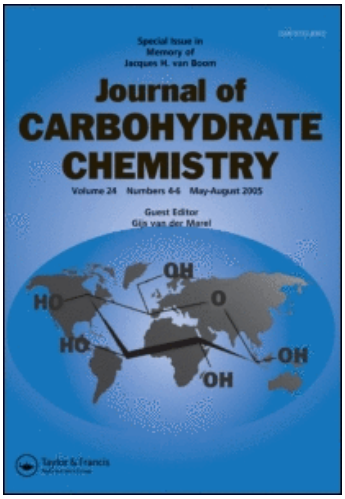

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X-Ray Structures of a 3-Amino-5- and a 3-Amino-6-Substituted Triazine, Produced as a Result of a Reaction of 3-Deoxy-D-Erythro-Hexos-2-Ulose (3-Deoxyglucosone) with Aminoguanidine

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X-RAY STRUCTURES OF A 3-AMINO-5- AND A 3-AMINO-6-SUBSTITUTED TRIAZINE, PRODUCED AS A RESULT OF A REACTION OF 3-DEOXY-D-ERYTHRO-HEXOS-2-ULOSE (3-DEOXYGLUCOSONE) WITH AMINOGUANIDINE.[1]

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ABSTRACT

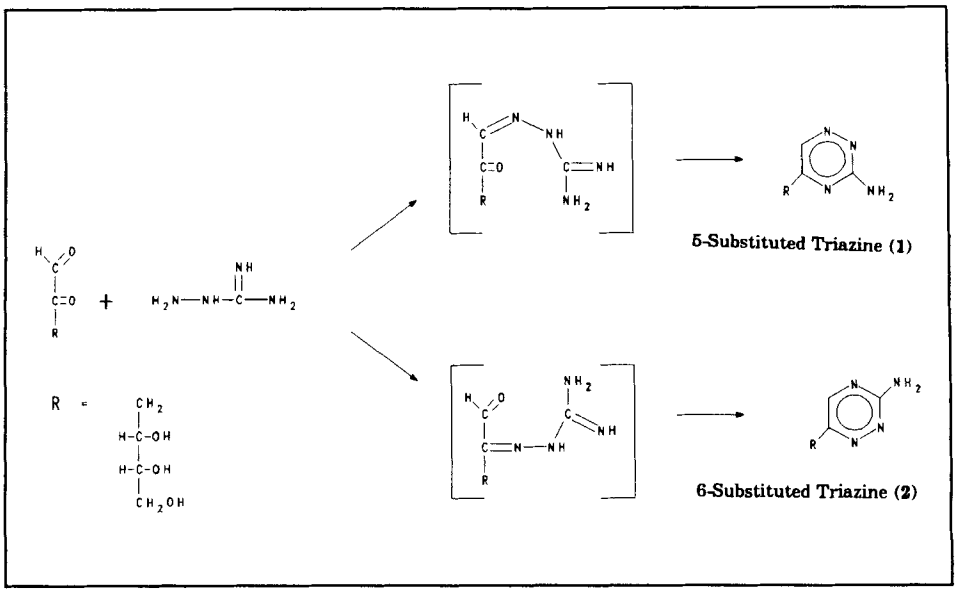
Aminoguanidine is a potent inhibitor of color formation during the Maillard reaction. The reaction of aminoguanidine with 3-deoxy-**D**-*erythro*-hexo-2-ulose ("3-deoxyglucosone"), a Maillard reaction intermediate, gives two triazines, 3-amino-5-([2*S*],[3*S*]-2,3,4-trihydroxybutyl)-1,2,4-triazine (**1**) and 3-amino-6-([2*S*],[3*S*]-2,3,4-trihydroxybutyl)-1,2,4-triazine (**2**) which have been obtained in the crystalline state. The structure of the triazines, as determined by X-ray diffraction, are reported herein.

