Aminosugars. XIX. On the Structure of 2-Deoxy-2-guanidino-D-glucose[1]

Juji YOSHIMURA, Tetsuo SEKIYA, and Takao IIDA

Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Meguro-ku, Tokyo

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It was found that 2-deoxy-2-guanidino-D-glucose prepared by guanidination of 2-amino-2-deoxy-D-glucose with cyanamide exists mainly as α-D-glucofurano[1′,2′;4,5]-2-imino-imidazolidine (*5*) which is easily converted into 2-imino-4-(D-*arabino*-tetrahydroxybutyl)imidazoline-4 (*6*) under alkaline conditions. Acetylation of *5* and *6* gave the corresponding hexa- and heptaacetate (*7* and *8*), respectively. Warming of *7* in alcohols gave addition compounds of alcohols to the imino double bond, and deacetylation with sodium alcoholate at a room temperature yielded 2-acetamido-4-(D-*arabino*-tetrahydroxybutyl)imidazole (*10*). Similar treatment of *8* in ethanol at elevated temperature gave an unknown addition compound in which two *N*-acetyl groups were eliminated, and deacetylation with a small amount of sodium methylate yielded a mixture of (2*R*,*S*)-2-acetamido-2-methoxy-4-(D-*arabino*-tetraacetoxybutyl)imidazoline-4 and tetra-*O*-acetyl derivative of *10* which was also obtained by acetylation of *10*.

Several natural guanidino-compounds such as streptidine,[2] viomycidine,[3] and tetrodotoxin[4] are known about their strong biological activities. Among them, the aminal ring between the guanidino and aldehyde group in tetrodotoxin is interesting in the structural feature. Odo and Kono[5] reported that 2-deoxy-2-guanidino-D-glucose hydrochloride which was obtained by guanidination of 2-deoxy-2-amino-D-glucose hydrochloride with cyanamide exists in an equilibration between the usual lactol (**1**) and the imidazoline ring structures (**2**) in aqueous solutions.

In this paper, the authors have found that 2-deoxy-2-guanidino-D-glucose exists mainly as α-D-glucofurano-[1′,2′;4,5]-2-imino-imidazolidine (**3**) which is easily converted to 4-(D-*arabino*-tetrahydroxybutyl)imidazoline-4 (**4**) under alkaline conditions, and examined a few chemical properties of them.

Results and Discussion

A neutral solution of 2-amino-2-deoxy-D-glucose hydrochloride and cyanamide in water was heated at 60°C for 7 hr, and then picric acid in methanol was added to the reaction mixture. After standing at 0°C for 2 days, the known picrate of needles (**3**)[5]; mp 180°C, and a new granular picrate (**4**); mp 178°C, were obtained in 23.6% and 15.4% yield, respectively. These picrates were then converted into hydrochlorides (**5** and **6**), respectively. Both of them were negative to ninhydrin, Fehling, and Sakaguchi reactions, and distinguishable each other in specific rotations and C–O stretching absorptions in the region between 1000—1100 cm^{-1} in IR spectra. No mutarotation of them indicated the absence of **1** in solutions.

Moreover, in UV spectrum, **5** showed no absorption other than end absorptions (<210 nm), but **6** had a maximum at 212 nm (ε 1.057×10^4). NMR spectra of **5** and **6** showed two characteristic doublets at 3.55 and 5.07 τ, and two singlets at 2.77 and 4.60 τ, respectively. These facts indicated a glucofurano-configuration for the former and a heterocyclic structure for the latter. Furthermore, the conversion of **5** to **6** was found in alkaline conditions. The doublet at 3.55 τ in NMR spectrum of **5** instantly disappeared by addition of alkali, and a singlet at 2.89 τ appeared, which is shifted to 2.77 τ by acidification. A maximum at 208 nm was also observed in UV spectrum of **5** at pH 10.4. Such a conversion was also occured by adjustment of the pH of a solution of **5** with Amberlite IRA-410, and in fact, **6** was isolated by acidification in 80% yield. Further conversion of **6** to an unknown compound by standing the alkalline solution for 2 or 3 days was indicated with the disappearance of characteristic singlet, however, no definite compound could be isolated.

