SYNTHESIS AND STRUCTURE OF A FLUORESCENT, TRICYCLIC ANALOGUE OF 2'-DEOXY-ADENOSINE AND OF A PRODRUG BY N-ANNELATION OF 2'-DEOXYGUANOSINE AND 9-[(2-HYDROXYETHOXY)METHYL]GUANINE (ACYCLOVIR), RESPECTIVELY†

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Abstract - Chemical modification of 2'-deoxyguanosine and of 9-[(2-hydroxyethoxy)-methyl]guanine, respectively, into a fluorescent, tricyclic analogue of deoxy-adenosine with potential for use as a probe for enzymatic reactions, and into a prodrug of an effective antiherpetic, acyclovir, is described. The X-ray structure determination of 8-amino-3,10-dihydro-10-oxo-3-(*β*-D-2-deoxyribofuranosyl)-3*H*-1,3,5-triazino[1,2-*a*]purine (dIdA'-metamorphosine) revealed that the nucleoside is in *syn* conformation, $\chi = 55.1°$, with an intramolecular hydrogen bond O(5')-H(5')---N(4)= 2.810Å. The 2'-deoxyribofuranosyl ring is in a 2'-*endo* envelope (^2E) conformation, and the conformation about the C(4')-C(5') bond is *gauche-gauche*.

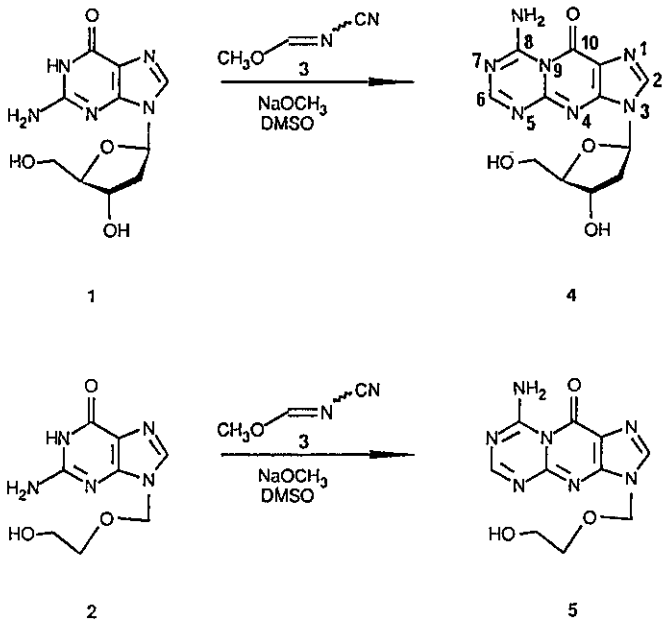
Dimensionally-extended analogues of purine nucleosides and nucleotides prepared in our laboratory have shown interesting activity in selected biological systems.[1] These stretched-out analogues are unique in retaining the terminal pyrimidine and imidazole rings. Thereby, the normal hydrogen bonding sites are retained, while a spacer is formally inserted between the terminal rings. Based on this concept, the conversion of guanosine into a structure that more closely resembles adenosine in the periphery, namely IA'-metamorphosine[2] (8-amino-3,10-dihydro-10-oxo-3-*β*-D-ribofuranosyl-1,3,5-triazino[1,2-*a*]purine), was recently reported from this laboratory.[3] The advent of these so-called metamorphosine compounds permits the conversion of other natural and unnatural nucleosides and related derivatives into fluorescent, tricyclic analogues by means of methyl *N*-cyanomethanimidate. The desired outcome of such an endeavor would be to produce compounds that utilize the metamorphosine with its new functionalities, or else release the original in alkaline environment, in specific biological

†This article is dedicated to Arnold Brossi, National Institutes of Health, Bethesda, Maryland, on the occasion of his sixty-fifth birthday.

applications. In the latter case a metamorphosine type may act as a prodrug. The work described herein briefly illustrates this concept.