INTRODUCTION

The Maillard reaction involves the initial interaction of an aldose with an amino group to give a 1-amino-1-deoxy-2-ketose (Amadori compound), followed by its degradation to (initially) highly reactive dicarbonyl sugar derivatives, followed by the production of brown pigments (Maillard polymers) and other degradation products. For a Maillard reaction involving **D**-glucose, the initially produced intermediate is 3-deoxy-**D**-*erythro*-hexo-2-ulose ("3-

deoxyglucosone"),[3] which participates in further degradative reactions, such as protein crosslinking[4] and the formation of ultraviolet absorbing compounds.[5,6] Aminoguanidine has recently been shown to function as a potent inhibitor of the Maillard reaction.[7] In some recent experiments,[8] we have shown that when aminoguanidine is incubated with 3-deoxyglucosone at physiological conditions (37 °C and pH 7.0), the two reagents react within a few minutes to give 5- and 6-substituted 3-amino triazine derivatives. This suggests that the mechanism for inhibition of *in vivo* Maillard reactions by aminoguanidine involves its reaction with dicarbonyl sugar intermediates, thereby removing them from participation in further degradative reactions. In an earlier report,[8] we reported that two different triazines are produced when 3-deoxyglucosone reacts with aminoguanidine and, based on NMR and MS data, the structures were proposed to be the 3-amino-5- and 3-amino-6- substituted triazines. Presumably, these are produced as a result of initial hydrazone formation at C-1 (giving the 5-substituted isomer, **1**) and at C-2 (giving the 6-substituted isomer, **2**) as shown in the Scheme below.

Scheme



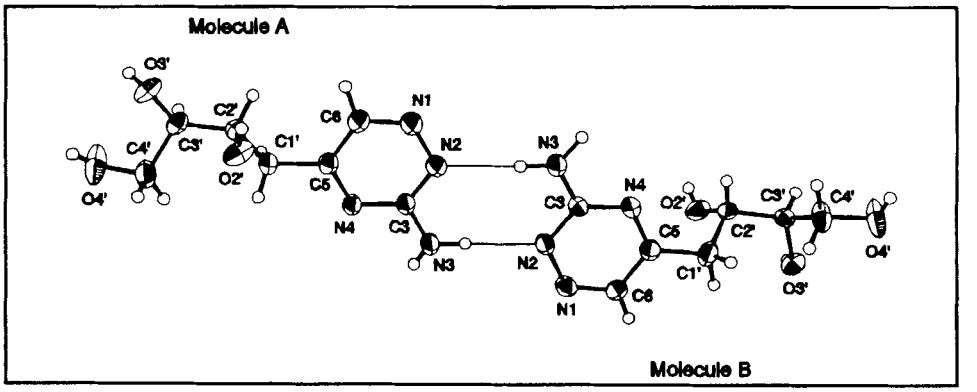


Figure 1. Perspective drawing of the crystal structure of **1**. Thermal ellipsoids are drawn at the 50% probability level.

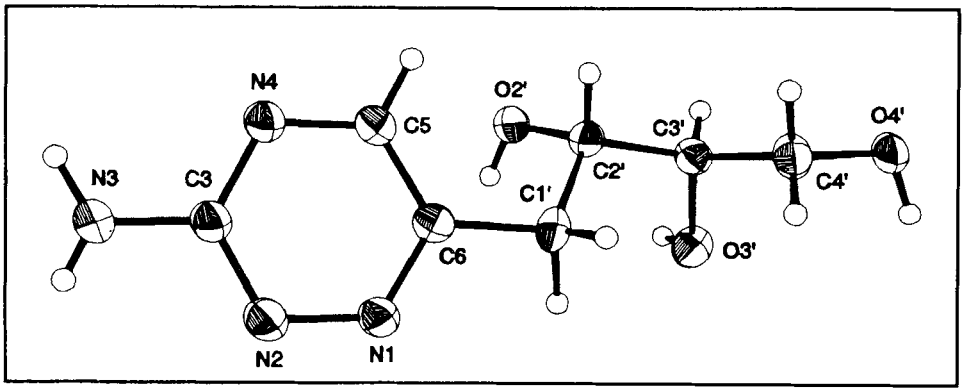


Figure 2. Perspective drawing of the crystal structure of **2**. Thermal ellipsoids are drawn at the 50% probability level.

