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The reaction of D-glucose with aminoguanidine ☆

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Abstract

The reaction of D-glucose with aminoguanidine was examined at pH 7.0 and 37°C (phosphate buffer). Under these conditions, the reaction requires ca. 42 days for 50% of the sugar to react, as measured by the disappearance of D-glucose, and at 60°C all the aminoguanidine had reacted within 72 h. The initial product, a β-D-glucopyranosyl aminoguanidine (**1**) was obtained in the crystalline state as the trifluoroacetate salt. Data collected on this compound suggests that, in solution, it is largely a glycosylamine in the β pyranose form. Acetylation gave a crystalline heptaacetate (**2**), which, in solution (as evidenced by NMR spectroscopy) exists in two different conformational forms. The crystal structure of the heptaacetate also includes two conformers. Both crystallographically independent molecules are in the normal β pyranose form, with the acetylated guanyl residue occupying different spatial positions relative to the ring.

Keywords: D-Glucose; Browning reaction; Maillard reaction; Amadori compound; Aminoguanidine; 1-Amino-1-deoxy-2-ketose

1. Introduction

Aminoguanidine (guanylhydrazine) represents an interesting compound in the sense that it has (apparently) a low toxicity level, and functions as an inhibitor of the Maillard reaction [1]. The latter reaction is a complex degradative pathway that initially involves the interaction of a reducing sugar with an amino group to give 1-amino-1-deoxy-2-ketose derivatives (Amadori compounds), which then decompose to give deoxydicarbonyl sugar

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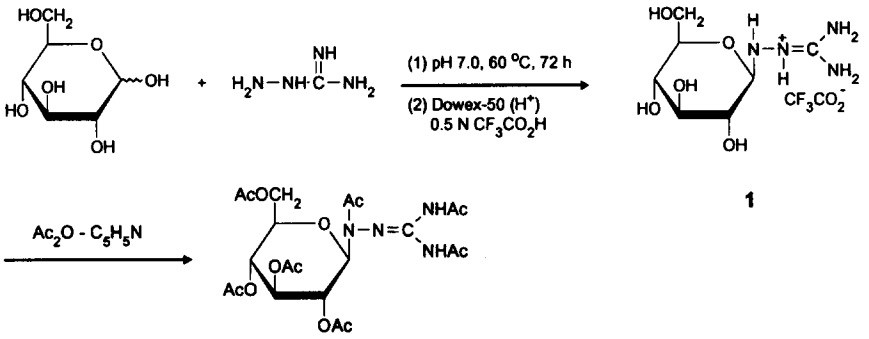

Scheme 1.

derivatives as initial degradation products [2–4]. Dicarbonyl sugar intermediates are known to serve as precursors of UV-absorbing compounds [1], of colored pigments (Maillard polymers) [5], as sources of reactants for Strecker degradation reactions (decarboxylation of amino acids) [6], and to be involved in protein cross-linking and possibly other modifications that are observed during Maillard reactions [7]. The Maillard reaction has recently received considerable interest because it has been shown to occur as an in vivo chemical reaction and has been proposed as a contributor to some of the pathophysiologies observed during aging [8], cataract formation [9], and the complications of diabetes [10]. The actual site of the inhibition of the Maillard reaction by aminoguanidine is still a subject of some debate and several scenarios have been proposed for this inhibition [11–15]. In earlier work in this laboratory, we have shown that, at pH 7.0 and 37°C, aminoguanidine reacts irreversibly and rapidly with a number of dicarbonyl sugar derivatives, including some that are produced during the Maillard reaction, to give 5- and 6-substituted triazine derivatives [16,17]. These reactions proceed in a matter of hours under these conditions, thus suggesting that this may be a major factor in the inhibition observed. It is noteworthy that Khatami and co-workers, in a study of the effect of aminoguanidine as an inhibitor of the reaction of D-glucose and albumin, showed that a discrete reaction product is formed between aminoguanidine and the sugar, but they did not identify this material [18]. It is also noteworthy that aldose–aminoguanidine condensation products were prepared at 100°C in concentrated solutions in water and studied by NMR spectroscopy [19]. The study reported herein describes an examination of the reaction of D-glucose with aminoguanidine at pH 7.0 and 37°C to give the cyclic glucopyranosyl aminoguanidine (**1**) (Scheme 1). Compound **1** was isolated as the crystalline trifluoroacetate salt and, on acetylation, a crystalline heptaacetate derivative (**2**) was also obtained.

