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SYNTHESIS AND STRUCTURE OF 6-SUBSTITUTED 9-(2-ETHOXY-1,3-DIOXAN-5-YL)PURINES

A. F. Mishnev, Ya. Ya. Bleidelis, É. É. Liepin'sh, N. P. Ramzaeva, and I. N. Goncharova

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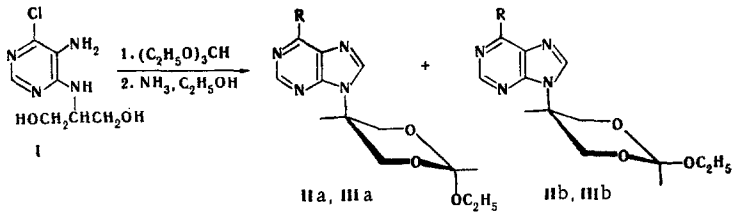
The reaction of 4-chloro-5-amino-6-(1,3-dihydroxy-2-propyl)aminopyrimidine with excess ethyl orthoformate gave a cyclic acetal, viz., 6-chloro-9-(2-ethoxy-1,3-dioxan-5-yl)purine, amination of which yielded 6-amino-9-(2-ethoxy-1,3-dioxan-5-yl)purine. The presence of two configurational isomers with a diaxial orientation of the purine ring and the ethoxy group in the trans isomer and an equatorial orientation of the ethoxy group in the cis isomer was established for these compounds by ^1H and ^{13}C NMR and IR spectroscopy. The three-dimensional structure of trans-6-chloro-9-(2-ethoxy-1,3-dioxan-5-yl)purine was determined by an x-ray difraction study, and the trans-diaxial orientation of the purine ring and the ethoxy group was confirmed; it is shown that the dioxane ring is in an anti conformation relative to the purine ring.

It has been previously shown [1, 2] that an imidazole ring is formed in the reaction of 4-chloro-5-amino-6-(1,3-dihydroxy-2-propylamino)pyrimidine (I) with ethyl orthoformate under acid catalysis conditions. However, under the same conditions, I, which contains a 1,3-dihydroxypropyl residue, undergoes transesterification with excess orthoester to give a cyclic derivative, viz., 6-chloro-9-(2-ethoxy-1,3-dioxan-5-yl)purine (II), the reaction of which with an alcohol solution of ammonia gave 6-amino-9-(2-ethoxy-1,3-dioxan-5-yl)purine (III).



II R=Cl; III R=NH_2

The interest in II and III, which contain a saturated six-membered heteroring in the 9 position of the purine ring, is due to the fact that, with respect to their biochemical properties, they may be classified as analogs of nucleosides, since some derivatives of this type are capable of forming complexes with enzymes that use natural nucleosides as substrates [3, 4] and display high physiological activity, including antitumorigenic activity [5]. In addition II and III also proved to be of interest in a stereochemical respect.

It is known that a chair conformation with an axial orientation of the alkoxy group (the anomeric effect) is preferred for 2-alkoxy-1,3-dioxane molecules [6]. At the same time, depending on the nature of the

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TABLE 1. Characteristics of the Compounds Obtained

Compound	Isomer	R	mp, °C	R_f	IR spectrum, ν, cm^{-1}	UV spectrum λ_{max}, nm	UV spectrum ε	Found, % C	Found, % H	Found, % N	Empirical formula	Calc., % C	Calc., % H	Calc., % N
IIa	trans	Cl	144—145	0,90	683	205	14300	46,1	4,6	19,5	$C_{11}H_{13}ClN_4O_3$	46,4	4,6	19,7
IIb	cis	Cl	139—140	0,83	700	205	13100	46,1	4,5	19,6	$C_{11}H_{13}ClN_4O_3$	46,4	4,6	19,7
IIIa	trans	NH_2	214—215	0,56	682	215	12500	49,3	5,6	26,3	$C_{11}H_{16}N_5O_3$	49,8	5,7	26,4
IIIb	cis	NH_2	163—164	0,38	690	215	8900	49,4	5,6	26,4	$C_{11}H_{15}N_5O_3$	49,8	5,7	26,4

heteroring, either the preferred axial orientation [e.g., in 9-(1,4-oxathian-3-yl)purine] or an equatorial orientation of the purine ring [for example, in 9-(tetrahydro-2-pyranyl)purine] is possible for 9-purinyl derivatives of saturated six-membered heterocycles [7].

