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Conformations of 2-*C* : 1-*N*-carbonyl-2-deoxy-D-glycopyranosylamines *

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ABSTRACT

Conformations of three derivatives of 2-*C*: 1-*N*-carbonyl-2-deoxy-D-glycopyranosylamines were investigated in the solid state, by use of X-ray. Quantitative conformational analysis (asymmetry parameters and puckering parameters), applied to the ring system in six crystallographically determined structures, revealed, for the pyranoid ring, conformations different from the initially observed half-chair conformation (*H*). Experimental conformations compared with molecular modelling-derived structures showed the importance of the *β*-lactam ring in shaping the pyranoid moiety. An entirely different hydrogen-bonding pattern, observed for molecules differing by one substituent, illustrates how easily the energy (conformation) of a molecule in solution or in the solid state could be influenced by intermolecular interactions. Substitution of the *β*-lactam nitrogen atom significantly changes the geometry of the four-membered ring.

INTRODUCTION

Previously, we have reported the synthesis and structural studies of a new class of bicyclic *β*-lactams[1]. Since X-ray studies, as well as molecular mechanics calculations, have shown that the conformations of the pyranoid rings in the *α*-D-*gluco*, *β*-D-*arabino*, and *β*-D-*altro* derivatives remain within the calculated global energy minimum assigned to the half-chair conformation, the ^{1}H and ^{13}C NMR data were interpreted in terms of two interconverting half-chair forms. Not all data, however, have been entirely consistent with the accepted model and we had to consider either distortion of the half-chair geometry or a conformational equilibrium involving more than two components. In the present studies, some additional crystal structure determinations gave, even for a molecule undisturbed by the effect of substitution, conformations different from those expected from our

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* Part II. For Part I, see ref 1.

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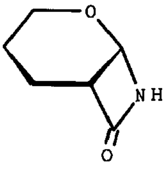
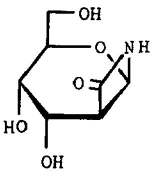
earlier studies. That prompted us to perform quantitative conformational analysis of all the crystal structures solved so far, along with a detailed analysis of the results obtained on the basis of molecular mechanics, in order to find not only the global minimum, but also the whole range of conformations within a wider energy window.

Now we report X-ray diffraction studies of 8-aza-2-oxabicyclo[4.2.0]octan-7-one[2] (**1**), 2-*C* : 1-*N*-carbonyl-2-deoxy-β-D-altropyranosylamine[3] (**2**), and 4-*O*-acetyl-3,6-anhydro-*N*-(*tert*-butyldimethylsilyl)-2-*C* : 1-*N*-carbonyl-2-deoxy-α-D-galactopyranosylamine[4] (**3**). Quantitative conformational studies were performed using the asymmetry and puckering parameters in order to specify the details of the ring conformations. These results were compared with the range of conformations generated by the RANDOMIZE procedure of the molecular mechanics PC-MODEL 4.0 program.



1



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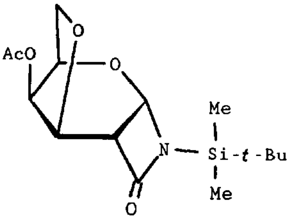

3

EXPERIMENTAL

X-ray structure determination.—Suitable crystals of the compounds were obtained from MeOH (**1** and **2**) and EtOAc–hexane (**3**).

Unit cell parameters were obtained by the least-squares fit of 25 reflections on an automated four-circle diffractometer. All experimental details regarding data collection and refinement are collected in Table I. Intensities were corrected by the Lorentz-polarization factors in the case of compounds **1** and **2**, and additionally for absorption for compound **3** (DIFABS program[5]).

Structures were solved using direct methods (Multan[6] and SHELX-86[7] programs) and refined by the full-matrix least-squares procedure to final convergence[8]. Hydrogens were found from $\Delta\rho$ maps and refined for compounds **1** and **2**, whereas they were kept at the calculated positions for compound **3**. Fractional atomic coordinates for **1**–**3** are presented in Table II, and other data from the structure determination in Tables III and IV *.

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* Atomic coordinates for these structures have been deposited with the Cambridge Crystallographic Data Centre. The coordinates may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ UK.