Because of the potential importance of this reaction in inhibiting the Maillard reaction, an absolute determination of the structures of the reaction products was deemed to be of value. Hence, in this paper, we wish to report the X-ray structures of 3-amino-5-([2*S*],[3*S*]-2,3,4-trihydroxybutyl)-1,2,4-triazine (**1**) and 3-amino-6-([2*S*],[3*S*]-2,3,4-trihydroxybutyl)-1,2,4-triazine (**2**), derived from the reaction of 3-deoxyglucosone and aminoguanidine.

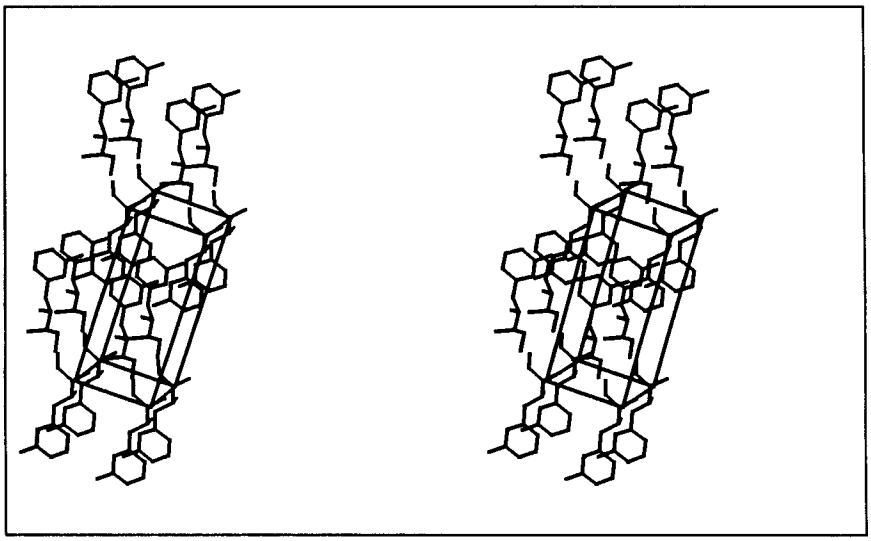


Figure 3. Stereo drawing of the packing interactions in the crystal structure of **1**.

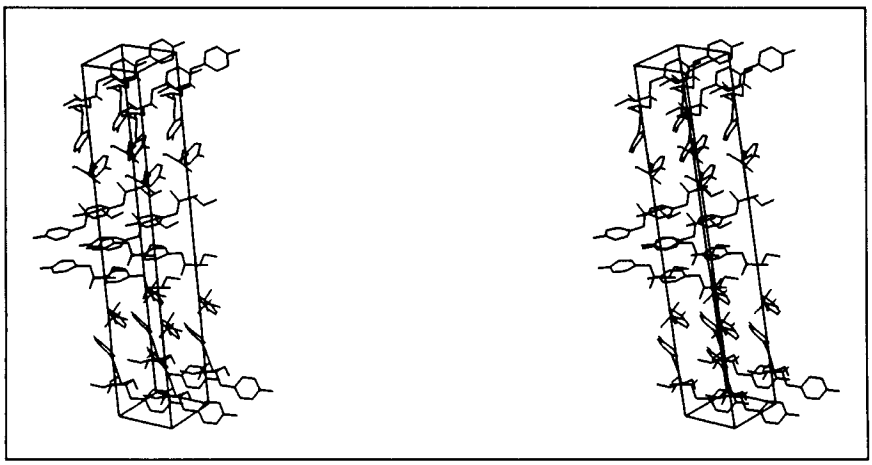


Figure 4. Stereo drawing of the packing interactions in the crystal structure of **2**.

Table 1. Atomic Parameters x,y,z and B_{eq} for 1.

