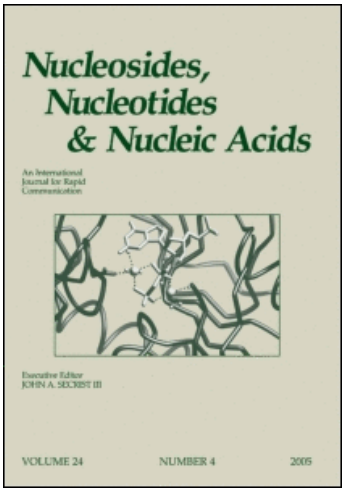

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The Novel 6-(*N*-Pyrrolyl)purine Acyclic Nucleosides: ^{1}H and ^{13}C NMR and X-ray Structural Study

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THE NOVEL 6-(*N*-PYRROLYL)PURINE ACYCLIC NUCLEOSIDES: ^{1}H AND ^{13}C NMR AND X-RAY STRUCTURAL STUDY†

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Abstract. Synthesis of the novel nucleoside analogues containing exocyclic pyrrolo moiety and acyclic side chains attached to the purine ring at N-9 and N-7 is described. The site of alkylation was determined by ^{1}H and ^{13}C NMR on the basis of chemical shifts, C-H coupling constants and connectivity in NOESY and HETCOR spectra. The N-9 substitution of **7** was proved by its X-ray crystallographic analysis.

Since the discovery of antiviral action of acyclovir intensive efforts of chemists and molecular pharmacologists have been directed toward the synthesis of its analogues as well as other acyclonucleosides with various side chains and aglycons.[1] A number of nucleoside analogues have been found to possess potent antiviral activities against HIV.[2-4] Certain analogues of adenine have also been used as plant growth factors (cytokinines) important for plant cell division and differentiation.[5] In the search of molecules related to these classes of biologically

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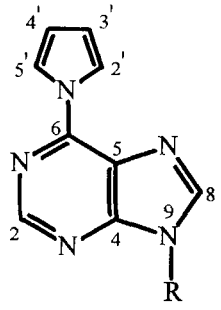
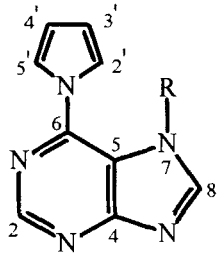




	R-(N-9)	R-(N-7)
1	H	-
2	$CH_2CH(OH)CH_3$	-
3	-	$CH_2CH(OH)CH_3$
4	$CH_2CHClCH_3$	-
5	$CH_2CH(OCOCH_3)CH_3$	-
6	-	$CH_2CH(OCOCH_3)CH_3$
7	$CH{=}CHCH_3$	-
8	$CH_2(1")CH(2")OHCH_2(3")OH$	-
9	-	$CH_2CH(OH)CH_2OH$
10	$CH_2CH(OH)CH_2$	-
11	$CH_2CH(OCOCH_3)CH_2(OCOCH_3)$	-
12	-	$CH_2CH(OCOCH_3)CH_2(OCOCH_3)$

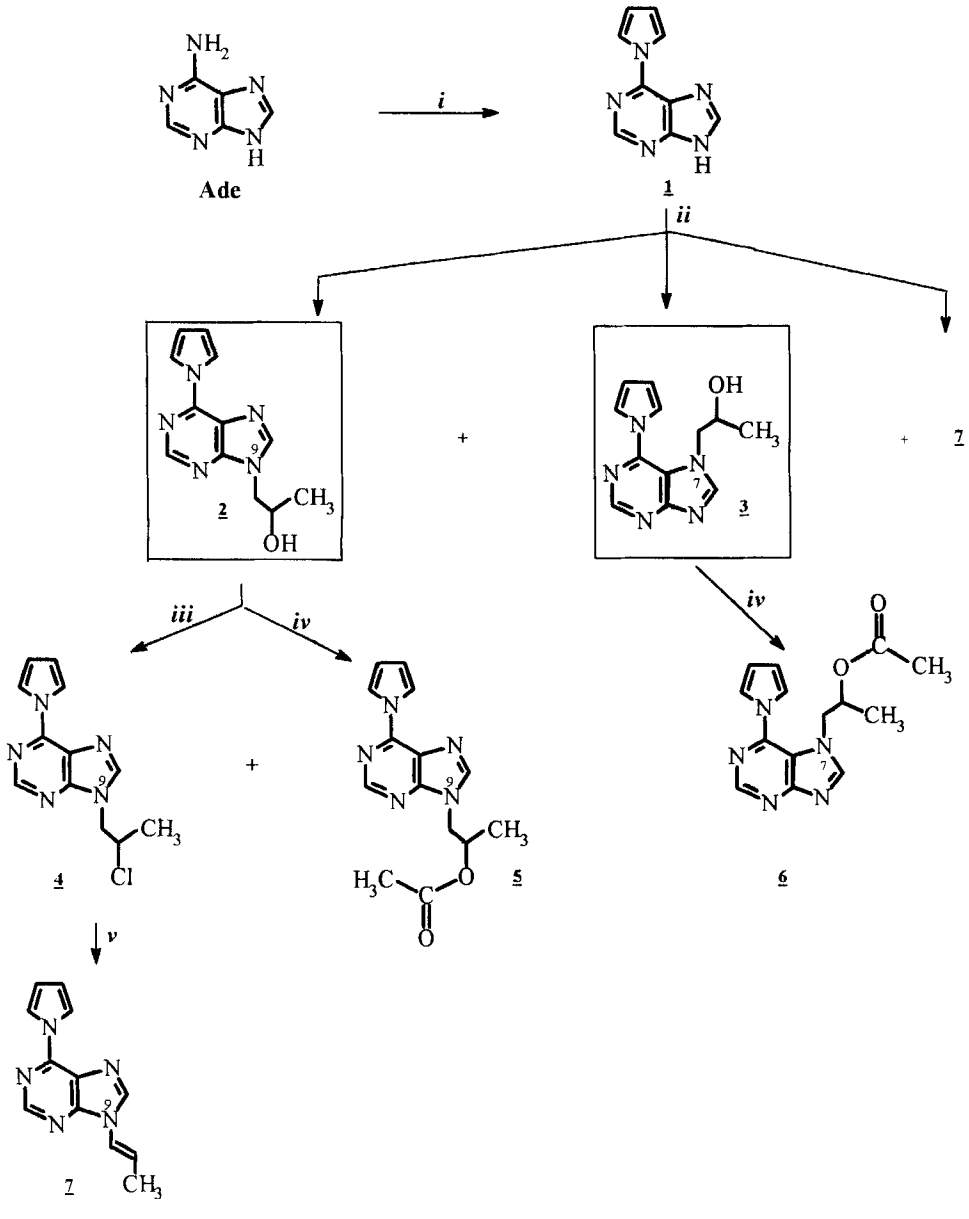
Scheme 1

and pharmacologically active compounds we have prepared the novel class of acyclic purine nucleosides **2-12** (Scheme 1). In order to determine the position of nitrogen substitution in the purine ring and to learn on stereochemistry of isolated products, NMR and X-ray crystallographic investigations were undertaken. The synthesis, ^{1}H and ^{13}C 1D and 2D NMR, as well as X-ray structural studies are reported in this paper.