TABLE I

Crystallographic parameters and details of data collection and refinement

Compound	1	2	3
Formula	$C_6H_9NO_2$	$C_7H_{11}NO_5$	$C_{15}H_{25}NO_4Si$
Mol wt	127.1	189.2	327.44
Crystal size (mm)	0.18×0.28×0.28	0.10×0.10×0.28	0.5×0.7×0.3
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
Cell parameters (Å, °)			
a	6.336(1)	4.999(1)	10.681(3)
b	9.774(2)	10.701(1)	8.149(2)
c	10.050(2)	14.675(2)	10.586(5)
β	–	–	98.73(4)
Volume (Å^3)	622.4(3)	785.1(2)	971(2)
Z	4	4	2
$F(000)$	272	400	352
Density calcd (g cm^{-3})	1.357	1.600	1.142
λ (Å)	1.54178	1.54178	1.54178
$\mu(\lambda)$ (cm^{-1})	8.12	11.35	12.510
Reflections measured	800	996	1843
Symmetry independent reflections with $F_o > 3\sigma$	752	946	1714
Number of refined parameters	118	151	226
Final residual factors			
R	0.036	0.034	0.058
R_w ($w = 1/\sigma^2$)	0.040	0.037	0.038
Abs correction (DIFABS)			
min	–	–	0.657
max	–	–	1.179
Diffractometer	CAD4	CAD4	KM4
	(Enraf–Nonius)		(KUMA Diffraction)

Molecular modelling.—The molecular mechanics program PCMODEL 4.0[9] was employed in order to explore the conformational space of the fused ring system. The model molecule was constructed and its geometry was optimized, then the RANDOMIZE option without any restriction was used in order to generate 640 conformations. In total, 54 low-energy conformations were found; among them, seven presented in Table V were unique.

RESULTS AND DISCUSSION

Table III presents the bond lengths and bond angles for the major ring system in compounds **1**, **2**, and **3**. There is a noteworthy equality (with respect to the 3 esd's) of the O-1–C-1, C-1–N-1, and O-1–C-5 distances, the two former being considered a measure of the endo-anomeric effect [1]. According to Table III, the N-1–C-7 distance in **1** and **2** is slightly longer than in the model β-lactam molecule azetidin-2-one (1.339 Å)[10], whereas in **3** it approximates the mean value 1.396 Å found by Wolfe et al.[11] for the β-lactam ring of penicillin derivatives. This longer

TABLE II

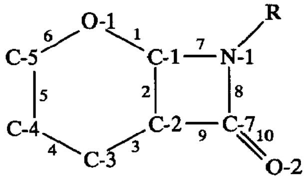
Fractional atomic coordinates of compounds **1–3** with esd's in parentheses

