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Original Scientific Paper

New Acyclic Purine Nucleoside Analogues Containing Exocyclic Pyrrolo Moiety: Synthetic, NMR and X-ray Crystal Structure Studies

Silvana Raić,[a] *Mario Pongračić,*[b] *Jasna Vorkapić-Furač,*[c] *Dražen Vikić-Topić,*[d] *Antonija Hergold-Brundić,*[e] *Ante Nagl,*[e] *and Mladen Mintas*[a,*]

[a]*Department of Organic Chemistry, Faculty of Chemical Engineering and Technology, University of Zagreb, Marulićev trg 20, 10000 Zagreb, Croatia*

[b]*Pliva Research Institute, Prilaz baruna Filipovića 25, 10000 Zagreb, Croatia*

[c]*Faculty of Food Technology and Biotechnology, University of Zagreb, 10000 Zagreb, Croatia*

[d]*Ruđer Bošković Institute, Laboratory of Molecular Spectroscopy, Bijenička 54, 10000 Zagreb, Croatia*

[e]*Laboratory of General and Inorganic Chemistry, Faculty of Science, University of Zagreb, Zvonimirova 8, 10000 Zagreb, Croatia.*

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The synthesis of novel 6-(*N*-pyrrolyl)purine nucleoside analogues containing acyclic side chains attached to the purine ring at N-9 is described. The structures were determined by ^{1}H and ^{13}C NMR on the basis of chemical shifts, substituent induced shifts, C-H coupling constants and connectivity in the COSY, NOESY and HETCOR spectra. Unequivocal proof for the stereostructure of **6** was obtained by its X-ray crystallographic analysis. Geometrical data from X-ray structural analysis showed that the two 6-(*N*-pyrrolyl)purine rings involved in the skeleton of **6** are *anti*-disposed but not centrosymmetric with respect to the central aliphatic bridge.

* Author to whom correspondence should be addressed.

INTRODUCTION

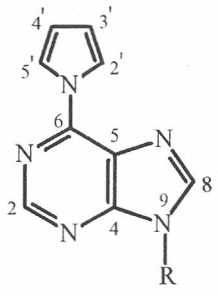
Open-chain sugar analogues of nucleosides have been made the object of intensive chemical and pharmacological investigation due to their potential activity as antiviral agents.[1–3] Among many viral diseases, the acquired immunodeficiency syndrome (AIDS) has evolved, despite intensive research on prevention and treatment, into a major epidemic in the last decade.[4] A lot of acyclic and carbocyclic analogues, modified in the heterocyclic base moiety as well as in the aliphatic chain attached to the base, were synthesized and evaluated for their biological activity, but only a few of them have been found to possess potent antiviral activities against HIV.[5–7] Furthermore, hydrophilic groups containing aliphatic chains extended by the basic *N,N*-diethylamino units are important constituents of many pharmacologically significant compounds, such as antihistaminic drugs: diphenhydramine, tripelennamine and pheniramine,[8] ranitidine,[9] as well as the antipsychotic agent chlorpromazine.[10] Certain analogues of adenine have also been used as plant growth factors (cytokinines) important for plant cell division and differentiation.[11] Searching for the compounds chemically related to such classes of biologically and pharmacologically active molecules and in connection with our previous studies,[12] we have prepared the new types of acyclic nucleoside analogues outlined in Scheme 1. The synthesis, ^{1}H and ^{13}C NMR, as well as X-ray structural studies are reported in this paper.

RESULTS AND DISCUSSION

Synthetic work

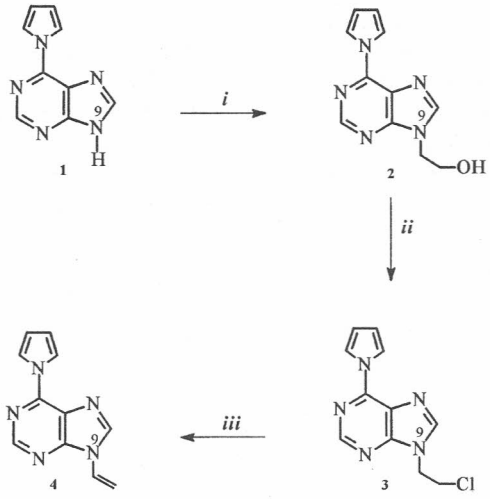
The novel nucleoside analogues with exocyclic pyrrolo moiety and aliphatic side chains attached to the N-9 position of the purine ring **2–5**, **7** and **8** (Scheme 1) were synthesized.

The preparation of the key-intermediate 6-(*N*-pyrrolyl)purine (**1**) was described in our previous paper.[12] The synthesis of the N-9 vinyl substituted

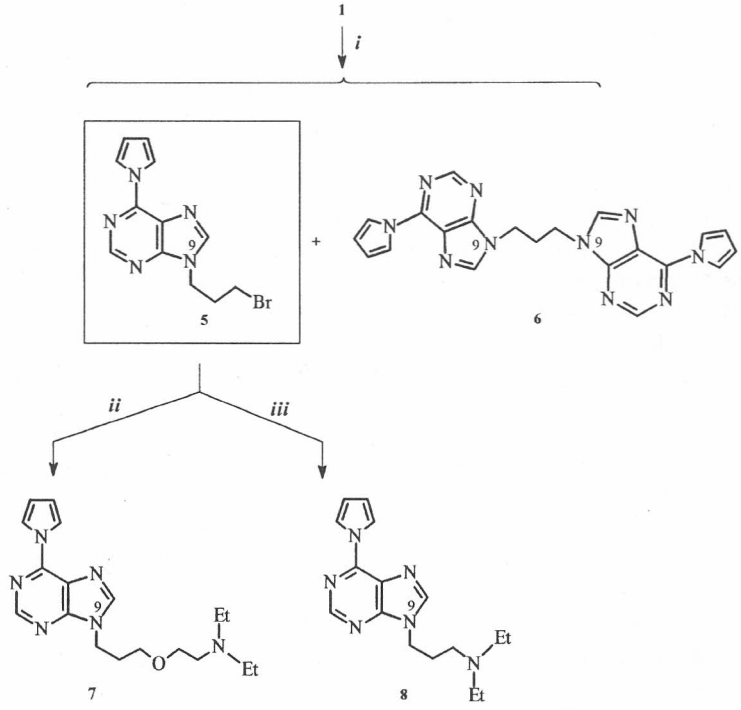


	R-(N-9)
1[9]	H
2	CH_2CH_2OH
3	CH_2CH_2Cl
4	$HC{=}CH_2$
5	$CH_2(1'')CH_2(2'')CH_2(3'')Br$
7	$CH_2CH_2CH_2\text{-}O\text{-}(CH_2)_2NEt_2$
8	$CH_2CH_2CH_2NEt_2$

Scheme 1.



Scheme 2. Reagents: *i*, NaOH/ethylene carbonate in DMF; *ii*, $SOCl_2$ in dioxane; *iii*, $NaOCH_3$ in dioxane.



