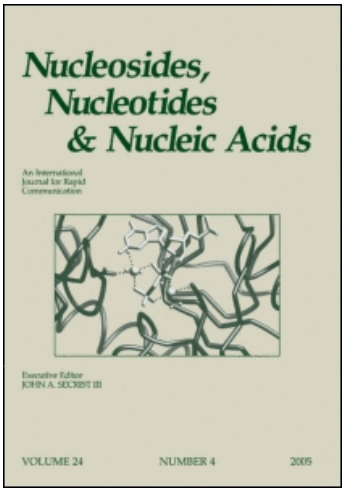

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Adenosine Receptor Agonists. X-Ray Crystal Structure of Neca 1-(6-Amino-9H-Purin-9-Yl)-1-Deoxy-N-Ethyl-β-D-Ribofuranuronamide

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ADENOSINE RECEPTOR AGONISTS. X-RAY CRYSTAL STRUCTURE OF NECA 1-(6-AMINO-9H-PURIN-9-YL)-1-DEOXY-N-ETHYL-β-D-RIBOFURANURONAMIDE

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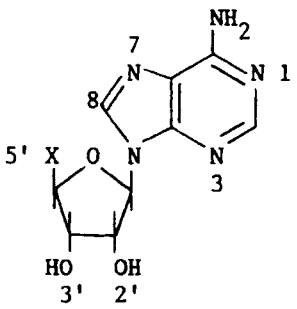
Abstract - The single crystal x-ray structure of NECA (1-(6-amino-9H-purin-9-yl)-1-deoxy-N-ethyl-β-D-ribofuranuronamide), a 5'-modified adenosine analogue, is reported. Crystallized from methanol as the monohydrate, NECA exists in a syn conformation (sugar syn to purine) in the solid state, consistent with both solution measurements and theoretical calculations. The biological profile of NECA may result from this conformational preference.

INTRODUCTION

Adenosine receptors, which mediate many of the biological effects of adenosine, have been divided into two main classes based upon effects on adenylate cyclase. A_1 (R_i) receptors inhibit and A_2 (R_a) receptors stimulate adenylate cyclase activity. Previous reports from our laboratory[1] have described A_1-selective ribose-modified adenosine analogues. The central role of the ribose-modified adenosine analogue, 1-(6-amino-9H-purin-9-yl)-1-deoxy-N-ethyl-β-D-ribofuranuronamide (NECA; 1; see FIG. 1), in establishing an A_2 binding assay,[2] coupled with the continuing interest in subtypes of adenosine receptors,[3] prompts us to disclose herein its single crystal x-ray structure.

Structure activity relationships of 5'-oxidized adenosine analogues with potential as antianginal agents were first described over a decade ago.[4] Nuclear Overhauser enhancement (NOE) studies of adenosine-5'-carboxylates (e.g., EAC; 2) showed the sugar conformation relative to the



5'-carboxamides: X=CONRR' (NECA (1): R=H,R'=Et)

5'-carboxylates: X=COOR (EAC (2): R=Et)

adenosine (3): $X=CH_2OH$

FIG. 1. Adenosine and 5'-oxidized analogues.

purine (the glycosidic torsional angle) to be intermediate between syn and anti.[5] Additional work with adenosine-5'-carboxamides led to NECA. NOE studies in the NECA series suggested that the syn conformation leads to increased biological activity.[6] Furthermore, conformational analyses supported the syn conformation as the biologically relevant one.[7]

Literature on the chemical and biological relevance of the syn versus the anti conformation is divided. Some workers[8] have concluded on the basis of nuclear magnetic resonance (NMR) and circular dichroism (CD) data that the existence of N-3/5'-OH hydrogen bonding is important in governing the conformation of adenosines, more important in some cases (e.g., 8,5'-radical cyclizations) than steric or electronic effects. However, other workers have proposed that the anti conformation is required for activation of adenylate cyclase.[9] For example, 8,5'-cycloadenosines are locked in an anti configuration by their 8,5'-bridge, and certain examples of these are pure antagonists. Because agonists and antagonists are believed to bind to adenosine receptors in the same way, this supports the anti conformation as the biologically relevant one.[10]