Atom	x	y	z	B_{eq}(Å^2) [a]
Compound **1**				
O-1	−0.1775(3)	0.4021(2)	0.4759(2)	4.58(3)
O-2	0.3629(3)	0.6568(2)	0.3861(2)	4.44(4)
N-1	0.0540(3)	0.5982(2)	0.5024(2)	3.74(4)
C-1	0.0127(4)	0.4525(2)	0.5250(2)	3.75(4)
C-2	0.2130(3)	0.4221(2)	0.4415(2)	3.14(4)
C-3	0.1587(4)	0.3492(2)	0.3130(2)	3.47(4)
C-4	−0.0266(4)	0.4189(3)	0.2469(2)	4.04(4)
C-5	−0.2192(4)	0.4245(3)	0.3364(3)	4.96(6)
C-7	0.2346(3)	0.5778(2)	0.4339(2)	3.17(4)
Compound **2**				
O-1	0.9781(4)	0.8632(1)	0.0705(1)	2.67(3)
O-2	0.4922(4)	1.0823(2)	−0.1233(1)	2.74(3)
O-3	1.1242(4)	1.1588(2)	0.0979(1)	2.73(3)
O-4	0.6875(4)	1.1112(2)	0.2150(1)	2.79(3)
O-5	0.7785(4)	0.7133(2)	0.2049(1)	3.02(4)
N-1	0.6742(4)	0.8999(2)	−0.0574(1)	2.45(4)
C-1	0.9412(5)	0.9132(2)	−0.0163(1)	2.04(4)
C-2	0.9080(5)	1.0562(2)	−0.0270(1)	1.89(4)
C-3	0.8680(5)	1.1265(2)	0.0618(1)	1.97(4)
C-4	0.7168(5)	1.0466(2)	0.1299(1)	2.01(4)
C-5	0.8505(5)	0.9203(2)	0.1488(1)	1.94(4)
Compound **3**				
O-1	0.5666(2)	0.0783(4)	0.3797(2)	3.46(9)
C-1	0.5719(4)	−0.0143(5)	0.2672(4)	4.4(1)
C-2	0.4642(4)	0.0104(5)	0.1518(4)	4.0(1)
C-3	0.3667(4)	0.1331(5)	0.1725(4)	3.8(1)
C-4	0.4326(3)	0.2745(5)	0.2479(4)	3.7(1)
C-5	0.4623(4)	0.1899(5)	0.3786(3)	3.7(1)
C-6	0.3401(4)	0.1048(6)	0.3864(4)	4.6(2)
O-3	0.2853(2)	0.0671(4)	0.2556(2)	4.3(1)
N-1	0.6628(3)	0.0496(5)	0.1877(3)	4.3(1)
C-7	0.5695(4)	0.0683(6)	0.0814(4)	4.2(1)
O-2	0.5780(2)	0.1143(4)	−0.0255(2)	5.5(1)
O-4	0.3402(2)	0.3999(3)	0.2536(2)	3.81(9)
C-8	0.3877(4)	0.5498(6)	0.2977(4)	3.9(2)
O-9	0.4962(2)	0.5779(4)	0.3278(2)	5.1(1)
C-10	0.2809(4)	0.6658(6)	0.3001(4)	6.0(2)
Si-11	0.8297(1)	0.0748(0)	0.2170(1)	5.65(4)
C-12	0.8850(4)	−0.0484(8)	0.3617(5)	8.9(3)
C-13	0.8960(4)	−0.0108(8)	0.0797(5)	8.9(3)
C-14	0.8670(4)	0.2982(6)	0.2415(4)	5.6(2)
C-15	1.0109(4)	0.3241(8)	0.2613(5)	9.6(2)
C-16	0.8094(5)	0.4048(7)	0.1260(5)	8.9(2)
C-17	0.8182(4)	0.3655(7)	0.3593(4)	7.5(2)

[a] Calculated from anisotropic thermal parameters as $B_{eq} = 8\pi D_u^{1/3}$, where D_u is the determinant of the U matrix

TABLE III

Essential bond lengths and bond angles characterizing the fused ring system

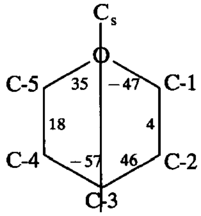
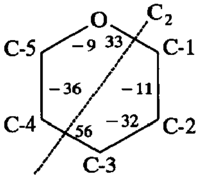
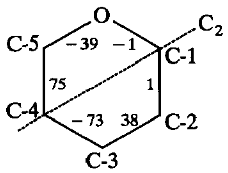


	1	**2**	**3**
Bond length (Å)			
1	1.392(3)	1.395(3)	1.418(5)
2	1.551(3)	1.548(3)	1.559(6)
3	1.515(3)	1.517(3)	1.484(6)
4	1.512(3)	1.516(4)	1.513(6)
5	1.517(4)	1.533(3)	1.535(5)
6	1.443(3)	1.449(3)	1.437(5)
7	1.466(3)	1.471(3)	1.473(6)
8	1.350(3)	1.361(3)	1.394(5)
9	1.530(3)	1.526(3)	1.516(6)
10	1.220(3)	1.214(3)	1.209(5)
Bond angle (deg)			
1–2	116.7(2)	119.1(2)	118.1(3)
1–6	116.8(2)	120.3(2)	117.4(2)
1–7	116.3(2)	117.2(2)	113.9(3)
2–3	111.4(2)	114.7(2)	115.0(3)
2–7	87.5(2)	87.5(2)	88.8(3)
2–9	84.8(1)	85.0(2)	84.9(3)
3–4	109.8(2)	110.7(2)	108.1(3)
3–9	116.5(2)	115.0(2)	116.9(4)
4–5	112.4(3)	113.5(2)	98.6(3)
5–6	115.1(3)	114.8(2)	110.2(3)
7–8	95.0(2)	94.2(2)	92.7(3)
8–9	92.7(2)	92.5(2)	93.6(3)
8–10	132.3(2)	133.0(2)	130.1(4)
9–10	135.1(2)	134.5(3)	136.4(4)