2. Results and discussion

When D-glucose and aminoguanidine were incubated (0.2 M phosphate buffer) at 37°C, and the progress of the reaction was followed by TLC, a new compound having R_f 0.7 (irrigant *A*) was slowly produced, and after six weeks of reaction, ca. 50% of the original

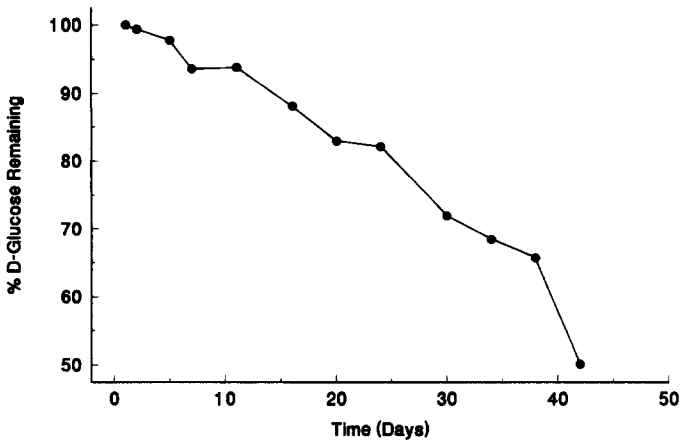

Fig. 1. Disappearance of D-glucose during incubation with aminoguanidine. Conditions for this experiment are detailed in the Experimental section.

D-glucose had reacted. At higher temperatures (60°C), the reaction was shown to be much faster, with all of the aminoguanidine having reacted within 72 h. Aliquots were treated with sodium borohydride, acetylated, and the unreacted glucitol hexaacetate was determined by GLC. A typical plot is shown in Fig. 1, which indicates the rate of disappearance of D-glucose for a reaction at 37°C and pH 7.0. TLC on fluorescent-absorbing plates indicated that no triazines (which show UV maxima at 320 nm) were produced throughout the reaction and that the only discernable product produced was the glucosylamine. For preparative purposes, this product was isolated by elution from an ion-exchange resin column with trifluoroacetic acid, and, on evaporation of the appropriate fractions, was obtained as the crystalline trifluoroacetate salt (**1**). Elemental analysis and NMR data (^1H and ^{13}C) were consistent [20,21] with the structure shown for **1** in Scheme 1, which shows the compound in the β-pyranose ring form. It is noteworthy that the hydrazone, when isolated by silica gel chromatography, was obtained as the free base in the form of a colorless syrup which was used for NMR measurements. These NMR data (D_2O) are in good agreement with those reported by Szilagyi and co-workers [19]. The NMR data, from a solution in Me_2SO-d_6, is also consistent with a β pyranose ring structure.

Acetylation of **1** gave a crystalline heptaacetate **2**, which was homogeneous as evidenced by TLC and had a sharp melting point. The ^1H and ^{13}C NMR spectroscopy ($CDCl_3$, 25°C) of **2**, however, indicated the presence of two different forms in solution in a ratio of ca. 1:0.6–0.7 (by integration of the ^1H NMR signals). The ^{13}C NMR data in Me_2SO-d_6 solution gave similar results. When the ^1H NMR spectrum was re-run at 50°C, it showed only a single set of NMR signals, which represented an average of the two sets of signals observed in the 25°C spectrum [22,23].

The structure of compound **2** was determined by single-crystal X-ray diffraction experiments. The results are given in Tables 1 and 2, along with experimental parameters. Perspective drawings (Fig. 2) show that both crystallographically independent molecules have the β pyranose structure, and that they differ mainly in the orientation of the acetylated guanyl group relative to the pyranose ring [2].

[2] Data relative to structure factors, anisotropic thermal parameters, bond distances, angles, and torsion angles have been deposited with the Cambridge Crystallographic Data Centre, 12 Union road, Cambridge, CB2 1EZ, UK.