The conversion of 2'-deoxyguanosine (**1**) and of 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir) (**2**)[4] by reaction with methyl *N*-cyanomethanimidate (**3**) and sodium methoxide in dry DMSO under anhydrous conditions provides new fluorescent compounds **4** and **5**, respectively (Scheme I). As

SCHEME I



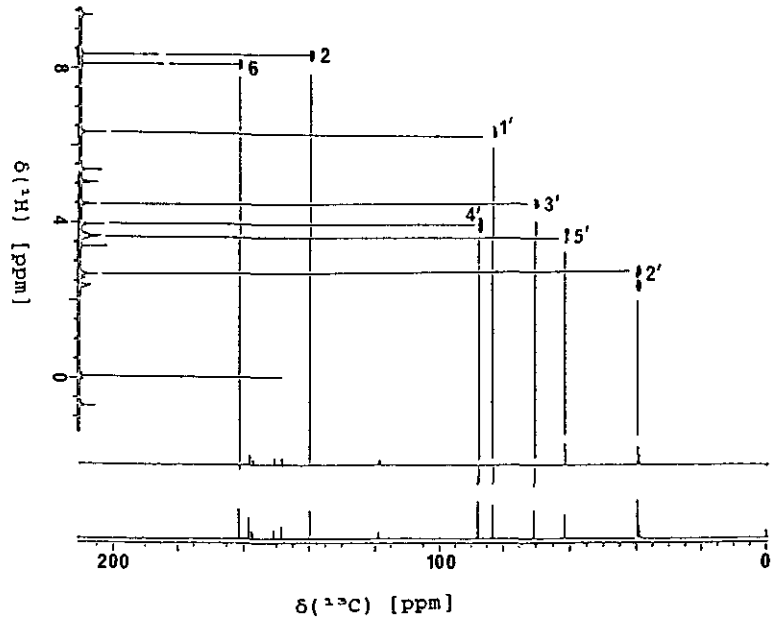
1 **4**

2 **5**

in the case of IA'-metamorphosine, the ^1H nmr spectra of **4** and **5** in $(CD_3)_2SO$ indicated two distinct exocyclic NH signals at δ 10.2 and 9.4 ppm, exchangeable in D_2O, and signals at δ ∿ 8.3 and 8.1, respectively, for the two protons attached at position 2 and 6. The chemical shifts of these latter two protons were determined unambiguously in IA'-metamorphosine with the aid of deuterium labelling at the 2 and 6 positions.[3] In the ^{13}C nmr spectrum of the 2'-deoxy compound **4**, the complete assignment of the carbon atoms to which hydrogens are attached was made by the use of ^1H-^{13}C heteronuclear correlation spectroscopy[5] (Figure 1). Since the order of C(4') and C(1') sugar signals in the ^{13}C nmr spectrum may differ from one 2'-deoxynucleoside to another,[6] we used this technique to establish the order of sugar signals as C(4')-C(1')-C(3')-C(5')-C(2') toward higher field. The FAB mass spectrum showed the expected $M^+ + 1$ and $B^+ + 2$ peaks at *m/z* 320 and 204, for **4**, and $M^+ + 1$ and $B^+ + 1$ peaks at m/z 278 and 203, respectively, for **5**.

Out of the four isomeric possibilities arising from different modes of condensation-cyclization of guanosine (N^2-1 vs N^2-3) and **3** (C = N vs C ≡ N) discussed in Ref. 3, the *N*-tricyclic portion

Figure 1. Two-dimensional [^1H, ^{13}C] heteronuclear correlation spectrum of **4** in $(CD_3)_2SO$.



of the product was confirmed by X-ray structure determination of the analogous product formed by the reaction of 9-benzyl-8-bromoguanine with **3**. We had been unsuccessful in obtaining X-ray quality crystals of IA'-metamorphosine itself. The X-ray structure determination of the fluorescent dIdA'-metamorphosine would provide useful information not only for affirmation of the mode of cyclization in this case but for determination of the sugar conformation and the intra- and intermolecular hydrogen bonding patterns. In the case of the product of 2'-deoxyguanosine (**1**) and methyl *N*-cyanomethanimidate (**3**), we were successful in obtaining X-ray quality crystals of **4**.

The transparent, colorless, prismatic crystals of **4** were grown from acetone-methanol (5:1) by slow evaporation. A crystal of size 0.1 x 0.1 x 0.2 mm was mounted on an Enraf-Nonius CAD4 automated *k*-axis diffractometer equipped with a graphite monochromator using MoK$\bar{\alpha}$

Table 1. Crystallographic data for compound **4**.

