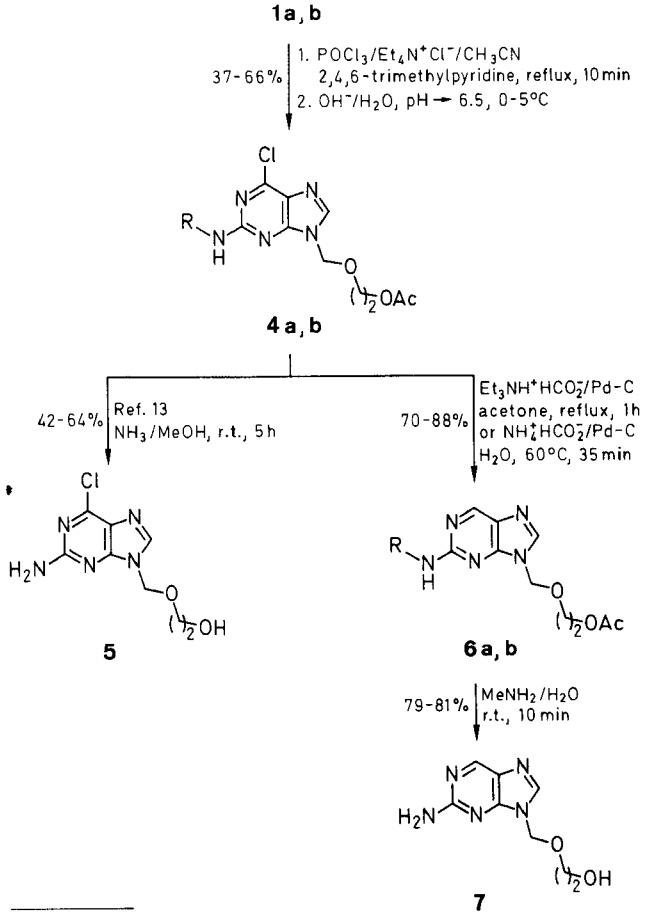


Scheme A

In a search for the best reagent for selective removal of the *N*-acetyl group in the presence of the *O*-acetyl group (and *vice versa*), smooth conversions of **1a** to **2** have been achieved in many instances (Scheme **A**) in addition to documented methods: ammonia in methanol[8,9] and hot aqueous methylamine.[7,10] Selective *N*-deacetylation of **1a** was successfully carried out with selected tertiary amines in refluxing methanol or ethanol. In general, reactions in ethanol, although 10–15 times slower than those in methanol, proceeded with better regioselectivity for the particular amine used. Triethylamine, ethyldiisopropylamine, tributylamine, [bis(2-hydroxyethyl)-amino]-tris(hydroxymethyl)methane (BIS-TRIS) and *N*,*N*,*N*′,*N*′-tetrakis(2-hydroxypropyl)ethylenediamine proved to be the best among amines tested for the regiospecific *N*-deacetylation of **1a** in ethanol as solvent, giving a product of greater than 98% purity. Triethylamine, exhibiting the highest rate of conversion, was finally adopted for the large scale synthesis of pure **1b** in an excellent yield. The use of strong bases gave rise to a selective *O*-deacetylation of **1a**. Thus, 8M solution of sodium methoxide in methanol yielded 78% of pure N^2-acetylacyclovir **(3)** under carefully controlled conditions. The same compound has been prepared recently using aqueous ammonia[9] or aqueous sodium hydroxide.[11] The latter procedure is especially noteworthy since **3** was obtained in a comparable yield (84%). Compound **3** is considered to be another structurally related prodrug of acyclovir, being approximately twice as soluble in water as the latter. Our methods for selective removal of acetyl

groups from N^2,*O*-diacetylacyclovir are more effective and simpler to perform compared to similar reported work.[9]

