ratio D_{56}/D_{35} is bracketed by the free and the eclipsed ratios. A preferentially eclipsed conformer would be indicated rather than staggered. The experimental ratio is much closer to the free rotation model than the fixed staggered model for a C–N bond length of 1.488 Å, suggesting a low barrier to internal rotation in the ion.

The Crystal and Molecular Structure of a Derivative of 1,N^6-Ethenoadenosine Hydrochloride. Dimensions and Molecular Interactions of the Fluorescent ϵ-Adenosine (ϵAdo) System

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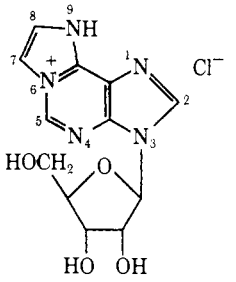
Abstract: The crystal structure of 7-ethyl-3-β-D-ribofuranosylimidazo[2,1-*i*]purine hydrochloride monohydrate (**3**) has been determined both to establish the direction of addition of chloroacetaldehyde to adenine in the preparation of ϵ-adenine derivatives and to probe the molecular interactions of the highly fluorescent ϵ-adenosine derivative. The crystals of **3** are monoclinic, with $a = 12.952$ (3), $b = 6.667$ (2), and $c = 9.679$ (2) Å, and $\beta = 101° 34'$ (1′). There are two molecules of $C_{14}H_{18}N_5O_4^+Cl^- \cdot H_2O$ in the space group $P2_1$. The structure has been refined to an R factor of 0.043 in 1373 nonzero reflections. The entire ϵ-adenine moiety is near-planar with a maximum deviation of 0.028 Å among the ring atoms. There are some minor differences in bond lengths in the adenine residue in **3** when compared to unbridged adenine rings, but the greatest differences involve the exocyclic angles at C(6). The arrangement about the glycosyl bond is syn ($\chi_{CN} = -109.1°$) and the ribose ring exists in the C(2′) endo–C(1′) exo conformation. The C(4′)–C(5′) exocyclic bond is in the trans–gauche arrangement. The N–H bond in the base, all three O–H bonds in the sugar, and the water molecules are involved in hydrogen bonding in the monohydrate. The crystal can be divided into successive regions (in the *a* direction) of polar and nonpolar character. In the nonpolar regions, there are infinite stacks (in the *b* direction) of ϵ-adenine rings, each of which overlap considerably with their neighbors with alternate ring–ring separations of 3.344 and 3.324 Å. These overlaps are compared with those found in related molecules.

The reaction of chloroacetaldehyde with adenosine and cytidine to produce fluorescent derivatives[1,2] is claiming increasing biochemical interest.[3] Two compounds that have been particularly useful as fluorescent probes in biochemical systems are 3-β-D-ribofuranosylimidazo[2,1-*i*]purine (1,N^6-ethenoadenosine or ϵAdo) and 5,6-dihydro-5-oxo-6-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidine (3,N^4-ethenocytidine or ϵCyd), each shown as the hydrochlorides, **1** and **2**,



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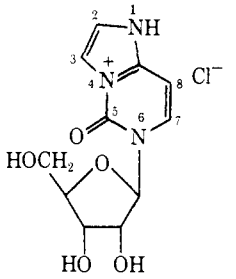


2

respectively. As an aid to understanding the fluorescent behavior of these compounds, in order to provide detailed molecular dimensions, and to explore their capability for intermolecular interactions, we have carried out single crystal X-ray studies on a derivative of ϵAdo, and on ϵCyd, both as hydrochloride salts. For the formation of ϵAdo as the hydrochloride salt from chloroacetaldehyde and adenosine, a logical mechanistic sequence was suggested that first involved alkylation at N(1) (according to convention for numbering in adenine) of the adenosine followed by ring closure of the aldehyde and 6-NH_2 groups with elimination of water.[2] A test of the direction of introduction of the etheno bridge can be made by utilizing the higher homologs, such as α-chloropropionaldehyde[4] or α-chloro-*n*-butyraldehyde. It has now been found that the latter reacts with adenosine more slowly than does chloroacetaldehyde but yields a pure ethyl-substituted ϵ-adenosine that exhibits a fluorescent emission maximum at 440 nm with a quantum yield of 0.33 and a lifetime of 17 nsec under neutral conditions. In order to gain the additional information required, we chose the product of the reaction of adenosine with α-chloro-*n*-butyraldehyde for the X-ray study of an example of an ϵ-adenosine derivative. The X-ray analysis establishes the product as 7-ethyl-3-β-D-ribofuranosylimidazo[2,1-*i*]purine hydrochloride monohydrate (EtϵAdo·HCl·H_2O) (**3**), thereby proving that N(1) (rather than N(6)) of adenosine reacts with the α carbon of the aldehyde.

(1) J. R. Barrio, J. A. Secrist III, and N. J. Leonard, *Biochem. Biophys. Res. Commun.*, **46**, 597 (1972).
(2) J. A. Secrist III, J. R. Barrio, N. J. Leonard, and G. Weber, *Biochemistry*, **11**, 3499 (1972).
(3) J. R. Barrio, L. G. Dammann, L. H. Kirkegaard, R. L. Switzer, and N. J. Leonard, *J. Amer. Chem. Soc.*, **95**, 961 (1973).
(4) N. K. Kochetkov, V. N. Shibaev, and A. A. Kost, *Dokl. Akad. Nauk. SSSR*, **205**, 100 (1972). These authors did not establish the structure of the product.

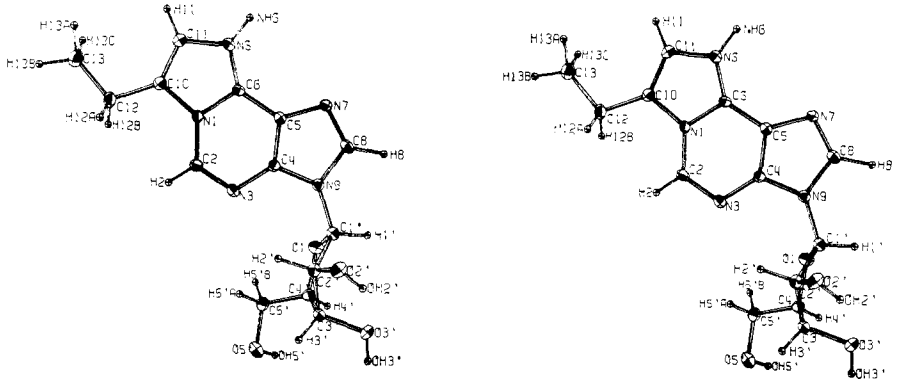
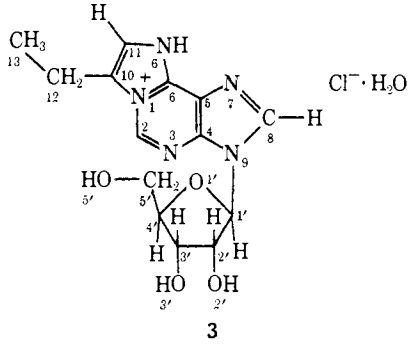


Figure 1. Stereoscopic view of the ϵAdo cation. The percentage probability of the ellipsoids is 20%.