Scheme 3. Reagents: *i*, NaH/1,3-dibromopropane in DMF; *ii*, $Na/Et_2N(CH_2)_2OH$ in THF; *iii*, Et_2NH in EtOH.

compound (**4**) consists of conversion of **1** to its N-9 hydroxyethyl derivative **2**, followed by chlorination to the N-9 chloroethyl compound **3** and dehydrochlorination to **4** (Scheme 2). This is in accord with a sequence of analogous reactions in the adenine series.[13] The N-9 substituted bromopropyl derivative **5** and 1,3-bis[6-(*N*-pyrrolyl)purin-9-yl]propane **6** were obtained by alkylation of the sodium salt of **1** with 1,3-dibromopropane using an analogous procedure to that for the preparation of 9-(3-bromopropyl)adenine[14] (Scheme 3). Introduction of the basic aminoethoxy group in **7**, with three methylene units in the side chain, was accomplished by coupling the sodium salt of 2-diethylaminoethanol[15] with bromo precursor **5**. The N-9 substituted diethylaminopropyl derivative **8** was prepared by condensation of **5** with diethylamine, analogously to the procedure given in the literature.[16]

NMR spectra

The assignment of ^{1}H and ^{13}C NMR spectra was performed on the basis of chemical shifts, substituent induced shifts, magnitude and multiplicity of H-H and C-H spin-spin coupling as well as connectivities in the COSY, NOESY and HETCOR spectra. The ^{1}H NMR data are displayed in Tables I and II, while ^{13}C data in Tables III and IV. The chemical shifts pattern of purine moiety in both ^{1}H and ^{13}C spectra as well as the substituent induced ^{13}C chemical shifts are consistent with those observed for other N-9 substituted compounds.[12,17,18] Thus, in all compounds H-2 is more deshielded than H-8, and the same is valid for C-2 and C-8. We confirmed this assignment by the magnitude and multiplicity of C-H couplings obtained from $^{13}C\{^{1}H\}$ gated decoupled spectra. Namely, in all N-9 derivatives C-2 displayed doublet, while C-8 doublet of triplets, with one-bond C-H coupling in the range of *ca.* 205–206 Hz and *ca.* 213–216 Hz, respectively. These one-bond coupling values are in accord with those observed at C-2 and C-8 in parent molecule **1** (Table III). In Figure 1, a part of the gated decoupled spectra of **1** (above) and **2** (below), displaying C-H coupling at C-2 and C-8, are shown. The additional triplet splitting at C-8 in N-9 derivatives, which is absent in the parent molecule **1**, arises from three-bond C-H coupling with the *N*-methylene protons of the acyclic side chain. The assignment of *N*-methylene protons was substantiated by the connectivity in COSY spectra (in Figure 2 displayed for **8**) as well. Theoretically possible N-3 substitution was disregarded, since in hypothetical N-3 substituted molecules an additional triplet would be at C-2, while C-8 would show only doublet splitting. In addition, in NOESY spectra of all compounds investigated here, the cross-peaks between *N*-methylene protons and H-8 have been observed, which would not be possible in the case of N-3 derivatives due to a much greater spatial distance between the corresponding protons. A part of the NOESY spectrum of **8**, displaying the mentioned cross-peaks, is shown in Figure 3. On the other hand, it has to be mentioned that for N-7 substitution the C-H splitting patterns at C-2 and C-8 would be the same as for N-9 substitution and the

TABLE I

^{1}H NMR chemical shifts (δ/ppm)[a] and H-H coupling constants (*J*/Hz)[b] for compounds **1–4** (*c.f.* Scheme 2)

Compound		**1**[c]	**2**	**3**	**4**
H-2	δ	8.70(s,1H)	8.73(s,1H)	8.75(s,1H)	8.98(s,1H)
H-8	δ	8.60(s,1H)	8.57(s,1H)	8.69(s,1H)	8.80(s,1H)
H-2',5'	δ	8.32(2H)	8.30(2H)	8.30(2H)	8.28(2H)
	J	2.2(t)	2.3(t)	2.1(t)	2.4(t)
H-3',4'	δ	6.43(2H)	6.44(2H)	6.45(2H)	6.46(2H)
	J	2.2(t)	2.3(t)	2.1(t)	2.3(t)
H-1"	δ		4.35(2H)	4.69(2H)	7.44(1H)
	J		(q)	5.8(t)	16.0; 9.2(dd)
H-2"	δ				6.13(1H)
	J		3.82(2H)	4.16(2H)	16.0; 1.1(dd)
	δ		(t)	5.8(t)	5.31(1H)
	J				9.2; 1.1(dd)
OH	δ		5.05(1H)		
	J		5.0(t)		

[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.

[b] Digital resolution ±0.25 Hz.

[c] Signal of NH at 13.74 ppm.

cross-peaks between *N*-methylene protons and H-8 would exist in the NOESY spectra of N-7 as well. However, N-7 substitution was excluded here on the basis of the magnitude of one-bond C-H coupling at C-2, substituent induced ^{13}C chemical shifts and HETCOR spectra. Thus, in the N-7 substituted molecules, the one-bond C-H coupling at C-2 amounts to *ca.* 202 Hz, while in **1** and N-9 derivatives it is *ca.* 3–4 Hz greater,[12] as it is here (Tables III and IV). In N-7 molecules, the C-2 is significantly deshielded (even for *ca.* 7 ppm) in comparison with C-2 in the parent molecule **1** and in N-9 molecules.[12] This is not the case for the substituent induced ^{13}C chemical shift (SCS) at C-2 in compounds investigated here, which is together with other SCS typical of N-9 molecules. Besides, HETCOR spectra substantiated the assignment of H-2 to the lower field than H-8, which is again in agreement with N-9 but not N-7 substitution, since for the latter it is *vice versa*. The aromatic part of the HETCOR spectrum of **8** is displayed in Figure 4. The N-9 substitution of **6** was confirmed by X-ray analysis as well. This molecule consists of the two 6-(*N*-pyrrolyl)purine rings connected *via* N-9 (see discussion on X-ray data). The peculiar structure of **6** was also recognized in ^{1}H NMR spectra because of a different ratio of integrals of **6** as compared to that of **5**

TABLE II

^{1}H NMR chemical shifts (δ/ppm)[a] and H-H coupling constants (*J*/Hz)[b] for compounds **5–8** (*c.f.* Scheme 3)

Compound		**5**	**6**[c]	**7**	**8**
H-2	δ	8.72(s,1H)	8.71(s,2H)	8.64(s,1H)	8.67(s,1H)
H-8	δ	8.08(s,1H)	8.21(s,2H)	8.25(s,1H)	8.05(s,1H)
H-2',5'	δ	8.32(2H)	8.31(4H)	8.27(2H)	8.30(s,2H)
	J	2.4(t)	2.2(t)	2.1(t)	
H-3',4'	δ	6.44(2H)	6.43(4H)	6.38(2H)	6.43(s,2H)
	J	2.2(t)	2.1(t)	2.1(t)	
CH_2N	δ	4.49(2H)	4.35(4H)	4.44(2H) 3.67(4H) 3.15(2H)	4.38(2H) 2.54(4H) 2.45(2H)
	J	6.6(t)	6.6(t)	6.9(t) 6.9(q) 7.0(t)	6.7(t) 7.0(q) 6.7(t)
CH_2[d]	δ	2.49(2H) 3.37(2H)	2.63(2H)	3.82(2H) 3.50(2H) 2.18(2H)	2.09(2H)
	J	6.4(qn) 6.1(t)	6.5(qn)	7.0(t) 7.0(t) 6.9(qn)	6.7(qn)
CH_3	δ			1.20(6H)	0.99(6H)
	J			7.0(t)	7.0(t)

[a] $CDCl_3$ 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, qn = quintet.

[b] Digital resolution ±0.25 Hz.

[c] Structure of **6** was confirmed by X-ray analysis as well.

[d] Other CH_2 groups in the molecule.

TABLE III

^{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 compounds **1–4** (*c.f.* Scheme 2)

Compound		**1**	**2**	**3**	**4**
C-2	δ	152.03	151.62	151.63	151.43
	SCS		–0.41	–0.40	–0.60
	J	205.40	205.50	205.00	205.10
C-4	δ	146.59	146.42	146.45	146.73
	SCS		–0.17	–0.14	0.14
C-5	δ	121.18	121.32	121.11	121.73
	SCS		0.14	–0.09	0.55
C-6	δ	154.50	153.43	153.16	152.03
	SCS		–1.07	–1.34	–2.47
C-8	δ	144.34	146.36	145.66	146.83
	SCS		2.02	1.32	2.49
	J	212.80	214.10	215.10	215.30
C-2',5'	δ	120.35	120.18	120.04	120.86
	SCS		–0.17	–0.31	0.51
C-3',4'	δ	112.52	112.47	112.31	112.76
	SCS		–0.05	–0.21	0.24
C-1''	δ		46.32	42.55	126.75
C-2''	δ		59.07	45.09	105.31

[a] DMSO-d_6 solutions. Chemical shifts referred to TMS.