Compounds **1a** and **1b** were chlorinated to give the corresponding 9-[(2-acetoxyethoxy)methyl]-2-acetylamino-6-chloro-9*H*-purine **(4a)** and 9-[(2-acetoxyethoxy)methyl]-2-amino-6-chloro-9*H*-purine **(4b)** using an excess of phosphoryl chloride and tetraethylammonium chloride in dry acetonitrile (Scheme **B**). For this purpose, we modified the reported procedure for the chlorination of 2',3',5'-tri-*O*-acetylguanosine,[12] by using 2,4,6-trimethylpyridine (*sym*-collidine) as a base instead of *N*,*N*-dialkylanilines in order to eliminate the formation of highly colored impurities. Due to the acid lability of the glycosidic bond, comparable to that of purine 2'-deoxyribonucleosides, the resulting aqueous phase during workup must be quickly adjusted to almost neutral pH at low temperature. This seems to be an essential modification of the reported procedure,[12] since stable products could be isolated only in this case. These conditions favored **1b** as a better substrate for chlorination than **1a** (yields 66% of **4b** vs. 37% of **4a**). The present method is expected to be general for chlorination of other acid-sensitive compounds. Compounds **4a** and **4b** were



1, 4, 6	R
a	Ac
b	H

Scheme **B**

Table. ^{13}C-NMR Spectral Data of Compounds **1–7** [δ, J(Hz)][a,b]

Product	C-2 (^3J)	C-4	C-5 (^3J, ^2J)	C-6 (^1J)	C-8 (^1J, ^3J)	C-1' (^1J, ^3J)	C-3' (^1J)	C-4' (^1J)	OCOCH$_3$ (^1J)	NHCOCH$_3$ (^1J)	OCOCH$_3$	NHCOCH$_3$ (^2J)
1a	148.0	148.8	120.2 (11, –)	154.9	139.7 (214, 4.5)	72.5 (158, 3)	66.9 (144)	62.6 (148.5)	20.3 (129.5)	23.6 (130)	170.0	173.3 (6.5)
1b	153.8	151.3	116.5 (11, –)	156.7	137.4 (214, 4.5)	71.9 (161, 3.5)	66.6 (144)	62.6 (148.5)	20.3 (130)	–	169.9	–
2	154.0	151.6	116.6 (11, –)	157.2	138.0 (213, 4)	72.3 (161)[c]	70.6 (142)	60.2 (140.5)	–	–	–	–
3	148.4	149.6	120.4 (11.5, –)	155.7	140.7 (214.5, 4.5)	73.3 (158.5)[c]	71.1 (142.5)	60.5 (141)	–	24.2 (130)	–	174.1 (6.5)
4a	152.6	153.1	127.2 (12, –)	149.4	146.5 (216, 4.5)	73.0 (162.5, 3)	67.7 (144.5)	62.9 (149)	20.6 (130)	24.7 (129)	170.3	169.0 (6.5)
4b	160.3	154.4	123.5 (12.3, –)	149.8	143.4 (213, 4.5)	72.4 (157.5, 3.5)	67.0 (144.5)	62.9 (149)	20.6 (130.5)	–	170.4	–
5	160.2	154.4	123.5 (12, –)	149.8	143.4 (216, 4.3)	72.6 (162)[c]	70.9 (143)	60.1 (141)	–	–	–	–
6a	153.5 (13)	152.4	130.3 (12, 6)	149.0 (185)	146.3 (214, 4)	72.3 (162, 2.8)	67.5 (144.5)	62.9 (148)	20.6 (130)	24.6 (128.5)	170.4	169.2 (6.5)
6b	160.9 (12)	153.4	126.9 (11.5, 6.5)	149.5 (181)	143.0 (213, 4)	71.9 (161, 2.8)	67.0 (144)	62.9 (148.5)	20.6 (129.5)	–	170.4	–
7	160.9 (12)	153.4	126.9 (11, 6)	149.5 (180.5)	143.1 (214, 4)	72.0 (161)[c]	70.8 (142.5)	60.2 (139.5)	–	–	–	–

[a] Recorded at 22.5 MHz on a Jeol FX 90Q spectrometer with DMSO-d_6 as solvent and reference (δ = 39.70).
[b] ^{13}C resonances were unambiguously assigned by heteronuclear gated decoupling, the decoupler being off during acquisition period. The values of appropriate coupling constants are placed in brackets.
[c] No ^3J-coupling could be detected.

smoothly deprotected with ammonia in methanol[13] to afford the reported 2-amino-6-chloro-9-[(2-hydroxyethoxy)methyl]-9*H*-purine **(5)** (Scheme **B**).