RESULTS AND DISCUSSION

NECA was crystallized from methanol as the monohydrate, which was subjected to single crystal x-ray analysis. The crystal structure was solved by direct methods. Full-matrix least squares refinement of

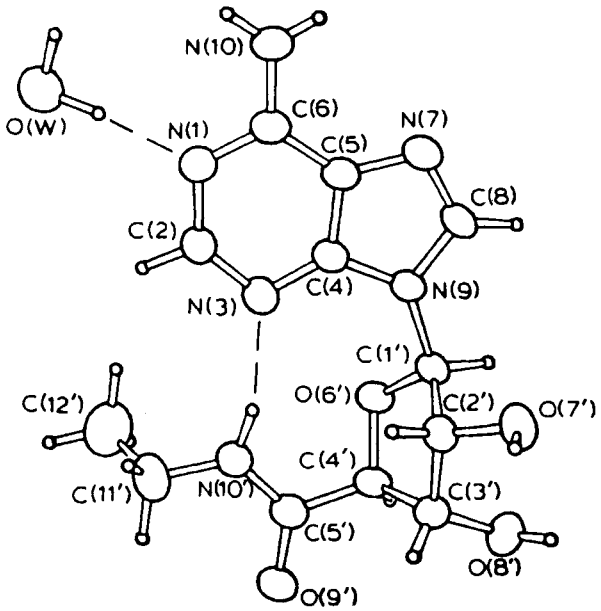


FIG. 2. Solid-state conformation of NECA in crystals of the monohydrate; small circles represent hydrogen atoms and broken lines indicate hydrogen bonds.

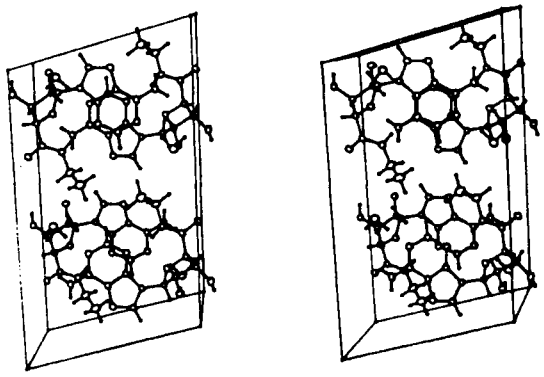


FIG. 3. Stereoview of the crystal packing arrangement for NECA monohydrate.

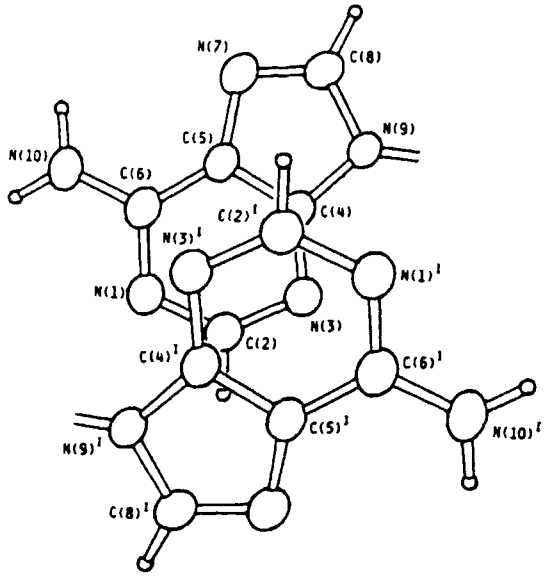


FIG. 4. Relationship of purine rings in adjacent NECA molecules, viewed perpendicular to N(1)-N(9) least-squares plane.