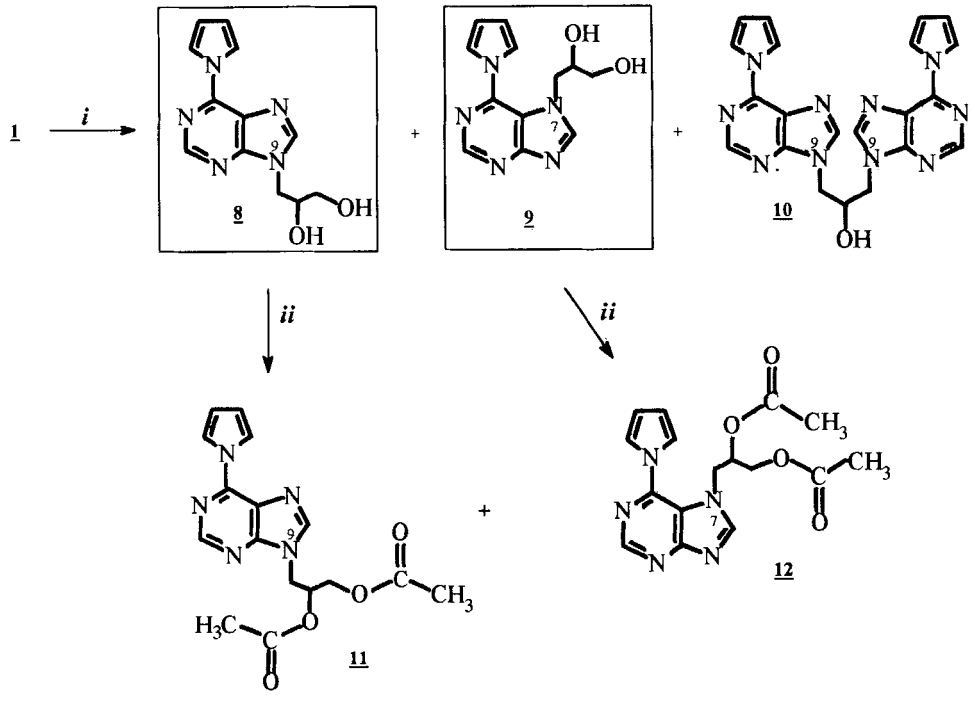
RESULTS AND DISCUSSION

Synthetic work. The 6-(*N*-pyrrolyl)purine containing exocyclic pyrrolo moiety and its derivatives with acyclic side chains attached to the N-9 or N-7 of the purine ring were synthesized (Scheme 1). The key intermediate, 6-(*N*-pyrrolyl)purine (**1**),[6] was prepared by introduction of the pyrrolo moiety in the purine ring, as outlined in the Scheme 2, using the method which has been previously applied for the preparation of various *N*-aryl substituted pyrroles.[7-10] The major products 9-(2-hydroxypropyl)-6-(*N*-pyrrolyl)purine (**2**) and 9-(propen-1-yl)-6-(*N*-pyrrolyl)purine (**7**), and the minor product 7-(2-hydroxypropyl)-6-(*N*-pyrrolyl)purine (**3**) were obtained simultaneously by alkylation of the sodium salt of **1** with propylene carbonate (Scheme 2) according to the procedure for the preparation of 9-(2-hydroxyethyl)adenine.[11] The synthesis of **7** was also achieved by chlorination of **2** to the 9-(2-chloropropyl) compound **4** and subsequent dehydrochlorination. The 9- and 7-(2,3-dihydroxypropyl)purine derivatives **8** and **9**, respectively, as well as 1,3-*bis*[6-(*N*-pyrrolyl)purinyl]propane-2-ol (**10**), were obtained by a modified procedure to that for the preparation of 9- and 3-(2,3-dihydroxypropyl)adenine[12] (Scheme 3). Formation of **10** may be explained by a subsequent reaction of the sodium salt of **1** with the product **8** to give **10**. In order to obtain crystals suitable for X-ray structure analysis the acetylated derivatives **5**, **6**, **11** and **12** were prepared (Schemes 2 and 3). Physical, analytical and UV data of **1-12** are summarized in TABLE 1.

UV spectra. Comparison of the UV spectral data in TABLE 1 showed that the two N-9 and N-7 regioisomers exhibit the following distinctive features: N-9 substituted derivatives **2** and **8** display two overlapped bands with absorption maxima in the region 298-296 nm and 288-285 nm, whereas the corresponding N-7 derivatives **3** and **9** have only one absorption band at shorter wavelength (289 nm). Furthermore, absorption bands at 297 and 287 nm were found in the UV spectra of N-9 acetylated derivatives **5** and **11**, while in the corresponding N-7



Scheme 2. Reagents: *i*, 2,5-dimethoxytetrahydrofuran in acetic acid; *ii*, NaOH or NaH and propylene carbonate in DMF; *iii*, thionyl chloride in dioxane; *iv*, acetic anhydride in pyridine; *v*, sodium methoxide in dioxane-methanol.



Scheme 3. Reagents: *i*, NaH and 3-chloro-1,2-propanediol in DMF; *ii*, acetic anhydride in pyridine.

derivatives **6** and **12** absorption bands at 314 and at 238 nm are seen. These pronounced differentiation in the UV spectra supplemented by NMR spectra allow one to distinguish N-9 and N-7 regioisomers. Similarly, differentiation between N-9 and N-7 substituted adenine derivatives by using UV and ^{1}H NMR spectroscopy has been reported by Townsend and coworkers.[13]

^{1}H and ^{13}C NMR spectra. In the synthesis of the purine nucleosides four regioisomers with acyclic substituents at N-9 , N-7 , N-3 or N-1 are theoretically possible. The N-9 regioselectivity of the coupling of heterocycle with acyclic residue was considered essential, as natural purine nucleosides are substituted at N-9.[14] Indeed, N-7-alkylated purines[15-17] have been hitherto isolated and characterized as well as a few N-1[18] and N-3[12] ones. The analysis of ^{1}H and ^{13}C