bond distance found in the penicillin family is attributed to the pyramidal β-lactam nitrogen. Comparison of the equivalent bond lengths and bond angles in six molecules of this family (compounds **1**–**3**, and three taken from ref 1) shows that the delocalization of electrons from the substituents located at the β-lactam nitrogen atom is mediated almost exclusively via the N-1–C-7 bond. This effect dominates any anomeric effects, which contribute a rather small energy portion to the global energy of the molecule (for example, 0.65 to 1.53 kcal mol^{-1} for the methoxy group in 2-methoxytetrahydropyrans, measured in different solvents)[12]. On the other hand, the nitrogen atom in the anomeric position affords a much smaller contribution to the conformational energy than such groups as OH, SH, and OAc. Analysis of the bond angles in the sugar moiety reveals, in **3**, an unusually small C-3–C-4–C-5 angle [98.6(3)°], along with shorter C-2–C-3, and

TABLE IV

Conformation of the sugar ring in compounds **1–3** (lines show location of the predominant element of symmetry in the ring)

Intracyclic torsion angles	1	2	3
			
	${}^{1,3}B$	${}^{4}S_{3}$	E_4
Puckering parameters			
Q (Å)	0.6312	0.5318	0.6803
ϕ (deg)	11.21	211.91	59.75
Θ (deg)	97.83	75.10	124.40
q_2 (Å)	0.6254	0.5139	0.5613
Asymmetry parameters (deg)			
ΔC_2		2.9	
ΔC_s	15.7		0.1

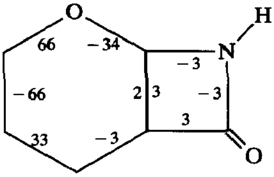
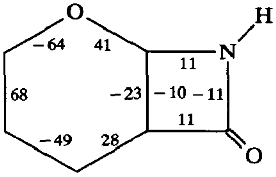
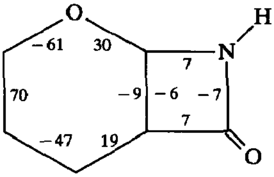
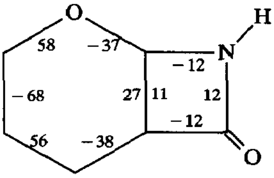
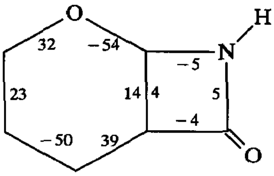
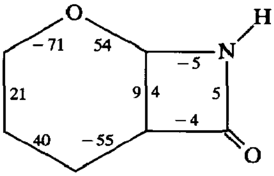
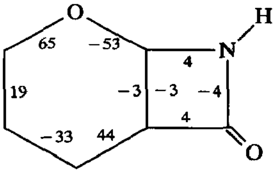
longer C-4–C-5 bond lengths. This is probably due to the presence of the extra five-membered ring in the molecule.

The conformation of the sugar ring was investigated in terms of symmetry of the torsion angles distribution (asymmetry parameters[13]), and of the puckering parameters[14] (see Table IV). In the case of the previously studied compounds[1] with relatively small hydroxyl residues, the sugar ring has been found to adopt quite distorted half-chair conformations. For **3**, where a tricyclic ring system is present, the sofa E_4 conformation of the ring is most obvious (Fig. 3). Compound **1**, which could be treated as a model compound, has a distorted boat conformation ${}^{1,3}B$ (see Fig. 1), whereas **2** has a skew ${}^{4}S_{3}$ conformation (see Fig. 2). As shown in Table IV, the asymmetry parameter for the model compound **1** is far from ideal, but the puckering parameters unequivocally locate the ring in the appropriate conformational region. Torsion angles in the β-lactam ring show its folding, usually larger in the case of substituted sugar rings.