atomic positional and thermal parameters converged to $\underline{R}$ = 0.037 ($\underline{R}_w$ = 0.048) over 1421 reflections. Final atomic positional parameters are listed in TABLES 1 and 2. Interatomic distances and angles involving non-hydrogen atoms are in TABLE 3. A view of the solid-state conformation adopted by NECA in crystals of the monohydrate is presented in FIG. 2. Atoms of the purine ring system and its directly bonded furanosidic carbon atom and trigonal planar amino nitrogen atom are approximately coplanar. The furanoside ring has an envelope conformation [a C(2')-endo pucker; pseudo-rotation parameters: $\tau_m = 38^\circ$ and $P = 156^\circ$] with C(2') displaced by 0.596 Å from the least-squares plane through the other four ring atoms, and its cis-related amide and 6-aminopurine substituents are linked via an intramolecular N-H···N hydrogen bond [N(10')···N(3) = 2.893(2) Å]. FIG. 3 provides a stereoview of the packing arrangement in the crystals. A pair of adjacent NECA molecules related by the crystallographic 2_1 screw axis along b, as viewed in projection onto the N(1)-N(9) plane, are shown in FIG. 4. The purine rings are oriented in an approximately parallel manner (dihedral angle = 17.2°) with overlap involving only the

TABLE 1. Non-hydrogen atom fractional coordinates and equivalent isotropic thermal parameters[a] ($\times 10^4$) for NECA monohydrate, with estimated standard deviations in parentheses

Atom	$10^5 x$	$10^4 y$	$10^5 z$	U_{eq} (Å^2)
N(1)	20423(8)	0(-)[b]	34216(13)	446(4)
C(2)	18788(10)	53(4)	45329(16)	510(5)
N(3)	23417(8)	-84(3)	56539(13)	502(5)
C(4)	30592(9)	-326(3)	55745(14)	379(4)
C(5)	33138(9)	-396(3)	45059(14)	422(4)
C(6)	27702(10)	-205(3)	33839(15)	419(4)
N(7)	40829(8)	-686(4)	47527(15)	594(6)
C(8)	42843(9)	-796(5)	59494(16)	542(6)
N(9)	36976(7)	-594(3)	65204(12)	386(4)
N(10)	29426(9)	-246(4)	22833(13)	589(6)
C(1')	37720(8)	-622(3)	78493(13)	323(4)
C(2')	37791(8)	1171(2)	84482(15)	328(4)
C(3')	35330(9)	698(3)	96369(14)	347(4)
C(4')	29720(9)	-797(3)	91946(14)	329(4)
C(5')	21493(9)	-232(3)	89845(15)	360(4)
O(6')	31336(6)	-1487(2)	80839(10)	355(3)
O(7')	44998(6)	1919(2)	86345(12)	410(3)
O(8')	41370(6)	11(3)	105588(10)	410(3)
O(9')	19034(6)	108(3)	99029(10)	460(4)
N(10')	17459(8)	-111(4)	78377(13)	552(5)
C(11')	9487(12)	354(7)	75090(24)	840(10)
C(12')	4910(13)	-1037(11)	67235(29)	1203(13)
O(W)	7746(8)	317(3)	13481(14)	517(4)

[a] $U_{eq} = (U_{11} + U_{22}\sin^2\beta + U_{33} + 2U_{13}\cos\beta)/3\sin^2\beta$.

[b] The y-coordinate of N(10) was held constant throughout the course of the analysis to define the origin in this direction.

pyrimidine rings; the shortest interplanar interatomic distance at 3.551(4) Å occurs between C(2) and C(4). NECA and water molecules are associated by an extensive network of hydrogen bonds involving one amino, both hydroxy, and both water molecule hydrogen bonds (TABLE 4). Thus, intermolecular O(7)-H···O(W) [O(7)···O(W) = 2.656(3) Å] and O(W)-H···N(1) [O(W)···N(1) = 2.862(2) Å] hydrogen bonds link NECA molecules along the b-direction. A pair of hydrogen bonds involving the

TABLE 2. Hydrogen atom fractional coordinates,[a] isotropic thermal parameters ($x10^3$), and bonded distances in NECA monohydrate; estimated standard deviations are in parentheses.