Table 1
Crystal data

Formula	$C_{21}H_{30}N_4O_{12}$
M_w (amu)	530.48
Space group	$P1$
a (Å)	9.4637(13)
b (Å)	10.078(2)
c (Å)	14.678(2)
α (°)	79.726(11)
β (°)	86.052(10)
γ (°)	77.223(11)
U (Å^3)	1342.7(4)
Z	2
D_c (g cm^{-1})	1.312
μ (cm^{-1})	8.6
$F(000)$	560
Radiation Cu$K\alpha$, graphite monochromator	$\lambda = 1.54056$Å
Diffractometer	Enraf–Nonius CAD4
Orienting reflections, range	25, $40 < \theta < 50°$
Temperature (°C)	22 ± 1
Scan method	$\omega - 2\theta$
Data collection range	$2.0 < 2\theta < 120°$
No. of unique data	4251
No. of observed data [$I > 1.8\sigma(I)$], N	3196
No. of parameters, P	454
R [a]	6.7%
R_w [b]	7.1%
S, goodness of fit [c]	1.77
Max. shift/error, final	0.007
Largest positive peak (e/Å^3)	0.27
Largest negative hole (e/Å^3)	−0.26

[a] $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$.
[b] $R_w = \{\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2\}^{1/2}$; $w = 1/[(\sigma F_o)^2 + 0.0005 * F_o 2]$.
[c] $S = [\Sigma w(|F_o| - |F_c|)^2/(N-P)]^{1/2}$.

3. Experimental

General methods.—Melting points were determined using a Thomas–Hoover melting point apparatus in open capillary tubes and are uncorrected. Optical rotations were measured at 24°C using a Perkin–Elmer Model 241 MC automatic polarimeter. TLC was performed on silica gel plates (Kieselgel 60F, 250 μm) using 9:1:0.75 pyridine–AcOH–water (irrigant *A*) and 5:1 $CHCl_3$–acetone (irrigant *B*). Detection was effected by spraying the plates with 5% ethanolic H_2SO_4 (spray *A*), ninhydrin (spray *B*), or by direct UV irradiation of the plate. Sprays *A* and *B* were followed by heating at 110°C for 10 min. Preparative column chromatography was performed using 200–400 mesh silica gel (Aldrich). ^{1}H (500 MHz, D_2O, internal reference) and ^{13}C NMR (125 MHz, 1,4-dioxane as external reference) spectra, COSY and HETCOR experiments were collected using a Bruker AMX 500 instrument. GLC was performed using a Varian 3400 instrument in the split mode. X-ray diffraction data were collected on an Enraf–Nonius CAD4 diffractometer using Cu$K\alpha$ radiation

Table 2
Atomic Parameters x, y, z, and B or B_{eq}. The esd's refer to the last digit printed