In order to clarify the structures, **5** and **6** was respectively acetylated with acetic anhydride in pyridine to the corresponding hexaacetate (**7**) and heptaacetate (**8**) in 83.3 and 50% yields. Both compounds showed UV absorptions of λ_{max}^{EtOH} 219 nm (ε 1.5×10^4) and 253 nm (ε 3.4×10^3), respectively. The NMR spectrum of **7** (Fig. 1) assigned by double resonance technique gave a very similar pattern of the ring-proton signals to 3′,5′,6′-tri-*O*-acetyl-α-D-glucofurano[1′,2′;4,5]-*N*-acetyloxazolidine-2-thion,[6] indicating the presence of α-D-glucofuranose configuration, and two acetyl signals appeared in lower field than other four acetyl signals are assignable to imino-acetyl and N_3-acetyl also by analogy to this compound. Therefore, **7** was determined to be 3′,5′,6′-tri-*O*-acetyl-α-D-glucofurano[1′,2′;4,5]-2-acetylimino-1,3-diacetylimidazolidine. It is interesting that such a ring formation in **7** as in glycosylamines is also seen in viomycidine[2] or anhydrotetro-

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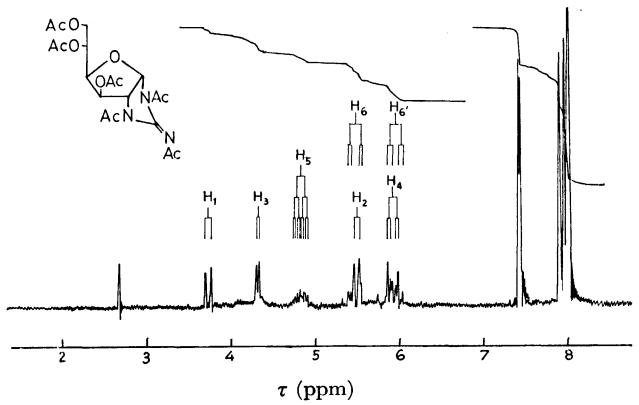


Fig. 1. The NMR spectrum of **7**.

dotoxin.[3]

On the other hand, the NMR spectrum of **8** (Fig. 2) showed again a closely similar pattern of sugar-chain protons to 2-methoxycarbonyl-4-(D-*arabino*-tetraacetoxybutyl)imidazole obtained by the reaction of 2-amino-2-deoxy-D-glucose and the corresponding iminoether,[7] indicating the presence of a five-membered heterocyclic structure. However, the difference of UV absorption between 8 and this compound (λ_{max} 260 nm; ε 1.05×10^4) and the presence of three acetyl groups in the heterocyclic part indicate a non-conjugated system. Consequently, **8** was concluded to be 2-acetylimino-1,3-diacetyl-4-(D-arabino-tetraacetoxybutyl)imidazolin-4.

Transformation of **1** to **3** or **4** mentioned above will be explained as follows (Scheme 1). Dehydration between the guanidino and aldehyde groups in the oxo-form of **1** give easily the intramolecular Schiff base which is equilibrating with the more stable imidazolidine structure at the pH region lower than 7. At a higher pH region, a prototropic shift is caused by the action of hydroxide ions to give the imidazoline derivative irreversibly. At the end of the condensation reaction of 2-amino-2-deoxy-D-glucose with cyanamide, the pH of the solution adjusted to 7 at the biginning has changed to 8.3. This change will be attributed to the reason for the formation of **3** and **4** at the same time. The participation of lone-paired electrons of nitrogen in the intramolecular Schiff base to the resonance stabilization of the imidazoline ring will accerelate the prototropic shift in the convesion into **4**.