TABLE 1. Physical, analytical and UV data for **1-12**

	Formula	M.p. (°C)	Anal.(HRMS)[a] Calcd.	Found	UV data[b] λ_{max}(nm)	logε
1[c]	$C_9H_7N_5$	281-283	C, 58.37 H, 3.81	C, 58.43 H, 3.61	296; 286	4.53; 4.49
2	$C_{12}H_{13}N_5O$	100-102	243.111461	243.111945	298; 288	5.31; 5.35
3	$C_{12}H_{13}N_5O$	189-190	243.111461	243.115965	289	6.76
4	$C_{12}H_{12}N_5Cl$	122-124	261.07757	261.077375	296; 286	6.78; 6.76
5	$C_{14}H_{15}N_5O_2$	96-97	285.122026	285.122570	297; 287	6.81; 6.79
6	$C_{14}H_{15}N_5O_2$	181-183	285.122026	285.124584	314; 238	7.05; 6.93
7	$C_{12}H_{11}N_5$	83-88	225.100896	225.104748	298; 288	6.83; 6.81
8	$C_{12}H_{13}N_5O_2$	154-155	259.106925	259.110351	296; 285	4.11; 4.15
9	$C_{12}H_{13}N_5O_2$	210-211	259.107474	259.108848	289	4.03
10	$C_{21}H_{18}N_{10}O$	212-218	426.166505	426.166500	297; 288	7.20; 7.19
11	$C_{16}H_{17}N_5O_4$	134.5-135	343.128055	343.128050	297; 287	6.83; 6.82
12	$C_{16}H_{17}N_5O_4$	135.5-136	343.128055	343.128050	314; 238	6.86; 6.83

[a] High resolution mass spectrometry, exact mass of the molecular ion.

[b] In absolute MeOH at 23°C.

[c] C% and H% determined by elemental analysis.

1D and 2D NMR spectra of the compounds synthesized here has shown that alkylation of the purine ring took place at N-9 and N-7 position. The assignment of spectra was performed on the basis of chemical shifts, substituent induced chemical shifts, signal intensities, magnitude and multiplicity of C-H *spin-spin* coupling constants as well as connectivity in COSY, NOESY and HETCOR spectra. The ^{1}H NMR data are given in TABLES 2 and 3. The most pronounced differences in N-9 and N-7 regioisomers are found for the proton signals of purine skeleton (H-2 and H-8). Thus, in N-9 substituted compounds (**2**, **4**, **5**, **7**, **8**, **10** and

TABLE 2. ^{1}H NMR chemical shifts (δ/ppm)[a] and H-H coupling constants (J/Hz)[b] for compounds **1-7** (*c.f.* Scheme 2).

Comp.		1[c]	2	3	4	5	6	7
H-2	δ	8.70(s,1H)	8.72(s,1H)	8.28(s,1H)	8.74(s,1H)	8.76(s,1H)	8.30(s,1H)	8.80(s,1H)
H-8	δ	8.60(s,1H)	8.54(s,1H)	8.79(s,1H)	8.65(s,1H)	8.63(s,1H)	8.90(s,1H)	8.72(s,1H)
H-2',5'	δ J	8.32(2H) 2.2(t)	8.39(2H) 2.3(t)	8.39(2H) 2.2(t)	8.29(2H) 2.3(t)	8.30(2H) 2.2(t)	8.38(2H) 2.3(t)	8.25(2H) 2.4(t)
H-3',4'	δ J	6.43(2H) 2.2(t)	6.48(2H) 2.3(t)	6.48(2H) 2.3(t)	6.43(2H) 2.2(t)	6.46(2H) 2.2(t)	6.50(2H) 2.2(t)	6.43(2H) 2.4(t)
CH_2N	δ J δ J		4.28(1H) 13.1;3.0(dd) 4.13(1H) 13.1;7.6(dd)	4.64(1H) 12.4;2.4(dd) 4.30(1H) 12.5;9.1(dd)	4.64(1H) 14.2;4.5(dd) 4.54(1H) 14.5;8.4(dd)	4.54(1H) 14.5;3.5(dd) 4.43(1H) 14.6;7.1(dd)	4.81(1H) 13.9;3.0(dd) 4.68(1H) 14.0;8.2(dd)	
CH	δ J δ J		4.09(1H) (m)	4.23(1H) (m)	4.71(1H) (m)	5.27(1H) (m)	5.45(1H) (m)	7.15(1H) 14.4;1.7(dq) 6.63(1H) 14.3;6.9(dq)
CHOH	δ J		5.11(1H) 4.6(d)	5.18(1H) 4.6(d)				
CH_3	δ J δ		1.13(3H) 5.8(d)	1.21(3H) 5.8(d)	1.6(3H) 6.6(d)	1.23(3H) 6.5(d) 1.89(s,3H)	1.34(3H) 6.2(d) 1.87(s,3H)	1.88(3H) 6.9;1.8(dd)

[a] DMSO-d_6 solutions, chemical shifts referred to TMS. Multiplicity of coupling and number of protons are given in brackets: s = singlet , d = doublet, t = triplet, q = quartet, m = complex multiplet.
[b] Digital resolution ±0.25 Hz.
[c] Signal of NH at 13.74 ppm.

TABLE 3. ^{1}H NMR chemical shifts (δ/ppm)[a] and H-H coupling constants (J/Hz)[b] for compounds **8-12** (*c.f.* Scheme 3).

Comp.		**8**	**9**	**10**	**11**	**12**
H-2	δ	8.75(s,1H)	8.29(s,1H)	8.73(s,2H)	8.76(s,1H)	8.31(s,1H)
H-8	δ	856(s,1H)	8.79(s,1H)	8.58(s,2H)	8.64(s,1H)	8.93(s,1H)
H-2',5'	δ J	8.32(2H) 2.3(t)	8.39(2H) 2.3(t)	8.29(4H) 2.3(t)	8.29(2H) 2.0(t)	8.38(2H) 2.0(t)
H-3',4'	δ J	6.46(2H) 2.3(t)	6.49(2H) 2.3(t)	6.44(4H) 2.3(t)	6.45(2H) 2.0(t)	6.50(2H) 2.2(t)
CH_2N	δ J δ J	4.48(1H) 13.8;3.3(dd) 4.17(1H) 13.9; 8.6(dd)	4.82(1H) 13.1; 3.1(dd) 4.35(1H) 13.1;9.1(dd)	4.48(2H) 13.1;3.4(dd) 4.31(2H) 13.6;7.2(dd)	4.32(1H) 12.1;3.6(dd) 4.15(1H) 12.1;5.8(dd)	4.40(1H) 12.2;3.5(dd) 4.25(1H) 12.3;5.4(dd)
CH	δ J	3.93(1H) (m)	4.08(1H) (m)	4.47(1H) (m)	5.44(1H) (m)	5.61(1H) (m)
CHOH	δ J	5.18(1H) 5.5(d)	5.28(1H) 5.5(d)	5.74(1H) 5.5(d)		
CH_2	δ J δ J	3.46(1H) (m) 3.40 (1H) (m)	3.56(1H) (m) 3.46(1H) (m)		4.62-4.59(2H) (m)	4.92(1H) 14.0;3.3(dd) 4.81(1H) 14.2;8.1(dd)
CH_2OH	δ J	4.90(1H) 5.6(t)	5.03(1H) 5.8(t)			
CH_3	δ δ				2.02(s,3H) 1.92(s,3H)	2.03(s,3H) 1.89(s,3H)

[a] DMSO-d_6 solutions, chemical shifts referred to TMS. Multiplicity of coupling and number of protons are given in brackets: s = singlet , d = doublet, t = triplet, q = quartet, m = complex multiplet.
[b] Digital resolution ±0.25 Hz.