E.S.Ds. refer to the last digit printed.

	x	y	z	B_{eq}
N1A	0.9272(5)	1.3938(4)	0.76101(17)	3.27(12)
N2A	1.0507(5)	1.2577(4)	0.72196(15)	2.73(10)
C3A	0.9633(5)	1.0315(5)	0.73942(17)	2.28(11)
N3A	1.0800(5)	0.8947(4)	0.69789(16)	2.88(10)
N4A	0.7679(4)	0.9319(4)	0.79683(14)	2.35(10)
C5A	0.6489(5)	1.0692(5)	0.83419(17)	2.37(12)
C6A	0.7292(6)	1.3044(5)	0.81500(21)	3.18(14)
C1'A	0.4253(6)	0.9541(5)	0.89526(18)	2.50(11)
C2'A	0.3689(5)	1.1146(5)	0.96753(18)	2.42(12)
O2'A	0.5875(4)	1.1921(4)	1.03201(14)	3.24(9)
C3'A	0.1030(5)	0.9931(5)	1.01014(17)	2.37(12)
O3'A	0.0637(4)	1.1537(4)	1.07685(13)	3.08(9)
C4'A	0.0775(7)	0.7700(6)	1.05005(21)	3.65(15)
O4'A	-0.18750	0.65270	1.07680	5.61(12)
N1B	-0.3480(5)	-0.0218(4)	0.54595(16)	2.70(10)
N2B	-0.4768(4)	0.1171(4)	0.57882(15)	2.57(10)
C3B	-0.3867(5)	0.3432(5)	0.55804(17)	2.24(12)
N3B	-0.5040(5)	0.4808(4)	0.59695(16)	2.91(11)
N4B	-0.1935(5)	0.4324(4)	0.49992(15)	2.64(10)
C5B	-0.0737(5)	0.2889(5)	0.46678(17)	2.49(12)
C6B	-0.1479(6)	0.0631(5)	0.49329(18)	2.67(12)
C1'B	0.1444(5)	0.3776(6)	0.40229(19)	3.12(14)
C2'B	0.0590(5)	0.4706(5)	0.32333(17)	2.19(11)
O2'B	-0.1716(4)	0.2891(4)	0.28099(15)	3.18(9)
C3'B	0.2845(6)	0.5477(5)	0.25808(17)	2.36(12)
O3'B	0.3724(4)	0.3619(3)	0.22908(12)	2.75(9)
C4'B	0.5294(7)	0.7498(5)	0.29978(22)	3.76(14)
O4'B	0.7271(6)	0.8335(4)	0.23587(19)	5.66(12)
H3A1	1.20(6)	0.954(5)	0.6571(19)	3.2
H3AB	1.047(6)	0.785(5)	0.7135(19)	3.2
H6A	0.648(6)	1.422(5)	0.8367(18)	3.2
H1'A1	0.469(6)	0.844(5)	0.9184(18)	3.2
H1'A2	0.260(6)	0.876(5)	0.8558(19)	3.2
H2'A	0.351(6)	1.244(5)	0.9399(19)	3.2
HO2'A	0.622(6)	1.332(5)	1.0488(19)	3.2
H3'A	-0.037(6)	0.941(5)	0.9657(19)	3.2
HO3'A	-0.078(6)	1.142(5)	1.0777(19)	3.2
H4'A1	0.124(6)	0.664(5)	1.0145(20)	3.2
H4'A2	0.212(6)	0.790(5)	1.1032(20)	3.2
HO4'A	-0.226(6)	0.699(6)	1.1181(19)	3.2

(continued)

Table 1. (continued)

H3B1	-0.636(6)	0.412(5)	0.6352(19)	3.2
H3B2	-0.428(6)	0.652(5)	0.5847(19)	3.2
H6B	-0.051(6)	-0.015(5)	0.4814(19)	3.2
H1'B1	0.319(6)	0.478(5)	0.4289(19)	3.2
H1'B2	0.199(6)	0.251(5)	0.3822(19)	3.2
H2'B	0.033(6)	0.613(5)	0.3453(19)	3.2
HO2'B	-0.281(6)	0.318(5)	0.2706(19)	3.2
H3'B	0.229(6)	0.602(5)	0.2098(20)	3.2
HO3'B	0.284(6)	0.295(5)	0.1945(20)	3.2
H4'B1	0.471(6)	0.869(5)	0.3163(19)	3.2
H4'B2	0.595(6)	0.685(5)	0.3560(18)	3.2
HO4'B	0.775(6)	0.969(5)	0.2478(19)	3.2