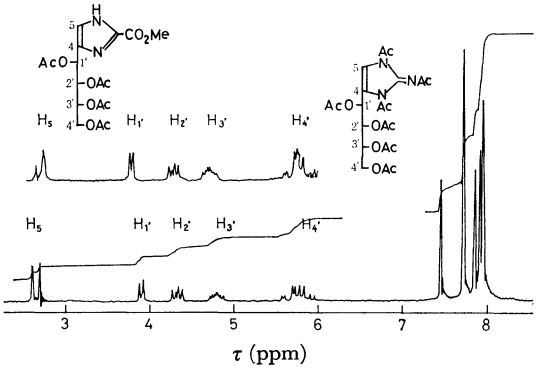
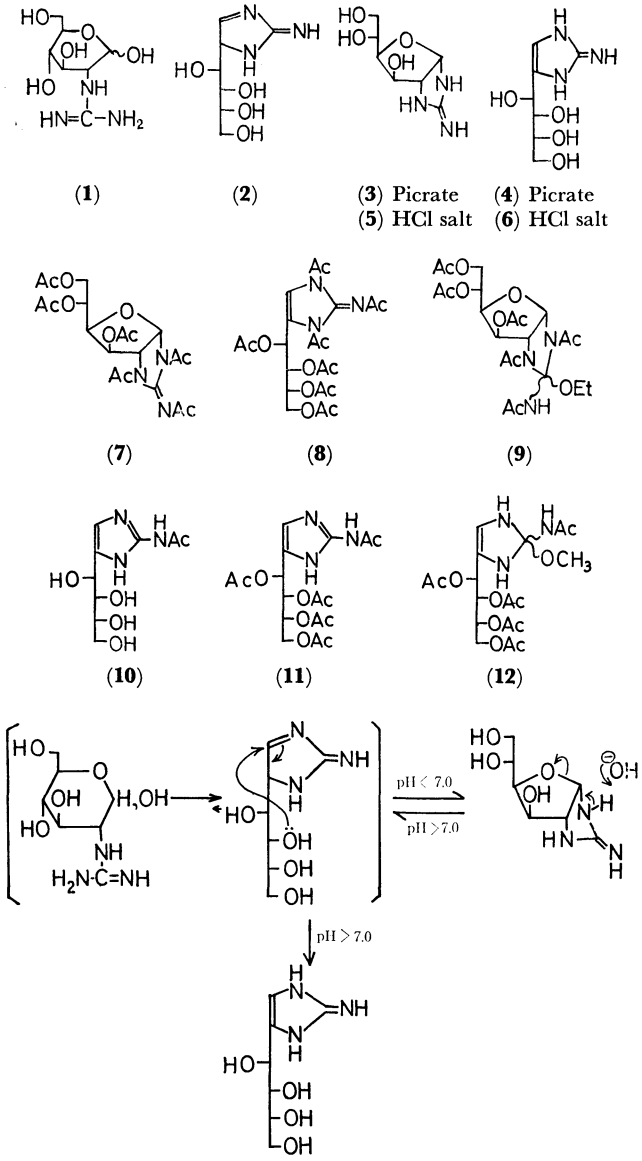


Fig. 2. The NMR spectrum of **8**.



Scheme 1

On the other hand, it was found that **7** was converted to an addition product of ethanol (**9**) in 66% yield by heating it in ethanol at 60°C for 4 hr. IR spectrum of **9** showed the appearrance of characteristic absorptions of N–H (3250, 3200, and 1540 cm^{-1}), and the NMR spectrum two kinds of ethyl signals (C–CH_3 at 8.78 and 8.84 τ; O–CH_2– at 6.31 and 6.89 τ), indicating the addition of ethanol to the 2-imino bond from the both side. Formation of analogous addition compound of methanol or isopropyl alcohol were also ascertained with NMR spectra. A similar reaction was reported in the case of triacetyl-2-imino-imidazolidine.[8] Similar treatment of **8** in ethanol at an elevated temperature gave also an addition compound in which elimination of two *N*-acetyl groups was indicated by NMR spectrum, however, no definite compound could be isolated.

Moreover, an attempted deacetylation of **7** with sodium methoxide at a room temperature gave 2-acetamido-5-(D-*arabino*-tetrahydroxymethyl)imidazole

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8) R. Greenhalgh and R. A. B. Bannard, *Can. J. Chem.*, **39**, 1017 (1961).