Atom	10^4x	10^3y	10^4z	$U(Å^2)$	$d(Å)$
H(2)	1346(14)	13(6)	4513(23)	47(9)	0.96(3)
H(8)	4814(10)	-106(3)	6377(19)	12(5)	0.99(2)
H(10A)	3450(14)	-32(5)	2237(23)	41(8)	0.94(3)
H(10B)	2601(13)	-10(5)	1561(22)	40(8)	0.90(2)
H(1')	4294(10)	-122(3)	8249(18)	9(5)	1.05(2)
H(2')	3375(11)	190(3)	7974(19)	12(5)	0.97(2)
H(3')	3284(10)	172(3)	9917(18)	10(5)	0.99(2)
H(4')	3064(10)	-167(3)	9779(18)	10(5)	0.92(2)
H(7')	4449(10)	307(4)	8673(20)	20(6)	0.89(3)
H(8')	4617(15)	77(6)	10720(24)	49(9)	1.03(3)
H(10')	2056(12)	-18(5)	7258(24)	32(7)	0.96(3)
H(11'A)[b]	882(-)	153(-)	7018(-)	84(-)	1.05(-)
H(11'B)[b]	755(-)	50(-)	8317(-)	84(-)	1.05(-)
H(12'A)[b]	-83(-)	-68(-)	6497(-)	120(-)	1.05(-)
H(12'B)[b]	681(-)	-119(-)	5912(-)	120(-)	1.05(-)
H(12'C)[b]	554(-)	-222(-)	7212(-)	120(-)	1.05(-)
H(OWA)	1071(16)	68(7)	726(30)	71(12)	1.01(4)
H(OWB)	1277(16)	50(6)	2056(31)	71(12)	1.07(3)

[a]Hydrogen atoms bear the same labels as the atoms to which they are bonded.

[b]These hydrogen atoms were included at their calculated positions and were assigned the equivalent isotropic thermal parameters of the atoms to which they are bonded.

amide oxygen atom O(9') [N(10)···O(9') = 2.884(2) Å, O(W)···O(9') = 2.899(2) Å] associate NECA/H_2O units related by unit translation along c, while NECA molecules related by the crystallographic two-fold axis are linked by hydrogen bonds involving their hydroxy groups [O(8')···O(9') = 2.833(2) Å].

The syn conformation [ψ_{CN} = 39.7(3)°] for NECA is surprising given that purine nucleosides (e.g., adenosine[11]) characteristically prefer the anti conformation. To explore the latter point more fully, we

TABLE 3. Interatomic distances (Å) and angles (deg.) for NECA monohydrate, with estimated standard deviations in parentheses.

(a) Bond Lengths

N(1)-C(2)	1.343(2)	C(1')-C(2')	1.529(3)
N(1)-C(6)	1.342(2)	C(1')-O(6')	1.414(2)
C(2)-N(3)	1.336(2)	C(2')-C(3')	1.541(2)
N(3)-C(4)	1.340(2)	C(2')-O(7')	1.399(2)
C(4)-C(5)	1.379(2)	C(3')-C(4')	1.536(3)
C(4)-N(9)	1.386(2)	C(3')-O(8')	1.416(2)
C(5)-C(6)	1.407(2)	C(4')-C(5')	1.520(2)
C(5)-N(7)	1.376(2)	C(4')-O(6')	1.441(2)
C(6)-N(10)	1.339(2)	C(5')-O(9')	1.240(2)
N(7)-C(8)	1.302(2)	C(5')-N(10')	1.319(2)
C(8)-N(9)	1.374(2)	N(10')-C(11')	1.451(3)
N(9)-C(1')	1.458(2)	C(11')-C(12')	1.501(7)