B_{eq} is the Mean of the Principal Axes of the Thermal Ellipsoid

RESULTS AND DISCUSSION

Final coordinates for **1** and **2** are given in Tables 1 and 2. Bond distances, angles and selected conformational angles for the non-hydrogen atoms are given in Tables 3 and 4. Figure 1 is a perspective drawing of the hydrogen bonded pair formed in the crystal packing of the two crystallographically independent molecules of **1**, and figure 2 gives a perspective view of **2**. Figures 3 and 4 show packing diagrams for **1** and **2**, respectively.

In both structures, the six-membered triazine rings are essentially planar (maximum deviations: 0.02Å and 0.04Å for **1**, molecules A and B, respectively; 0.03Å for **2**. Equivalent bond distances and angles among the three molecules in the two structures agree well and are also in good agreement with expected values. The conformations of the side chains are determined by packing interactions. The primary conformational differences between molecules A and B of **1** are seen in the angles about the C5-C1' and C2'-C3' bonds. In all three molecules, the conformations about C2'-C3' are *gauche*, leading to less than fully extended side chains.

Table 2. Atomic Parameters x,y,z and B_{eq} for 2.

E.S.Ds. refer to the last digit printed.

	x	y	z	B_{eq}
N1	0.5270(4)	0.8130(4)	0.02056(6)	2.14(11)
N2	0.3604(5)	0.7099(4)	0.01351(7)	2.45(12)
C3	0.3164(5)	0.5528(5)	0.03277(8)	2.14(13)
N3	0.1418(5)	0.4617(6)	0.02808(9)	3.36(15)
N4	0.4357(4)	0.4815(4)	0.05729(7)	2.25(11)
C5	0.5999(5)	0.5833(5)	0.06284(9)	2.37(14)
C6	0.6455(5)	0.7564(5)	0.04526(8)	1.91(12)
C1'	0.8235(5)	0.8871(6)	0.05261(9)	2.37(14)
C2'	0.8852(5)	0.8875(5)	0.08937(8)	1.87(12)
O2'	0.7181(3)	0.9191(4)	0.11069(6)	2.33(10)
C3'	1.0448(5)	1.0424(5)	0.09691(8)	2.00(13)
O3'	0.9815(4)	1.2366(4)	0.08740(6)	2.39(10)
C4'	1.2408(5)	1.0021(6)	0.08027(11)	2.54(16)
O4'	1.3957(4)	1.1249(4)	0.09259(6)	2.87(11)
H3A	0.079(6)	0.498(6)	0.0131(9)	2.4
H3B	0.103(6)	0.367(6)	0.0427(9)	2.4
H5	0.684(5)	0.531(6)	0.0790(10)	2.4
H1'A	0.938(6)	0.848(6)	0.0382(9)	2.4
H1'B	0.781(6)	1.032(6)	0.0439(9)	2.4
H2'	0.937(6)	0.755(6)	0.0951(8)	2.4
HO2'	0.642(6)	1.000(6)	0.1025(9)	2.4
H3'	1.062(5)	1.045(5)	0.1183(9)	2.4
HO3'	0.910(6)	1.278(6)	0.1016(9)	2.4
H4'A	1.235(6)	1.015(6)	0.0573(9)	2.4
H4'B	1.272(6)	0.877(7)	0.0877(9)	2.4
HO4'	1.401(6)	1.234(6)	0.0814(9)	2.4

B_{eq} is the Mean of the Principal Axes of the Thermal Ellipsoid

Table 3. Bond Distances (Å), angles (°) and Selected Torsion Angles (°) for 1.