On the basis of the difference in the chemical shifts and the integral curve in the PMR spectrum of 6-chloropurine II in chloroform we have shown that the compound contains two stereoisomers in a ratio of 60:40. An analysis of the PMR spectrum of III showed that it is also a mixture of two isomers in the same ratio. It should be noted that the stereoisomeric pairs of acetals II and III proved to be chromatographically homogeneous in various systems [paper chromatography and thin-layer chromatography (TLC)], and we were able to detect isomers of II and III only on Silufol in a chloroform–ethanol system. Repeated recrystallization and separation with a column filled with silical gel made it possible at best to obtain only substances containing 90-95% of the principal stereoisomer. The complete separation of the isomers (Table 1) was accomplished on preparative TLC plates on silica gel with monitoring of the degree of purity of the individual isomers on analytical TLC plates.

We will show below that data from an x-ray diffraction analysis of the high-melting isomers of 6-chloropurine IIa and 6-aminopurine IIIa [8] demonstrated unambiguously that the purine residue in the 5 position of the dioxane ring is axially oriented.

It is apparent from an analysis of the PMR spectra of isomers IIa,b and IIIa,b (Fig. 1 and Table 2) that the position of the resonance signals of the protons of the purine ring are actually unchanged for the two isomers. The close values of the constants of spin–spin coupling of the H_5, proton with the methylene protons in the 4 and 6 positions of the dioxane residue make it possible to speak of the identical character of the conformation of the steric center in the 5 position for both stereoisomers and, further, to draw the conclusion that the purine residue in the 5 position of the dioxane ring is axially oriented in both the high-melting and low-melting isomers.

On the basis of the significant nonequivalence of the methylene protons in the 4 and 6 positions of the dioxane ring and the spin–spin coupling constants (SSCC) of the geminal protons it may be concluded that the high-melting isomers exist in the chair conformation [9, 10]. Additional multiplicity (J = 0.4 Hz) due to long-range spin–spin coupling of this proton with the equatorial protons of the methylene groups is observed for the 2'-H proton, which resonates at 5.64 ppm; this confirms the equatorial character of this proton, and consequently, the axial orientation of the 2-ethoxy group, i.e., high-melting isomers IIa and IIIa have a trans configuration. The 6 ppm shift to strong field of the $C_{4'}$ and $C_{6'}$ resonance signals in the ^{13}C NMR spectrum of high-melting isomer IIIa as compared with low-melting isomer IIb also provides evidence for an axial orientation of the ethoxy group in IIIa [11].

In contrast to the spectra of IIa and IIIa, additional multiplicity due to long-range spin–spin couplings of the 2'-H proton with the equatorial protons of the methylene groups in the 4 and 6 positions of the dioxane ring is completely absent in the PMR spectra of low-melting isomers IIb and IIIb, and this constitutes evidence

TABLE 2. PMR Spectra of Dioxanylpurines II and III

Compound	Isomer	Chemical shifts, δ, rpm 2-H	8-H	NH_2	5'-H	H_A	H_B	2'-H	OCH_2	CH_3	5' A	5' B	AB	2' B	CH_2CH_3
II a	trans	8,69	8,78	—	4,78	3,91	4,72	5,64	3,68	1,31	1,8	1,8	10,5	0,4	6,9
II b	cis	8,69	8,77	—	4,74	4,36	4,36	5,46	3,83	1,27	2,2	2,2	—	0	6,9
IIIa	trans	8,29	8,45	5,9	4,61	3,90	4,67	5,61	3,66	1,30	1,9	2,0	10,5	0,4	6,8
IIIb	cis	8,30	8,43	5,8	4,64	4,32	4,32	5,43	3,82	1,27	2,5	2,5	—	0	6,9

