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Synthesis of Glycoamidines Using a Mercury-Promoted Reaction†

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Abstract. Glycoamidines are readily prepared by a mercury-promoted reaction of the corresponding thioamides with amines. The reaction appears to involve the participation of bidentate mercury complexes with *N*-monosubstituted thioamides, whereas *N,N*-disubstituted derivatives form presumably monocoordinated species. In the light of these assumptions, two different mechanistic pathways can be applicable depending on the starting thioamide. In addition, this protocol enhances the versatility of transformations of organosulfur compounds in the presence of transition metal ions and illustrates novel features.

Key Words. Amidine, carbohydrates, glycosylamine, mercury compounds, metal complex, organosulfur reagents, thioamide

The crucial importance of glycoconjugates in many biological processes needs no comment. The development of efficient methods for the direct syntheses of tailored complex glycosides and glycosylamines, which could potentially be used to study these processes, is therefore a research field of great interest, in particular in medicinal and bioorganic chemistry.[1] As evidence in support of these premises, several oligosaccharides linked by amidine spacers having significant biological activity, have been recently isolated from natural sources. These include, among others, lipopolysaccharides from *Pseudomonas aeruginosa*,[2,3] and *Vibrio cholerae*,[4] which have the *N*-acetylimidoyl group covalently linked to aminosugars. Moreover, different glycoamidines are powerful glycosidase inhibitors, such as trehazolin,[5,6] a trehalase inhibitor, isolated from culture broths of *Amycolatopsis trehalostatica* and *Micromonospora* strain SANK 62390. Likewise, several saccharide amidines, amidrazones, and amidoximes,[7] as well as amidine pseudo-disaccharides[8] have been synthesized and further evaluated as glycosidase inhibitors.

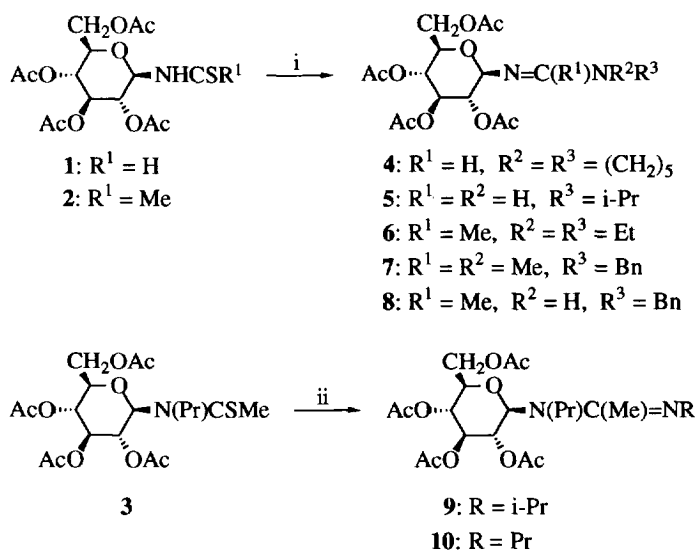
Glycoamidines can be prepared by reaction of amines or ammonia with activated amides,[8,9] isonitriles,[10] or thioamides.[7,8] The latter approach requires a rapid access to the corresponding raw materials, amino- or

thioamido-sugars.[11,12] Another important strategy involves the intermediacy of transition metal ions. It has been known that some reactions of organosulfur compounds can be activated by soft metal ions.[13] Thioamides do react with bases or nucleophiles in the presence of such metal ions to give a variety of functionalized substances, such as amides or nitriles in aqueous media.[13,14] Very recently, we have reported the smooth transformation of thioamides into amides, imides, and nitriles by reaction with silver carboxylates in aprotic solvents.[15] Activation of thioamides either with Hg(II) or Ag(I) is a common resource for the preparation of simple amidines,[16] but this strategy has not yet been explored with amidosugars.

Herein, we wish to describe the effectiveness of Hg(II)-promoted reactions of thioamidosugars with amines in organic solvents. We have also carried out structural studies on the mercury complexes, which along with mechanistic considerations allow us to expand and understand the versatility of the process. In addition, these synthetic glycoamidines share the structural requirements found in other glycosidase inhibitors. Thus, the strong inhibition requires that the basic nitrogen atom be directly joined to the anomeric carbon atom,[17] though other amidines which have been found to be glycosidase inhibitors share other features such as sp^2 hybridization at the anomeric center.[7a]

Results and discussion

Syntheses of amidines. *N*-Thioformyl,[12a] *N*-thioacetyl,[12b] and *N*-propyl-*N*-thioacetyl[12b] glucopyranosylamines (**1**-**3**) react with *N*-alkyl or *N*,*N*-dialkylamines in the presence of stoichiometric amounts of Hg(II) compounds to afford the corresponding amidines **4**-**10** (Scheme 1).