[b] SCS in **2–4** referred to **1**.

[c] *J*, digital resolution ±1.18 Hz. At C-2 doublet, while at C-8 doublet of triplets.

but also due to the existence of weak NOE between the H-2 of the one ring (A) and the H-8 of the other (B), *c.f.* Figure 5. The latter finding is in accord with molecular modelling,[19] which showed that the distance between the corresponding protons is 4.89 Å.

X-ray Crystal Structure Study

In order to determine the position of nitrogen substitution at the purine ring and the exact stereostructure of **6**, its X-ray structure analysis was undertaken. Bond lengths and angles of **6** are summarized in Table V. The perspective views with atom numbering and packing of molecules in the unit cell of **6** are displayed in Figures 5 and 6, respectively. The skeleton of **6** consists of two coplanar 6-(*N*-pyrrolyl)purine rings linked at N-9 positions

TABLE IV

^{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 compounds **5–8** (*c.f.* Scheme 3)

Compound		**5**	**6**	**7**	**8**
C-2	δ	152.12	152.33	151.74	152.02
	SCS	–0.09	–0.30	0.29	0.01
	J	206.30	205.80	206.30	206.50
C-4	δ	147.76	147.97	147.45	147.78
	SCS	1.17	1.38	0.86	1.19
C-5	δ	122.15	122.21	121.89	122.26
	SCS	0.97	1.03	0.71	1.08
C-6	δ	153.00	153.30	152.22	153.29
	SCS	–1.50	–1.20	–2.28	–1.21
C-8	δ	143.28	143.31	143.95	143.84
	SCS	–1.06	–1.03	–0.39	–0.50
	J	216.00	215.40	216.50	216.50
C-2',5'	δ	120.45	120.64	120.34	120.61
	SCS	0.10	0.29	–0.01	0.26
C-3',4'	δ	112.48	112.74	111.30	112.45
	SCS	–0.04	0.22	–1.22	–0.07
C-1"	δ	42.18	41.17	41.18	42.13
C-2"	δ	29.34	30.48	29.46	26.93
C-3"	δ	31.55		67.89	49.31
CH_2[d]	δ			65.15	
	δ			51.28	
	δ			47.54	46.44
CH_3	δ			8.57	11.14

[a] $CDCl_3$ solutions. Chemical shifts referred to TMS.

[b] SCS in **5–8** referred to **1**.

[c] *J*, digital resolution ±1.18 Hz. At C-2 doublet, while at C-8 doublet of triplets.

[d] Other CH_2 groups in the molecule.

with the 1,3-propylene aliphatic chain. It is seen that heteroaromatic moieties are *anti*-disposed relative to the plane defined by the bridging atoms C(1"1)-C(2)-C(1"2). The angles between the least-square (l.s.) planes **A** and **B** (*c.f.* Figure 5) and the plane defined by the bridging atoms C(1"1)-C(2)-C(1"2) amount to 86.7(4) and 86.1(4)°, respectively. It means that planes **A** and **B** are perpendicular with respect to the plane of the bridging atoms.

TABLE V

Bond lengths (Å) and angles (°) for **6**

N(11)-C(61)	1.360(9)	N(1'2)-C(62)	1.395(9)
N(11)-C(21)	1.329(9)	N(1'2)-C(2'2)	1.393(10)
C(21)-N(31)	1.313(9)	N(1'2)-C(5'2)	1.397(10)
N(31)-C(41)	1.338(9)	C(2'2)-C(3'2)	1.355(12)
C(41)-N(91)	1.361(10)	C(3'2)-C(4'2)	1.409(12)
C(41)-C(51)	1.403(11)	C(4'2)-C(5'2)	1.356(11)
C(51)-N(71)	1.390(10)	C(1"2)-N(92)	1.448(9)
C(51)-C(61)	1.375(11)	C(1"2)-C(2)	1.515(10)
C(61)-N(1'1)	1.395(10)	N(12)-C(22)	1.338(10)
N(71)-C(81)	1.316(10)	N(12)-C(62)	1.319(9)
C(81)-N(91)	1.352(10)	C(22)-N(32)	1.321(10)
N(91)-C(1"1)	1.467(10)	N(32)-C(42)	1.344(9)
N(1'1)-C(5'1)	1.365(10)	C(42)-C(52)	1.354(11)
N(1'1)-C(2'1)	1.384(10)	C(42)-N(92)	1.381(10)
C(2'1)-C(3'1)	1.348(11)	C(52)-N(72)	1.393(10)
C(3'1)-C(4'1)	1.403(11)	C(52)-C(62)	1.412(12)
C(4'1)-C(5'1)	1.334(11)	N(72)-C(82)	1.306(11)
C(1"1)-C(2)	1.521(9)	C(82)-N(92)	1.365(11)
C(61)-N(11)-C(21)	116.8(7)	C(62)-N(1'2)-C(5'2)	125.4(8)
N(31)-C(21)-N(11)	129.5(9)	C(2'2)-N(1'2)-C(5'2)	107.0(8)
C(21)-N(31)-C(41)	111.9(7)	C(3'2)-C(2'2)-N(1'2)	107.7(9)
N(91)-C(41)-N(31)	128.1(9)	C(2'2)-C(3'2)-C(4'2)	109.6(9)
N(91)-C(41)-C(51)	106.0(8)	C(5'2)-C(4'2)-C(3'2)	106.2(9)
N(31)-C(41)-C(51)	125.8(9)	C(4'2)-C(5'2)-N(1'2)	109.6(9)
N(71)-C(51)-C(61)	135.3(8)	N(92)-C(1"2)-C(2)	111.8(7)
N(71)-C(51)-C(41)	109.0(8)	C(22)-N(12)-C(62)	118.9(8)
C(61)-C(51)-C(41)	115.7(9)	N(12)-C(22)-N(32)	129.5(9)
N(11)-C(61)-C(51)	120.2(8)	C(42)-N(32)-C(22)	108.4(8)
N(11)-C(61)-N(1'1)	116.0(8)	N(32)-C(42)-C(52)	129.8(9)
C(51)-C(61)-N(1'1)	123.9(8)	N(32)-C(42)-N(92)	124.4(8)
C(81)-N(71)-C(51)	104.6(8)	C(52)-C(42)-N(92)	105.7(9)
N(71)-C(81)-N(91)	113.5(8)	C(42)-C(52)-N(72)	112.8(9)
C(41)-N(91)-C(81)	106.8(8)	C(42)-C(52)-C(62)	114.8(9)
C(41)-N(91)-C(1"1)	125.1(8)	N(72)-C(52)-C(62)	132.4(9)
C(81)-N(91)-C(1"1)	128.0(8)	N(12)-C(62)-N(1'2)	117.0(8)
C(5'1)-N(1'1)-C(61)	124.8(8)	N(12)-C(62)-C(52)	118.4(7)
C(5'1)-N(1'1)-C(2'1)	109.7(8)	N(1'2)-C(62)-C(52)	124.5(8)
C(61)-N(1'1)-C(2'1)	125.4(8)	C(82)-N(72)-C(52)	101.1(8)
C(3'1)-C(2'1)-N(1'1)	107.1(8)	N(72)-C(82)-N(92)	116.1(8)
C(2'1)-C(3'1)-C(4'1)	106.8(8)	C(82)-N(92)-C(42)	104.3(7)
C(5'1)-C(4'1)-C(3'1)	109.9(8)	C(82)-N(92)-C(1"2)	128.2(9)
C(4'1)-C(5'1)-N(1'1)	106.5(8)	C(42)-N(92)-C(1"2)	127.3(8)
N(91)-C(1"1)-C(2)	115.6(7)	C(1"1)-C(2)-C(1"2)	109.4(4)
C(62)-N(1'2)-C(2'2)	127.6(8)		