In this paper we describe the crystal and molecular structures and molecular interactions of EtϵAdo·HCl·H_2O. We have also determined the structure of ϵCyd·HCl.[5] In order to facilitate comparisons with related adenine molecules, the conventional atom numbering for adenine, as shown in **3**, is used in this paper.



3

Experimental Section

7-Ethyl-3-β-D-ribofuranosylimidazo[2,1-*i*]purine Hydrochloride Monohydrate (EtϵAdo·HCl·H_2O) (3). The compound was made in a manner similar to the reaction of chloroacetaldehyde with adenosine.[1,2] To 1.0 g of adenosine suspended in 20 ml of water was added 4.0 g of freshly prepared α-chloro-*n*-butyraldehyde. The mixture was stirred at *ca.* 40°, pH 4–4.5, until all of the adenosine had reacted as judged by tlc on cellulose in 1-butanol saturated with water. This required about 5.5 days. Ether (20 ml) was added, and the aqueous layer was separated and treated with decolorizing charcoal. The filtrate was evaporated to small volume and acetone was added. After refrigeration overnight, the colorless crystals were collected by filtration, washed with acetone, and dried: yield 71%; mp 149°; λ_{max} (0.1 *N* HCl) 279 nm (ϵ 11,200), λ_{min} 248 (4000); $\lambda_{max}^{H_2O}$ 0.05 *M* phosphate 263 nm (sh), 270 (ϵ 6200), 281 (6300), 302 (2900), λ_{min} 251 (4100), 276 (5100), 290 (2800); λ_{max} 0.1 *N* NaOH 263 nm (sh), 270 (ϵ 8200), 280 (7800), λ_{min} 253 (6700), 276 (7200); fluorescent emission max 440 nm, quantum yield 0.33, lifetime 17.2 nsec.

Anal. Calcd for $C_{14}H_{18}N_5ClO_4 \cdot H_2O$: C, 44.98; H, 5.39; N, 18.74. Found: C, 44.54; H, 5.54; N, 18.46.

Crystallographic Study of 3. The crystals of **3** are colorless, transparent, rectangular-shaped plates with well-developed (100) faces, and elongated in the *b* direction.

Crystal Data. $C_{14}H_{18}N_5O_4^+Cl^- \cdot H_2O$, mol wt 373.8, monoclinic, a = 12.952 (3), b = 6.667 (2), and c = 9.679 (2) Å, β = 101° 34 (1)′, V = 818.9 Å^3, d_{meas} = 1.50 g cm^{-3}, Z = 2, d_{calcd} = 1.497 g cm^{-3}, $F(000)$ = 392, μ(Cu K$\bar{\alpha}$) = 24.1 cm^{-1}. Systematic absences for $0k0$, when $k = 2n + 1$, indicated that the space group is either $P2_1$ or $P2_1/m$. Since the compound is optically active, the former must be the correct space group. The density was measured by flotation in a mixture of hexane and carbon tetrachloride and the cell data were obtained by a least-squares fit to the hand-centered settings for 12 reflections on a Picker FACS-1 diffractometer ($\lambda_{CuK\bar{\alpha}}$ = 1.5418 Å).

Table I. Final Atomic Coordinates in Fractions of the Unit Cell Edge[a]

	x	y	z
Cl	0.3019 (1)	0.2500[b]	0.1777 (1)
W	0.7411 (3)	0.1286 (8)	0.6328 (4)
N(1)	0.0207 (3)	0.1382 (8)	0.3803 (4)
C(2)	0.1280 (3)	0.1379 (10)	0.3857 (5)
N(3)	0.1967 (3)	0.1394 (8)	0.5024 (4)
C(4)	0.1541 (3)	0.1394 (9)	0.6200 (5)
C(5)	0.0505 (3)	0.1374 (9)	0.6290 (4)
C(6)	−0.0226 (3)	0.1351 (9)	0.4993 (5)
N(6)	−0.1270 (3)	0.1345 (7)	0.4603 (4)
N(7)	0.0366 (3)	0.1406 (8)	0.7671 (4)
C(8)	0.1339 (4)	0.1447 (9)	0.8387 (5)
N(9)	0.2102 (3)	0.1422 (7)	0.7595 (4)
C(10)	−0.0632 (3)	0.1404 (10)	0.2616 (5)
C(11)	−0.1524 (3)	0.1376 (9)	0.3131 (5)
C(12)	−0.0418 (4)	0.1511 (11)	0.1143 (5)
C(13)	−0.1434 (4)	0.1594 (11)	0.0051 (5)
C(1′)	0.3226 (4)	0.1506 (9)	0.8127 (5)
C(2′)	0.3890 (4)	0.0005 (9)	0.7498 (5)
C(3′)	0.4955 (4)	0.1034 (9)	0.7829 (5)
C(4′)	0.4661 (4)	0.3234 (9)	0.7634 (5)
C(5′)	0.4773 (4)	0.4090 (9)	0.6215 (6)
O(1′)	0.3581 (3)	0.3409 (6)	0.7776 (4)
O(2′)	0.3827 (3)	−0.1958 (6)	0.8036 (4)
O(3′)	0.5454 (3)	0.0648 (7)	0.9258 (3)
O(5′)	0.5840 (3)	0.4208 (7)	0.6091 (4)
WH(1)	0.729 (5)	0.004 (11)	0.677 (6)
WH(2)	0.692 (4)	0.191 (9)	0.625 (5)
H(2)	0.157 (4)	0.142 (13)	0.307 (6)
NH(6)	−0.180 (4)	0.124 (10)	0.520 (5)
H(8)	0.163 (4)	0.166 (9)	0.957 (5)
H(11)	−0.227 (3)	0.152 (8)	0.268 (4)
H(12A)	−0.001 (4)	0.022 (9)	0.102 (5)
H(12B)	0.007 (5)	0.287 (12)	0.101 (6)
H(13A)	−0.205 (6)	0.025 (13)	0.010 (7)
H(13B)	−0.146 (4)	0.193 (9)	−0.107 (6)
H(13C)	−0.191 (4)	0.268 (11)	0.010 (6)
H(1′)	0.337 (3)	0.142 (8)	0.918 (4)
H(2′)	0.353 (3)	0.010 (7)	0.643 (4)
H(3′)	0.538 (3)	0.049 (8)	0.722 (4)
H(4′)	0.504 (4)	0.394 (8)	0.832 (5)
H(5′A)	0.441 (6)	0.361 (14)	0.544 (8)
H(5′B)	0.433 (4)	0.552 (9)	0.598 (5)
OH(2′)	0.427 (4)	−0.197 (8)	0.875 (5)
OH(3′)	0.604 (4)	0.032 (8)	0.927 (5)
OH(5′)	0.613 (5)	0.503 (7)	0.674 (5)

[a] Standard deviations in parentheses. [b] The y coordinate of the Cl ion was held constant to define the origin in the *b* direction.