(b) Bond Angles

C(2)-N(1)-C(6)	117.9(1)	N(9)-C(1')-O(6')	108.3(1)
N(1)-C(2)-N(3)	129.4(2)	C(2')-C(1')-O(6')	105.3(1)
C(2)-N(3)-C(4)	110.8(2)	C(1')-C(2')-C(3')	101.0(1)
N(3)-C(4)-C(5)	126.4(1)	C(1')-C(2')-O(7')	110.2(1)
N(3)-C(4)-N(9)	128.4(2)	C(3')-C(2')-O(7')	114.9(1)
C(5)-C(4)-N(9)	105.2(1)	C(2')-C(3')-C(4')	101.8(1)
C(4)-C(5)-C(6)	117.2(2)	C(2')-C(3')-O(8')	112.4(1)
C(4)-C(5)-N(7)	111.5(1)	C(4')-C(3')-O(8')	107.2(2)
C(6)-C(5)-N(7)	131.3(2)	C(3')-C(4')-C(5')	112.9(2)
N(1)-C(6)-C(5)	118.2(2)	C(3')-C(4')-O(6')	107.2(1)
N(1)-C(6)-N(10)	118.6(1)	C(5')-C(4')-O(6')	111.5(1)
C(5)-C(6)-N(10)	123.2(2)	C(4')-C(5')-O(9')	117.8(1)
C(5)-N(7)-C(8)	103.9(2)	C(4')-C(5')-N(10')	118.0(2)
N(7)-C(8)-N(9)	114.1(1)	O(9')-C(5')-N(10')	124.2(2)
C(4)-N(9)-C(8)	105.3(1)	C(1')-O(6')-C(4')	109.3(1)

(table continued)

TABLE 3. (Continued)

C(4)-N(9)-C(1')	129.5(1)	C(5')-N(10')-C(11')	123.6(2)
C(8)-N(9)-C(1')	125.2(1)	N(10')-C(11')-C(12')	110.7(4)
N(9)-C(1')-C(2')	114.9(2)		

(c) Torsion Angles[a]

C(6)-N(1)-C(2)-N(3)	-0.6(4)	C(8)-N(9)-C(1')-C(2')	100.5(3)
C(2)-N(1)-C(6)-C(5)	1.6(3)	C(8)-N(9)-C(1')-O(6')	-142.2(3)
C(2)-N(1)-C(6)-N(10)	-179.5(2)	N(9)-C(1')-C(2')-C(3')	157.7(1)
N(1)-C(2)-N(3)-C(4)	-0.8(4)	N(9)-C(1')-C(2')-O(7')	-80.4(2)
C(2)-N(3)-C(4)-C(5)	1.3(4)	O(6')-C(1')-C(2')-C(3')	38.7(2)
C(2)-N(3)-C(4)-N(9)	-177.2(3)	O(6')-C(1')-C(2')-O(7')	160.6(1)
N(3)-C(4)-C(5)-C(6)	-0.4(4)	N(9)-C(1')-O(6')-C(4')	-150.3(2)
N(3)-C(4)-C(5)-N(7)	-179.1(3)	C(2')-C(1')-O(6')-C(4')	-26.9(2)
N(9)-C(4)-C(5)-C(6)	178.4(2)	C(1')-C(2')-C(3')-C(4')	-34.9(2)
N(9)-C(4)-C(5)-N(7)	-0.3(3)	C(1')-C(2')-C(3')-O(8')	79.5(2)
N(3)-C(4)-N(9)-C(8)	179.0(3)	O(7')-C(2')-C(3')-C(4')	-153.4(1)
N(3)-C(4)-N(9)-C(1')	-2.6(4)	O(7')-C(2')-C(3')-O(8')	-39.0(2)
C(5)-C(4)-N(9)-C(8)	0.3(3)	C(2')-C(3')-C(4')-C(5')	-102.5(2)
C(5)-C(4)-N(9)-C(1')	178.7(2)	C(2')-C(3')-C(4')-O(6')	20.6(2)
C(4)-C(5)-C(6)-N(1)	-1.2(3)	O(8')-C(3')-C(4')-C(5')	139.3(1)
C(4)-C(5)-C(6)-N(10)	179.9(3)	O(8')-C(3')-C(4')-O(6')	-97.6(2)
N(7)-C(5)-C(6)-N(1)	177.3(2)	C(3')-C(4')-C(5')-O(9')	-71.2(3)
N(7)-C(5)-C(6)-N(10)	-1.6(4)	C(3')-C(4')-C(5')-N(10')	107.9(2)
C(4)-C(5)-N(7)-C(8)	0.3(3)	O(6')-C(4')-C(5')-O(9')	168.1(2)
C(6)-C(5)-N(7)-C(8)	-178.3(3)	O(6')-C(4')-C(5')-N(10')	-12.9(3)
C(5)-N(7)-C(8)-N(9)	-0.1(4)	C(3')-C(4')-O(6')-C(1')	3.6(2)
N(7)-C(8)-N(9)-C(4)	-0.1(4)	C(5')-C(4')-O(6')-C(1')	127.6(2)
N(7)-C(8)-N(9)-C(1')	-178.6(3)	C(4')-C(5')-N(10')-C(11')	177.8(3)
C(4)-N(9)-C(1')-C(2')	-77.7(3)	O(9')-C(5')-N(10')-C(11')	-3.2(5)
C(4)-N(9)-C(1')-O(6')	39.7(3)	C(5')-N(10')-C(11')-C(12')	-123.0(3)