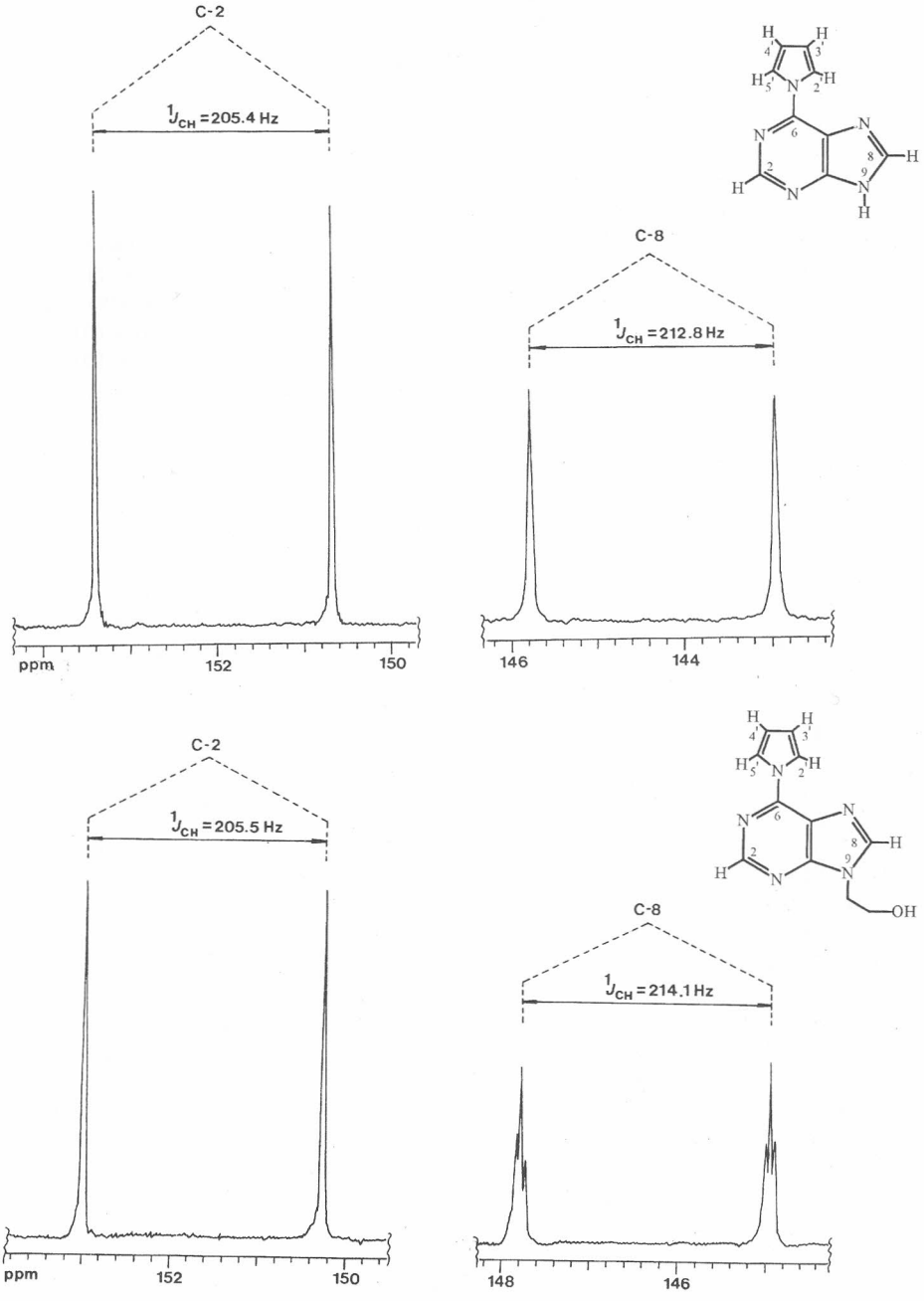


Figure 1. A part of the gated decoupled spectra of **1** (above) and **2** (below), displaying C-H coupling at C-2 and C-8. Additional triplet splitting at C-8 in **2** arises from the three-bond C-H coupling with the N-methylene protons of the acyclic side chain.

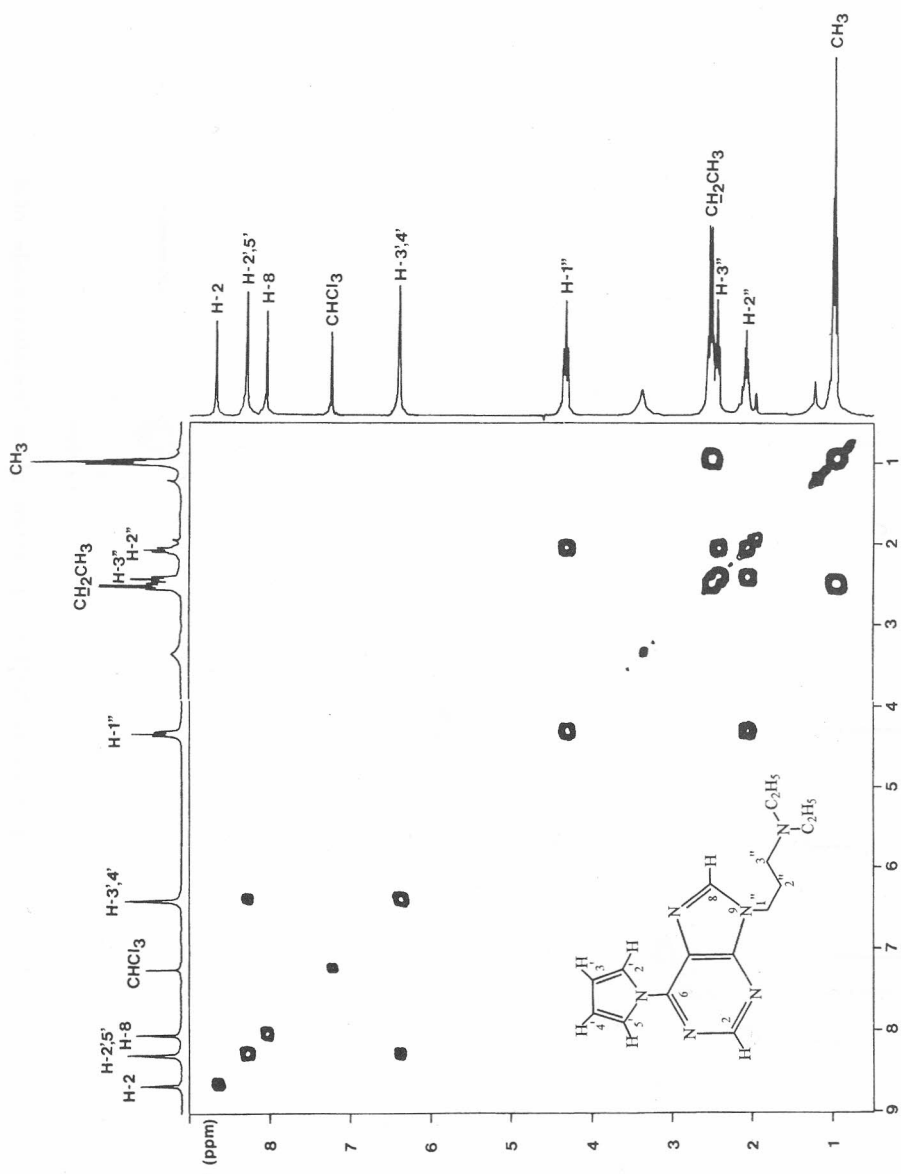


Figure 2. The COSY spectrum (magnitude mode) of 8.