A crystal 0.5 mm in the *b* direction and 0.2 × 0.06 mm in cross section was used for data collection. The general procedures for data collection were as described previously.[6] The octants of

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(6) J. K. Frank and I. C. Paul, *J. Amer. Chem. Soc.*, **95**, 2324 (1973).

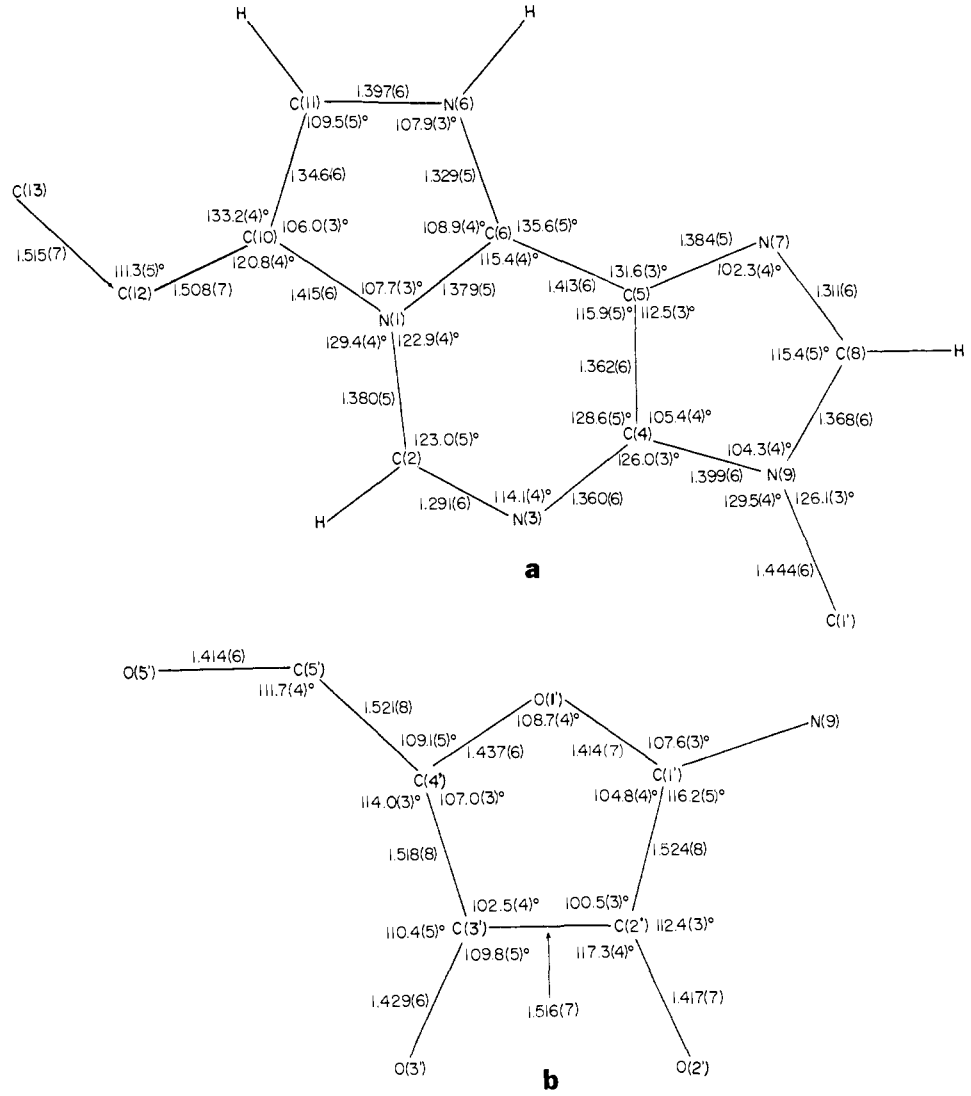

Figure 2. (a) Bond distances and angles involving non-hydrogen atoms in the ϵAde base. (b) Bond distances and angles in the ribose ring The range of C–H distances is 0.88 (6) to 1.20 (8) Å and of O–H distances is 0.75 (5) to 0.96 (7) Å.

data *hkl* and $\bar{h}kl$ were measured to $2\theta = 130°$. No evidence for crystal deterioration or loss of intensity was noted. Of 1526 possible unique reflections, 1373 were considered to be significantly above background, using a 2σ criterion based on counting statistics. The data were corrected for Lorentz and polarization effects, but not for absorption.

The structure was solved by the heavy atom method based on chlorine. Full-matrix least-squares refinement varying positional and isotropic temperature factors for the nonhydrogen atoms gave an R factor of 0.104 and R_2, $[\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$, of 0.122. All reflections were given weights using a program written by Dieterich,[7] which uses essentially the method described by Corfield, Doedens, and Ibers[8] and the quantity minimized was $\Sigma w(|F_o| - |F_c|)^2$.

Introduction of anisotropic temperature factors for the non-hydrogen atoms into the refinement reduced the R factor to 0.065 and a difference map was calculated at this stage which showed clearly the positions of all the hydrogen atoms. When the model included positional parameters for all atoms, anisotropic thermal parameters for the non-hydrogen atoms, and isotropic thermal parameters for the hydrogen atoms, full-matrix least-squares refinement gave final values of R and R_2 of 0.043 and 0.045, respectively, on all observed reflections. A final difference map contained no peaks greater than 0.3 e/Å^3. The final values for the positional parameters are listed in Table I.[9]

The scattering curves for Cl^-, C, N, and O used in the analysis were taken from the compilation by Cromer and Mann,[10] and the one for hydrogen was that calculated by Stewart, *et al.*[11]

Results and Discussion

Molecular Dimensions of the ϵ-Adenine Ring. A stereoscopic view of the EtϵAdoH$^+$ cation, looking normal to the plane of the ϵAde moiety, is shown in Figure 1. The bond lengths and angles involving non-hydrogen atoms are shown in Figure 2. A rigid body analysis[12] of the thermal motion in the ϵ-adenine moiety, while showing that the ring system could be treated as a good rigid body (rms Δ of $U(i,j)$ is 0.0027 Å^2), resulted in corrections to the bond lengths of 0.003 Å or less. In subsequent discussions, the uncorrected values are used. The site of protonation in the EtϵAdo cation is the N(6) position. Other purine nucleosides that have been investigated as monocations in halide salts include formycin hydrobromide,[13] aristeromycin

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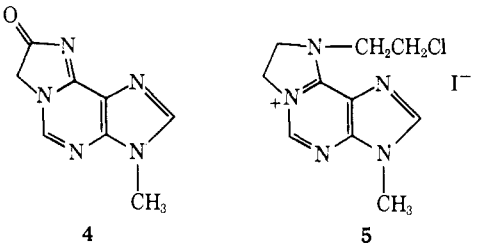
hydrobromide,[14] 2′,3′-*O*-isopropylideneadenosine hydroiodide,[15] 5′-methylammonium-5′-deoxyadenosine iodide monohydrate,[16] and adenosine hydrochloride.[17] While hydrogens atoms were not included in several of these analyses, there is no evidence that the sugar rather than the nucleic acid base was the site of protonation.