Formula: $C_{12}H_{13}N_4O_4 \cdot H_2O$	$F(000)$ = 352.0
Molecular weight = 337.30	Z = 2
Space group $P2_1$	ρ calcd = 1.609 g/cm^3
Crystal size 0.1 x 0.1 x 0.2 mm	λ (MoK$\bar{\alpha}$) = 0.71073Å
a = 6.410(1)Å	No. of unique reflection 1519
b = 10.138(5)Å	Reflections with I > 2.58 σ (I) 1096
c = 10.714(3)Å	R = 0.043
V = 696.2(6)Å	R_w = 0.046
β, deg 90.78(2)	largest peak in Δ_F map, eÅ^{-3} +0.23, -0.27

(λ = 0.71073Å). The crystal and structure data are given in Table 1. The lattice parameters were refined using 15 reflections with 2θ values between 13.0 and 27.1°; 1,519 unique reflections were measured (±h, +k, -l) to the limit of $2\theta < 53.0°$ using ω/θ scans 2-8°/min variable through an ω-angle of 1.50[1.00 + 0.35 tan (θ)]° with a background/scan time ratio of 0.33. Three standard reflections were measured per 90 min exposure time, and an examination of these at the end of the data collection showed insignificant crystal decomposition. Data were corrected for anomalous dispersion, Lorentz and polarization effects,[7] but not for extinction or absorption. The structure was solved by DIDRIF[8] using a misplaced fragment of 13 atoms deduced from an E-map generated by MULTAN.[9] After the correct origin was determined, the remaining non-hydrogen atoms were located in a weighted difference Fourier map calculated by DIDRIF. In the final cycle of least squares, the oxygen and nitrogen atoms were refined with anisotropic thermal coefficients, the carbon atoms were refined with isotropic thermal coefficients, and the hydrogen atoms were refined with an isotropic group thermal parameter. The scattering factors were taken from the *International Tables for X-ray Crystallography*.[10] The final agreement

Table 2. Final positional parameters for non-hydrogen atoms in **4** with e.s.d.'s in parentheses.

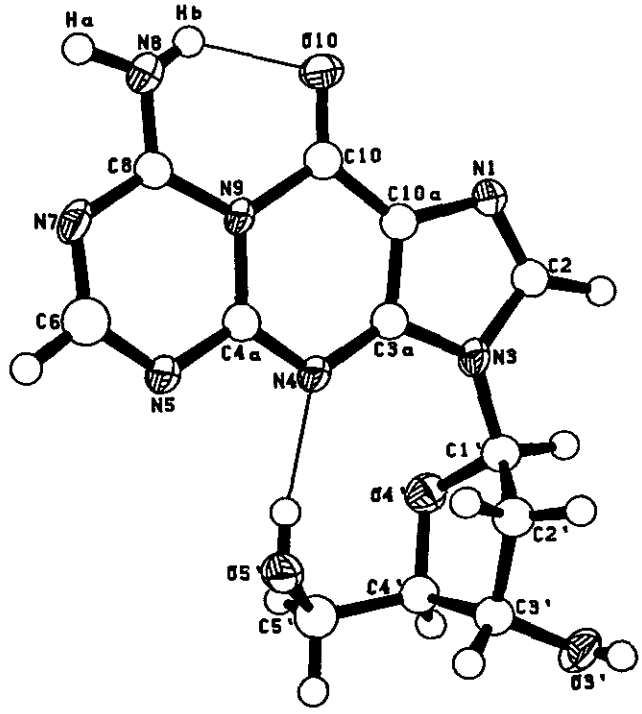
Atom	x	y	z
N(8)	0.7604(8)	0.3395(7)	0.6171(4)
N(1)	0.7606(6)	-0.1800(6)	0.5384(3)
N(3)	0.7515(6)	-0.1918(6)	0.3305(3)
N(4)	0.7417(6)	0.0383(5)	0.2768(3)
N(5)	0.7216(8)	0.2592(6)	0.2478(4)
N(7)	0.7307(7)	0.4093(6)	0.4182(4)
N(9)	0.7458(6)	0.1784(6)	0.4584(4)
C(2)	0.7585(8)	-0.2582(7)	0.4434(4)
C(3a)	0.7491(7)	-0.0613(7)	0.3592(4)
C(4a)	0.7365(7)	0.1551(6)	0.3269(4)
C(6)	0.7149(9)	0.3766(8)	0.2977(6)
C(8)	0.7462(7)	0.3107(7)	0.4982(5)
C(10)	0.7553(7)	0.0693(7)	0.5482(4)
C(10a)	0.7538(7)	-0.0540(7)	0.4866(4)
C(1')	0.7509(8)	-0.2534(7)	0.2072(4)
C(2')	0.5576(8)	-0.2275(7)	0.1287(5)
C(3')	0.6386(8)	-0.2467(7)	-0.0013(5)
C(4')	0.8633(8)	-0.1995(7)	0.0072(4)
C(5')	0.8975(9)	-0.0610(7)	-0.0404(5)
O(10)	0.7630(7)	0.0894(6)	0.6602(3)
O(3')	0.6443(6)	-0.3832(5)	-0.0328(3)
O(4')	0.9192(5)	-0.2025(5)	0.1399(3)
O(5')	0.7664(6)	0.0336(6)	0.0152(3)
O(W)	0.7631(8)	0.6000	0.7103(4)