(**10**) in 80% yield. Reacetylation of **10** by the usual method gave a mixture of the corresponding *N,O*-pentaacetate (**11**) and another product. The presence of two kind of C_4- and C′-proton signals indicate that the structure of the latter is similar to the former. One attempted acetylation of **6** gave incidentally **11** as the main product, from which pure sample was isolated by preparative thin layer chromatography. Comparatively large molecular coefficency of the absorption of **11** [λ_{max}^{EtOH} 246 nm (ε 7.08×10^3)] and the presence of characteristic absorptions of secondary amide (1675 and 1520 cm^{-1}), esters (1745 cm^{-1}), monoacetylguanidine (1595 cm^{-1})[8] in IR spectrum indicated the presence of imidazole structure in **11**. Because of its insolubility NMR and UV spectrum of **10** could not be examined, however, the IR spectrum showed absorptions of secondary amide (1675 and 1530 cm^{-1}), monoacetylguanidine (1600 cm^{-1}), and characteristic C–O stretching in the region between 1000—1100 cm^{-1} as was observed that of **4** and **6**.

For the transformations of **7** to **10** and **10** to **11**, the following considerations will be given; (i) treatment of **7** with sodium methoxide caused the elimination of feasible *N*-acetyl groups attached to guanidine-type structure[9] as well as de-*O*-acetylation, and moreover, the skeletal conversion as shown in Scheme 1 is accompanied with the shift of *exo*-double bond to give more stable imidazole structure. Thus, the usual 2-acetamido group in **10** is remained intact. (ii) Because *N*-acetylation of heterocycles such as imidazole can be accomplished only by refluxing with acetic anhydride,[10] the usual acetylation of **10** gave the *N,O*-pentaacetate.

Similar deacetylation of **8** with a small amount of sodium methoxide gave again a mixture of **11** and another addition compound of methanol. From the integration of NMR spectrum the latter was deduced to be (2*R*,*S*)-2-acetamido-2-methoxy-4-(D-*arabino*-tetraacetoxybutyl)imidazoline-4 (**12**). The analitical data of the mixture consisted with that a mixture of them in the ratio estimated from the NMR spectrum. Treatment of **11** with excess amounts of ethoxide gave again crude **10**. These results indicate that guanidine-type *N*-acetyl groups are more labile than *O*-acetyl groups, and nucleophilic additions to the *exo*-double bond in **8** are also possible depending on condition used.

Many works on electrophillic reactions of triheterocarbonium ions including oxygen, nitrogen and sulfur as heteroatoms[11] have been done, but, the trinitrogen-system of guanidines has been considered to be rather stable than others. The result obtained in this work seems likely to suggest that *N*-acylation activates this system, and more simple model compound will be suitable to study for this aspect.

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10) L. Birkofer, *Chem. Ber.*, **76**, 769 (1943); J. A. Montgomery *J. Amer. Chem. Soc.*, **78**, 1928 (1956).
11) H. Prinzbach and E. Futter, "Advances in Heterocyclic Chemistry", Vol. 7, ed. by A. R. Katritzky and A. J. B. Boulton, Academic Press, (1967) p. 103; A. H. Land, "Heterocyclic Compounds", Vol. 5, ed. by R. C. Elderfield, John Wiley & Sons Inc., (1967) p. 484; T. Nakai, *Yuki Gosei Kagaku Kyokai Shi*, **28**, 708 (1970).

Experimental

All melting points are uncorrected. The solutions were evaporated under diminished pressure at a bath temperature not exceeding 45°C. Specific rotations were measured in a 0.5-dm tube, with a Carl Zeiss LEP Al Polarimeter. The IR spectra were recorded with a Hitachi Model EPI-GS grating IR spectrophotometer. The NMR spectra were taken with a JMN-4H-100MHz Spectrometer in deuteriochloroform unless otherwise stated, using tetramethylsilane as an internal standard. Chemical shifts and coupling constants were recorded in τ and Hz units, and IR frequencies in cm^{-1}.