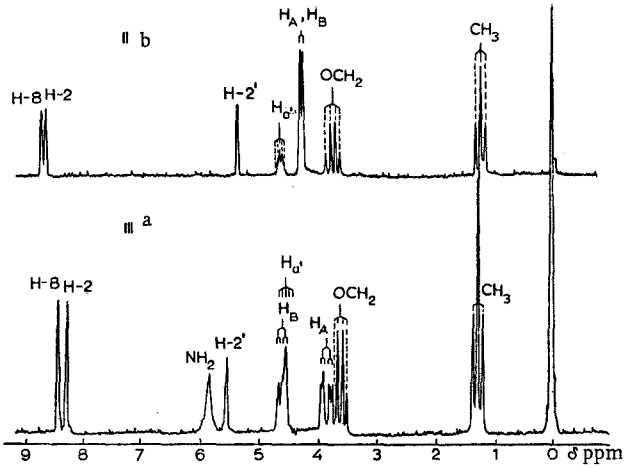

Fig. 1. PMR spectra of cis-6-chloro-9-(2-ethoxy-1,3-dioxan-5-yl)purine (IIb) and trans-6-amino-9-(2-ethoxy-1,3-dioxan-5-yl)purine (IIIa).

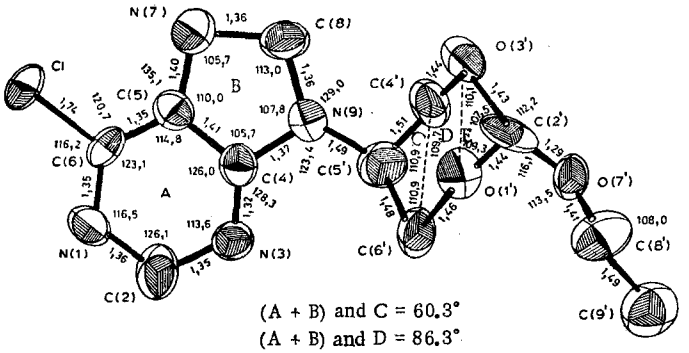

Fig. 2. Projection of the molecule on the average plane of the purine two-ring system, bond lengths, valence angles, and the most important dihedral angles of the trans isomer of 6-chloro-9-(2-ethoxy-1,3-dioxan-5-yl)purine (IIa).

for an axial orientation of the 2'-H proton and, correspondingly, for equatorial character of the ethoxy group, i.e., low-melting stereoisomers IIb and IIIb have a cis configuration. However, the signals of the 4- and 6-H protons resonate at 4.36 (IIb) and 4.32 ppm (IIIb) in the form of a doublet with $J_{5'A} = J_{5'B} = 2.2$ Hz and $J_{5'A} = J_{5'B} = 2.5$ Hz, respectively; this is explained by degeneracy of the AA'BB'X spin system to an A_4X system as a consequence of this magnetic-anisotropic effect of the surrounding atoms on the shielding constants, which makes the H_A and H_B protons equivalent. A similar peculiarity in the spectra was observed in the case of cis isomers and dioxanes and dithianes with a branched alkyl substituent in the 5(*a*) position [9, 10]. In this case the authors assume that there is distortion of the "ideal" chair conformation in the $C_4-C_5-C_6$ region. In conformity with the information stated above, we will also assume a chair conformation for the cis form. However, taking into account the fact that the low-temperature PMR spectra recorded for isomers IIb and IIIb in deuteroacetone at −80°C indicate that they have high conformational lability, we hope to subsequently refine the structures of isomers IIb and IIIb by means of x-ray diffraction analysis.

It was shown by PMR spectroscopy that the spectra of the stereoisomeric pairs of II and III recorded in deuterochloroform remained unchanged after definite intervals, and this confirms their configurational stability under these conditions [12]. We were unable to detect isomerization even in the case of initiation of the process by the addition of iodine in deuteromethanol to a solution of II in deuterochloroform. However, judging from the PMR spectrum, the compound underwent more profound transformations in this case.