factors for 1,096 reflections with I > 2.58 σ (I) were R = 0.043, Rw = 0.046, and goodness-of-fit E = 1.32.[11] The final difference Fourier map showed no significant features. The atomic coordinates for nonhydrogen atoms are listed in Table 2.

Results and Discussion

Although the crystals of **4** were grown from acetone-methanol solution, the structure determination of **4** revealed a molecule of water (not shown in Fig. 2) participating in an intermolecular hydrogen bond with Ha of the NH_2 group. An ORTEP view of the molecule of **4** along with atom numbering is given in Fig. 2. Selected bond lengths and angles are provided in Table 3. The molecule is nearly planar through the entire tricyclic base moiety with an

Figure 2. An *ORTEP* drawing (Johnson, 1965) of the molecule (**4**) with the atom numbering. Intramolecular hydrogen bonds are shown by thin lines.



interplanar angle of 1.42° about the C(3a)-C(10a) vector. The central ring of the base is somewhat wider at the top (N(9)-C(10a) distance = 2.375(9)Å) than at the bottom (C(4a)-C(3a) distance = 2.222(9)Å). The torsional angle values of N(7)-C(8)-N(8)-H(a) and N(7)-C(8)-N(8)-H(b), -3(4)° and 177(5)°, respectively, are indicative of the the approximate coplanarity of the two amino hydrogen atoms with the tricyclic ring.

Table 3. Selected bond lengths (Å) and bond angles (°) for **4**.[a]

Bond Lengths

Bond	Length, Å	Bond	Length, Å
N(1)-C(2)	1.290(7)	C(8)-N(9)	1.408(9)
C(2)-N(3)	1.385(7)	N(9)-C(10)	1.466(8)
N(3)-C(3a)	1.359(9)	C(10)-O(10)	1.218(6)
C(3a)-C(10a)	1.366(6)	C(10)-C(10a)	1.414(9)
C(3a)-N(4)	1.342(8)	C(10a)-N(1)	1.393(9)
N(4)-C(4a)	1.301(8)	N(3)-C(1')	1.461(7)
C(4a)-N(9)	1.429(6)	C(1')-C(2')	1.511(7)
C(4a)-N(5)	1.356(8)	C(2')-C(3')	1.505(7)
N(5)-C(6)	1.305(10)	C(3')-C(4')	1.519(7)
C(6)-N(7)	1.336(8)	C(4')-C(5')	1.512(10)
N(7)-C(8)	1.320(8)	C(4')-O(4')	1.462(6)
C(8)-N(8)	1.308(7)	O(4')-C(1')	1.403(6)