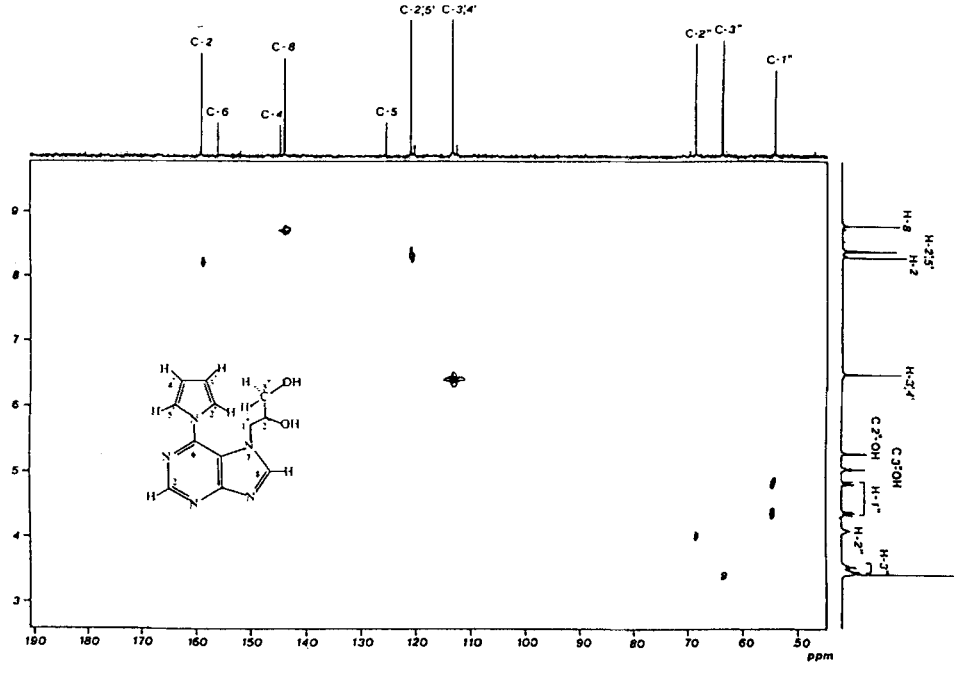


FIG. 1. HETCOR (^{1}H-^{13}C) spectrum of **9**.

11) H-2 is more deshielded (8.72-8.80 ppm) than H-8 (8.54-8.72 ppm), like in parent molecule **1** and purine itself, while in N-7 derivatives (**3**, **6**, **9** and **12**) it is *vice versa* (H-2; 8.28-8.31 ppm, and H-8; 8.79-8.93 ppm). The latter was proved by carbon-proton connectivity in HETCOR spectra, which is displayed for **9** in FIG. 1. Therefore, the signal of H-8 in the N-7 molecules is shifted downfield relative to the H-8 signal of the corresponding N-9 molecules. The similar behaviour was found earlier for variously alkylated purine[18] and guanosine analogues.[19] On the contrary, the signal of H-2 is shifted upfield in N-7 isomers relative to H-2 signal in corresponding N-9 isomers. The both proton pairs, H-2',5' and H-3',4', of the pyrrolo moiety in N-7 molecules are deshielded relative to corresponding pairs in N-9 molecules. In all compounds investigated here the nonequivalency of methylene protons exists, more for N-CH_AH_B than for O-CH_AH_B pair. The *N*-methylene protons are more deshielded than *O*-methylene

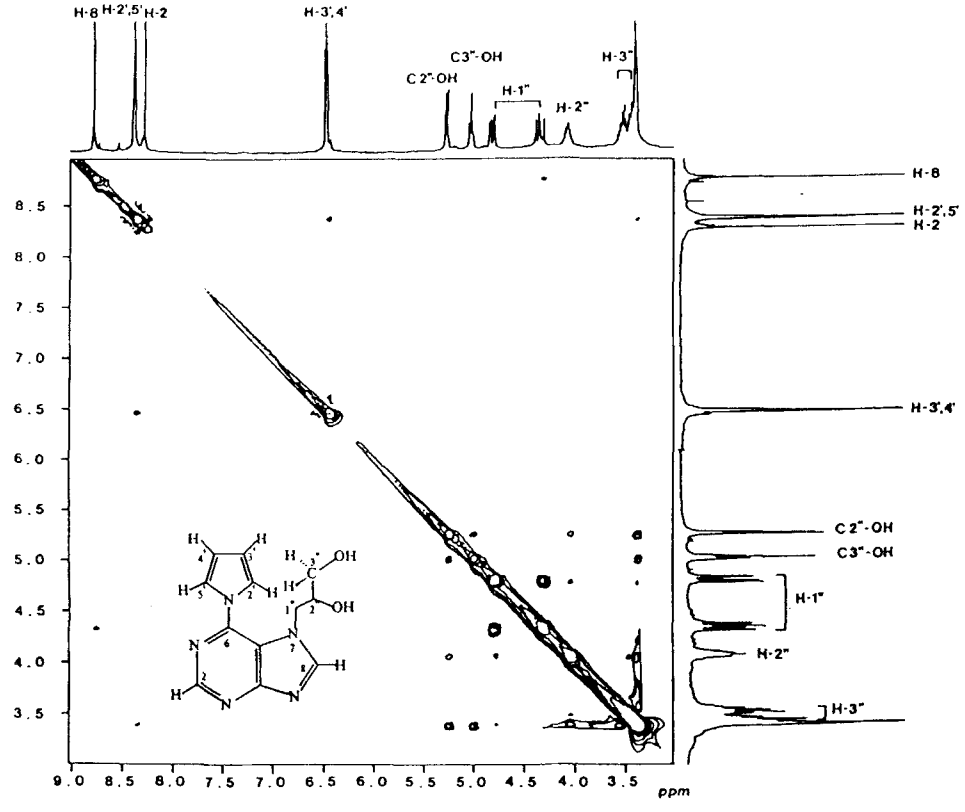


FIG. 2. NOESY spectrum of **9**.

ones which was confirmed by COSY and HETCOR spectra (FIG. 1). In N-7 molecules both pairs of methylene protons are shifted downfield relative to the corresponding proton pairs in N-9 molecules. The chemical shift difference between nonequivalent *N*-methylene protons is greater in N-7 than in corresponding N-9 molecules. The geminal coupling of *N*-methylene protons is somewhat smaller in N-7 than in N-9 molecules (*c.f.* N-9/N-7 pairs **2/3** and **8/9**), while vicinal couplings vary from 2.40 to 9.13 Hz, depending on HCCH dihedral angle. The methine, hydroxyl and methyl protons in the N-7 substituted compounds are also shifted downfield relative to the corresponding protons in the N-9 derivatives (note N-9/N-7 pairs: **2/3**, **5/6**, **8/9** and **11/12** in TABLES 2 and 3).