α-D-Glucofurano[1′,2′;4,5]-2-iminoimidazolidine picrate (3) and 2-imino-4-(D-arabino-tetrahydroxybutyl)imidazoline picrate (4). A solution of D-glucosamine hydrochloride (4.30 g, 20 mmol) and cyanamide (1.26 g, 30 mmol) in water (20 m*l*) was neutralized with 5N-sodium hydroxide to pH 7.0, stirred at 60°C for 7 hr, and then picric acid (10.2 g) in methanol (140 m*l*) was added to the reaction mixture. After standing this solution at 0°C for 2 days, picrate of needle crystal (**3**) was obtained in 23.6% yield (2.02 g). Mp 180°C; IR: 1670 (C=N), 1560 (NO_2).

Found: C, 35.96; H, 3.70; N, 19.38%. Calcd for $C_{13}H_{16}N_6O_{11}$: C, 36.13; H, 3.73; N, 19.44%.

The mother liquor was suitably concentrated, and the precipitate appeared was gathered. This powder (8.50 g) was washed three times with benzene (25 m*l*) at 60°C to remove excess picric acid. The residue was recrystallized from hot water to give granular picrate (**4**) (1.33 g) in 15.4% yield. Mp 178°C; IR: 1680 (C=C), 1668 (C=N), 1550 (NO_2).

Found: C, 35.96; H, 3.76; N, 20.47%. Calcd for $C_{13}H_{16}N_6O_{11}$: C, 36.13; H, 3.73; N, 19.44%.

α-D-Glucofurano[1′,2′;4,5]-2-iminoimidazolidine hydrochloride (5). To a solution of **3** (1.4 g) in water (30 m*l*) was added 10% hydrochloric acid (10 m*l*) at 50°C, kept at the same temperature for ten minutes and then cooled to room temperature. After separating picric acid by filteration, the mother liquor was extracted several times with ether (15 m*l*× 5) to remove the picric acid. The water solution was adjusted to pH 5.0 with Amberlite IRA-410, decolorized with active carbon, concentrated, and the residual sirup was crystallized by addition of ethanol to give 0.6 g (77%) of colorless prisms which was recrystallized from water-ethanol. IR: 1674 (C=N); NMR (D_2O): 3.55 ($H_{1'}$; d, $J_{1,2}$=6.3); 5.07 ($H_{2'}$; d); 5.17 (1H; s) and 5.5—6.0 (4H; m), ($H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'a}$, $H_{6'b}$). $[\alpha]_D^{23}$ −25.4° (*c* 1.0, water).

Found: C, 35.08; H, 6.07; N, 17.46%. Calcd for $C_7H_{14}N_3O_4Cl$: C, 35.07; H, 5.89; N, 17.53%.

2-Imino-4-(D-arabino-tetrahydroxybutyl)imidazoline-4 hydrochloride (6). The picrate **4** (1.0 g) was treated by the same method as mentioned above, and the corresponding hydrochloride was obtained as colorless needles in 72% (0.4 g) yield. Mp 171°C; $[\alpha]_D^{23}$ −11.7° (*c* 1.0, water); IR: 1664 and 1575 (C=N and C=C); NMR (D_2O): 2.77 (H_5; s); 4.60 ($H_{1'}$; s); 5.6—5.9 ($H_{2'}$, $H_{3'}$, $H_{4'a}$, $H_{4'b}$, m).

Found: C, 34.48; H, 5.59; N, 17.69%. Calcd for $C_7H_{14}N_3O_4Cl$: C, 35.07; H, 5.89; N, 17.53%.

Conversion of 5 into 6. A solution of **5** (1.00 g) in water (30 m*l*) was adjusted to pH 11.8 with Amberlite IRA-410 and kept at room temperature for thirty minutes. After checking the appearrance of the UV absorption (λ_{max} 208 nm) the solution was adjusted to pH 4.8 with 4N-HCl (*ca.* 8 m*l*), and evaporated to give a sirup which was crystallized by addition of ethanol. Yield, 0.8 g (80%). Physical properties of this crystals consisted with the authentic specimen.