TABLE 3. Equations of the Average Planes of the Planar Fragments of the Molecule and Deviations of the Atoms from Them

Plane	Atoms of the plane	Deviations from the atoms from the plane, A	Equation of the plane: Ax + By + Cz − D = O			
			A	B	C	D
A	N (1)	−0,004	−0,1234	−0,6587	−0,7422	−6,3698
	C (2)	−0,002				
	N (3)	0,004				
	C (4)	−0,002				
	C (5)	−0,004				
	C (6)	0,007				
B	C (4)	−0,005	−0,1161	−0,6389	−0,7605	−6,4291
	C (5)	0,003				
	N (7)	0,000				
	C (8)	−0,003				
	N (9)	0,005				
(A+B)	N (1)	0,007	−0,1208	−0,6505	−0,7498	−6,3767
	C (2)	0,005				
	N (3)	−0,003				
	C (4)	−0,020				
	C (5)	−0,018				
	C (6)	0,008				
	N (7)	−0,003				
	C (8)	0,011				
	N (9)	0,012				
	Cl*	0,076				
	C (5')*	0,035				
C	C (4')		−0,9016	−0,1145	−0,4172	1,1531
	C (5')					
	C (6')					
D	O (1')	−0,007	0,9136	0,1612	−0,3734	−7,4661
	O (3')	0,007				
	C (4')	−0,006				
	C (6')	0,006				
	C (2')*	−0,733				
	C (5')*	0,617				
E	O (1')		−0,7846	−0,0835	−0,6143	−2,2337
	C (2')					
	O (3')					

*These atoms were not taken into account in the calculation of the corresponding plane.

The existence of configurational isomerism of purines IIa,b and IIIa,b is also confirmed by the IR-spectroscopic data. The IR spectra of trans isomers IIa and IIIa contain characteristic bands of skeletal vibrations at 683 and 682 cm^{-1}, respectively, while the spectra of cis isomers IIb and IIIb contain bands at 700 and 690 cm^{-1}; this coincides with the general principle in the dioxane series that is used for the identification of cis and trans isomers [12].

Thus, the presence of two configurational isomers with an axial orientation of the ethoxy group in the trans isomer and an equatorial orientation of the ethoxy group in the cis isomer was established for II and III by NMR and IR spectroscopy. To confirm the data obtained and to make a more detailed study of purine compounds in order to investigate the conformations of the purine and dioxane rings, as well as their relative orientation, we investigated the molecular-crystal structure of high-melting isomer IIa by x-ray diffraction analysis.

The projection of the molecule on the average plane of the purine two-ring system is shown in Fig. 2 with an indication of the bond lengths and valence angles; the angles between the average planes of the most important fragments of the IIa molecule are also presented.

As in the case of purine bases in nucleic acids, a small deviation of the purine ring from planarity (the deflection of the two-ring system along the C_4-C_5 bond is only 1.6°) is observed in the IIa molecule. In addition, it should be noted that the exocyclic substituents deviate only slightly from the plane of the purine two-ring system, so that the chlorine atom deviates 0.08 Å on the same side as the $C_{5'}$ atom, the deviation of which is 0.03 Å. The equations of the average planes of the planar fragments of the IIa molecule and the deviations of the atoms from these planes are presented in Table 3.

It follows from a comparison of the interatomic distances and valence angles of the purine ring in the IIa molecule and other purine compounds that within the limits of 0.05 Å and 4°, the geometry of the purine fragment of the IIa molecule corresponds to the geometry of purine [13], 9-methyladenine [14], and their derivatives

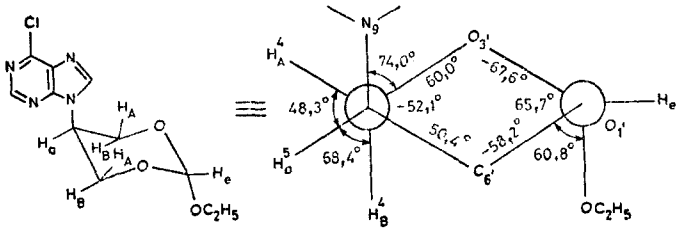

Fig. 3. Torsion angles of the 1,3-dioxane fragment of the IIa molecule.