Since the N(6) and N(1) atoms are linked by the 1,-N^6-etheno bridge and constrained in a five-membered ring, some differences in the bond lengths and angles involving these two atoms can be anticipated when dimensions are compared with those of an unbridged adenine moiety, whether neutral or protonated. Table II lists the average values of the dimensions in the pyrimidine ring of a protonated adenine in 12 different molecules.[18–26] The values for another somewhat similar, although neutral, compound, 3-methyl-3*H*-imidazo[2,1-*i*]purin-8(7*H*)-one (**4**),[27] are also included in the table. Another adenine derivative (**5**) with a C_2 bridge between N(1) and N(6) has also been studied by X-ray diffraction, but was not refined to a stage that merits detailed discussion of the molecular dimensions.[28] As has been pointed out previously,[24,29–32] formation of a bond to a third atom by the atom N(1) in an adenine ring leads to an increase in the C(2)–N(1)–C(6) angle by 4–5° over what it would be in unsubstituted adenine. Most of the dimensions in **3**, including the C(2)–N(1)–C(6) angle, agree well with the other values in the table. Thus, the size of the C(2)–N(1)–C(6) angle seems to be independent of whether N(1) is protonated or, as in **4**, uncharged but substituted with a methylene group. It has recently been shown that an N-oxide at N(1) also causes a large C(2)–N(1)–C(6) angle.[33]

Table II. Comparison of the Bond Lengths (Å) and Angles (deg) of the Pyrimidine Ring in EtϵAdo·HCl (**3**), with Those in 3-Methyl-3*H*-imidazo[2,1-*i*]purin-8(7*H*)-one (**4**), and the Averaged Values of 12 Protonated Adenine Moieties

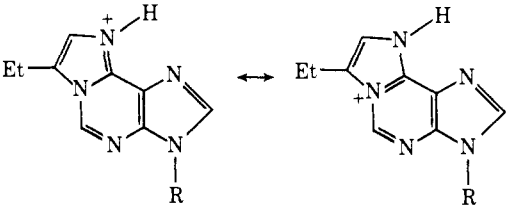
Bond lengths	**3**[a]	**4**[b]	Av[c,d]
N(1)–C(2)	1.380 (5)	1.363 (3)	1.356 ± 0.012
N(1)–C(6)	1.379 (5)	1.381 (3)	1.368 ± 0.012
C(2)–N(3)	1.291 (6)	1.308 (3)	1.307 ± 0.012
N(3)–C(4)	1.360 (6)	1.358 (3)	1.358 ± 0.010
C(4)–C(5)	1.362 (6)	1.383 (3)	1.373 ± 0.015
C(5)–C(6)	1.413 (6)	1.404 (3)	1.414 ± 0.017
C(6)–N(6)	1.329 (5)	1.326 (3)	1.312 ± 0.012
Bond angles			
C(2)–N(1)–C(6)	122.9 (4)	124.9 (1)	123.8 ± 0.9
N(1)–C(2)–N(3)	123.0 (5)	123.2 (2)	126.0 ± 0.9
C(2)–N(3)–C(4)	114.1 (4)	112.9 (1)	111.2 ± 0.9
N(3)–C(4)–C(5)	128.6 (5)	128.3 (2)	128.0 ± 1.1
C(4)–C(5)–C(6)	115.9 (5)	117.1 (2)	117.7 ± 1.0
C(5)–C(6)–N(1)	115.4 (4)	113.6 (1)	113.6 ± 0.8
N(1)–C(6)–N(6)	108.9 (4)	114.6 (2)	121.1 ± 1.2
N(6)–C(6)–C(5)	135.6 (5)	131.8 (1)	125.5 ± 1.3

[a] This work. [b] Reference 27. [c] Averaged values among adenosine hydrochloride,[17] 5′-AMP,[18] 3′-AMP,[19] A(2′-5′)U,[20] 3′-deoxy-3′-(dihydroxyphosphinylmethyl)adenosine,[21] 5′-methyleneadenosine 3′,5′-cyclic monophosphonate monohydrate,[22] puromycin dihydrochloride pentahydrate,[23] $AdeH^+$-C_3-Nic^+,[24] and uridylyl-(3′–5′)-adenosine hemihydrate.[25,26] [d] The crystals of uridylyl-(3′–5′)-adenosine hemihydrate have two independent molecules in the asymmetric unit and were studied by two different groups.[25,26] Thus, four sets of values for this molecule were included in the average.



4 **5**

The N(1)–C(6)–N(6) angle of 108.9 (4)° in the ϵ-adenosine is considerably smaller than the averaged value of 121.1° given in Table II for protonated adenine groups. Similarly, the C(5)–C(6)–N(6) angle of 135.6 (5)° in ϵAdo is greater than the averaged value of 125.5°. The C(2)–N(3)–C(4) angle of 114.1 (4)° is larger than the averaged value of 111.2° among the protonated adenine rings, while the N(1)–C(2)–N(3) angle in **3** (123.0 (5)° as compared to 126.0°) is smaller. The values found in **4** are rather similar to those in **3**. The C(4)–N(9)–C(1′) angle of 129.5 (4)° is greater than



6 **7**

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Table III. Least-Squares Planes for the Base and Sugar and the Deviations of the Atoms from the Planes in Å[a,b]

Atoms	Plane I	II	III	IV	V	VI	VII
N(1)	**0.003**	**0.001**	**0.007**				
C(2)	**−0.007**	0.012	**−0.006**				
N(3)	**−0.005**		**−0.002**	0.020			
C(4)	**−0.007**		**0.004**	**0.005**			
C(5)	**−0.013**	−0.032	**0.002**	**−0.002**			
C(6)	**−0.019**	**−0.001**	**−0.008**	0.010			
N(6)	**−0.014**	**0.000**	−0.002				
N(7)	**0.005**		0.026	**−0.002**			
C(8)	**0.023**		0.044	**0.006**			
N(9)	**0.004**		0.019	**−0.004**			
C(10)	**0.028**	**−0.002**	0.030				
C(11)	**0.014**	**0.001**	0.020				
C(12)	0.103	−0.047	0.097				
C(13)	0.169	−0.093	0.162				
C(1′)	0.050			0.034	**−0.228**	**−0.015**	−0.084
C(2′)					**0.263**	0.615	0.548
C(3′)					**−0.176**	**0.014**	**0.000**
C(4′)					**0.049**	**−0.023**	**0.000**
O(1′)					**0.057**	**0.013**	**0.000**
C(5′)					1.350	1.132	1.195
χ^2	67.5	0.2	5.4	2.3	7410	55.5	0.0
P[c]	≪0.01	0.90	0.20	0.30	<0.005	<0.01	