N1A-N2A	1.338(3)	N1B-N2B	1.338(3)
N1A-C6A	1.320(4)	N1B-C6B	1.310(4)
N2A-C3A	1.344(4)	N2B-C3B	1.359(3)
C3A-N3A	1.331(4)	C3B-N3B	1.321(4)
C3A-N4A	1.360(3)	C3B-N4B	1.347(3)
N4A-C5A	1.316(4)	N4B-C5B	1.327(4)
C5A-C6A	1.405(4)	C5B-C6B	1.392(4)
C5A-C1'A	1.510(4)	C5B-C1'B	1.497(4)
C1'A-C2'A	1.512(4)	C1'B-C2'B	1.515(4)
C2'A-O2'A	1.431(3)	C2'B-O2'B	1.422(3)
C2'A-C3'A	1.513(4)	C2'B-C3'B	1.522(4)
C3'A-O3'A	1.419(3)	C3'B-O3'B	1.417(3)
C3'A-C4'A	1.509(4)	C3'B-C4'B	1.518(4)
C4'A-O4'A	1.405(3)	C4'B-O4'B	1.418(4)
N2A-N1A-C6A	119.8(3)	N2B-N1B-C6B	118.9(2)
N1A-N2A-C3A	117.5(2)	N1B-N2B-C3B	118.0(2)
N2A-C3A-N3A	117.3(2)	N2B-C3B-N3B	116.5(2)
N2A-C3A-N4A	125.3(2)	N2B-C3B-N4B	124.7(2)
N3A-C3A-N4A	117.4(2)	N3B-C3B-N4B	118.8(2)
C3A-N4A-C5A	116.0(2)	C3B-N4B-C5B	115.7(2)
N4A-C5A-C6A	120.1(2)	N4B-C5B-C6B	120.1(2)
N4A-C5A-C1'A	115.5(2)	N4B-C5B-C1'B	118.4(3)
C6A-C5A-C1'A	124.5(3)	C6B-C5B-C1'B	121.4(3)
N1A-C6A-C5A	121.3(3)	N1B-C6B-C5B	122.2(3)
C5A-C1'A-C2'A	116.7(2)	C5B-C1'B-C2'B	114.2(2)
C1'A-C2'A-O2'A	108.8(2)	C1'B-C2'B-O2'B	108.4(2)
C1'A-C2'A-C3'A	111.8(2)	C1'B-C2'B-C3'B	111.8(2)
O2'A-C2'A-C3'A	110.3(2)	O2'B-C2'B-C3'B	109.5(2)
C2'A-C3'A-O3'A	108.6(2)	C2'B-C3'B-O3'B	111.6(2)
C2'A-C3'A-C4'A	115.5(2)	C2'B-C3'B-C4'B	111.0(2)
O3'A-C3'A-C4'A	108.6(2)	O3'B-C3'B-C4'B	107.2(2)
C3'A-C4'A-O4'A	111.4(2)	C3'B-C4'B-O4'B	110.1(3)
N4A-C5A-C1'A-C2'A	154.0(3)	N4B-C5B-C1'B-C2'B	-55.0(2)
C5A-C1'A-C2'A-C3'A	166.4(3)	C5B-C1'B-C2'B-C3'B	-177.3(3)
C1'A-C2'A-C3'A-C4'A	57.9(2)	C1'B-C2'B-C3'B-C4'B	-62.6(2)
C2'A-C3'A-C4'A-O4'A	-171.7(3)	C2'B-C3'B-C4'B-O4'B	-174.6(3)

Table 4. Bond Distances (Å), angles (°) and Selected Torsion Angles (°) for 2.