Compounds **4a** and **4b** could also be reductively dehalogenated to give 9-[(2-acetoxyethoxy)methyl-2-acetylamino-9*H*-purine **(6a)** and 9-[(2-acetoxyethoxy)methyl]-2-amino-9*H*-purine **(6b)**, respectively, by catalytic transfer hydrogenolysis with formic acid based hydrogen donors.[14] Quantitative conversions have been achieved in less than one hour using either an excess of aqueous ammonium formate at 60 °C or triethylammonium formate in refluxing acetone in the presence of 5 or 10% palladium on carbon (Scheme **B**). These reactions are considerably faster than related hydrogenolysis of 2-amino-9-[(2-benzoyloxyethoxy)-methyl]-6-chloro-9*H*-purine by molecular hydrogen.[5] The optimized conditions, e. g. the choice of catalyst, donor quantity, temperature and solvent effects for dehalogenation of chloroaromatics, that have just been reported,[15] are in good agreement with our findings. Final deprotection of compounds **6a** and **6b** with aqueous methylamine yielded one of the target compounds 6-deoxyacyclovir **(7)** (Scheme **B**).

In conclusion, the overall yield of the stepwise conversion to **7**, starting from the commercially available intermediate for acyclovir synthesis **1a**, principally depends on the choice of starting material suitable for chlorination. Namely, the overall yield of **7** *via* chlorination of **1a**, subsequent hydrogenolysis of chlorine and deprotection (**1a** → **4a** → **6a** → **7**) was found to be 26%, but raised to 45% by previous regioselective *N*-deacetylation of **1a** to **1b**, followed by the same sequence of reactions **1a** → **1b** → **4b** → **6b** → **7**. Thus this sequence can be easily adapted for a large scale preparation.

Melting points were determined on a Kofler apparatus and are uncorrected. Mass spectra were measured on a CEC 21-110B spectrometer at the "Jožef Stefan" Institute, Ljubljana. Microanalyses were performed at the Institute of Chemistry, Technology and Metallurgy, Belgrade, ^{1}H-NMR spectra were recorded at 60 MHz on a Varian EM 360L spectrometer using TMS as internal standard. ^{13}C-NMR data are very indicative for the structural assignment and are, for that reason, collectively presented in the Table. Flash chromatography was carried out on silica gel 60 (40–63 μm, Merck) and analytical TLC on precoated plates (silica gel 60 F_{254}, Merck). HPLC data were obtained on a Varian 8500 instrument under the following conditions: reverse phase column Spherisorb S10 ODS1, eluent H_2O/CH_3CN (8:1), flow rate 1 mL/min, detection UV 254 nm.

Starting material **1a** is commercially available from Krka, 68000 Novo mesto, Yugoslavia. Reagents and solvents were of commercial quality and were used without further purification except CH_3CN, which was refluxed with, and then distilled from CaH_2 and stored over 4 A molecular sieves. Continuous extractions refer to the use of rotational perforators for liquid-liquid extraction with either specific lighter or heavier solvent (Normag, D-6328 Hofheim, West Germany).

9-[(2-Acetoxyethoxy)methyl]-2-amino-1,9-dihydro-6*H*-purin-6-one (1b):

A suspension of 9-[(2-acetoxyethoxy)methyl]-2-acetylamino-1,9-dihydro-6*H*-purin-6-one[7] (**1a**; 15.5 g, 0.05 mol) in 1 M solution of Et_3N in 95–96% EtOH (200 mL) is heated with stirring at reflux for 10 h. The reaction is allowed to cool to r. t., the colorless crystals are filtered, washed with EtOH, and dried *in vacuo* at 110 °C overnight to give **1b** in >98% purity (HPLC); yield: 13.00 g (97%); mp 240–242 °C; analytical sample: mp 243–245 °C (DMF); (Lit.[7] mp 240–241 °C). ^{1}H-NMR data agree with the literature values.[9]

MS: m/z = 267 (M^+).