[a] The distances in boldface are for the atoms included in the best plane calculation. [b] In these calculations, the atoms were weighted as $1/\sigma^2$, where σ is the standard deviation from the least-squares results. [c] The probability (on the basis of the χ^2 test) that the deviations of the atoms from the plane form a normal distribution.

the C(8)–N(9)–C(1′) angle of 126.1 (3)° as a result of the syn conformation of the molecule as will be described in a subsequent section. Similar differences have also been noted in many purine nucleosides with the syn conformation.[16,22,34–37]

It is of interest to note that the ethyl side chain on the etheno bridge assumes a conformation such that the terminal C(13) methyl group points away from the purine ring system. In many N^6-monosubstituted adenine derivatives, such as N^6-methyladenine,[38] N^6-(Δ^2-isopentenyl)adenine (i^6Ade),[39] and N^6-(Δ^2-isopentenyl)-2-methylthioadenine (i^6ms^2Ade),[40] aliphatic substituents at the N(6) position tend to point away from the C(4)–N(9) imidazole ring. The ethyl group on the etheno bridge is almost coplanar with the plane of the ϵ-adenosine base. Such a coplanar conformation may be anticipated on two counts. It allows both methylene hydrogen atoms on C(12) to be gauche to the C(10)–N(1) bond so that the C(13) methyl group approaches the H(11) atom on C(11). The stability of this arrangement is also enhanced by the large C(11)–C(10)–C(12) exocyclic angle of 133.2 (4)°. The coplanarity of the ethyl group with the ϵ-adenine ring would also facilitate a crystal packing arrangement in which there would be stacking by the flat portions of the molecule. In the N^6-monosubstituted adenine derivatives,[38–40] the amino nitrogen atom N(6) and its immediate substituents are also essentially coplanar with the purine ring.

The atoms composing the ring system of the ϵ-adenine cation are not quite coplanar with a maximum deviation of 0.028 Å (plane I in Table III). However, when the groups of atoms of the three rings are considered individually, all are quite planar. Plane II and plane IV (Table III) each make an angle of 1.0° with plane III and form a slight "U" shape when looking from the edge side. The atoms of the two five-membered rings all lie on the *same* side of the best plane through the six-membered ring, that of C(8) being as great as 0.044 Å. While N(6) is almost in the plane of the six-membered ring, C(10), C(11), C(12), and C(13) lie 0.030, 0.020, 0.097, and 0.162 Å, respectively, from that plane. In the case of the molecule **4**, it is the carbon atom of the methylene group (in a position corresponding to C(10) in **3**) that lies in the best plane of the six-membered ring, while the atoms in positions corresponding to N(6) and C(11) lie 0.009 and 0.046 Å from the plane. Whereas in **3** the imidazole ring [C(4), C(5), N(7), C(8), and N(9)] is bent from the plane of the six-membered ring, in **4** it is twisted with N(9) being 0.024 Å from the plane on the *same* side as the deviation of the other five-membered ring and N(7) being 0.024 Å on the *opposite* side.

Molecular Dimensions of the Ribose Ring. In the ϵ-adenosine derivative, the best four-atom plane in the ribose ring is defined by the atoms C(1′), C(3′), C(4′), and O(1′) (Table III). The atom C(2′) lies 0.615 Å on the same side of this plane as C(5′). The conformation of the ribose is thus C(2′) endo, which is one of the common puckering modes of the ribose ring in nucleosides, nucleotides, and nucleic acids.[41] When referred to the three-atom plane, C(3′), C(4′), and O(1′), the puckering of the ribose ring is C(2′) endo–C(1′) exo($^2T_1$) with C(2′) and C(1′) lying on opposite sides of the plane at distances of 0.548 and −0.084 Å, respectively. This mode of puckering is commonly found among purine

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Table IV. Torsion Angles (deg) at the Ribose Ring of the ϵ-Adenosine Derivative[a]

C(4′)–O(1′)–C(1′)–C(2′)	−27.6	C(4)–N(9)–C(1′)–O(1′)	67.6
O(1′)–C(1′)–C(2′)–C(3′)	40.0	C(4)–N(9)–C(1′)–C(2′)	−49.6
C(1′)–C(2′)–C(3′)–C(4′)	−36.4	C(8)–N(9)–C(1′)–O(1′)	−109.1
C(2′)–C(3′)–C(4′)–O(1′)	21.3	C(8)–N(9)–C(1′)–C(2′)	133.7
C(3′)–C(4′)–O(1′)–C(1′)	3.6	O(1′)–C(4′)–C(5′)–O(5′)	172.1
		C(3′)–C(4′)–C(5′)–O(4′)	−68.5

[a] The torsion angle A–B–C–D is considered positive if, when looking along the bond from B to C, atom A has to be rotated clockwise to eclipse atom D.

nucleosides.[42] The atom O(2′) is in an equatorial position, while O(3′) and C(5′) are in axial orientations.

The bond lengths and angles of the ribose ring are quite normal when compared to the most recently compiled set of average values.[43] The torsion angles of the ribose ring are shown in Table IV and they agree quite well with the averaged values found in C(2′) endo nucleosides.[43] The torsion angles about the C(4′)–C(5′) exocyclic bond are rather unusual, assuming a trans–gauche conformation with $\phi_{OO} = 172.1°$ and $\phi_{OC} = -68.5°$, respectively.[44] Although theoretical calculations[45] have predicted that the trans–gauche conformation about the C(4′)–C(5′) bond is slightly more stable than the gauche–trans conformation in ribonucleosides having the C(2′) endo conformation of the ribose ring and the syn arrangement about the glycosyl bond, this is only the second purine nucleoside that has been shown to have this conformation in the solid state; the first example was in the complex of 5′-bromo-5′-deoxyadenosine with riboflavine.[46] However, this conformation has been noted frequently in the case of pyrimidine nucleosides.[47–50]

Molecular Conformation of the ϵAdo Cation. The glycosyl torsion angle, χ_{CN}, which describes the relative orientation of the base with respect to the sugar is −109.1° in EtϵAdo·HCl (see Figure 1). Thus, the conformation about the glycosyl bond is syn. This value of χ_{CN} lies to the end of the syn conformation range with smallest negative torsion angles. The only other purine nucleoside with a value of χ_{CN} in this region is N^2-dimethylguanosine[34] where the angle is −103.9°.

Crystal Structure. The crystal structure is shown in the stereoscopic pictures, Figures 3 and 4. In the *a* direction, regions of a nonpolar or hydrophobic nature alternate with polar regions. These nonpolar and polar regions extend in the *b* and *c* directions. A structure with a similar nonpolar band containing perpendicular stacks of bases and extending in two directions was found in the crystal of 4-thiouridine hemihydrate.[51,52] The nonpolar area is characterized by stacking of the EtϵAdeH$^+$ bases; the polar region contains ribose residues, water molecules, and chloride ions, linked together by ionic contacts and hydrogen bonding.