N1-N2	1.345(4)	C6-C1'	1.511(5)
N1-C6	1.325(4)	C1'-C2'	1.529(5)
N2-C3	1.339(4)	C2'-O2'	1.425(4)
C3-N3	1.335(5)	C2'-C3'	1.523(5)
C3-N4	1.354(4)	C3'-O3'	1.423(4)
N4-C5	1.316(4)	C3'-C4'	1.500(5)
C5-C6	1.392(5)	C4'-O4'	1.415(4)
N2-N1-C6	120.6(3)	C5-C6-C1'	124.0(3)
N1-N2-C3	117.9(3)	C6-C1'-C2'	113.7(3)
N2-C3-N3	118.3(3)	C1'-C2'-O2'	111.3(3)
N2-C3-N4	124.4(3)	C1'-C2'-C3'	112.5(3)
N3-C3-N4	117.3(3)	O2'-C2'-C3'	109.5(3)
C3-N4-C5	115.7(3)	C2'-C3'-O3'	111.2(3)
N4-C5-C6	122.1(3)	C2'-C3'-C4'	113.9(3)
N1-C6-C5	119.0(3)	O3'-C3'-C4'	108.0(3)
N1-C6-C1'	117.0(3)	C3'-C4'-O4'	112.6(3)
N1-C6-C1'-C2	148.9(4)	C6-C1'-C2'-C3'	-171.7(4)
C1'-C2'-C3'-C4'	-65.8(3)	C2'-C3'-C4'-O4'	-168.6(4)

EXPERIMENTAL

Preparation of 3-amino-5-([2*S*],[3*S*]-2,3,4-trihydroxybutyl)-1,2,4-triazine (1) and 3-amino-6-([2*S*],[3*S*]-2,3,4-trihydroxybutyl)-1,2,4-triazine (2). These compounds were prepared by reaction of 3-deoxy-D-*erythro*-hexos-2-ulose ("3-deoxyglucosone") with aminoguanidine and were isolated by silica gel chromatography as described in an earlier report.[8] The crude crystals were dissolved in methanol and slowly recrystallized at room temperature over a period of 48 h. The resulting crystals were used for the X-ray studies.

X-ray studies. Experimental details of the crystallographic studies are given in Table 5. Both structures were solved using the direct methods program SHELX86[9] and refined by full-matrix least squares techniques using the NRCVAX[10] suite of programs. Data were corrected for Lorentz and polarization effects, but not for absorption. Non-hydrogen atoms were refined

Table 5. Crystal data

	1	2
Formula	$C_7H_{12}N_4O_3$	$C_7H_{12}N_4O_3$
M(a.m.u.)	200.19	200.19
Space group	P1	$P4_12_12$
a(Å)	5.309(2)	6.7117(4)
b(Å)	6.130(2)	
c(Å)	15.249(5)	40.037(9)
α(°)	95.31(2)	
β(°)	90.00(2)	
γ(°)	111.52(2)	
U(Å^3)	459.4(3)	1803.5(4)
Z	2	8
D_c(g.cm^{-1})	1.45	1.48
μ(cm^{-1})	1.1	1.2
F(000)	212	848
Radiation MoKα		
Graphite monochromator	λ=0.71073Å	λ=0.71073Å
Diffractometer	Enraf-Nonius CAD4	Enraf Nonius CAD4
Orienting reflections		
Range	25, 11<θ<15	25,11<θ<14
Temperature (°C)	22	22
Scan method	ω-2θ	ω-2θ
Data collection range	2.5<2θ<48	2.5<2θ<50
No. of unique data	2862	1033
No. observed data (I>2.5σ(I)), N	2483	875
No. of parameters, P	322	164
R[a]	4.1%	3.6%
R_w[b]	5.1%	5.6%
S, goodness of fit[c]	1.25	1.49
Max. shift/error, final	0.015	0.004
Largest positive peak (e/Å^3)	0.19	0.17
Largest negative hole (e/Å^3)	-0.23	-0.18

[a] $R=\Sigma(|Fo|-|Fc|)/\Sigma|Fo|$. [b] $R_w=\{\Sigma w(|Fo|-|Fc|)^2/\Sigma w|Fo|^2\}^{1/2}$; $w=1/[(\sigma Fo)^2+0.001*Fo^2]$; [c] $S=[\Sigma w(|Fo|-|Fc|)^2/(N-P)]^{1/2}$

with anisotropic thermal parameters. Hydrogen atoms were located in difference Fourier maps and were refined with fixed isotropic thermal parameters. Atomic scattering factors and anomalous-dispersion corrections from *International Tables for X-ray Crystallography* (1974).[11,12]

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