Bond Angles

Type[b]	Angle, °	Type[b]	Angle, °
H(2)-C(2)-N(1)	129(3)	C(10a)-C(10)-O(10)	127.4(6)
H(2)-C(2)-N(3)	118(3)	O(10)-C(10)-N(9)	121.4(6)
N(1)-C(2)-N(3)	113.0(6)	C(10)-N(9)-C(8)	121.3(4)
C(2)-N(3)-C(3a)	106.0(4)	C(8)-N(9)-C(4a)	117.1(5)
C(2)-N(1)-C(10a)	104.4(4)	N(9)-C(4a)-N(5)	119.3(5)
N(3)-C(3a)-N(4)	125.7(4)	C(4a)-N(5)-C(6)	117.2(5)
N(3)-C(3a)-C(10a)	106.2(5)	N(5)-C(6)-N(7)	128.3(6)
C(3a)-C(10a)-N(1)	110.4(5)	C(6)-N(7)-C(8)	116.4(6)
N(1)-C(10a)-C(10)	128.6(4)	N(7)-C(8)-N(8)	117.8(6)
C(3a)-C(10a)-C(10)	120.9(6)	N(8)-C(8)-N(9)	120.5(6)
C(10a)-C(3a)-N(4)	128.1(6)	N(7)-C(8)-N(9)	121.7(5)
C(3a)-N(4)-C(4a)	114.5(4)	C(8)-N(8)-H(a)	113(3)
N(4)-C(4a)-N(5)	116.9(4)	C(8)-N(8)-H(b)	121(5)
N(4)-C(4a)-N(9)	123.8(5)	H(a)-N(8)-H(b)	126(5)
C(4a)-N(9)-C(10)	121.5(5)	C(3a)-N(3)-C(1')	128.4(5)
N(9)-C(10)-C(10a)	111.1(4)	C(2)-N(3)-C(1')	125.6(5)

[a]The numbers in parentheses are the estimated standard deviations in the last significant digit. [b]Atoms are labeled in agreement with structure **4** (Fig. 2).

The nucleoside has the *syn* conformation with the glycosidic torsional angle, C(3a)-N(3)-C(1')-O(4'), $\chi = 55.1(7)°$. Generally, the naturally occurring purine nucleosides lacking substituent at the C-8 position, e.g., crystalline adenosine,[12] 2'-deoxyadenosine,[13] and guanosine,[14] have been found to have the *anti conformation* by X-ray crystallography, while N^2-methylguanosine,[15] N^2-dimethylguanosine,[16] and guanosine 5'-monophosphate[17] have adopted the *syn* conformation. The stability of the *syn* conformation of the 2'-deoxynucleoside **4** is probably

enhanced by the intramolecular O(5')-H(5')---N(4) hydrogen bond indicated by a thin line in Fig. 2. The 2'-deoxyribofuranosyl ring has a C2'-endo envelope (^2E) conformation[18] with pseudo-rotational phase angle P = 156.6(5)° and amplitude of puckering τ_m = 35.95°. The conformation across the C(4')-C(5') bond[19] is *gauche-gauche* (i.e., O(5') is *gauche* to C(3'), ϕ_{gg} = 53.6° and *gauche* to O(4'), ϕ_{gg} = 64.0°). The 5'-*hydroxy bond* O(5')-H(5') has rotated to form an intramolecular hydrogen bond with N(4) of the base with a torsional angle of H(5')-O(5')-C(5')-C(4') = 62.0(4)°. The other torsional angles of importance are given in Table 4.

There are two intramolecular hydrogen bonds, between N(8)-H(b)---O(10) and O(5')-H(5')---N(3), which are shown in Fig. 2 by thin lines. There are also five intermolecular hydrogen bonds. The bond lengths and angles for the hydrogen bonds are provided in Table 5.

Table 4. Selected torsional angles (°) of the aglycone and ribose in **4**.

C(1')-C(2')-C(3')-C(4')	-33.0(5)	O(4')-C(1')-N(3)-C(3a)	55.1(7)
C(2')-C(3')-C(4')-O(4')	19.6(5)	O(4')-C(1')-N(3)-C(2)	-123.7(5)
C(3')-C(4')-O(4')-C(1')	3.0(6)	N(7)-C(8)-N(8)-H(a)	-3(4)
C(4')-O(4')-C(1')-C(2')	-24.6(5)	N(7)-C(8)-N(8)-H(b)	177(5)
O(4')-C(1')-C(2')-C(3')	35.9(5)	N(9)-C(8)-N(8)-H(a)	177(4)
O(4')-C(4')-C(5')-O(5')	-64.0(6)	N(9)-C(8)-N(8)-H(b)	-3(5)
C(3')-C(4')-C(5')-O(5')	53.6(7)		

Table 5. Hydrogen bonding interactions in crystalline **4**.