Hydrogen Bonding. Compared to protonated adenine nucleosides, the ϵ-adenosine derivative has lost considerable hydrogen-bonding capability in the heterocyclic base. The only hydrogen bond formed by the ϵAdo cation (with the possible exception of a very weak C(2)–H···Cl$^-$ interaction (see below)) is one of length 2.617 (5) Å through the N(6) proton to a water molecule at $-1 + x, y, z$ (Table V). The water molecule acts as a hydrogen bonding donor to the O(5′) hydroxyl group and to the chloride anion at $1 - x, -\frac{1}{2} + y, 1 - z$. The arrangement of the three non-hydrogen atoms participating in hydrogen bonds with the water molecule is nearly trigonal planar. The oxygen atom of the water molecule lies 0.236 (4) Å from the plane defined by the other three atoms.

Table V. Molecular Dimensions Relevant to the Hydrogen Bonding Scheme and Short Contacts[a]

Hydrogen bond D–H···A	Distances, Å D···A	Distances, Å H···A	Angles, deg D–H···A
N(6)–H···W^{II}	2.617 (5)	1.64 (5)	172 (5)
O(2′)–H···O(3′)^{I}	2.804 (5)	2.31 (5)	120 (3)
O(2′)–H···O(3′)^{III}	3.048 (5)	2.47 (5)	130 (4)
O(3′)–H···Cl^{IV}	3.180 (4)	2.56 (5)	137 (4)
O(3′)–H···O(1′)^{III}	3.255 (5)	3.08 (5)	96 (4)
O(5′)–H···Cl^{V}	3.168 (4)	2.34 (5)	169 (2)
W–WH1···Cl^{IV}	3.234 (5)	2.29 (7)	168 (4)
W–WH2···O(5′)^{I}	2.792 (6)	2.06 (6)	166 (5)
C(8)–H···Cl^{VI} [b]	3.624 (5)	2.57 (5)	154 (4)
C(2)–H···Cl^{I} [b]	3.392 (5)	2.56 (6)	151 (3)

[a] D refers to donor, A, acceptor; I, x, y, z; II, $-1 + x, y, z$; III, $1 - x, -\frac{1}{2} + y, 2 - z$; IV, $1 - x, -\frac{1}{2} + y, 1 - z$; V, $1 - x, \frac{1}{2} + y, 1 - z$; VI, $x, y, 1 + z$. [b] Short contacts.

The chloride ion is also an acceptor for two hydrogen bonds that serve to link two ϵ-adenosine molecules. The donor atoms are O(5′) in the molecule at $1 - x, -\frac{1}{2} + y, 1 - z$, and O(3′) in the molecule at $1 - x, \frac{1}{2} + y, 1 - z$. The chloride ion is also approached by a C(2)–H group from the reference molecule and by a C(8)–H group from the molecule at $x, y, -1 + z$. The H···Cl$^-$ distances of 2.56 (6) and 2.57 (5) Å are approximately 0.25 Å less than the sum of the van der Waals radius of hydrogen[53] either with the van der Waals radius of covalently bound chlorine[54] or with the

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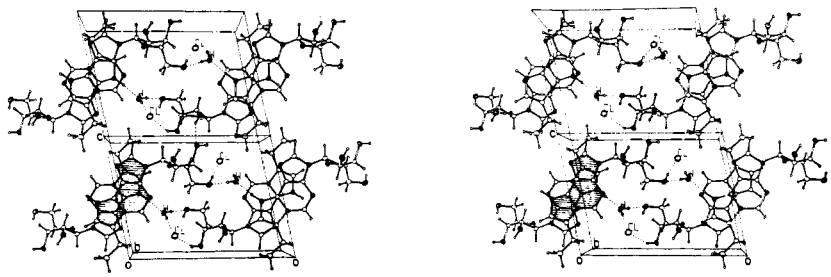


Figure 3. Stereoscopic view of the packing in the crystal of **3** looking almost along the *b* axis. The ϵ-adenine group in the reference molecule (*i.e.*, the one whose coordinates are given in Table I) is shaded. This figure illustrates well the successive region of nonpolar and polar character in the *a* direction.

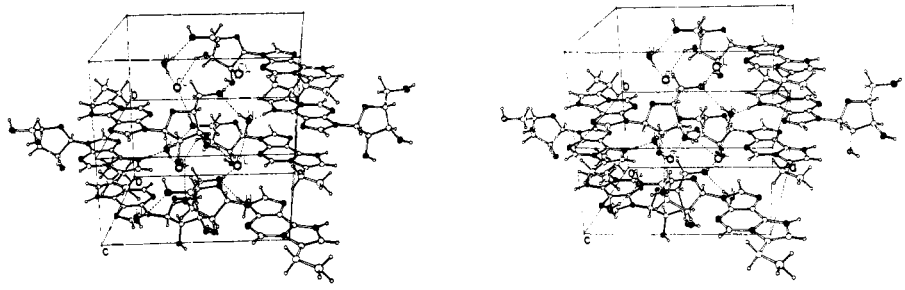
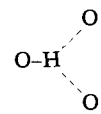


Figure 4. Stereoscopic view of the crystal of **3**, looking at an angle to the stacks of the ϵ-adenine bases. The reference molecule is shown by heavy lines.

ionic radius of the chloride anion.[55] Whether such contacts can properly be considered as hydrogen bonds is really a matter of individual classification. Certainly, the stronger hydrogen bonds all lie on the opposite side of the chloride ion from the C–H···Cl^- interactions.

All the hydroxyl groups in the sugar residue are involved in hydrogen bonding. The atoms O(3′) and O(5′) act as both donors and acceptors for hydrogen bonds. The O(2′)–H···$O(3')^{III}$ interaction is the only direct hydrogen bond between the two ϵAdo groups.

In the case of the hydrogen bonds involving the hydroxyl groups with O(2′) and O(3′), the H···A distances were quite long and the D–H···A angles vary greatly from linearity. We have considered the possibility of bifurcated hydrogen bonds involving these two hydroxyl groups. The atom O(2′) appears to interact intramolecularly to O(3′) and intermolecularly to O(3′) in the molecule at $1 - x, -1/2 + y, 2 - z$. The intramolecular O(2′)···O(3′) and H···O(3′) distances are 2.804 (5) and 2.31 (5) Å and the O(2′)–H···O(3′) angle is 120 (3)°. The corresponding intermolecular distances are 3.048 (5) and 2.47 (5) A and the angle is 130 (4)°. A rather similar



intramolecular–intermolecular bifurcated hydrogen bond was reported in the structure of 3-deazauridine.[56] The atom O(3′) interacts with Cl^- at $1 - x, -1/2 + y, 1 - z$ and with O(1′) in the molecule at $1 - x, -1/2 + y, 2 - z$. The O(3′)···Cl^{-IV} and H···Cl^{-IV} distances are 3.180 (4) and 2.56 (5) Å and the O(3′)–H···Cl^{-IV} angle is 137 (4)°, whereas the O(3′)···$O(1')^{III}$ and H···$O(1')^{III}$ distances are 3.255 (5) and 3.08 (5) Å and the O(3′)–H···$O(1')^{III}$ angle is 96 (4)°.