3′,5′,6′-Tri-O-Acetyl-α-D-glucofurano[1′,2′;4,5]-2-acetylimino-1,3-diacetylimidazolidine (7). To a suspension of **5** (1.20 g, 5.0 mmol) in pyridine (8.0 m*l*) was added acetic anhydride

(6.0 ml, 64 mmol) with stirring under cooling at 0°C. After standing the reaction mixture at room temperature for 2 days, it was poured into ice-water (30 ml) with stirring to give white crystals, which was gathered on a filter paper, washed with cold water, and then recrystallized from chloroform–petroleum ether. Yield, 1.89 g (83.3%); mp 155°C; $[\alpha]_D^{23}$ +26.0° (*c* 2.00, chloroform); IR: 1745 (OAc), 1685 (C=N), 1640 (*tert.* amide); NMR: 3.73 ($H_{1'}$; d, $J_{1',2'}$=6.5), 5.49 ($H_{2'}$; d), 4.32 ($H_{3'}$; d, $J_{3',4'}$=3.0), 5.91 ($H_{4'}$; q, $J_{4',5'}$= 10.0), 4.82 ($H_{5'}$; oct, $J_{5',6'_a}$=3.0), 5.47 ($H_{6'_a}$; q, $J_{6'_a,b}$= 12.5), 5.94 ($H_{6'_b}$; q, $J_{5',6'_b}$=5.5), 7.42 and 7.44 (N_3-Ac and imino-Ac), 7.90, 7.96, and 8.01 (N_1-Ac and 3×OAc).

Found: C, 50.01; H, 5.89; N, 9.23%. Calcd for $C_{19}H_{25}N_3O_{10}$: C, 50.11; H, 5.53; N, 9.23%.

*2-Acetylimino-1,3-diacetyl-4-(*D-arabino-*tetraacetoxybutyl)imidazoline-4 (8).* To a suspension of **6** (0.6 g, 2.5 mmol) in pyridine was added acetic anhydride (3.0 ml), and the reaction mixture was treated by the usual method to give the heptaacetate (0.65 g) in 50% yield, which was recrystallized from chloroform-petroleum ether. Mp 151°C; $[\alpha]_D^{23}$ −13.6° (*c* 1.01, chloroform); IR: 1740 (OAc), 1720 (NAc); NMR: 2.61 (H_5; s), 3.89 ($H_{1'}$; d, $J_{1',2'}$=4.5), 4.32 ($H_{2'}$; q, $J_{2',3'}$=8.5), 4.77 ($H_{3'}$; sex, $J_{3',4'_a}$=3.0, $J_{3',4'_b}$=6.0), 5.66 ($H_{4'_a}$; q, $J_{4'_a,b}$=12.0), 5.86 ($H_{4'_b}$; q), 7.45 (-NAc), 7.72 (2 NAc), 7.86, 7.92, and 7.95 (4 OAc).

Found: C, 49.85; H, 5.41; N, 9.02%. Calcd for $C_{21}H_{27}N_3O_{11}$: C, 50.11; H, 5.53; N, 9.23%.

*3',5',6'-Tri-*O*-acetyl-α-*D*-glucofurano[1',2';4,5]-(2*R,S*)-2-acetamido-1,3-diacetyl-2-ethoxyimidazolidine (9).* A solution of **7** (0.45 g, 1.0 mmol) in ethanol (5 ml) was heated at 60°C for 4 hr, and the crystals appeared was filtered to give colorless crystals (0.33 g) in 66% yield. Mp 225°C (decom); IR: 3250, 3200, 1540 (NH).

Found: C, 50.00; H, 6.13; N, 8.52%. Calcd for $C_{21}H_{31}N_3O_{11}$: C, 50.29; H, 6.13; N, 8.78%.

*2-Acetamido-5-(*D-arabino-*tetrahydroxybutyl)imidazole (10).* To a solution of **7** (470 mg, 1.04 mmol) in aboslute methanol was added two drops of 2N-sodium methoxide at room temperature, and then white solid precipitated was filtered, washed with absolute methanol to give 0.2 g (79%) of the monoacetate. Mp 200°C (decomp). It was insoluble in methanol, water and DMSO. IR: 1675 and 1530 (*sec*-amide), 1600 (mono-acetylguanidine).