A-H---B	H---B	A---B	<A-H---B
	Intramolecular		
N(8)-H(b)---O(10)	1.99(6)	2.578(9)	134(6)
O(5')-H(5')---N(4)	2.01(6)	2.810(5)	159(5)
	Intermolecular		
N(8)-H(a)---O(W)	1.87(6)	2.823(7)	164(5)
O(W)-H(W2)---O(3')	2.07(6)	2.872(6)	170(6)
O(W)-H(W1)---N(1)	2.15(6)	2.892(6)	149(5)
C(2)-H(2)---N(7)	2.29(6)	3.386(9)	174(4)
O(3')-H(3')---O(5')	2.00(5)	2.773(6)	175(6)

Both compound **4** and compound **5**, the corresponding product of the reaction between 9-[2-hydroxyethoxy)methyl]guanine (**2**) and **3**, are fluorescent and have potential for use as probes for binding to biomolecules in a manner similar to that used for *1in*-benzoadenosine and related compounds.[1] In addition, compound **5** might be used as a prodrug for acyclovir since it has already been demonstrated that IA'-metamorphosine is readily reconverted into guanosine upon mild treatment with aqueous base.[3]

Problems associated with oral drug delivery in the case of acyclovir related to gastrointestinal absorption have been explored through the preparation of more highly soluble derivatives and other alternatives.[20] Compound 5, which is less soluble than acyclovir, was administered orally and intraperitoneally against HSV-1 in mice and intravaginally against HSV-2 in guinea pigs. No advantage of the compound over its parent was detected under these test conditions. Nevertheless, the possibility remains that compound 5, if it passes into the basic environment of the gut, would there release acyclovir by hydrolysis of the terminal triazine ring.

Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C nmr spectra were recorded an a QE-300 spectrometer at 300 MHz and 75.5 MHz, respectively. Fast atom bombardment (FAB) mass spectra were recorded on a VG-ZAB-1 HF spectrometer and uv spectra on a Beckman Acta MVI spectrophotometer. Elemental analyses were performed by Mr. Josef Nemeth and his staff at the University of Illinois.

***8*-Amino-3,10-dihydro-10-oxo-3-(*β*-D-2-deoxyribofuranosyl)-3*H*-1,3,5-triazino[1,2-*a*]purine (dIdA'-metamorphosine) (4).** To a stirred suspension of dry 2'-deoxyguanosine (1) (0.588 g, 2.2 mmol) in anhydrous DMSO (12 ml) at room temperature and under nitrogen was added a solution of sodium *methoxide* prepared from sodium (115 mg, 5 mmol) and methanol (6 ml). The clear solution so formed was treated with methyl *N*-cyanomethanimidate (3) (1.26 g, 15 mmol) introduced through a hypodermic syringe. The bulky, white precipitate which separated initially gradually dissolved again on heating at 55 °C, and heating was continued for 15 h. The reaction mixture was cooled, ethyl acetate-ether (1:1 v/v, 40 ml) was added, and the resulting solid was collected by filteration. To the filtrate was added 150 ml of ether, and the oily residue that resulted on trituration with ethanol gave a solid that was combined to give 340 mg of impure product. This was dissolved in minimum amount of DMF (5 ml) mixed with silica gel (4 g), and evaporated to dryness on a rotary evaporator at < 40 °C. The residue was loaded on a column of the same silica gel (60 g) and eluted with acetone and then with acetone-methanol (9:1). The fractions containing a single fluorescent compound were pooled and evaporated to give dIdA'-metamorphosine (4) as a white solid (0.240 g, 34%): mp 167-169 °C; ^1H nmr ($(CD_3)_2SO$) δ 10.24 (s, 1, NHb, exchangeable with D_2O), 9.41 (s, 1, NHa, exchangeable with D_2O), 8.33 (s, 1, 2-H), 8.07 (s, 1, 6-H), 6.29 (t, J = 6.6 Hz, 1, 1'-H, 5.35 (d, J = 4.2 Hz, 1, 3'-OH, exchangeable with D_2O), 5.04 (t, J = 5.4 Hz, 1, 5'-OH, exchangeable with D_2O), 4.40 (m, 1, 3'-H), 3.89 (m, 1, 4'-H), 3.55 (m, 2, 5'-CH_2), 2.61 and 2.31 (m, 2, 2'-Ha and Hb); ^{13}C nmr ($(CD_3)_2SO$) δ 161.53 (C6), 158.54 (C8 or C4a), 157.58 (C10), 150.90 (C4a or C8), 148.58 (C3a), 139.76 (C2), 119.03