There is also a short intramolecular N(3)···H(2′) distance of 2.37 (5) Å (Figure 1).

Molecular Overlap of Bases. A most striking aspect of the structure is the great overlap of the ϵAde bases in the stacks built along the *b* axis. The plane of the base is almost exactly perpendicular to the *b* axis (Figure 4). Adjacent ϵ-adenine rings in the stack are mutually inclined at an angle of 0.8°. Figure 5a shows the overlap of the ϵAde bases with one ϵ-adenine group projected onto the plane of the reference ϵ-adenine moiety. The projection of the ϵ-adenine on the other side onto the reference ϵ-adenine is almost identical (as a consequence of the base being perpendicular to the *b* axis). The interplanar spacing between the reference molecule and the one at $-x, 1/2 + y, 1 - z$ is 3.344 Å; that between the reference molecule and the one at $-x, -1/2 + y, 1 - z$ is 3.324 Å. Bugg, Thomas, Sundaralingam, and Rao, after a survey of base stacking in crystals, concluded that extensive overlap of bases is rather unusual.[57] Some overlap arrangements involving adenine groups were discussed recently by Johnson, Maier, and Paul.[58] Among adenine derivatives that show extensive overlap are 9-methyladenine[59] and 9-ethyladenine in the complex with 1-methyluracil.[60] It is particularly interesting in the present context to note that the ring formed by the etheno bridge is almost completely overlapped by the purine portion of the adjacent molecule. If one focusses on the atoms of the adenine moiety, the main

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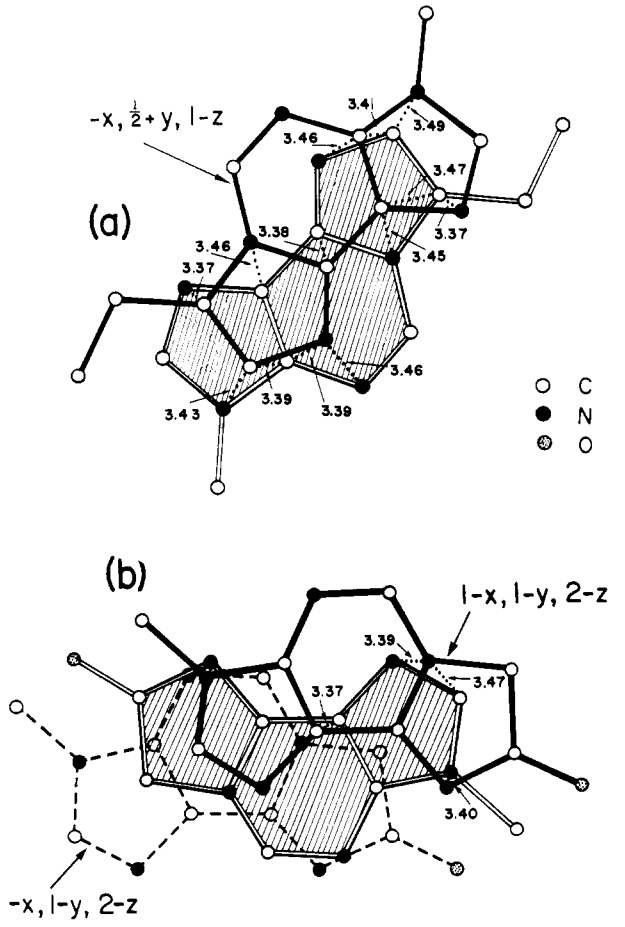

Figure 5. (a) Overlap of the ϵ-adenine moiety in the molecule at $-x, \frac{1}{2} + y, 1 - z$ onto the best plane through the 12 ring atoms of the ϵ-adenine moiety of the reference molecule (shaded). Interaction distances <3.5 Å are marked. (b) Overlap of the two adjacent molecules of **4** onto the best plane of the 12 ring atoms in the reference molecule (shaded).

overlap is of the C(6)–N(6) bond with the center of the pyrimidine ring. This type of spatial relationship between adenine rings was also found in the structure of α-D-2′-amino-2′-deoxyadenosine monohydrate.[61] In that structure there was also an infinite stack of adenine rings related by a twofold screw axis.

It is also rather unusual to find a continuous stack of the heterocyclic bases as in the present case. Such an arrangement was, however, noted in the crystal structure of the hydrated sodium salt of adenosine triphosphate.[62] In the structure of ATP, however, the overlap was between crystallographically independent molecules and the C(6)–NH_2(6) group pointed in the same general direction for adjacent overlapping molecules.

The projections of the two adjacent neighbors onto the plane of the reference molecule of the neutral analog **4** are shown in Figure 5b. These drawings were calculated by us from the coordinates presented in ref 27. In that paper, the discussion of molecular overlap was confusing and misleading in that the projections of molecules onto exact molecular planes were not made, but rather overlap was discussed with reference to a rather arbitrary plane through the entire crystal. There are only two distinct overlaps in the crystal of **4** as shown in Figure 5b. In the stacking shown with the dashed line in Figure 5b, there is almost complete overlap of the pyrimidine and 1,N^6 five-membered ring portions of adjacent molecules. The orientation of this overlap is rather similar to the one found by us in the ϵ-adenosine derivative, although the average interplanar spacing (3.520 Å) is greater in the case of **4** than in **3** (3.324 or 3.344 Å). If the difference in interplanar spacing is neglected, there is greater overlap in the case of **4** than in **3**. In the other stacking in the structure of **4** (heavy line in Figure 5b), the greatest overlap is with the two different types of five-membered ring. In this interaction, the interplanar spacing is 3.360 Å. In the structure of ATP,[62] where there is a stack of interleaved crystallographically independent adenine residues, the plane of one adjacent adenine is closer (average distance 3.26 Å) than the other (average distance 3.42 Å) to the plane of the reference molecule. In the case of both ATP molecules, adjacent adenine rings are inclined at an angle of 3.3°, compared to 0.8° in **3** and exact parallelism in **4**.

There was no base–base overlap in the crystal structure of **5**.[28] The main interaction in that crystal appeared to be an ion–ion contact between the positively charged heterocyclic base and the iodide ion.

Polymers of ϵ-adenine derivatives have recently been prepared and studied.[63,64] The present analysis clearly indicates that under acid conditions, N(6) will be protonated in the ϵAde series and that the formation of a pair of N(6)–H···N(7) hydrogen bonds should be possible between two ϵAde moieties, thus allowing a double-stranded polymer to be formed. However, unlike the case in crystals of many adenine structures,[24,58] where the adenine residues form a pair of N(6)–H···N(7) hydrogen bonds, in the present crystal such an arrangement appears to be sacrificed so that base stacking can occur. Both studies of polymers of ϵ-adenosine derivatives noted a significant change in properties in going from acid to neutral pH conditions. Lehrach and Scheit[64] observed less quenching of fluorescence upon polymerization of ϵADP as compared to other fluorescent nucleotide derivatives, and they postulated that this may be due to reduced stacking interactions in the polymer on account of steric hindrance caused by the additional ring. Our results do not support such an idea in view of the large overlap of the ϵ-adenine rings of **3** observed in the crystal.[65,66]

Acknowledgment. We thank Professor N. J. Leonard for introducing us to the problem and for his generous and valuable criticism of our paper. This work was supported by National Institutes of Health Grants GM 19336 and GM 05829 and by a grant for computer time from the Research Board at the University of Illinois.