	x	y	z	B or B_{eq} [a]
O-2A	0.0166(8)	0.7896(7)	0.9749(5)	4.7(3)
O-3A	−0.0062(8)	0.8985(8)	0.7836(5)	4.7(3)
O-4A	−0.2759(8)	1.1102(7)	0.7508(5)	4.7(3)
O-5A [b]	−0.37270	0.86210	0.94200	3.8(3)
O-6A	−0.6522(8)	1.0448(8)	0.8918(5)	4.6(3)
O-1′A	−0.3608(9)	0.8715(7)	1.1606(5)	4.6(3)
O-4′A	−0.2128(9)	0.1922(8)	0.9981(6)	6.3(4)
O-6′A	0.0571(9)	0.2738(8)	1.1706(6)	5.5(3)
O-8′A	0.1103(11)	0.5894(10)	0.9274(8)	9.4(5)
O-10′A	0.0523(10)	1.1031(9)	0.7721(7)	7.7(5)
O-12′A	−0.2398(13)	1.0357(10)	0.6161(6)	8.9(6)
O-14′A	−0.6428(10)	1.2635(8)	0.8386(7)	8.9(5)
N-1′A	−0.2536(9)	0.7227(8)	1.0663(6)	3.8(3)
N-2′A	−0.2554(9)	0.5959(8)	1.0344(6)	3.7(3)
N-3′A	−0.1524(9)	0.3627(8)	1.0518(6)	3.9(3)
N-4′A	−0.0575(9)	0.5011(8)	1.1339(6)	3.8(3)
C-1A	−0.2430(10)	0.8356(9)	0.9920(6)	3.4(2)
C-2A	−0.1156(11)	0.8063(10)	0.9269(7)	3.8(2)
C-3A	−0.1207(10)	0.9316(9)	0.8509(6)	3.4(2)
C-4A	−0.2656(10)	0.9741(9)	0.8032(7)	3.4(2)
C-5A	−0.3899(10)	0.9857(9)	0.8743(6)	3.3(2)
C-6A	−0.5335(11)	1.0032(10)	0.8305(7)	4.1(2)
C-1′A	−0.3407(10)	0.7547(10)	1.1426(7)	3.5(2)
C-2′A	−0.4012(12)	0.6455(11)	1.2011(7)	5.2(2)
C-3′A	−0.1608(10)	0.4948(10)	1.0722(7)	3.5(2)
C-4′A	−0.2342(11)	0.3176(11)	0.9951(7)	4.3(2)
C-5′A	−0.3452(14)	0.4151(13)	0.9370(9)	7.1(3)
C-6′A	0.0450(11)	0.3956(10)	1.1800(7)	4.0(2)
C-7′A	0.1403(12)	0.4366(10)	1.2406(8)	5.0(2)
C-8′A	0.1258(14)	0.6812(13)	0.9657(9)	6.3(3)
C-9′A	0.260(2)	0.6946(13)	1.0090(10)	8.2(3)
C-10′A	0.0685(13)	0.9945(12)	0.7491(8)	5.1(2)
C-11′A	0.174(2)	0.9474(14)	0.6778(10)	7.9(3)
C-12′A	−0.2566(13)	1.1244(12)	0.6609(9)	6.0(3)
C-13′A	−0.266(2)	1.275(2)	0.6204(11)	8.8(3)
C-14′A	−0.6980(13)	1.1828(12)	0.8879(8)	5.5(2)
C-15′A	−0.8263(14)	1.2133(12)	0.9543(9)	7.1(3)
O-2B	0.0265(8)	0.6720(8)	0.4245(5)	4.0(3)
O-3B	−0.1226(8)	0.6266(7)	0.6145(5)	4.5(3)
O-4B	−0.4209(9)	0.6329(8)	0.5923(5)	4.6(3)
O-5B	−0.3359(8)	0.8685(7)	0.3888(5)	4.3(3)
O-6B	−0.5658(9)	0.9817(8)	0.5026(6)	6.2(3)
O-1′B	−0.0346(8)	0.7355(7)	0.2107(5)	4.2(3)
O-4′B	−0.1968(11)	1.4217(8)	0.3802(6)	7.3(5)
O-6′B	−0.4639(9)	1.3367(8)	0.2057(7)	6.7(4)
O-8′B	0.1521(9)	0.7265(9)	0.5313(6)	7.1(4)
O-10′B	0.0266(10)	0.4341(9)	0.5809(6)	7.1(4)
O-12′B	−0.4527(11)	0.7421(10)	0.7128(6)	8.1(5)
O-14′B	−0.6340(13)	1.1327(12)	0.3760(9)	13.1(7)

Table 2 (continued)