[15-18]. The increase in the endocyclic valence angle at the C_6 atom from 119° in the purine molecule to 123° in the IIa molecule, like the shortening of the C_5-C_6 bond, is evidently associated with the effect of the chlorine atom. Identical C_4-N_9 and C_5-N_7 bond lengths in the purine molecule (1.37 Å) were noted in [13]. However, in the IIa molecule this value is retained only for the C_4-N_9 bond, whereas the length of the C_5-N_7 bond is increased by 0.03 Å. This fact and the lengthening of the C_8-N_9 bond from 1.31 Å in the purine molecule to 1.36 Å in the IIa molecule, which leads to equalization of the bond lengths in the $N_7-C_8-N_9$ fragment in the imidazole part of the molecule, in all likelihood reflects the role of the dioxane residue attached to the nitrogen atom in the 9 position and of the chlorine atom in the 6 position of the purine ring.

The dioxane ring has a chair conformation; this follows from the data presented in Table 3 and Fig. 2. The $C_{5'}$ and $C_{2'}$ atoms deviate 0.62 and 0.73 Å, respectively on opposite sides from the strictly planar D fragment formed by the $O_{1'}$, $O_{3'}$, $C_{4'}$, and $C_{6'}$ atoms. The endocyclic valence angles of the IIa molecule correspond, within the limits of 2-3°, to those in the 1,3-dioxane fragment [19-21]. It should be noted that the C-C bonds in the dioxane ring in IIa undergo additional shortening to 1.48-1.51 Å as compared with unsubstituted 1,3-dioxane, and the $O_{1'}-C_{2'}-O_{3'}$ angle is 107.5°.

The torsion angles in the IIa molecule (Fig. 3) constitute evidence for further compression of the hydrocarbon part of the dioxane ring ($\psi = 50.4°$ and $\psi = 52.1°$) as compared, for example, with unsubstituted 1,3-dioxane [22], the torsion angle of which is 54°, and for an increase in the folding of the ring in the oxygen part of the residue ($\psi = 65.7°$, and $\psi = 67.6°$).

The results of an x-ray diffraction analysis provide unambiguous evidence for the axial orientation of the purine ring with respect to the dioxane residue. Thus the dihedral angle formed by the plane of the purine ring and the average square plane of dioxane is 100.7°, while the dihedral angles formed by the plane of purine and the planar C and D fragments are 60.3 and 86.3°, respectively.

The preferableness of an axial or equatorial orientation of the purine ring with respect to the six-membered saturated residue is explained in [7] by manifestation of the gauche effect in the O(S)-C-C-N fragment and the possible formation of a hydrogen bond between the 8-H proton of purine and the oxygen atom in the dioxane or oxathian ring. In our case the preferableness of the axial orientation of the purine ring is also determined, in all likelihood, by the gauche effect [23] of the $N_9-C_{5'}-C_{4'}-O_{3'}$ and $N_9-C_{5'}-C_{6'}-O_{1'}$ fragments, which is responsible for the conformational stability of this structure. Evidence for this is provided by the dihedral angle ($\theta = 74°$) between the planes that pass through the $C_{5'}-C_{4'}-O_{3'}$ and $N_9-C_{5'}-C_{4'}$ fragments and, correspondingly, the angle ($\theta = 74.6°$) between the planes that pass through the $C_{5'}-C_{6'}-O_{1'}$ and $N_9-C_{5'}-C_{6'}$ fragments.

At the same time, the calculations showed that the formation of a hydrogen bond between the 8-H proton of the purine ring and the oxygen atom of the dioxane residue, as assumed in [7] for compounds that contain 1,4-dioxane and 1,4-oxathiane residues in the 9 position of the purine ring, is impossible for IIa in the crystalline state, since the $C_8-N\ldots O$ distance in the IIa molecule is 3.09 Å.