2-Acetylamino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one (3):

Compound **1a** (6.18 g, 20 mmol) is added to a freshly prepared solution of sodium (0.92 g, 40 mmol) in anhydrous MeOH (50 mL). The solution is stirred at 21 °C for 16 min, then the reaction is quenched by the addition of 1.4 M aq HCl (30 mL). Stirring of the mixture is continued at r. t. overnight, the resulting colorless solid is collected by filtration, washed with H_2O (30 mL) and EtOH (30 mL) to give **3**; yield: 4.19 g (78%); mp 214–215 °C; (Lit.[11] mp 212–214 °C); which contains less than 4% of acyclovir (HPLC). Crystallization from MeOH/H_2O (1:1) with addition of charcoal affords **3**; yield: 3.06 g (57%); mp 217–218 °C; colorless crystals 99.9% purity (HPLC).

^{1}H-NMR (DMSO-d_6, TMS): δ = 2.17 (s, 3 H, $NHCOCH_3$), 3.49 (m, 4 H, H-3′ + H-4′), 4.69 (br s, 1 H, OH), 5.44 (s, 2 H, H-1′), 8.06 (s, 1 H, H-8), 10.65, 10.95 (2 br s, 2 × 1 H, 2 NH).

MS (FAB): m/z = 268 (MH^+).

9-[(2-Acetoxyethoxy)methyl]-2-amino-6-chloro-9*H*-purine (4b):

CH_3CN (70 mL) is distilled directly from P_2O_5 into a flask containing **1b** (6.68 g, 25 mmol; predried *in vacuo* at 110 °C overnight over P_2O_5) and Et_4NCl (6.6 g, 40 mmol; predried *in vacuo* at 85 °C overnight over P_2O_5). 2,4,6-Trimethylpyridine (3.30 mL, 25 mmol; distilled from CaH_2) and freshly distilled $POCl_3$ (13.7 mL, 0.15 mol) are added to the stirred suspension at r. t. The mixture is heated with stirring under reflux for 10 min with exclusion of moisture. Volatile materials are evaporated *in vacuo* at a temperature below 45 °C to give a partially solidified yellow oil. This is dissolved in ice cold water (200 mL) and the pH of this solution is adjusted to above 6 with careful addition of sat. aq $NaHCO_3$ at a temperature below 5 °C in an ice-bath. The ice-bath is then removed, while the pH of the solution is still maintained between 6 and 6.5. The addition of base is finished in ~3 h, when the pH value of 6.5 remains constant for at least 15 min. About 110 mL of sat. aq $NaHCO_3$ is consumed altogether. The resulting solution is continuously extracted with pentane for 12 h to remove 2,4,6-trimethylpyridine. The extraction is repeated with CH_2Cl_2 (4 × 100 mL). The combined CH_2Cl_2 extracts are dried (Na_2SO_4) and evaporated to give a yellow solid (6.36 g), which is purified by flash chromatography on silica gel (300 g; 8 × 16 cm). Elution is performed with benzene/EtOAc (1:1) and fractions containing the product (R_f = 0.18 in eluent) are combined and evaporated to give the crude material (5.42 g, 76%). Crystallization from 2-propanol (50 mL) affords a slightly yellow amorphous product; yield: 4.74 g (66%); mp 125–126 °C, (Lit.[13] mp 132–133 °C). An analytical sample of **4b**, mp 126–127 °C, is obtained as a colorless solid after two subsequent crystallizations from ethyl propionate with addition of charcoal.

^{1}H-NMR (DMSO-d_6/TMS): δ = 1.94 (s, 3 H, $OCOCH_3$), 3.69 (A_2B_2m, 2 H, H-3′), 4.05 (A_2B_2m, 2 H, H-4′), 5.45 (s, 2 H, H-1′), 6.92 (br s, 2 H, NH_2), 8.21 (s, 1 H, H-8). ^{1}H-NMR data ($CDCl_3$) agree with the literature values.[13]

MS: m/z = 285 (M^+).