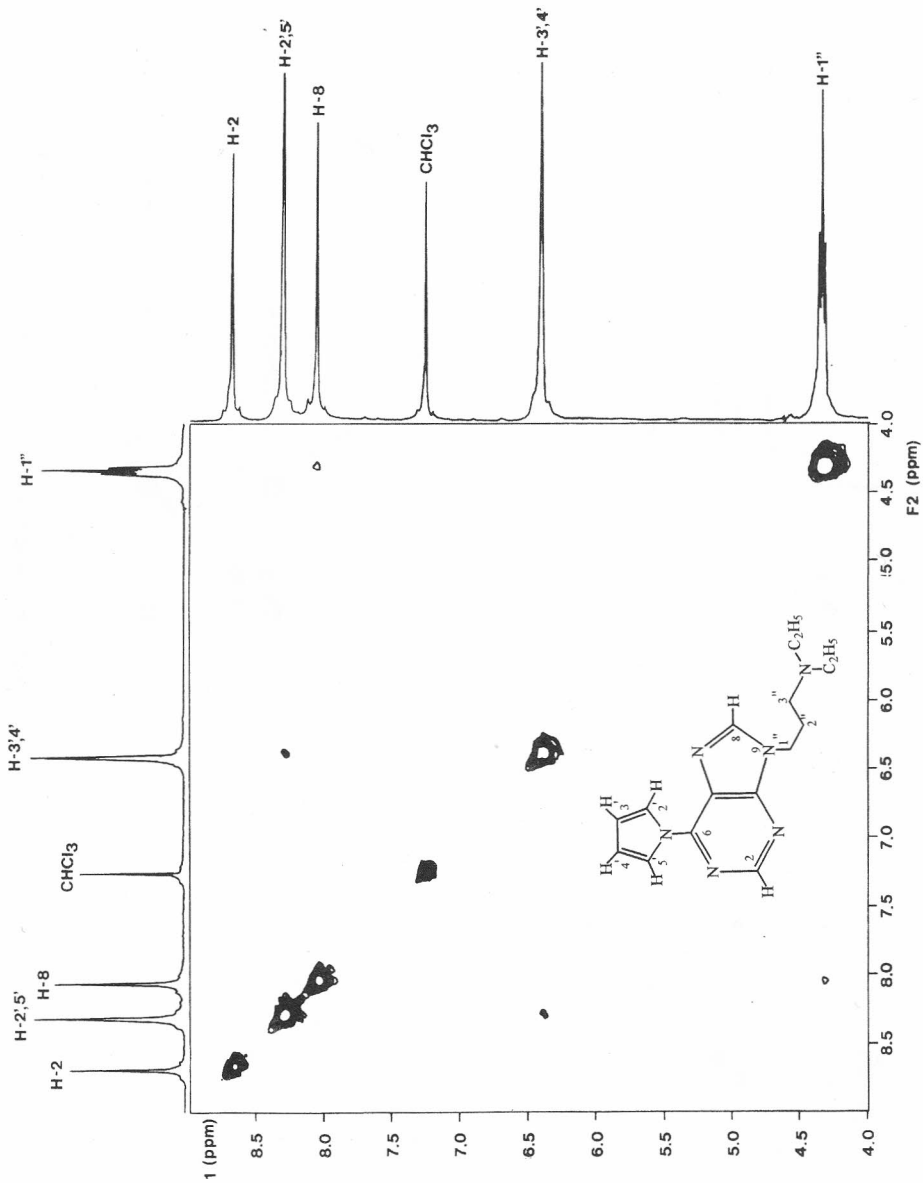


Figure 3. A part of the NOESY spectrum (phase sensitive mode) of 8.

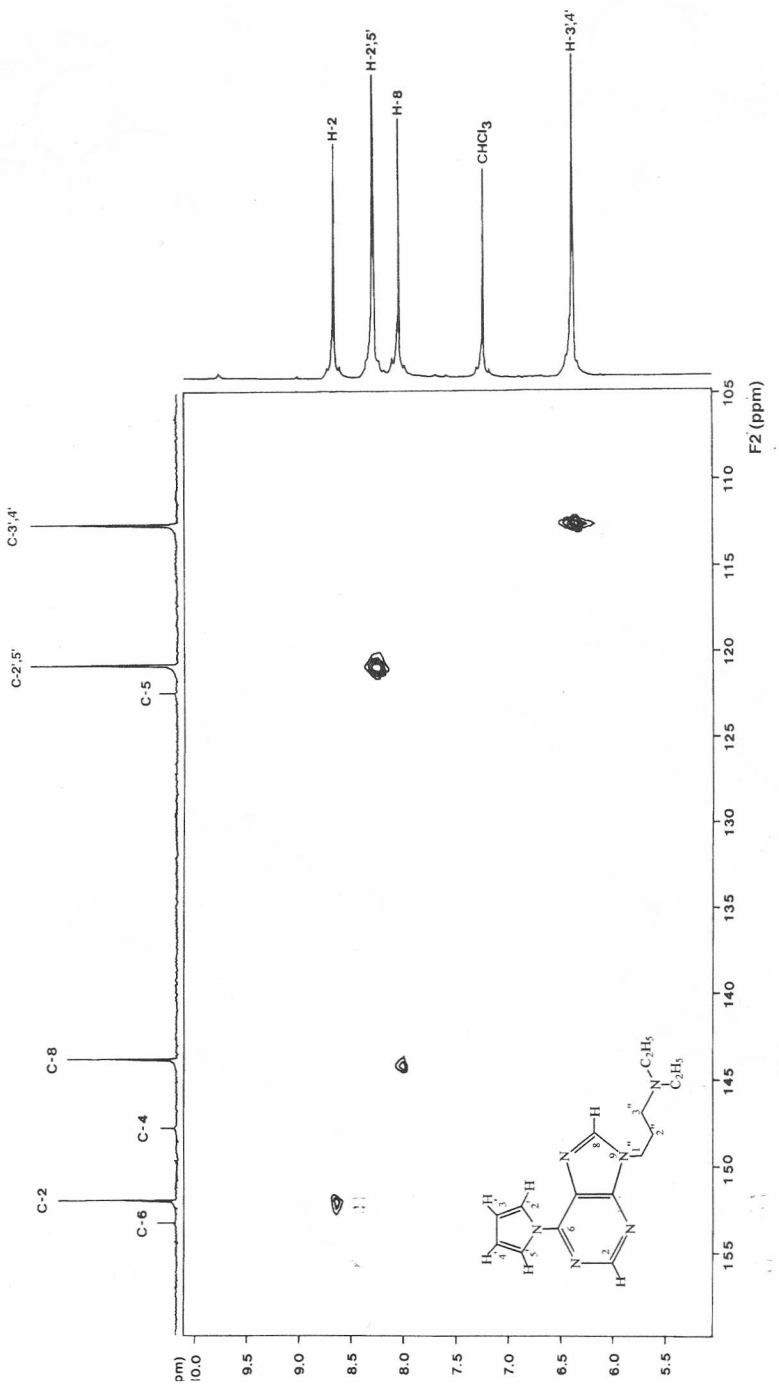


Figure 4. The aromatic part of the two-dimensional $^{1}H/^{13}C$ heteronuclear correlation (HETCOR) spectrum of **8**.