The magnitude of the dihedral angle between the planes that pass through the $C_{6'}-O_{1'}-C_{2'}$ and $O_{1'}-C_{2'}-C_{7'}$ fragments ($\theta = 60.8°$) also serves as a confirmation of the axial orientation of the 2-ethoxy group.

It should be noted that the $C_{5'}-N_9$ bond in the IIa molecule is 1.49 Å and, with respect to its length and chemical properties (with respect to acid and alkaline hydrolysis), correspond to the glycoside bond in the purine bases of nucleic acids, whereas the dioxane ring exists in an anti conformation with respect to the purine ring with $\chi = -13.4°$.

The packing of the molecules in the unit cell of the crystal is realized at distances that are no shorter than the sum of the van der Waals radii of the corresponding atoms indicated in [24, 25].

TABLE 4. Coordinates of the Atoms

Atoms	x	y	z	Atoms	x	y	z
Cl	0,071 (03)	0,439 (00)	0,263 (2)	O (7′)	−0,865 (10)	0,190 (9)	0,572 (4)
C (6)	−0,155 (12)	0,445 (15)	0,281 (5)	C (8′)	−0,956 (16)	0,287 (14)	0,618 (7)
N (1)	−0,249 (13)	0,541 (11)	0,242 (5)	C (9′)	−1,151 (17)	0,258 (18)	0,612 (7)
C (2)	−0,428 (16)	0,543 (13)	0,254 (6)	H1C (4′)	−0,816	0,067	0,450
N (3)	−0,519 (11)	0,457 (12)	0,300 (4)	H2C (4′)	−0,612	0,035	0,419
C (4)	−0,417 (14)	0,368 (12)	0,337 (5)	H1C (9′)	−1,251	0,349	0,648
C (5)	−0,230 (13)	0,355 (14)	0,330 (5)	H2C (9′)	−1,162	0,206	0,647
N (7)	−0,168 (11)	0,246 (12)	0,375 (5)	HC (8)	−0,333	0,100	0,450
C (8)	−0,318 (16)	0,195 (13)	0,408 (5)	H1C (8′)	−0,915	0,231	0,662
N (9)	−0,468 (11)	0,264 (10)	0,386 (4)	H2C (8′)	−0,880	0,369	0,625
C (5′)	−0,657 (13)	0,239 (13)	0,409 (5)	H1C (6′)	−0,846	0,403	0,464
C (6′)	−0,727 (14)	0,356 (13)	0,455 (5)	H2C (6′)	−0,696	0,477	0,453
O (1′)	−0,653 (9)	0,350 (10)	0,532 (4)	H3C (9′)	−1,195	0,239	0,552
C (2′)	−0,698 (19)	0,217 (13)	0,565 (5)	HC (2)	−0,461	0,675	0,247
O (3′)	−0,606 (10)	0,111 (9)	0,524 (4)	HC (5′)	−0,732	0,220	0,359
C (4′)	−0,678 (16)	0,101 (14)	0,449 (6)	HC (2′)	−0,622	0,239	0,617

Thus, the geometry and conformation of high-melting isomer IIa were determined by the x-ray diffraction study, the trans-diaxial orientation of the substituents in the 5 and 2 positions of the dioxane residue was confirmed, and it was shown that the dioxane ring exists in the anti conformation with respect to the purine ring.

EXPERIMENTAL

Thin-layer chromatography (TLC) was carried out on 0.25-mm thick DC-Fertigplatten Kieselgel $60F_{254}$ plates, and preparative TLC was accomplished on 2-mm thick PSC-Fertigplatten Kieselgel $60F_{254}$ plates in a chloroform–ethanol system (9:1) with development in UV light with a UPM apparatus. The UV spectra of solutions of the compounds in ethanol were obtained with a Specord UV-vis spectrophotometer. The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer. The NMR spectra of $CDCl_3$ solutions were recorded with a Brucker WH-90 spectrometer with tetramethylsilane as the internal standard.