(C10a), 87.96 (C4'), 83.30 (C1'), 70.66 (C3'), 61.57 (C5'), 39.72 (C2'); uv λ_{max} nm (ε): (EtOH) 334 (9780), 313 (9270), 254 (sh) (7400), 245 (sh) (9440) (pH ~ 1) 330 (8440), 310 (8700), 252 sh (8850), 242 (sh) (10,800); mass spectrum (FAB) m/z 320 (M^+ + 1), 204 (B^+ + 2); fluorescence (glycerol at 20 °C) λ_{max}^{ex} 350 nm, λ_{max}^{em} 424 nm. Anal. Calcd for $C_{12}H_{13}N_7O_4 \cdot H_2O$: C, 42.73; H, 4.48; N, 29.07. Found: C, 42.66; H, 4.40; N, 29.02.

8-Amino-3,10-dihydro-3-[(2-hydroxyethoxy)methyl]-10-oxo-1,3,5-triazino[1,2-a]purine (5). Acyclovir (2) (3.1 g, 13.8 mmol) was dissolved in 80 ml of DMSO and to this was added a solution of sodium methoxide, prepared from 0.72 g of sodium and 40 ml of methanol. The solution became slightly cloudy. Methyl *N*-cyanomethanimidate (3) (8.4 ml, approx. 100 mmol) was added dropwise via syringe and the solution became clear. The solution was warmed to 55 °C for 7 h and then 2.2 g of solid was collected and washed with methanol. The combined filtrate was stirred at 55 °C for 3 days, and an 1.1 g additional (total 3.3 g, 86%) of a faintly colored powder, mp 258-260 °C dec, was obtained: tlc (1:1 MeOH/CH_2Cl_2 containing 5 drops of NH_4OH) R_f 0.77 (light blue fluorescence ~ long wave length irradiation). A sample was recrystallized from water and provided colorless needles of 5: mp 260-261 °C dec; ^1H nmr ($(CD_3)_2SO$) δ 10.23 and 9.39 (2s, 2, NHb and NHa, respectively, exchangeable with D_2O), 8.24 (s, 1, 2-H), 8.06 (s, 1, 6-H), 5.51 (s, 2, N-CH_2-O), 4.71 (t, J = 5 Hz, 1, OH), 3.50 (m, 4, O-CH_2CH_2-O); ^{13}C nmr ($(CD_3)_2SO$) δ 161.47 (C6), 158.52 (C8), 157.63 (C10), 151.1 (C4a), 149.24 (C3a), 141.90 (C2), 118.61 (C10a), 72.24 (N-CH_2-O), 70.78 (O-CH_2CH_2-O), 59.8 (CH_2-OH). uv λ_{max} nm (ε): (H_2O) 329 (11,100), 313 (10,500), 252 (sh) (6,850), 243 (sh) (10,350) (pH ~1) 326 (8,775), 309 (8,890), 251 (sh) (7,620), 242 (sh) (9,700); fluorescence (glycerol at 20 °C) λ_{max}^{ex} 350 nm, λ_{max}^{em} 425 nm; mass spectrum (FAB), m/z 278 (M^+ + 1), 203 (B^+ + 1); high-resolution mass spectrum, m/z calcd for $C_{10}H_{12}N_7O_3$ 278.1002, found 278.1004. Anal. Calcd for $C_{10}H_{11}N_7O_3 \cdot \frac{1}{2} H_2O$: C, 42.63; H, 4.11; N, 34.80. Found: C, 42.50; H, 4.02; N, 34.45.

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References

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