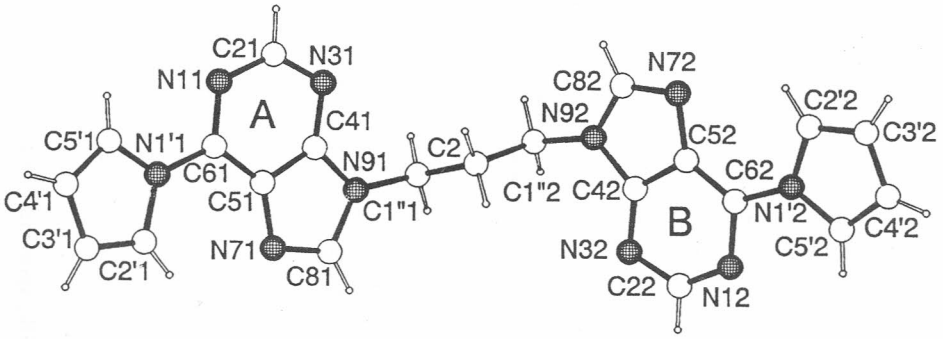


Figure 5. Perspective view with atom numbering for **6**.

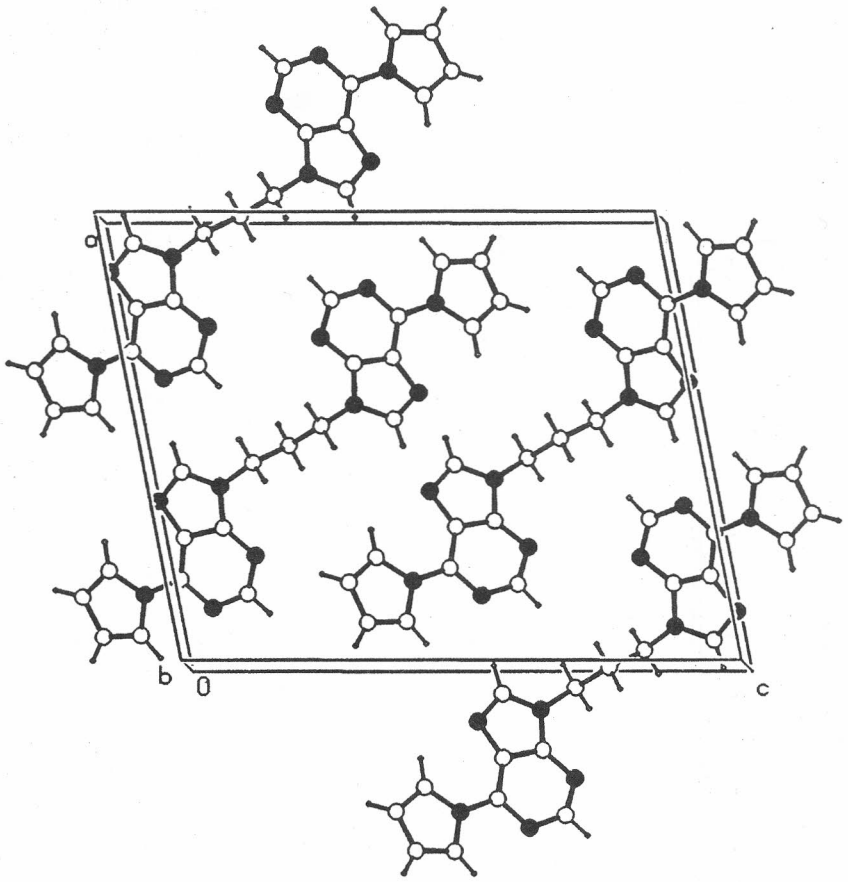


Figure 6. Packing diagram in the unit cell of **6**.

The angle between the l.s. planes **A** and **B** amounts to 58.8(1)°. This means that these heterocyclic rings are not centrosymmetric relative to the central aliphatic bridge. In addition to that, torsional angles N(91)-C(1"1)-C(2)-C(1"2) and C(1"1)-C(2)-C(1"2)-N(92) amount to 174.6(7) and 173.7(7)°, respectively. These findings indicate also the unsymmetrical feature of the molecule. The observed values for bond lengths and angles of purine rings are in agreement with those found in the related 9-methyladenine[20] and purine itself.[21]

Conclusions: ^{1}H and ^{13}C NMR chemical shifts, substituent induced chemical shifts and one-bond C-H couplings have proved to be useful in determination of the N-9 substitution. This was substantiated by the connectivities in NOESY and HETCOR spectra. Conformational X-ray structural analysis showed that the two 6-(*N*-pyrrolyl)purine rings of **6** are *anti*-disposed and not centrosymmetric with respect to the central aliphatic bridge.

EXPERIMENTAL

Melting points (uncorrected) of **1–6** were determined on a Kofler micro hot-stage (Reichert, Wien). Pre-coated Merck silica gel 60F-254 plates were used for qualitative and preparative 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; the 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 = CH_2Cl_2-MeOH (18 : 1); S_4 = CH_2Cl_2-MeOH (10 : 1); DMF was dried by keeping it over type-4 Å molecular sieves with occasional shaking. UV spectra were recorded in absolute MeOH at 23 °C on a Hitachi Perkin-Elmer 124 spectrophotometer. The electron impact mass spectra were recorded on the EXTREL FT MS 2001 instrument. The ^{1}H and ^{13}C NMR spectra of **1–8** were recorded on a JEOL FX-90Q and on a Varian Gemini 300 spectrometers, operating at 22.05 and 75.46 MHz for the ^{13}C nucleus, respectively. The samples were measured from DMSO-d_6 and $CDCl_3$ solutions at 21 °C in 5 mm NMR tubes. Chemical shifts, in ppm, were referred to TMS. Digital resolution in ^{1}H NMR spectra was 0.25 Hz while in ^{13}C NMR spectra it was 1.18 Hz per point. The following techniques were used: broadband proton decoupling, gated decoupling, APT, COSY, NOESY and HETCOR. COSY spectra were obtained in magnitude mode, while NOESY spectra in phase-sensitive mode. For both COSY and NOESY 1024 points in F2 dimension and 256 increments in F1 dimension, the latter was subsequently zero-filled to 1024 points. Increments were obtained with 16 scans each, using 4500 Hz spectral width and a relaxation delay of 1 s. The resolution was 8.8 Hz/point and 17.8Hz/point in F2 and F1 dimensions, respectively. NOESY spectra were measured at several mixing times (0.45–0.60 s). HETCOR spectra were measured with 2048 points in F2 dimension and 256 increments in F1 dimension, which were zero-filled to 512 points. Increments were obtained using 128 scans, with a relaxation delay of 1 s and a spectral width of 19000 Hz in F2 and 4500 Hz in F1 dimensions, respectively. The resulting resolution was 18.6 Hz/point in F2 and 17.6 Hz/point in F1 dimension, re-

spectively. All two-dimensional experiments were performed by standard pulse sequences, with proton decoupling by Waltz-16 modulation.

*9-(2-Hydroxyethyl)-6-(N-pyrrolyl)purine (**2**)*

A solution containing **1** (2.10 g, 0.011 mol), ethylene carbonate (1.00 g, 0.011 mol) and pulverized sodium hydroxide (20 mg) in dry DMF (40 ml) was heated under reflux for 2 hours. The main part of the solvent was removed by evaporation under reduced pressure. The residual DMF was removed by codistillation *in vacuo* with ethanol and acetone. The crude solidified residue was dried overnight in a *vacuum* desiccator and purified by column chromatography (S_1). Recrystallization of the separated solidified product from water gave colourless crystals of **2**: yield 45%, m.p. 123–124 °C; MS (15 eV) *m/z* (rel. intensity): 230(10), 229(78), 199(45), 198(47), 186(17), 185(100), 159(10), 158(23), 131(31) and 104(10); found M^+ 229.094407; calcd. for $C_{11}H_{11}N_5O$: 229.095811; UV: λ_{max} (log ε) 294 (4.07) and 285 (4.09).