For **4** and **7**, all resonances are shifted downfield due to the presence of chlorine atom and vinyl group, respectively. The N-9 substitution of derivative **7**, obtained from **2** (Scheme 2), was confirmed by X-ray analysis as well. In the NOESY spectrum of **9** (FIG. 2), weak but recognizable cross peak between the *O*-methylene protons (at C-3") and pyrrolo H-2',5' has been observed. Molecular modelling[20] showed that in **9**, these protons may spatially approach each other to the distance of 3.9 Å. The NOE between *O*-methylene and H-2',5' pyrrolo protons in **9** also substantiates the N-7 substitution, since in the N-9 substituted regioisomer **8** and in corresponding hypothetical N-3 substituted derivative, where the spatial distance between these protons is greater than 5 Å, this NOE would not be expected. In agreement with this, the NOESY spectra of **8** displayed no cross peak between *O*-methylene and H-2',5' pyrrolo protons. As one can see from FIG. 2, the NOESY spectrum of **9** shows also the cross peak between H-8 and one of the *N*-methylene protons (at C-1"), which together with mentioned interaction between pyrrolo and *O*-methylene protons clearly disregards the N-3 substitution. The proton spectra of **10** (Scheme 3) show features of symmetrical structure: (*i*) the protons in aromatic region of **10** have doubled intensities relative to those of **8**; (*ii*) only three aliphatic signals exist in spectrum of **10**, contrary to four signals in spectrum of **8**; and (*iii*) in spectrum of **10,** methylene protons have four times greater intensity than methine and hydroxyl protons, while in **8** only two times. Thus, ratio of integrals in **10** is 2:2:4:4:1:1:4, while in **8** is 1:1:2:2:1:1:2, both for H-2:H-8:H-2',5':H-3',4':CH:OH:CH_2. The structure of **10** was proved by its high resolution mass spectrum and it is in agreement with the structure of closely related compound, 1,3-*bis*[6-(*N*-pyrrolyl)purinyl]propane, which exact geometry was established by X-ray crystallographic analysis.[21] In **11** and **12,** the chemical shift nonequivalence of *N*-methylene and *O*-methylene protons is diminished, as a consequence of substituent effect of acetoxy groups and their different spatial arrangement at N-7 and N-9. The latter is also reflected on side-chain vicinal H-H couplings which have much smaller range (3.47-5.77 Hz) than in derivatives with less bulky acyclic residues (2.40-9.08 Hz).

TABLE 4. ^{13}C NMR chemical shifts (δ/ppm)[a], substituent induced chemical shifts (SCS/ppm)[b] and one-bond C-H coupling constants (*J*/Hz)[c] for **1-7** (*c.f.* Schemes 1 and 2).

Comp.		1	2	3	4	5	6	7
C-2	δ	152.03	151.81	159.14	151.83	152.10	159.12	152.10
	SCS		-0.22	7.11	-0.20	0.07	7.16	0.07
	J	205.40	205.90	202.00		206.40	202.40	
C-4	δ	146.59	146.60	144.65	146.48	146.40	144.37	146.50
	SCS		0.01	-1.94	-0.11	-0.19	-2.22	-0.09
C-5	δ	121.18	121.29	125.55	120.07	121.40	125.23	121.40
	SCS		0.11	4.37	-1.11	0.22	4.05	0.22
C-6	δ	154.50	153.75	156.02	153.30	153.90	155.95	151.70
	SCS		-0.75	1.52	-1.20	-0.60	1.45	-2.80
C-8	δ	144.34	146.67	143.85	146.00	146.90	143.22	143.20
	SCS		2.33	-0.49	1.66	2.56	-1.12	-1.10
	J	212.80	214.50	215.10		215.40	214.80	
C-2',5'	δ	120.35	120.31	120.95	120.10	120.50	120.83	120.10
	SCS		-0.04	0.60	-0.25	0.15	0.48	-0.25
C-3',5'	δ	112.52	112.57	113.43	112.50	112.90	113.40	112.50
	SCS		0.05	-0.91	-0.02	0.38	0.88	-0.02
C-1''	δ		50.60	57.54		48.20	54.07	
C-2''	δ		64.58	63.69		69.50	67.79	
C=O	δ					170.70	169.79	
CH_3	δ		20.85	20.84		17.40 20.70	17.37 20.75	

[a] DMSO-d_6 solution, chemical shifts referred to TMS.
[b] SCS in **2-7** referred to **1**.
[c] Doublet at C-2, while doublet of triplets at C-8. Digital resolution ±1.18 Hz.

The ^{13}C NMR data are given in TABLES 4 and 5. Generally, the ^{13}C spectra of N-9 and N-7 regioisomers show seven signals in the aromatic region and three to five signals in aliphatic region, depending on the type of alkyl residue. The $^{13}C\{^1H\}$ gated decoupled spectra of the purine moiety in all derivatives showed doublet for C-2 and doublet of triplets for C-8 resonances, which is in accord with

TABLE 5. ^{13}C NMR chemical shifts (δ/ppm)[a], substituent induced chemical shifts (SCS/ppm)[b] and one-bond C-H coupling constants (J/Hz)[c] for **8-12** (*c.f.* Schemes 1 and 3).

Comp.		**8**	**9**	**10**	**11**	**12**
C-2	δ	151.82	159.03	151.98	152.14	159.37
	SCS	-0.21	6.97	0.05	0.11	7.34
	J	206.0	201.9	206.2	206.5	202.4
C-4	δ	146.60	144.70	146.67	146.72	144.59
	SCS	-0.01	-1.89	0.08	0.13	-2.0
C-5	δ	121.36	125.47	121.38	121.21	125.36
	SCS	0.18	4.29	0.20	0.03	4.18
C-6	δ	153.75	155.97	153.78	153.80	156.15
	SCS	-0.75	1.47	-0.72	-0.70	1.65
C-8	δ	146.88	143.90	146.77	146.33	143.51
	SCS	2.54	-0.44	2.43	1.99	-0.83
	J	214.6	214.8	215.6	215.5	214.8
C-2',5'	δ	120.33	120.96	121.38	120.31	120.99
	SCS	-0.02	0.61	1.03	-0.04	0.64
C-3',5'	δ	112.62	113.44	112.72	112.73	113.59
	SCS	0.12	0.92	0.20	0.21	1.07
C-1''	δ	47.10	54.27	47.23	43.70	50.71
C-2''	δ	69.59	68.65	66.97	69.28	68.83
C-3''	δ	63.72	63.74		62.63	62.76
C=O	δ				170.36	169.95 170.37
CH_3	δ				20.55 20.51	20.52