The three-dimensional set of intensities of the reflections was obtained with a $P2_1$ automatic four-disk diffractometer with a 0.20 by 0.25 by 0.30 mm colorless single crystal with a prismatic habitus. The following crystallographic characteristics of the unit cell of a rhombic crystal with the composition $C_{11}H_{13}C_1N_4O_3$ were obtained: $a = 7.505(2)$ Å, $b = 9.550(1)$ Å, $c = 17.756(2)$ Å, $V = 1272.68(36)$ Å^3, $M = 284.72$, $d_{calc} = 1.49$ g-cm^{-1}, $Z = 4$, $\mu(CuK_\alpha) = 27.9$ cm^{-1}, space group Pc2n, and $F_{000} = 592$. The intensities of 821 independent nonzero reflections were measured by the $\theta/2\theta$ scanning method in monochromatic copper emission (with a graphite monochromator) up to $2\theta_{max} = 150°$. A total of 783 reflections with $1 \geq 2\sigma$ were used in the calculation. The structure was decoded with an XTL system for the determination of structures. A model of the molecule was found by a direct method from a MULTAN program [26]. An E synthesis carried out with respect to the best set of phases made it possible to localize all 19 of the nonhydrogen atoms of the molecule. Subsequent refinement within the total-matrix isotropic approximation (two cycles) reduced the R factor from 0.35 to 0.18. Further refinement by the method of least squares within the total matrix isotropic approximation (the chlorine atom was refined anisotropically) led to R = 0.11. In this stage the positions of all 13 hydrogen atoms were determined from differential synthesis. Further refinement of the nonhydrogen atoms within the anisotropic approximation (171 parameters) with allowance for all of the hydrogen atoms ($B_{isotr} = 6.0$ Å^{-2}) led to a final R value of 0.059. The accuracies in the determination of the interatomic distances and valence angles were 0.01 Å and 1°, respectively. The coordinates of the atoms are presented in Table 4.

6-Chloro-9-(2-ethoxy-1,3-dioxan-5-yl)purine (II). A solution of 4.3 g (0.015 mole) sample of I was refluxed in a mixture of 25 ml of acetic anhydride and 25 ml of ethyl orthoformate for 1 h, after which the solvent was removed by distillation, and the residue was crystallized from absolute ethanol to give 3.2 g (57%) of a mixture of IIa,b with mp 125-127°C. Separation by TLC of preparative plates in a chloroform–ethanol system (9:1) with elution of the pure isomers by chloroform yielded the trans (IIa) and cis (IIb) isomers (Table 1) in a ratio of 3:2. ^{13}C NMR spectrum of IIb: δ 152.4 (C_6 and C_4), 151.5 (C_2), 141.7 (C_8), 132.1 (C_5), 111.3 ($C_{2'}$), 66.9 ($C_{4'}$ and $C_{6'}$), 6.17 (OCH_2), 47.6 ($C_{5'}$), and 15.0 ppm (CH_3).

6-Amino-9-(2-ethoxy-1,3-dioxan-5-yl)purine (III). A solution of 1.4 g (0.005 mole) of a mixture of IIa,b in 30 ml of absolute ethanol saturated with ammonia at 0°C was heated in a sealed ampul at 60°C for 15 h, after which the solvent was removed by distillation, and the residue was crystallized from ethanol to give 1.2 g (86%)

of a mixture of IIIa,b with mp 100-105°C. Separation by TLC on preparative plates in a chloroform–ethanol system (9:1) and elution of the isomers with chloroform yielded the trans (IIIa) and cis (IIIb) isomers in a ratio of 3:2. ^{13}C NMR spectrum of IIIa: δ 155.1 (C_6), 152.2 (C_2), 149.1 (C_4), 139.7 (C_8), 118.6 (C_5), 107.1 ($C_{2'}$), 61.3 (OCH_2), 60.8 ($C_{4'}$ and $C_{6'}$), 47.2 ($C_{5'}$), and 14.6 ppm (CH_3).

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