Anal. Calcd. for $C_{11}H_{11}N_5O$ (229.24): C 57.63, H 4.84, N 30.55; found: C 57.35, H 4.72, N 30.80%.

*9-(2-Chloroethyl)-6-(N-pyrrolyl)purine (**3**)*

A stirred mixture of **2** (0.92 g, 0.004 mol) and thionyl chloride (0.8 mL, 0.011mol) in dioxane (50 mL) containing catalytic amount of pyridine was heated under reflux for 30–40 min. After evaporation of the solvent and excess thionyl chlorideunder reduced pressure, an oily residue was formed. Recrystallization of this crude product from ethanol-water (1:1) gave colourless crystals of **3**: yield 46%, m.p. 98–101 °C; MS (20 eV): 249 (11), 247 (38), 186 (7), 185 (100), 159 (6), 158 (51), 131 (28), 104 (14), 77 (5) and 50 (6); found M^+ 247.055519 calcd. for $C_{11}H_{10}N_5Cl$ 247.061927. UV: λ_{max} (log ε): 296 (4.44) and 286 (4.45).

Anal. Calcd. for $C_{11}H_{10}N_5Cl$ (247.69): C 53.34, H 4.07, N 28.28; found: C 53.20, H 3.96, N 28.48%.

*9-Vinyl-6-(N-pyrrolyl)purine (**4**)*

The procedure essentially follows that reported for 9-vinyladenine,[13] substituting 9-(2'-chloroethyl)adenine with the appropriate 6-(N-pyrrolyl)purine derivative **3**. The isolation procedure was modified as follows: a crude oily product (0.30 g) obtained after removal of water from the neutralized water solution was purified by column chromatography (S_2). Recrystallization of the separated crystalline product from ethanol-water (1:1) gave colourless crystals of **4:** yield 24%; m.p. 109–112 °C; MS (70 eV) 212 (8) 211 (100), 185 (6), 184 (12) and 158 (6); found M^+ 211.083116 calcd. for $C_{11}H_9N_5$ 211.085246; UV: λ_{max} (log ε) 298, sh (6.80) and 287 (6.78).

Anal. Calcd. for $C_{11}H_9N_5$ (211.23): C 62.55, H 4.29, N 33.16; found: C 62.33, H 4.17, N 33.07%.

*9-(3-Bromopropyl)-6-(N-pyrrolyl)purine (**5**) and*
*1,3-bis-6-(N-pyrrolyl)purin-9-ylpropane (**6**)*

A solution containing **1** (1.38 g, 0.007 mol) and sodium hydride, 55%, (0.35 g 0.008 mol) in dry DMF (30 mL) was stirred under nitrogen at room temperature for 1 hour. 1,3-Dibromopropane (1 mL, 0.007 mol) was then added and stirring was con-

tinued for 48 hours. The solvent was evaporated and the remaining DMF was removed by codistillation with acetone. An oily residue was purified by column chromatography (S_2) to give crystalline products of **5**: yield 14%, m.p. 181–183 °C; MS *m/z* (rel. intensity): 305 (7), 225 (23), 224 (25), 212 (38), 199 (27), 198 (59), 95 (100), 81 (90) and 61 (83); found M^+ 305.038453 calcd. for $C_{12}H_{12}N_5Br$ 305.027057; UV: λ_{max} (log ε) 298 (6.92) and 289 (6.90).

Anal. Calcd. for $C_{12}H_{12}N_5Br$ (306.17): C 47.08, H 3.95, N 22.87; found: C 46.94, H 3.82, N 22.90%.

and **6**: yield 21%, m.p. 170–173 °C; UV $_{max}$ (log) 298 (6.88) and 288 (6.86).

Anal. Calcd. for $C_{21}H_{18}N_{10}$ (410.44): C 61.45, H 4.42, N 34.13; found: C 61.42, H 4.29, N 34.15%.

*9-3-(2-Diethylaminoethoxy)propyl-6-(*N*-pyrrolyl) purine (**7**)*

To a stirred solution of 2-diethylaminoethanol[15] (1.5 mL, 0.01 mol) in THF (30 mL), small pieces of sodium (0.03 g, 0.0013 gatom) were added and the mixture was boiled under reflux for 2 hours. Compound **5** (0.38 g, 0.0013 mol) was then added and sodium bromide gradually separated. After cooling, further pieces of sodium (0.03 g, 0.0013 gatom) were added, the reaction mixture was warmed until all the sodium had reacted and a further quantity of **5** (0.38 g, 0.0013 mol) was added. Boiling under reflux was continued for 24 hours. The precipitated sodium bromide was filtered off and the solvent evaporated. The crude product was purified by double column chromatography (S_3), providing a slightly yellowish oil of **7**: yield 36%, UV λ_{max} (log ε) 287 (6.90) and 297 (6.92).

*Anal.*Calcd. for $C_{18}H_{26}N_6O$(342.44): C 63.13, H 7.65, N 24.54; found: C 63.11, H 7.54, N 24.57%.

*9-(3-Diethylaminopropyl)-6-(*N*-pyrrolyl)purine (**8**)*

A mixture containing **5** (0.61 g, 0.002 mol) and diethylamine (13.23 mL, 0.128 mol) in EtOH (10 mL) was heated in a sealed ampule at 100 °C for 90 min. After being cooled to 0 °C, the ampule was opened and the reaction mixture was extracted twice with ether (100 mL). The organic phases were washed with water (3 × 100 mL), dried over asuhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the oily residue by double column chromatography (S_4) gave a colourless oil of **8**: yield 50%. Final purification was effected by preparative thin layer chromatography (S_4). Trituration of the oily residue thus obtained with acetone gave slightly yellowish crystals, m. p. 148–150 °C which were used for spectroscopic measurements. UV λ_{max} (log ε) 288 (6.56) and 297 (6.58).

Anal. Calcd. for $C_{16}H_{22}N_6$ (298.39): C 64.39, H 7.44, N 28.18; found: C 64.13, H 7.31, N 27.92%.

X-ray Crystal Structure Study

A single crystal of **6**, suitable for X-ray structure analysis, was prepared by growth under slow evaporation at room temperature of a dilute solution of EtOAc : EtOH (1 : 10) . A colourless crystal, dimensions 0.30 × 0.45 × 0.55 mm, was mounted on a Philips PW 1100 diffractometer upgraded by Stoe; data were collected in the

$\Theta - 2\Theta$ scan mode ($3 - \Theta - 63.5°$), graphite-monochromated Cu K_α radiation; lattice parameters from least-squares refinement of 20 reflections ($15.62 - 2\Theta - 52.50°$); monitored reflections (–6,2,0; –4,0,2 and –3,–1,4) showed only statistical variations of intensities; 3221 independent reflections were measured (h = –16,16; k = 0,9; l = 0,20), 1038 ≥ $2\sigma(I)$; Lorentz-polarization corrections were applied; the structure was solved by direct methods, the full matric least-squares refinement, H atoms were generated and allowed to ride at fixed distances from the attached atoms, isotropic thermal parameters were refined for two groupings of H atoms; R = 0.080 and

TABLE VI

Atomic coordinates (× 10^4) and equivalent isotropic parameters (Å^2 × 10^3) for **6**