[a]The torsion angle A-B-C-D is defined as positive if, when viewed along the B-C bond, atom A must be rotated clockwise to eclipse atom D.

TABLE 4. Hydrogen-bonded distances and angles for NECA monohydrate, with estimated standard deviations in parentheses.

X-H...Y	X...Y(Å)	X-H(Å)	H...Y(Å)	X-H...Y(°)
N(10)-H(10B)...O(9')^{I}	2.884(2)	0.90(2)	1.99(2)	175(3)
O(7')-H(7')...O(W)^{II}	2.656(3)	0.89(3)	1.77(3)	173(2)
O(8')-H(8')...O(7')^{III}	2.833(2)	1.03(3)	1.82(3)	167(3)
N(10')-H(10')...N(3)	2.893(2)	0.96(3)	1.98(3)	159(2)
O(W)-H(OWA)...O(9')^{I}	2.899(2)	1.07(3)	2.00(4)	147(4)
O(W)-H(OWB)...N(1)	2.862(2)	1.01(4)	1.84(3)	159(4)

[a]Roman numeral superscripts refer to atoms at the following equivalent positions: I x, y, $-1+z$; II $\frac{1}{2}-x$, $\frac{1}{2}+y$, $1-z$; III $1-x$, y, $2-z$.

searched the Cambridge Crystallographic Database using an unsubstituted furanyl-adenine fragment as the template. Of 111 structures that matched the template, 29 were bibliographic entries only (no atomic coordinates available), four were complex structures such as DNA dimer models, and two contained heterocyclic rings fused to the sugar. Of the 76 remaining structures, 60 displayed anti and 16 syn conformations. Among the 16 compounds possessing a syn conformation, five were poorly refined ($R > 0.09$) or contained disorder in the structure, and thus were not considered further. Seven were 8-substituted, wherein steric interactions (and perhaps other interactions,[8] *vide supra*) between the sugar and the 8-substituent resulted in the syn conformation being more favorable. The 5'-OH was hydrogen bonded to N-3 in the 8-substituted compounds. N-[1'-(9-Adenyl)-β-D-ribofuranuronosyl]-L-phenylalanine,[12] a carboxamide unrelated to NECA, crystallized as independent zwitterions, one anti and the other syn. Finally, 5'-methylammonium-5'-deoxyadenosine,[13] 3'-O-acetyladenosine,[14] and a complex of adenosine and 5-bromouracil[15] were syn with hydrogen bonds to N-3. In the complex, unusual molecular packing forces are a likely explanation for the syn, hydrogen-bonded structure.

Thus, in the absence of other factors, the syn conformation is found only in purine nucleosides with 8-substitution, 3-O-acylribosides,

or 5'-substitution that provides enhanced hydrogen bond donating capability. The 5'-carboxamide substitution of NECA clearly falls into the latter category.

CONCLUSIONS

Solid state (x-ray) data demonstrate the propensity of NECA to adopt a syn conformation, in concert with previous solution (NOE) and theoretical (molecular modeling) results. It is interesting to speculate that this conformational preference imparts the balanced A_1/A_2 profile observed for NECA and related analogues. In any event, questions regarding biologically relevant conformations at adenosine receptors warrant further consideration.