Found: C, 44.10; H, 6.72; N, 17.63%. Calcd for $C_9H_{17}N_3O_6$: C, 44.08; H, 6.17; N, 17.14%.

*2-Acetamido-5-(*D-*arabino-tetraacetoxybutyl)imidazole (11).*

i) From 6; To a suspension of **6** (0.48 g, 2 mmol) in pyridine was added acetic anhydride (0.3 ml) under cooling at 0°C. After stirring at room temperature for two days on a magnetic stirrer, the warm reaction mixture was poured into ice water (30 ml). As any crystals could not be obtained, the resulted solution was extracted four times with chloroform (40 ml), and the extracts were washed with 2N-sulfuric acid (30 ml), saturated aqueous sodium bicarbonate (30 ml) and water. The extract was then evaporated to give a sirup (0.53 g). This sirup showed three bands on preparative tlc (Wakogel B-5 UA; 10% methanol in benzene), and the main band which had the greatest R_f value was collected, and eluted with chloroform to give a sirup in 21% (0.17 g) yield. $[\alpha]_D^{23}$ −10.8° (*c* 0.52, ethanol); UV: λ_{max}^{EtOH} 246 nm (ε 7.08×10³); IR: 1740 (OAc), 1680 and 1520 (*sec*-amide), 1595 (monoacetylguanidine); NMR: 3.22 (H_4; s), 3.96 ($H_{1'}$; d, $J_{1',2'}$=4.8), 4.47 ($H_{2'}$; q, $J_{2',3'}$=7.0), 4.12 ($H_{3'}$; m), 5.76 ($H_{4'_a}$; q, $J_{3',4'_a}$=3.5, $J_{4'_ab}$=13.0), 5.90 ($H_{4'_b}$; q, $J_{3',4'_b}$= 5.8), 7.73 (NAc), 7.92, 7.96, and 7.98 (OAc).

Found: C, 49.72; H, 6.05; N, 9.53%. Calcd for $C_{17}H_{24}N_3O_9$: C, 49.27; H, 5.84; N, 10.14%.

ii) From 10; To a solution of **10** (0.11 g, 0.45 mmol) in pyridine (1 ml) was added acetic anhydride (1 ml) at room temperature, and the reaction mixture was kept for three days with stirring, poured into ice–water. The resulted solution was extracted with benzene, and the extract was evaporated to give a sirup. This sirup showed the presence of two kinds of products in the NMR spectrum in which a series of proton chemical shifts of the main product consisted with that of **11**. Another one showed H_5-proton signal at 2.98 τ (s) and $H_{1'}$ at 4.03 τ (d, $J_{1',2'}$=5.0), respectively.

Attempted deacetylation of 8 with sodium methoxide. To a solution of **8** (0.5 g, 1 mmol) in absolute methanol (2 ml) was added five drops of 2N-sodium methoxide at room temperature. After standing overnight, the reaction mixture was neutralized with five drops of 2N-acetic acid and evaporated. A solution of the resulted sirup in chloroform (10 ml) was washed three times with water, dried and evaporated. The resulted sirup showed two bands on a preparative tlc (Wakogel B-5 UA; 10% methanol in benzene), and the main band which had larger R_f value was collected. The NMR sepctrum of the resulted sirup indicated the presence of two products in which the proton chemical shifts of the main product consisted with that of **11**. Another one showed H_5-proton signal at 3.23 τ (s), H_1' at 4.01 τ (d, $J_{1',2'}$=4.8), OCH_3 at 6.79 τ (s) indicating the presence of the addition product of methanol. The ratio of the both compounds was deduced to be 3: 1 from intensities of OCH_3 and other proton signals. UV spectrum of the mixture showed at 247 nm. (Found: C, 48.78; H, 5.58; N, 9.52%. Calcd as 3: 1 mixture of the both compounds: C, 49.39; H, 5.95; N, 9.88%).

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