9-[(2-Acetoxyethoxy)methyl]-2-acetylamino-6-chloro-9*H*-purine (4a):

Following the above procedure, from **1a** (7.73 g, 25 mmol), an orange red solid (5.82 g) is obtained after extraction with CH_2Cl_2 (5 × 100 mL), which is purified by flash chromatography on silica gel (210 g). Elution is performed with benzene/EtOAc (1:1) and fractions containing the product (R_f = 0.13 in eluent) are combined and evaporated to give the crude material (4.07 g, 50%). Crystallization from EtOAc (60 mL) affords pure **4a** as a colorless solid; yield: 3.01 g (37%); mp 150–150.5 °C.

$C_{12}H_{14}ClN_5O_4$	calc.	C 43.98	H 4.31	N 21.37
(327.7)	found	43.75	4.48	21.40

^{1}H-NMR (DMSO-d_6/TMS): δ = 1.94 (s, 3H, $OCOCH_3$), 2.23 (s, 3H, $NHCOCH_3$), 3.78 (A_2B_2m, 2H, H-3'), 4.07 (A_2B_2m, 2H, H-4'), 5.61 (s, 2H, H-1'), 8.59 (s, 1H, H-8), 10.75 (br s, 1H, NH).

MS: m/z = 327 (M^+).

2-Amino-6-chloro-9-[(2-hydroxyethoxy)methyl]-9*H*-purine (5):
This compound is prepared from either **4a** or **4b** according to the procedure, described in the literature for **4b**.[13] Crystallization of crude solids from 2-propanol with addition of charcoal affords **5** as colorless plates (42% from **4a**, mp 194–195.5°C; 64% from **4b**, mp 193–195.5°C); (Lit.[13] mp 204–205°C); purity: >98% (HPLC). ^{1}H-NMR data agree with the literature values.[13]

9-[(2-Acetoxyethoxy)methyl]-2-amino-9*H*-purine (6b):
Method A: To a solution of **4b** (7.15 g, 25 mmol) in acetone (100 mL) and Et_3N (35 mL, 0.25 mol) is added 98% HCO_2H (5 mL, 0.13 mol) and 10% Pd-C (1 g). The mixture is heated with stirring at reflux for 1 h, then the catalyst is filtered off and washed with hot acetone. The filtrate is evaporated *in vacuo* and the residue dissolved in water (100 mL). The solution is continuously extracted with CH_2Cl_2 for 9 h, the extract is dried (Na_2SO_4) and evaporated *in vacuo*. The residue (6.25 g) is crystallized from absolute EtOH (50 mL) to give **6b** as colorless needles; yield: 5.51 g (88%); mp 133–133.5°C; (Lit.[6] mp 135–136°C). ^{1}H-NMR data agree with the literature values.[6]

MS: m/z = 251 (M^+).

Method B:A mixture of **4b** (1.43 g, 5 mmol) in 1M ammonium formate (60 mL) and 5% Pd-C (0.2 g) is heated at 60°C with stirring in a water bath for 35 min (the initial evolution of gas ceases in about 30 min). The catalyst is filtered off and the filtrate is extracted with EtOAc (8 × 50 mL). The combined extracts are dried (Na_2SO_4), evaporated *in vacuo*, and the crude product (1.13 g, 90%) is crystallized from 2-propanol to give pure **6b** as colorless needles; yield: 0.88 g (70%); mp 133–135°C; which is identical with the product obtained by Method A.

9-[(2-Acetoxyethoxy)methyl]-2-acetylamino-9*H*-purine (6a):
Following the procedure given under Method A, starting from **4a** (3.28 g, 10 mmol), a crude product is obtained after evaporation of the CH_2Cl_2 extract *in vacuo*. This material is crystallized from absolute EtOH (30 mL) to give **6a** as colorless needles; yield: 2.56 g (87%); mp 134.5–135.5°C.