MM2 calculations.—According to Table V, the β-lactam ring introduces the same conformational constraints as the epoxide ring in 2,3- (ref 15) or 3,4-anhydro sugars[16–18], e.g., it forms energetically favorable conformations with planar elements located at the C-1–C-2 bond (torsion angle close to 0°). In our case, the two isoenergetically lowest energy conformations were: sofa E_5 and flattened chair forms (conformations I and II in Table IV). The ${}^{5}H_{4}$ half-chair distorted into the sofa (E) conformation was found to have an energy higher by 0.71 kcal (conforma-

TABLE V

Unique conformations obtained during molecular modelling

Energy	Torsion angles	Conformation
I $E = 47.06$ (kcal/mol)		Sofa ^5E
II $E = 47.06$ (kcal/mol)		Flattened chair $^5C_2$
III $E = 47.78$ (kcal/mol)		Half-chair $^4H_5$
IV $E = 48.87$ (kcal/mol)		Half-chair $^5H_4$
V $E = 50.05$ (kcal/mol)		Boat + 1,3-diplanar $^{1,3}B + {}^4S_3$
VI $E = 51.19$ (kcal/mol)		Boat $B_{0,3}$
VII $E = 51.20$ (kcal/mol)		Boat $^{1,3}B$

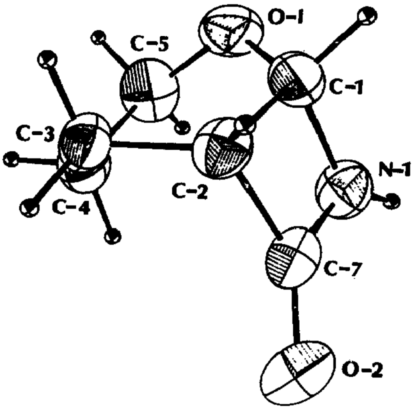


Fig. 1. Atom numbering and thermal ellipsoids (50%) of compound **1**.

tion III). The quite symmetrical $^4H_5$ and a hybrid of the boat and 1,3-diplanar forms (conformations IV and V) are followed by the $B_{1,3}$ and $^{1,3}B$ conformations of the boat family (conformations VI and VII). The first half-chair conformation (III) has bond distances and torsion angles close to those found in the crystal structure. The second conformation (IV), which was found more frequently in the solid state, displays quite different bond distances and torsion angles. Their energy minima are located quite apart, with a noticeable difference in the torsion term. The sofa conformation is generally considered to be a form of higher energy compared with the half-chair. In our case, when the C-1–C-2 bond length is longer than usual, and when the atom with smaller steric hindrance (O-atom) is located next to this bond, the standard force field may produce, for this form, energy slightly lower than for the half-chair form. We calculated the asymmetry parameters for the two calcu-

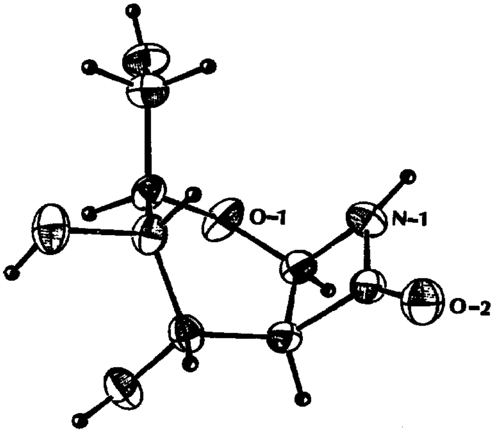


Fig. 2. Perspective view of compound **2**.

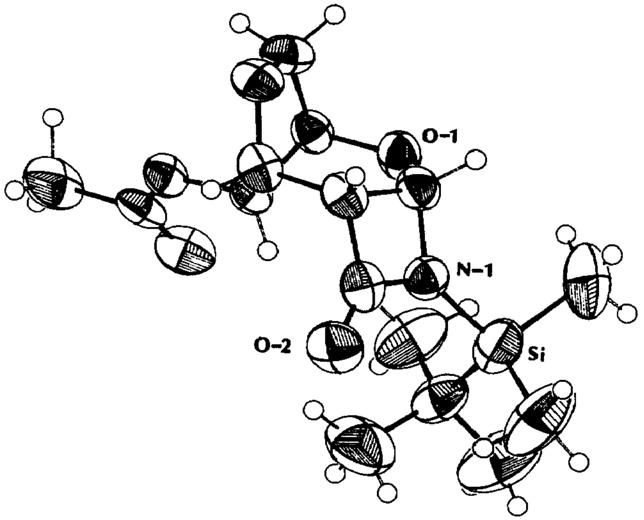


Fig. 3. Perspective view of compound 3.

lated model conformations from ref 1, in order to evaluate the degree of distortion from the half-chair conformation. It appears that the ${}^{4}H_{5}$ conformation is indeed rather the ${}^{4}E + {}^{4}H_{5}$ form, whereas the ${}^{5}H_{4}$ conformation is a ${}^{5}E + {}^{5}H_{4}$ hybrid. In the case of 2,3- and 3,4-dehydrohexopyranosides, it was observed that the pure half-chair form exists rather rarely[15], whereas the distorted half-chair or a mixture of the sofa and half-chair ($E + H$) conformations are present quite often[16–18].