[a] DMSO-d_6 solutions, chemical shifts referred to TMS.
[b] SCS in **8-12** referred to **1**.
[c] Doublet at C-2, while doublet of triplets at C-8. Digital resolution ±1.18 Hz.

substitution at N-9 or N-7 but not at N-3. The additional triplet splitting at C-8 arises from three-bond C-H coupling with two *N*-methylene protons of the acyclic residue at N-9 or at N-7, what was confirmed by coupled spectra of the parent molecule **1**, where only a doublet for C-8 was observed. In corresponding hypothetical N-3 substituted molecules a doublet of triplets for C-2 and only a doublet for C-8 would have been expected. The C-2 and C-8 resonances were

distinguished on the basis of chemical shifts (C-2 is more deshielded than C-8) and magnitude of one-bond C-H coupling constants (for C-2 *ca* 202-206 Hz while for C-8 *ca* 213-215 Hz). This assignment is in accordance with the literature data for purine, adenine and other related molecules.[18,19,22] From TABLES 4 and 5 one can recognize that N-9 and N-7 derivatives show systematic trend in their ^{13}C chemical shifts which can be used for their differentiation on the basis of substituent induced chemical shifts (SCS/ppm). In the purine skeleton the significant change of ^{13}C chemical shift exists for C-8 in N-9 derivatives and for C-2, C-4, C-5 and C-6 in N-7 derivatives. The C-8 is deshielded in N-9 derivatives for *ca* 3 ppm with respect to the corresponding C-atom in parent molecule **1** and in N-7 derivatives. The similar behaviour has been reported in some other acyclic purine nucleosides[14], while the opposite one in some substituted purines[18] and guanines[19]. The most significant difference of SCS between N-7 and N-9 regioisomers was revealed for C-2. This carbon is deshielded in N-7 substituted molecules for even *ca* 7 ppm with respect to that of N-9 derivatives and **1**. In addition to this, the magnitude of one-bond C-H spin-spin coupling at C-2 is *ca* 4 Hz smaller in N-7 than in N-9 derivatives (See TABLES 4 and 5), while that at C-8 remains constant in both series of regioisomers. The great long range SCS and decrease of C-H coupling, both at C-2 in N-7 derivatives, might be explained by the fact that N-7 substituents are placed at *para*-, while N-9 substituents at *meta*-position with respect to the C-2. In N-7 regioisomers the C-4 is shielded for *ca* 2 ppm, while C-5 and C-6 are deshielded for *ca* 4 ppm and 2 ppm, respectively, in comparison with corresponding C-atoms in N-9 regioisomers. The C-4 and C-6 were distinguished on the basis of C-H coupling patterns (C-4 doublet, C-6 unresolved multiplet) and by comparison with chemical shifts of corresponding C-atoms in related molecules[22]. The assignment of C-5 to the highest field is in agreement with theoretical predictions that this carbon would have the highest π-electron density[23] but also in accord with other experimental data.[18, 22] The C-5 is rather sensitive to the type of substituent at N-7 site since in some cases this carbon is more shielded in N-7 than in N-9 derivatives [18,19] while in some cases

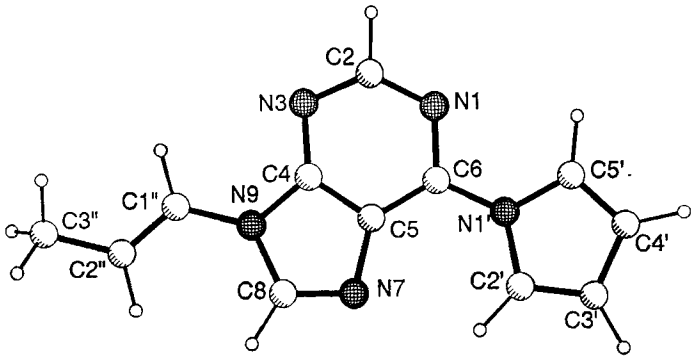


FIG. 3. Perspective view with atom numbering for **7**.

(as was found here) it is *vice versa*.[14] In fact, for almost all C-atoms of purine skeleton of N-9/N-7 regioisomers investigated here, the trend of SCS is opposite to the one found in variously alkylated N-9/N-7 purines by Townsend et al.[18] This may be explained by different steric and electronic influences of pyrrolo and acyclic moieties than those of alkyl and ribosyl moieties on the purine skeleton. The carbon atoms of pyrrolo moiety are more deshielded in N-7 than in N-9 derivatives. Although, these effects are rather small, they are two times greater in N-7 than in N-9 regioisomers. This also corroborates that substitution takes place at N-7 , but not at N-3. Out of the purine skeleton the most pronounced difference in chemical shifts between N-7 and N-9 derivatives was observed for *N*-methylene carbon (C-1") of the acyclic residue. This carbon is deshielded in N-7 derivatives with respect to the corresponding one in N-9 derivatives for *ca* 7 ppm. Contrary to this, the methine carbon (C-2") in N-7 derivatives is shielded against that in N-9 derivatives (for *ca* 1 ppm). The only exception is **10** (N-9 regioisomer) where this carbon is even more shielded (*ca* 1.50 ppm) than in corresponding N-7 regioisomer **9**, which is a consequence of dimeric structure of **10**.

X-ray structure analysis. Molecule **7** crystallizes in the triclinic centrosymmetric space group $P\bar{1}$. Perspective view of **7** with atom numbering is

TABLE 6. Selected bond lengths (Å) and angles (°) with e.s.d.'s in parenthesis of 7.