	x	y	z	B or B_{eq} [a]
N-1'B	−0.1344(9)	0.8949(8)	0.2997(6)	3.4(3)
N-2'B	−0.1290(9)	1.0215(8)	0.3294(6)	3.8(4)
N-3'B	−0.2438(10)	1.2518(8)	0.3191(6)	4.2(3)
N-4'B	−0.3357(10)	1.1130(8)	0.2368(6)	4.1(4)
C-1B	−0.1937(11)	0.7978(9)	0.3680(7)	3.6(2)
C-2B	−0.10 78(11)	0.74 96(9)	0.45 52(7)	3.6(2)
C-3B	−0.1880(11)	0.6564(9)	0.5256(7)	3.5(2)
C-4B	−0.3418(11)	0.7311(10)	0.5402(7)	4.0(2)
C-5B	−0.4175(11)	0.7836(10)	0.4481(7)	4.1(2)
C-6B	−0.5674(13)	0.8674(12)	0.4567(8)	5.8(2)
C-1'B	−0.0467(10)	0.8507(10)	0.2269(7)	3.6(2)
C-2'B	0.0274(13)	0.9574(11)	0.1689(8)	5.6(2)
C-3'B	−0.2336(11)	1.1211(10)	0.2968(7)	3.6(2)
C-4'B	−0.1611(12)	1.2995(12)	0.3715(8)	4.8(2)
C-5'B	−0.0316(13)	1.2081(12)	0.4200(8)	5.8(2)
C-6'B	−0.4444(11)	1.2147(11)	0.1963(7)	4.7(2)
C-7'B	−0.5446(13)	1.1727(12)	0.1388(8)	5.7(2)
C-8'B	0.1468(13)	0.6708(12)	0.4653(9)	5.4(2)
C-9'B	0.276(2)	0.5826(13)	0.4257(9)	7.0(3)
C-10'B	−0.0190(13)	0.5089(13)	0.6347(9)	5.7(2)
C-11'B	0.025(2)	0.4876(14)	0.7318(10)	8.2(3)
C-12'B	−0.4759(12)	0.6536(11)	0.6763(8)	5.1(2)
C-13'B	−0.57 08(14)	0.5570(12)	0.7160(8)	6.2(2)
C-14'B	−0.602(2)	1.1100(17)	0.4554(12)	8.5(3)
C-15'B	−0.591(2)	1.211(2)	0.5142(14)	12.6(5)

[a] B_{eq} is the mean of the principal axes of the thermal ellipsoid.
[b] The coordinates of O-5A were held constant in order to define the origin.

($\lambda = 1.54056$ Å). The structure was solved by direct methods and completed by successive Fourier calculations. The structure was refined by full-matrix least squares methods. Due to sparse data the N and O atoms were refined with anisotropic thermal parameters, while the C atoms were refined with isotopic thermal parameters. All H atoms, except some of the methyl group H atoms, could be located in difference Fourier maps, and all H atoms were included in the final model at calculated positions with isotropic thermal parameteres equal to 1.3 times that of the attached atom. All calculations were performed with the NRCVAX program package [24]. Details of the X-ray experiment, crystal data, data collection, reduction, and refinement are given in Table 1.

*Preparation of β-*D*-glucopyranosyl aminoguanidine trifluoroacetate salt* (**1**).—D-Glucose (900 mg, 5 mmol) and aminoguanidine (bicarbonate salt, 685 mg, 5 mmol) were dissolved in distilled water (45 mL) and kept at 60°C (oil bath) for 72 h, when TLC showed that no aminoguanidine (R_f 0.3, irrigant *A*, spray *B*) was present in the mixture. The resulting dark-yellow solution was evaporated to ca. 15 mL in a flash evaporator (bath temperature 45°C) and placed on a 1.5 × 20 cm column of Dowex-50 ion-exchange resin (H^+ form). The column was then eluted with ca. 400 mL of water (to remove 600 mg, 66.7% of unreacted D-glucose), and the product was eluted by washing with 400 mL of 0.5 N CF_3CO_2H. The eluant was evaporated to dryness, 30 mL of water was added, and the