Atom	x	y	z	U_{eq}*
N(11)	8585(5)	–86(11)	9428(3)	68(3)
C(21)	8286(6)	–851(11)	8757(4)	65(3)
N(31)	7454(5)	–1532(10)	8480(3)	59(2)
C(41)	6835(7)	–1323(12)	8953(5)	55(3)
C(51)	7032(6)	–543(11)	9679(4)	47(2)
C(61)	7941(6)	79(12)	9900(4)	50(3)
N(71)	6219(5)	–599(11)	10004(4)	63(2)
C(81)	5582(6)	–1384(12)	9490(5)	70(3)
N(91)	5921(5)	–1889(10)	8863(4)	60(2)
N(1'1)	8264(5)	912(10)	10596(4)	53(2)
C(2'1)	7720(7)	1259(11)	11147(5)	63(3)
C(3'1)	8285(6)	2102(13)	11721(4)	68(3)
C(4'1)	9165(6)	2335(11)	11493(4)	63(3)
C(5'1)	9153(6)	1588(11)	10815(5)	60(3)
C(1"1)	5411(6)	–2797(11)	8185(4)	68(3)
N(1'2)	1736(5)	928(10)	4421(4)	54(2)
C(2'2)	2251(7)	1277(12)	3845(5)	67(3)
C(3'2)	1675(7)	2159(13)	3287(5)	75(3)
C(4'2)	773(7)	2366(14)	3488(5)	80(4)
C(5'2)	825(6)	1601(12)	4180(4)	60(3)
C(1"2)	4576(6)	–2831(12)	6821(5)	73(3)
N(12)	1438(4)	–84(10)	5580(4)	58(2)
C(22)	1711(6)	–897(14)	6248(4)	78(4)
N(32)	2551(5)	–1539(11)	6553(4)	67(3)
C(42)	3135(6)	–1351(11)	6046(5)	52(3)
C(52)	2978(6)	–585(12)	5349(5)	53(3)
C(62)	2051(6)	80(12)	5114(4)	55(3)
N(72)	3777(5)	–597(11)	5003(4)	68(3)
C(82)	4389(6)	–1403(12)	5520(5)	72(3)
N(92)	4074(5)	–1872(10)	6172(4)	60(2)
C(2)	4993(7)	–1713(6)	7495(5)	64(1)

* $U_{eq} = 1/3\ \Sigma_i\ \Sigma_j\ U_{ij} a_i^* a_j^* \mathbf{a}_i \mathbf{a}_j$

R_ω = 0.207 for 282 parameters and 1038 reflections, $\omega = 1/[\sigma^2(F^2) + 0.1000(P)^2 + 0.0000P]$, $P = \max 1/3\ (F_o^2 + 2F_c^2)$; $(\Delta/\sigma)_{max} = 0.051$; largest peaks in the final difference map: +0.45 and –0.43 eÅ^{-3}. All calculations were performed using the SHELXS-86[22] and SHELXL-93[23] on a IBM PC/AT compatible microcomputer. Atomic coordinates with equivalent isotropic thermal parameters and bond distances with bond angles are given in Table VI. Crystal data for $C_{21}H_{18}N_{10}$: space group $P2_1/n$ with a = 14.277(4), b = 7.971(3), c = 17.662(5) Å, β = 101.00(4)°, V = 1793.0(11) Å^3, Z = 4, d_{calc} = 1.382 gcm^{-3} and μ(Cu Kα) = 0.736 cm^{-1}.

Additional X-ray crystallographic data, *i.e.* full tables of anisotropic thermal parameters, hydrogen atomic coordinates with isotropic thermal parameters, as well as the observed and calculated structure factors (11 pages) are given as deposit.

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REFERENCES

1. H. Vanderhaeghe, P. Herdewijn, and E. De Clercq in: *A Textbook of Drug Design and Development,* P. Krogsgaard-Larsen and H. Bundgaard (Eds.), Harwood Academic Publishers, Chur 1994, p. 577.
2. J. P. H. Verheyden in: *Chronicles of Drug Discovery* **3**, D. Lednicer(Ed.), American Chemical Society, Washington (1993) p. 299.
3. C. K. Chu and S. J. Cutler, *J. Heterocyclic Chem.* **23** (1986) 289.
4. M. Hoffman, *Science* **252** (1991) 372.
5. R. F. Schinazi, J. R. Mead, and P. M. Feorino, *Aids Res. Human Retrovirus* **8** (1992) 963.
6. E. De Clercq and J. Balzarini in: *Design of anti AIDS Drugs*, E. De Clercq (Ed.), Elsevier, Amsterdam 1990, p. 175.
7. M. Nast, C. Litterst, and J. Mc Gowan, *Antiviral Res.* **14** (1990) 125.
8. A. Barnett and M. J. Green in: *Cronicles of Drug Discovery* **3**, D. Lednicer (Ed.), American Chemical Society, Washington 1993, p. 83.
9. J. Bradshow in:. *Chronicles of Drug Discovery*, **3** (Ed. D. Lednicer), American Chemical Society, Washington 1993, p. 45.
10. T. Högberg and U. Norinder in: *A Textbook of Drug Design and Development,* P. Krogsgaard-Larsen and H. Bundgaard (Eds.), Harwood Academic Publishers, Chur 1994, p. 56.
11. K. Bajrović, Z. Kniewald, and J. Vorkapić-Furač, *Pharmazie* **48** (1993) 787, and references cited therein.
12. S. Raić, M. Pongračić, J. Vorkapić-Furač, D. Vikić-Topić, A. Hergold-Brundić, A. Nagl, and M. Mintas, *Nucleosides & Nucleotides* **15** (1996) 937.
13. N. Ueda, K. Kondo, M. Kono, K. Takemoto, and M. Imoto, *Macromol. Chem.* **120** (1968) 13.
14. I. Gryczynski, A. Kawski, S. Paszyc, M. Rafalska, and B. Skalski, *Bull. Acad. Polon. Sci. Ser. Sci. Phys. Astronom.* **27**(1979) 271.
15. *Org. Syntheses*, Coll. Vol. *2* (1950) 183.

16. J. R. Hardcastle, M. G. Rowlands, J. Houghton, J. B. Parr, G. A. Potter, and M. Jarman, *J. Med. Chem.* **38** (1995) 241.
17. M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, *J. Amer. Chem. Soc.* **97** (1975) 4627.
18. G. Jähne, H.Kroha, A. Müller, M. Helsberg, I. Winkler, G. Gross, and T. Scholl, *Angew. Chem. Int. Ed. Engl.* **33** (1994) 562.
19. Computational results obtained using software programs Discover/InsightII from Biosym. Technologies of San Diego, CA, U.S.A.
20. T. J. Kistenmacher and M. Rossi, *Acta Cryst.* **B 33** (1977) 253.
21. D. G. Watson, R. M. Sweet, and R. E. Marsh, *ibid.*, **19**, (1965)573.
22. G. M. Sheldrick, *SHELXS86. Program for the Automatic Solution of Crystal Structures,* University of Göttingen, Federal Republic of Germany, 1986.
23. G. M. Sheldrick, *SHELXL93. Program for the Automatic Solution of Crystal Structures,* University of Göttingen, Federal Republic of Germany, 1993.

SAŽETAK

Novi aciklički analozi purinskih nukleozida koji sadržavaju egzocikličku pirolnu jezgru: sintetsko, NMR i rentgensko strukturno istraživanje

Silvana Raić, Mario Pongračić, Jasna Vorkapić-Furač, Dražen Vikić-Topić, Antonija Hergold-Brundić, Ante Nagl i Mladen Mintas

Opisana je sinteza novih nukleozidnih analoga 6-(*N*-pirolil)purina koji sadržavaju acikličke lance pripojene na purinsku jezgru u položaju N-9. Strukture su određene spektroskopijom ^{1}H i ^{13}C NMR na temelju kemijskih pomaka, pomaka induciranih supstituentima, konstanata sprege C-H i povezanosti u spektrima COSY, NOESY i HETCOR. Nedvojbeni dokaz za stereostrukturu spoja **6** dobiven je rentgenskom strukturnom analizom. Geometrijski podaci iz te analize pokazuju da su dva 6-(*N*-pirolil)purinska prstena, koji sačinjavaju kostur spoja **6**, međusobno u *anti*-položaju, ali ne i centrosimetrični u odnosu na središnji alifatski most.