EXPERIMENTAL

X-Ray Crystal Structure. Crystals of the monohydrate of NECA were grown from methanol by slow evaporation in the open atmosphere. Crystal data: $C_{12}H_{16}N_6O_4 \cdot H_2O$, M_r = 326.31, monoclinic, a = 18.166(3) Å, b = 7.674(1) Å, c = 11.165(2) Å, β = 103.74(1)°, V = 1511.9 Å^3, Z = 4, $D_{calcd.}$ = 1.433 g cm^{-3}, μ(Cu-Kα radiation, λ = 1.5418 Å) = 9.2 cm^{-1}. Space group $C2(C_2^3)$ from the systematic absences: $hk\ell$ when $h + k \neq 2n$, and NECA is chiral. Sample dimensions: 0.15 x 0.30 x 0.70 mm.

Preliminary unit-cell parameters and space group information were derived from oscillation, Weissenberg, and precession photographs. Intensity data ($+h$, $+k$, $\pm \ell$) to θ = 67° were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu-Kα radiation, incident-beam graphite monochromator; ω - 2θ scans). From a total of 1470 non-equivalent reflections recorded, those 1421 with $I > 3.0\sigma(I)$ were retained for the structure analysis, and the usual Lorentz and polarization corrections were applied. Refined unit-cell parameters were computed from the diffractometer setting angles for 25 reflections (56° < θ < 67°) widely separated in reciprocal space.

The crystal structure was solved by direct methods by using the program MULTAN 11/82. All crystallographic calculations were performed on a PDP 11/44 computer by use of the Enraf-Nonius SDP suite of programs. Approximate coordinates for the non-hydrogen atoms were

obtained from an E-map. Several rounds of full-matrix least-squares adjustment of the atomic positional and anisotropic thermal parameters were followed by evaluation of a difference Fourier synthesis which revealed positive regions corresponding to calculated hydrogen atom positions. Continuation of the least-squares iterations, with hydrogen atom positional and isotropic thermal parameters included as variables, yielded physically unacceptable values for hydrogen atoms of the N-ethyl group, and so these five hydrogen atoms were included at their calculated positions in the subsequent least-squares iterations. These iterations converged at $\underline{R} = 0.037$ ($\underline{R}_{\underline{w}} = 0.048$), where $\underline{R} = \Sigma||\underline{F}_o| - |\underline{F}_c||/\Sigma|\underline{F}_o|$ and $\underline{R}_{\underline{w}} = \sqrt{[\Sigma\underline{w}(|\underline{F}_o| - |\underline{F}_c|)^2/\Sigma\underline{w}|\underline{F}_o|^2]}$. Final fractional atomic coordinates are reported in TABLES 1 and 2. For the structure-factor calculations, neutral atom scattering factors were taken from the literature.[16] In the least squares iterations, $\Sigma\underline{w}\Delta^2$ [$\underline{w} = 1/\sigma^2(|\underline{F}_o|)$, $\Delta = (|\underline{F}_o| - |\underline{F}_c|)$] was minimized.

Non-hydrogen atom positional and anisotropic temperature factor parameters, bond lengths and angles, and hydrogen atom positional and isotropic thermal parameters have been deposited with the Cambridge Crystallographic Data Centre.

Cambridge Crystallographic Database Search/Analysis. Databases and associated software from the Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, England, were obtained through the Medical Foundation of Buffalo, Inc., 73 High Street, Buffalo, NY. A search query in Cambridge format was constructed using the SYBYL/Cambridge interface within the molecular modeling package SYBYL (CAMBRIDGE command). SYBYL (Tripos Release 3.4, Parke-Davis Version 5.0.2)[17] analyses were performed using a Digital Equipment Corp. VAX Cluster containing a VAX 11/785 and a MicroVAX-II. Standard SYBYL procedures were used for all operations; defaults were used wherever possible. Valencies of atoms were left unfilled so that any attachments to these atoms would be allowed in the search. Single, double, aromatic, or delocalized bond types were allowed for all bonds in the purine ring, including the bond to N-6; those in the sugar were restricted to single bonds. The resulting hits were extracted from the database, transferred to SYBYL, and displayed on an Evans & Sutherland PS 350 graphics terminal. Syn/anti assignments were made visually.

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