$C_{12}H_{15}N_5O_4$	calc.	C 49.14	H 5.16	N 23.88
(293.3)	found	49.34	5.03	23.80

^{1}H-NMR (DMSO-d_6/TMS): δ = 1.92 (s, 3H, $OCOCH_3$), 2.25 (s, 3H, $NHCOCH_3$), 3.78 (A_2B_2m, 2H, H-3'), 4.07 (A_2B_2m, 2H, H-4'), 5.61 (s, 2H, H-1'), 8.50 (s, 1H, H-8), 8.90 (s, 1H, H-6), 10.5 (br s, 1H, NH).

MS: m/z = 293 (M^+).

2-Amino-9-[(2-hydroxyethoxy)methyl]-9*H*-purine (7):
Either **6a** (20 mmol) or **6b** (20 mmol) is dissolved in water (50 mL) at ~60°C, followed by 40% aq $MeNH_2$ (25 mL). The solution is stirred at r.t. for 10 min and evaporated several times *in vacuo* with successive addition of water. The residue is crystallized from absolute EtOH with addition of charcoal to give **7** as colorless needles; yield: 3.3–3.4 g (79–81%); mp 192.5–193.5°C; (Lit.[5] mp 187–189°C; Lit.[6] mp 193.5–194.5°C). The product is 99.8% pure according to HPLC. ^{1}H-NMR data agree with the literature values.[5,6]

MS: m/z = 209 (M^+).

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(1) Elion, G.B.; Furman, P.A.; Fyfe, J.A.; deMiranda, P.; Beauchamp, L.; Schaeffer, H.J. *Proc. Natl. Acad. Sci. USA* **1977**, *74*, 5716.
(2) Schaeffer, H.J.; Beauchamp, L.M.; deMiranda, P.; Elion, G.B.; Bauer, D.J.; Collins, P. *Nature (London)* **1978**, *272*, 583.
(3) *Drugs of the Future* **1986**, *11*, 92.
(4) Selby, P.; Powless, R.L.; Blake, S.; Stolle, K.; Mbidde, E.K.; McElwain, T.J.; Hickmott, E.; Whiteman, P.D.; Fiddian, A.P. *Lancet* **1984**, *2*, 1428.
(5) Krenitsky, T.A.; Hall, W.W.; deMiranda, P.; Beauchamp, L.M.; Schaeffer, H.J.; Whiteman, P.D. *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 3209.
(6) Kusmierek, J.T.; Czochralska, B.; Johansson, N.G.; Shugar, D. *Acta Chem. Scand.* **1987**, *B41*, 701.
(7) Schaeffer, H.J. *US Patent* 4146715, (1979), Burroughs Wellcome Co. *WPI*, 78-20879A/11.
(8) Radl, S.; Zikan, V. *Cesk. Farm.* **1987**, *36*, 58; *C.A.* **1987**, *107*, 236341.
(9) Matsumoto, H.; Kaneko, C.; Yamada, K.; Takeuchi, T.; Mori, T.; Mizuno, Y. *Chem. Pharm. Bull.* **1988**, *36*, 1153.
(10) Madre, M.A.; Zhuk, R.A.; Lidak, M.J. *Khim.-Farm. Zh.* **1985**, *19*, 1371; *C.A.* **1986**, *105*, 6748.
(11) Zhuk, R.A.; Lidak, M.J.; Madre, M.A.; Votyakov, V.I.; Andreeva, O.T.; Boreko, E.I.; Korobchenko, L.V.; Rusyaev, V.A.; Starkova, O.I. *PCT Int. Appl.* WO 88/03923 (1988); *C.A.* **1989**, *110*, 114574.
(12) Robins, M.J.; Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2601.
(13) Robins, M.J.; Hatfield, P.W. *Can. J. Chem.* **1982**, *60*, 547.
(14) Ram, S.; Ehrenkaufer, R.E. *Synthesis* **1988**, 91.
(15) Anwer, M.K.; Sherman, D.B.; Roney, J.G.; Spatola, A.F. *J. Org. Chem.* **1989**, *54*, 1284.