	Å		o		o
N1'- C2'	1.386(5)	C2' - N1' - C5'	108.3(4)	N1' - C6 - N1	116.4(4)
N1' - C5'	1.385(6)	C2' - N1' - C6	126.3(4)	N1' - C6 - C5	125.1(4)
N1' - C6	1.378(6)	C5' - N1' - C6	125.4(4)	N1 - C6 - C5	118.6(4)
N1 - C2	1.331(6)	C2 - N1 - C6	118.4(4)	N7 - C8 - N9	115.4(4)
N1 - C6	1.347(5)	C2 - N3 - C4	110.8(4)	N9 - C1" - C2"	125.9(4)
N3 - C2	1.342(6)	C5 - N7 - C8	103.1(4)	C1"- C2" - C3"	125.2(5)
N3 - C4	1.326(5)	C4 - N9 - C8	104.9(4)		
N7 - C5	1.402(5)	C4 - N9 -C1"	126.8(4)		
N7 - C8	1.300(6)	C8 - N9 -C1"	128.3(4)		
N9 - C4	1.375(6)	N1' - C2' - C3'	108.1(5)		
N9 - C8	1.365(5)	C2' - C3' - C4'	106.8(5)		
N9 - C1"	1.409(6)	C3' - C4' - C5'	108.6(5)		
C2' - C3'	1.362(8)	N1' - C5' - C4'	108.2(5)		
C3' - C4'	1.426(7)	N1 - C2 - N3	128.6(4)		
C4' - C5'	1.334(7)	N3 - C4 - N9	126.3(4)		
C4 - C5	1.380(6)	N9 - C4 - C5	106.5(4)		
C5 - C6	1.390(7)	N7 - C5 - C4	110.2(5)		
C1" - C2"	1.310(7)	N7 - C5 - C6	133.3(4)		
C2" - C3"	1.473(8)	C4 - C5 - C6	116.6(4)		

shown in FIG. 3. Bond lengths and angles of **7** are summarized in TABLE 6. One can see that the skeleton of the molecule consists of two almost coplanar pyrrolo and purine rings substituted at the position N-9 of the purine moiety by acyclic chain. The observed values for bond lengths and angles of the purine ring in **7** are in good agreement with the corresponding values found in related 9-methyladenine[24] and purine itself.[25]

Conclusions. Alkylation of the 6-(*N*-pyrrolyl)purine gave, both, N-9 and N-7 substituted acyclic derivatives. The N-9 regioisomers were predominant

in all cases. ^{1}H and ^{13}C NMR chemical shifts and the connectivity in NOESY and HETCOR spectra have proved to be useful for differentiating N-9 and N-7 substituted regioisomers. The N-9 substitution in regioisomer **7** and its conformation were unambiguously confirmed by X-ray structure analysis.

EXPERIMENTAL

General methods. Melting points (uncorrected) of **1**, **4**, **7**, and **2**, **3**, **5**, **6**, **8-12** were determined with a Kofler micro hot-stage (Reichert, Wien) and Fisher-Jones instruments, respectively. Precoated Merck silica gel 60F-254 plates were used for thin layer chromatography (**TLC**) and the spots were detected under UV light (254 nm). Column chromatography was performed using silica gel (0,05-0,2 mm) Merck; glass column was slurry-packed under gravity. Solvent systems used for **TLC** and column chromatography were as follows: S_1=CH_2Cl_2-MeOH (5:1); S_2=$CHCl_3$-MeOH (20:1); S_3=$CHCl_3$-MeOH (6:1); S_4=CH_2Cl_2-MeOH (6:1); S_5=CH_2Cl_2-MeOH (18:1); S_6=CH_2Cl_2-MeOH (9:1). Elemental analysis of **1** was performed by the Central Analytical Service of the "Rudjer Bošković" Institute, Zagreb, Croatia. UV spectra were recorded on Hitachi Perkin-Elmer 124 spectrophotometer.

Mass spectra. The high resolution electron impact mass spectra of **1-4**, **6**, **7** and **9** were recorded with an EXTREL FT MS 2001 instrument, while the ones of **5**, **8**, and **10-12** with a Varian MAT 95 double focussing mass spectrometer with ionizing energy 70 eV.

NMR spectra. The ^{1}H and ^{13}C 1D and 2D NMR spectra were recorded on a Varian Gemini 300 spectrometer, operating at 75.46 MHz for the ^{13}C resonance The samples were dissolved in DMSO-d_6 and measured at 21 °C in 5 mm NMR tubes. The ^{1}H and ^{13}C chemical shift values are in ppm, referred to TMS. Digital resolution in ^{1}H spectra was 0.25 Hz while in ^{13}C spectra 1.18 Hz per point. The

TABLE 7. Summary of crystal data, intensity measurements and structure refinement for compound **7**.

Formula	$C_{12}H_{11}N_5$	Radiation	MoK_α (λ=0.71073 Å)
Formula weight	225.3	Monochromator	graphite
Colour	colourless	μ (cm^{-1})	0.812
Crystal dimension (mm)	0.45 x 0.30 x 0.08	2θ range (^{o})	4 - 60
Space group	$P\bar{1}$, triclinic	Scan type	Θ-2Θ
a (Å)	7.102(4)	Scan width(^{o})	1
b (Å)	7.770(5)	Standard reflections*	-2 2 -1; 0 -2 3; -2 1 0
c (Å)	10.785(6)	Index ranges	-10,10; -11,11; -15 ,15
α (^{o})	92.10(4)	Independent reflections	3250 [$821 \geq 2\sigma(I)$]
β (^{o})	107.42(5)	Number of parameters	156
γ (^{o})	99.24(3)	Final R, R_w	0.049; 0.069
V (Å^3)	558.2(6)	$(\Delta/\sigma)_{max.}$	0.002
Z	2	S	0.6339
D_x (gcm^{-3})	1.340	Residual peaks ($eÅ^{-3}$)	-0.23; 0.20
F(000)	236	Weighting scheme	$w = 1/[\sigma^2(Fo) + 0.0125Fo^2]$

*measured every 100 min.

techniques used were the following: broadband proton decoupling, gated decoupling, APT, COSY, NOESY and HETCOR. The NOESY spectra were measured with several mixing times (0.45-0.80 s).

Crystallography. Single crystal of **7** was prepared by growth under slow evaporation at room temperature of a very dilute solution of ethyl acetate-ethanol (1:10). Data collection was performed at room temperature on a Philips PW1100 diffractometer upgraded by STOE. Lattice parameters were refined from a least-squares refinement of 24 reflections (12.46-2θ-24.74°). Diffracted intensities were corrected for Lorentz-polarization but not for absorption. The structures was solved by direct methods (SHELXS86).[26] Structure of **7** was refined by full-matrix least squares technique (CRYSRULER package).[27] All coordinates of H atoms

were calculated and were allowed to ride at fixed distances from attached atoms. Crystal and refinement data are given in the TABLE 7.

The illustrations were prepared with the aid of PLUTON-89 program.[28] Additional X-ray crystallographic data: atomic coordinates for nonhydrogen atoms, full tables of bond distances and angles, tables of anisotropic thermal parameters, hydrogen atomic coordinates with isotropic thermal parameters, as well as the observed and calculated structure factors are given as deposit (61 pages).

6-(*N*-Pyrrolyl)purine (1). A stirred mixture containing adenine (6.3 g, 47 mmol) and 2,5-dimethoxytetrahydrofuran (6.5 mL, 50 mmol) was refluxed in acetic acid (9 mL) for approximately 2 h, and thereafter all methanol formed in the reaction was separated in Dean-Stark apparatus. The reaction mixture was then cooled to room temperature and acetic acid-water (1:1, 50 mL) was added. The light yellow crystals obtained were recrystallized from ethanol-water (1:1) to give colourless crystals of **1** (6.0 g, 69%).