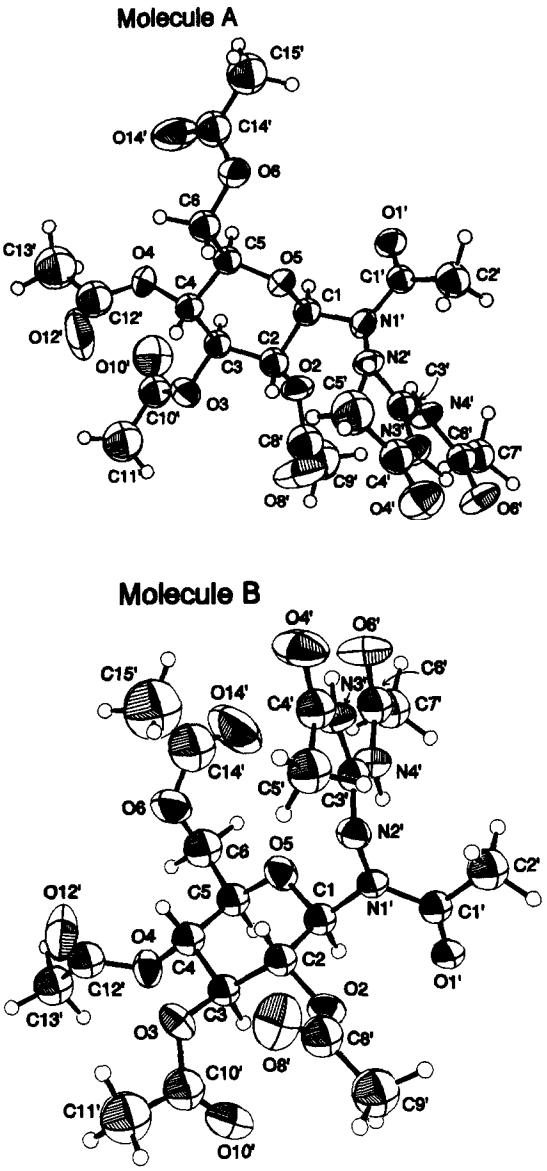

Fig. 2. Perspective drawings (molecules A and B) of two isomeric β-D-glucopyranosyl aminoguanidine heptaacetates.

solution was again evaporated to dryness. This procedure was repeated two additional times. The resulting hygroscopic compound **1** (350 mg, 29.7%; 89.7% of the reacted D-glucose, R_f 0.7, irrigant *A*, spray *A*) crystallized from MeOH as the trifluoroacetate salt; mp 166–167°C; $[\alpha]_D$ −11.8° (*c* 1.15, H_2O). The following data were collected for **1** (where the numbering is the same as for the original carbon atoms of D-glucose). ^{1}H NMR data (D_2O): δ 3.98 (d, 1 H, $J_{1,2}$ 9.1 Hz, H-1), 3.76 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6a,6b}$ 12.1 Hz, H-6a), 3.57 (dd,

1 H, $J_{5,6b}$ 5.8 Hz, H-6b), 3.35 (dd, unresolved, 1 H, $J_{2,3}$ 9.1 Hz, H-3), 3.28 (ddd, 1 H, $J_{4,5}$ 9.8 Hz, H-5), 3.22 (dd, unresolved, 1 H, H-4), 3.17 (dd, unresolved, 1 H, H-2). ^{13}C NMR data (^{1}H decoupled, D_2O): δ 159.42 (guanyl carbon), 90.28 (C-1), 77.71 (C-5), 77.43 (C-3), 71.31 (C-2), 70.38 (C-4), 61.78 (C-6). ^{13}C NMR data (^{1}H decoupled, Me_2SO-d_6): δ 158.47 (guanyl carbon), 90.25 (C-1), 77.83 (C-5), 76.82 (C-3), 70.99 (C-2), 70.06 (C-4), 61.55 (C-6). Anal. Calcd for $C_9H_{17}F_3N_4O_7$: C, 30.86; H, 4.89; N, 16.01; F, 16.27. Found: C, 30.66; H, 4.85; N, 16.03; F, 15.91.

Measurement of the progress of the reaction of D-*glucose with aminoguanidine.*—The reaction rate was determined by measuring the D-glucose present in the solution as a function of time. A solution composed of D-glucose (900 mg, 5 mmol), aminoguanidine (bicarbonate salt, 685 mg, 5 mmol), and D-mannitol (910 mg, 5 mmol, internal standard) in 0.2 M phosphate buffer (pH 7.0, 45 mL) at 37°C was used in the experiment. For analytical data collection, 1.0-mL aliquots were removed at intervals, and the reaction was terminated by adding 1.0 mL of a freshly prepared 10% solution of sodium borohydride. After 30 min, the solution was evaporated to dryness and acetylated (1 h, 65°C, and 1:2 pyridine–Ac_2O), and the acetylation solution was evaporated to dryness and then taken up in 1.0 mL of CH_2Cl_2. A 1-μL aliquot was used for GLC analysis, and the amount of D-glucitol present was determined by comparison with D-mannitol (internal standard).