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Supplementary Material Available. The final values for the thermal parameters and the list of $h, k, l, |F_o|, |F_c|$, and α will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-1205.

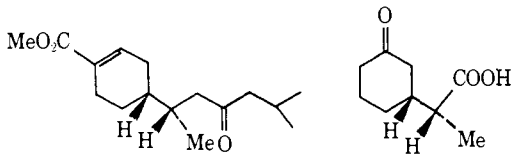
Communications to the Editor

Stereospecific Synthesis of *dl*-Juvabione

Sir:

We wish to describe in this communication the first stereospecific synthesis of *dl*-juvabione (**1**), a sesquiterpene which shows its juvenile hormone activity selectively on the insects of the Pyrrhocoridoe family. The absolute configuration of the natural enantiomer *d*-juvabione has been established by X-ray analysis[1] as 4(*R*) and 8(*S*), as shown in **1**.

Previous syntheses of juvabione[2] required separation of diastereoisomers, a reflection of the difficulty presented by the fact that one of the two asymmetric centers is in a free-rotating side chain. We have recently reported a method[3,4] which appeared suitable for the solution of this type of problem, since it allows the preparation of the keto acid **2**,[4b] free of its diastereo-

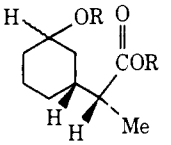


1 **2**

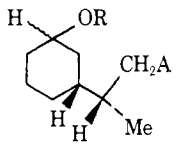
isomer. The application of our method to the synthesis of *dl*-juvabione is especially attractive as it resolves the problem of stereospecific construction at the very beginning of the synthesis.

Various strategies are conceivable for the transformation of the keto acid **2** to *dl*-juvabione (**1**). In the one we describe here, we first elaborate the side chain, and then the unsaturated ester component. To allow eventual differentiation of the ring carbonyl, which will serve to introduce the unsaturated ester function, from that which must be placed in the side chain of juvabione, the keto acid **2**[4b] (mp 76°; nmr[5] ($CDCl_3$) δ 1.15 ppm (d, 3)) was first reduced catalytically (PtO_2–H_2, dioxane, 25°, 1 atm, drop of hydrochloric acid) to produce in quantitative yield the hydroxy acid **3a** as a mixture of cyclohexanol epimers (ir (film) 3700–2300 and 1710 cm^{-1}; nmr ($CDCl_3$) δ 4.05 ppm (m, 1)); one of the epimers was obtained crystalline, mp 109° (chloroform–hexane). That **3a** is produced as an epimeric mixture is, of course, irrelevant to the overall stereospecificity since the center involved will again become trigonal. The cyclohexanol hydroxyl was, then, protected by reaction with ethyl vinyl ether (ether–HCl), which also esterified the carboxyl function, to give **3b** (bp 120–125° (0.1 mm); ir (film) 1730 cm^{-1}; nmr (CCl_4) δ 4.65 (q, 1) and 5.8 ppm (q, 1)), which was then reduced ($LiAlH_4$, ether, reflux) to the alcohol **4a** (bp 90° (0.015 mm); ir (film) 3350 cm^{-1} (broad), nmr (CCl_4) δ 4.65 ppm (q, 1)). The removal of the carboxyl function in the side chain, at this early stage, ensures that no subsequent epimerization of the adjacent center can take place. The stereochemical integrity at this stage was established by Jones oxidation of the glycol **4b** to the starting keto acid **2**.

Elaboration of the ketonic side chain of juvabione was achieved by the use of the Stork–Maldonado ketone synthesis,[6] starting with the bromide **4c** (bp



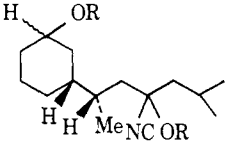
3a, R = H
b, R = CH(Me)OEt



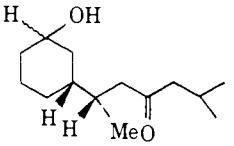
4

4a, R = CH(Me)OEt; A = OH
b, R = H; A = OH
c, R = CH(Me)OEt; A = Br

97–98° (0.2 mm); nmr (CCl_4) δ 3.85 (m, 1) and 4.65 ppm (q, 1)) derived from **4a**.[7] The sequence, initiated by reaction of **4c** with 1.5 equiv of the anion of the protected cyanohydrin of isovaleraldehyde, led, in quantitative yield, *via* **5a** and **5b** to the hydroxy ketone **6**: bp 130–135° (0.4 mm); ir (film) 3400 (broad) and 1710 cm^{-1}; nmr (CCl_4) δ 4.05 ppm (m, 1).



5a, R = CH(Me)OEt
b, R = H



6

The synthesis of the hydroxy ketone **6**, thus available in 50% overall yield starting from the initial keto acid

(1) J. F. Blount, B. A. Pawson, and G. Saucy, *Chem. Commun.*, 715 (1969).

(2) (a) K. S. Ayyar and G. S. K. Rao, *Tetrahedron Lett.*, **43**, 4677 (1967); *Can. J. Chem.*, **46**, 1467 (1968); (b) K. Mori and M. Matsui, *Tetrahedron*, **24**, 3127 (1968; (c) B. A. Pawson, H. C. Cheung, S. Gurbaxani, and G. Saucy, *Chem. Commun.*, 1057 (1968); *J. Amer. Chem. Soc.*, **92**, 336 (1970); (d) A. J. Birch, P. L. Macdonald and V. H. Powell, *Tetrahedron Lett.*, 351 (1969); *J. Chem. Soc. C*, 1469 (1970); (e) G. Farges and H. Veschambre, private communication.

(3) J. Ficini and A. Krief, *Tetrahedron Lett.*, **18**, 1431 (1969); **17**, 1397 (1970).

(4) (a) J. Ficini and A. M. Touzin, *Tetrahedron Lett.*, **21**, 2093 (1972); (b) *ibid.*, **21**, 2097 (1972).

(5) The nmr spectra of all intermediates are recorded on a Varian T.60 (60 MHz) instrument.

(6) G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, **93**, 5286 (1971).

(7) The bromide **4c** is prepared from **4a** by the procedure described by J. Hooz and S. S. H. Gilani, *Can. J. Chem.*, **46**, 86 (1968); using CBr_4 and $(C_6H_5)_3P$ in ether, with 1 equiv of pyridine, at 0°, then 3 hr at 25°.