9-(2-Hydroxypropyl)-6-(*N*-pyrrolyl)purine (2) *and* **7-(2-Hydroxypropyl)-6-(*N*-pyrrolyl)purine (3)**. **Procedure A**. A solution of **1** (3.70 g, 20 mmol), propylene carbonate (2.25 g, 22 mmol) and pulverized sodium hydroxide (30 mg) in dry DMF (100 mL) was heated under reflux with stirring for 9 h. The reaction solution was concentrated *in vacuo* and residual DMF and propylene carbonate were removed by distillation (0.01 Torr). The main part of solid residue was dissolved in ethyl acetate (50 mL), the undissolved material filtered off and the clear solution concentrated. The crude product was submitted to column chromatography (S_6) yielding pure **2** (4.3 g, 88,5%, R_f 0.53) and **3** (0.16 g, 3.3%, R_f 0.33). A repeated synthesis of compounds **2** and **3** by a modified procedure (**B**), in which sodium hydride was used as a base, gave in addition to **2** and **3** the product 7. **Procedure B**. A mixture of **1** (1.85 g, 10 mmol) and sodium hydride (0.46 g, 55% , 10.5 mmol) in dry DMF (50 mL) was stirred at room temperature

for 1 h to give a turbid solution of the sodium salt of **1**. The solution was concentrated *in vacuo* and propylene carbonate (35 mL, 413 mmol) added to the residue. The turbid reaction mixture was heated at 155-160 °C with stirring for 6 h, cooled and the undissolved material filtered off. Propylene carbonate was removed by distillation (0.01 Torr, b.p. 38-42 °C) and the residual dark brown oil (2.42 g) was submitted to column chromatography (S_6) yielding pure **2** (0.88 g, 36,2%,R_f 0.53), **3** (0.04 g, 1.6%, R_f 0.33), and **7** (0.63 g, 28%, R_f 0.87).

9-(2-Chloropropyl)-6-(*N*-pyrrolyl)purine (**4**). To a solution of **2** (0.49 g, 2 mmol) in dioxane (12 mL) a few drops of pyridine and thionyl chloride (0.66 g, 5.5 mmol) dissolved in dioxane (12 mL) were added. After the reaction mixture was gently boiled under reflux for 35 minutes, the solvent was evaporated and thick oily residue was purified by column chromatography (S_3). Recrystallization of the separated product from ethanol-water (96:4) gave colourless crystals of **4** (0.47 g, 91%).

9-(2-Acetoxypropyl)-6-(*N*-pyrrolyl)purine (**5**). A solution of **2** (0.49 g, 2 mmol) in a mixture of pyridine (6 mL) and acetic anhydride (2.5 mL, 26 mmol) was allowed to stand at room temperature for about 20 h, then poured onto ice and extracted with chloroform (2x20 mL). The organic phase was washed with water (20 mL), 5% citric acid solution (20 mL), 5% sodium bicarbonate solution (20 mL) and water (20 mL), dried (Na_2SO_4) and concentrated. The residual pyridine was removed by codistillation *in vacuo* with methanol. After drying in a vacuum dessicator, the crude product was recrystallized from absolute ethanol yielding pure **5** (0.24 g, 42 %).

7-(2-Acetoxypropyl)-6-(*N*-pyrrolyl)purine (**6**). **3** (0.16 g, 0.66 mmol) was treated in the same way as described for **5**. The crude product was recrystallized from ethyl acetate-ethanol (1:10) yielding pure **6** (0.17 g, 89.5%).

9-(Propen-1-yl)-6-(*N*-pyrrolyl)purine (**7**). To a solution of **4** (0.67 g, 2.6 mmol) in dioxane (50 mL) a methanol solution of sodium methoxide, prepared

from methanol (14 mL) and sodium (0.41 g, 0.018 gatom), was added. After stirring at room temperature for 24 h, water was added until solution became clear. Solution was then treated with Dowex 50 (H^+) to be neutral and evaporated to dryness. Purification of the crude oily product by column chromatography (S_2) and recrystallization of the separated crystalline product from ethyl acetate-light petroleum (40-70 °C, 1:1) gave colourless crystals of **7** (0.05 g, 8.6%).

9-(2,3-Dihydroxypropyl)-6-(*N*-pyrrolyl)purine (8), 7-(2,3-Dihydroxy propyl)-6-(*N*-pyrrolyl)purine (9) and 1,3-*bis*[6-(N-pyrrolyl)purinyl]propene-2-ol (10). A solution of **1** (4.1 g, 22 mmol) and sodium hydride (1.0 g, 55% in oil, 23 mmol) in dry DMF (150 mL) was stirred at 25-30 °C for 1h. A solution of 3-chloro-1,2-propanediol (2.7 g, 24.4 mmol) in dry DMF (10 mL) was then added and stirring was continued at 95 °C for 12 h. The precipitated sodium chloride was filtered off from the cooled (5 °C) reaction mixture and the solvent evaporated; the remaining DMF was removed by codistillation with acetone. The crude product was triturated with acetone (25 mL) and the solid was collected with suction and washed with acetone (5 mL). This product (4.0 g) contains only the regioisomers **8** and **9** as established by TLC (S_4), whereas the solid residue (2.4 g) obtained after concentration of the acetone solution contains **8**, **9**, **10** and traces of **1**. Those crude products were submitted to column chromatography (S_4) providing pure **8** (2.81 g total, 49.3%, R_f 0.51), **9** (0,57 g total, 10%, R_f 0.38) and **10** (0.13 g, 2.8%, R_f 0.67). Recrystallization from ethanol-water (95:5) afforded analytical samples of **8** and **9**.

9-(2,3-Diacetoxypropyl)-6-(*N*-pyrrolyl)purine (11). A solution of **8** (0.31 g, 1.2 mmol) in a mixture of pyridine (4 mL) and acetic anhydride (1.5 mL, 15.9 mmol) was allowed to stand at room temperature for about 20 h and then worked up as described for **5**. A crude product was recrystallized from absolute ethanol yielding pure **11** (0.39 g, 95%).

7-(2,3-Diacetoxypropyl)-6-(*N*-pyrrolyl)purine (12). A solution of a product containing predominantly **9** and less **8** (0,34 g, 1.3 mmol), in a mixture of pyridine (13 mL) and acetic anhydride (2 mL, 21 mmol) was allowed to stand at room temperature for about 20 h. The isolation procedure was the same as described for **5**. The crude solid product (0.43 g, 95,5%) was submitted to column chromatography (S_5), which yielded pure **11** (0.11 g, 24%, R_f 0.75) and pure **12** (0.2 g, 44.4%, R_f 0.36). Recrystallization of **11** and **12** from ethyl acetate-ethanol (1:10) afforded analytical samples.

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