Preparation of β-D-*glucopyranosyl aminoguanidine heptaacetate* (**2**).—Compound **1** (500 mg) was acetylated in the usual way with 1:1 pyridine–Ac_2O (4 mL) at room temperature for 24 h. This preparation (R_f 0.25, irrigant *B*, spray *A*) was purified by silica gel column (2.4 × 20 cm) chromatography after the usual workup, and gave the heptaacetate (**2**) in crystalline form (440 mg, 42.7%). After recrystallization from EtOH, the following analytical data were collected for compound **2**; mp 166–167°C; $[\alpha]_D$ −2.1° (*c* 1.17, $CHCl_3$). Crystals for X-ray studies were prepared from the crude material by dissolving them in 1-butanol followed by 4 days crystallization at room temperature. ^{1}H NMR data (500 MHz, $CDCl_3$): major component: δ 12.91 (s, 1 H, NH), 10.57 (s, 1 H, NH_2), 5.94 (d, 1 H, $J_{1,2}$ 9.4 Hz, H-1), 5.22 (dd, unresolved, 1 H, $J_{3,4}$ 9.4 Hz, H-3), 5.08 (dd, unresolved, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 4.94 (dd, unresolved, 1 H, $J_{2,3}$ 9.3 Hz, H-2), 4.21 (dd, 1 H, $J_{5,6a}$ 1.7, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.10 (dd, $J_{5,6b}$ 4.1 Hz, H-6b), 3.81 (m, H-5), 2.25–1.95 (m, $NCOCH_3$, $COCH_3$); minor component: δ 12.85 (s, 1 H, NH), 10.77 (s, 1 H, NH_2), 5.85 (d, 1 H, $J_{1,2}$ 7.3 Hz, H-1), 5.32 (dd, unresolved, 1 H, H-3), 4.94 (dd, unresolved, 1 H, H-4), 4.87 (dd, unresolved, 1 H, H-2), 4.16 (dd, unresolved, 1 H, H-6a), 4.03 (dd, unresolved, 1 H, H-6b), 3.81 (m, 1 H, H-5), 2.25–1.95 (m, $NCOCH_3$, $COCH_3$). ^{13}C NMR data (H-1 decoupled, $CDCl_3$): major component: 173.47–169.25 (7 C, N*C*OCH$_3$, *C*OCH$_3$), 155.63 (guanyl carbon), 79.67 (C-1), 74.03 (C-3), 73.57 (C-5), 67.24 (C-4), 67.11 (C-2), 61.32 (C-6), 28.54–20.46 (NCO*C*H$_3$, CO*C*H$_3$); in Me_2SO-d_6: δ 153.23 (guanyl carbon), 81.26 (C-1), 73.04 (C-3), 72.13 (C-5), 67.67 (C-4), 67.56 (C-2), 61.70 (C-6), $J_{C\text{-}1,H\text{-}1}$ 162.2 Hz; minor component: 172.90–169.54 (N*C*OCH$_3$, *C*OCH$_3$), 155.63 (guanyl carbon), 80.09 (C-1), 73.57 (C-5), 72.12 (C-3), 68.98 (C-2), 68.18 (C-4), 61.72 (C-6), 28.66–20.46 (NCO*C*H$_3$, CO*C*H$_3$); in Me_2SO-d_6: δ 149.01 (guanyl carbon), 84.46 (C-1), 72.13 (C-5), 71.30 (C-3), 68.31 (C-2), 67.12 (C-4), 61.40 (C-6), $J_{C\text{-}1,H\text{-}1}$ 159.7 Hz. Anal. Calcd for $C_{21}H_{30}N_4O_{12}$: C, 47.55; H, 5.70; N, 10.56. Found: C, 47.44; H, 5.72; N, 10.65.

Views of the two crystallographically independent molecules are given in Fig. 2, and the final atomic coordinates are given in Table 2.

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