Since it remains controversial whether the development and use of an individual set of force-field parameters is reasonable, we also applied the set developed by Wolfe et al.[11] for parametrization of the β-lactam ring in penicillins. This time the RANDOMIZE procedure afforded only one unique conformation which was assigned to the half-chair with the O-1–C-1–C-2–C-3 torsion angle of 26.58° (similarly to conformation IV in Table V). A comparison of molecular geometry of the above molecule showed that several bonds failed to be well reproduced: the C-1–C-2 bond expanded to 1.57–1.58 Å (in the standard minimization not more than 1.57 Å). In our case, however, the mean value of this distance, calculated for six compounds of this type, was 1.553 Å. In contrast, the C-7–N-1 distance 1.34 Å (resembling that found for amides or peptides) reproduced well that observed in our compound without a substituent at the N-atom. It is also worth mentioning that the very flexible 1,3-diplanar and twist conformations were not generated by the above procedure.

Summing up, the conformations of the pyranoid ring obtained by the modelling procedure showed a wide variety of structural possibilities. The X-ray structures presented here, as well as the three structures previously solved[1], are far from the expected half-chair conformations. The three lowest energy conformations display energy differences within the range of 1 kcal. Their irregularities, caused by the

TABLE VI

Hydrogen bonding pattern in compounds **1** and **2**

Bridge	Symmetry	D···A(Å)	D-H(Å)	H···A(Å)	D-H···A(deg)
Compound **1**					
N-1–H(N-1)···O-2	$-1/2+x, 3/2-y, 1-z$	2.908	0.874	2.037	174.1
Compound **2**					
N-1–H(N-1)···O-1	$x-1/2, 3/2-y, -z$	2.987	0.903	2.152	153.4
O-4–H(O-4)···O-5	$2-x, 1/2+y, 1/2-z$	3.115	0.915	2.202	175.0
O-3–H(O-3)···O-2	$1/2+x, 5/2-y, -z$	2.872	0.941	2.007	152.0
O-4–H(O-4)···O-3	x, y, z	2.825	0.915	2.449	104.8
O-5–H(O-5)···O-4	$1-x, 3/2+y, 1/2-z$	2.829	0.775	2.080	162.5

presence of the ring oxygen atom and ring fusion, are similar to those observed in the crystal structures. For example, the half-chair form always exhibits unsymmetrical torsion angles located at the O-1–C-1 or C-2–C-3 bonds. The torsion angle at C-5–O-1, both in the calculated and experimental structures, is often smaller than expected, confirming the smaller steric requirement of the oxygen atom. Most of the bond distances were reproduced fairly well, except for the C-1–C-2 bond length. Torsion angles found in the four-membered ring vary, depending on the conformation. The highest values are observed in the case of the half-chair and flattened chair conformations of the six-membered ring. Bond lengths and bond angles within the anomeric region of the molecule suggest dominance of the strain introduced by the β-lactam ring over any steric effects characteristic of the sugar ring.

Conformational analysis of the sugar moiety present in the six compounds investigated by us by X-ray diffraction, as well as molecular mechanics calculations, explain why the chemical shifts and coupling constants collected in ref 1 for a large group of derivatives could not be interpreted by exclusive use of the half-chair geometry.

Hydrogen bonding pattern.—It was of interest to determine whether the hydrogen bonding patterns were changed with small alterations of the molecular formula. Compound **1** exemplifies the simplest hydrogen bond between the strongest proton donor and proton acceptor in the molecule (see Table VI). Compound **2**, which additionally has a hydroxymethyl group at C-5, does not show any similarities with 2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabinopyranosylamine (compound **13** ref 1); none of the hydrogen bonds were replicated. Compound **2** forms one intramolecular hydrogen bond and four intermolecular hydrogen bonds with neighboring molecules (Table VI).

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