1: R^1 = H
2: R^1 = Me

4: R^1 = H, $R^2 = R^3 = (CH_2)_5$
5: $R^1 = R^2$ = H, R^3 = i-Pr
6: R^1 = Me, $R^2 = R^3$ = Et
7: $R^1 = R^2$ = Me, R^3 = Bn
8: R^1 = Me, R^2 = H, R^3 = Bn

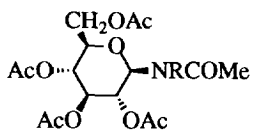
3

9: R = i-Pr
10: R = Pr

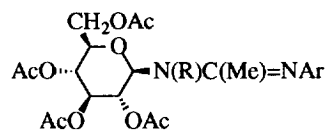
Scheme 1. *Reagents:* i, R^2R^3NH, HgO; ii, RNH_2, HgO

Although $HgCl_2$ has been usually utilized for the preparation of simple amidines,[16,18] this salt was ineffective for the synthesis of glycosylamidines, presumably due to the release of hydrogen chloride that complicates the work-up procedure. In contrast, HgO associates the inherent advantages of Hg(II) as promoter in reactions of organosulfur compounds[13] and the absence of side reactions, attributed to counterions, because of the transformation of the oxygen into water as by-product. The use of Hg(II) carboxylates was avoided since it is known that these anions favor the formation of amide and imide derivatives.[15,19] In the absence of metal ions, side reactions such as S/O exchange and deprotection of hydroxyl groups take place. Thus, reaction of thioamide **2** with diethylamine gave a complex mixture, from which amide **11** could be isolated. On the other hand, reactions of **2** and **3** with HgO alone afforded exclusively glycosylamides **11** and **12**, respectively, by O/S exchange as well.

The reactions of thioamides **2** and **3** with 4-methoxyaniline and aniline, respectively, in the presence of HgO afforded amidines **13** and **14**. In stark contrast, the reaction of **2** with aniline under identical conditions gave amide **11**. However, the addition of catalytic amounts of triethylamine did lead to the formation of glycoamidine **15** in good yield.



11: R = H
12: R = Pr

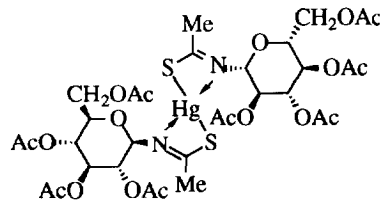


13: R = H, Ar = 4-$MeOC_6H_4$
14: R = Pr, Ar = Ph
15: R = H, Ar = Ph

Mechanism. Reactions of organosulfur compounds promoted by metal ions usually involve coordination equilibria,[13] in which thioamides can serve either as mono- or bidentate donor ligands.[20] Reactions of thioamides **1** and **2** with amines and HgO were monitored by thin layer chromatography or NMR analyses indicating the formation of coordinated species, which were transformed into the corresponding amidines. Moreover, the complex **16**, a yellowish solid, was isolated in the reactions of thioamide **2** with diethyl or triethylamine. This complex did not display the typical thioamide I band in the IR spectrum. However, its NMR spectrum in $CDCl_3$ revealed a 1.5:1 mixture of the coordination complex **16** and thioamide **2**, evidencing the equilibrium of both species in solution. Remarkably, the reaction of crude **16** with *N*-methylbenzylamine gave the amidine **7**. The presence of an amine of sufficient basicity, even in catalytic amounts, is essential for the formation of the mercury complex. This explains the unsucessful reaction of thioamide **2** with HgO alone or in the presence of aniline, leading exclusively to glycosylamide **11** in both cases.

The stoichiometry of the coordination complex **16** was determined by using Job's method of continuous variation adapted for NMR studies.[21] By adding triethylamine to a solution of **2** in $CDCl_3$, the coupling between H-1 and NH was lacking due to hydrogen exchange. Further addition of HgO resulted in the

appearance of a new signal set attributed to the formation of **16**. Chemical shifts were shifted to highfield upon addition of more HgO, which indicated a relatively slow ligand exchange on the NMR time scale.



16

Consequently, the ratio between complexed and total (free plus complexed) sugar in solution (X_c) was easily determined by proton integration of appropriate signals. A plot of a measurable property of the complex as a function of the mole fraction of HgO (or thioamide) added, shows a maximum at the point corresponding to the stoichiometric amounts of sugar and metal in the complex. Figure 1 displays a Job plot of X_c (in percentage), *versus* the mole fraction of HgO added. A maximum occurs at the experimental point for X_{HgO} = 0.34, in accordance with a 2:1 ligand:metal stoichiometry. Unfortunately, an accurate binding constant of the complex could not be determined by ^{1}H-NMR titration experiments because of the insolubility of HgO, in excess of this oxide. Furthermore, any concentration of HgO less than stoichiometric amounts did not give satisfactory results, which is presumably on account of other equilibria in solution. It should be noted, however, that sharp breaks in the Job plot are indicative of complexes with large formation constants, whereas those with small formation constants give smoother curves, being difficult to determine their maxima.

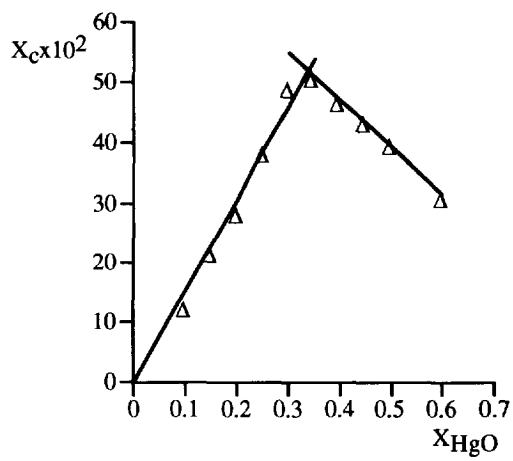


Figure 1. Determination of stoichiometry of complex **16** by Job's method (Δ, experimental data).

Inasmuch as complex **16** could not be crystallized, a plausible structure was elucidated using spectroscopic experiments. Firstly, the NH signal is lacking in both IR and ^{1}H-NMR spectra and, H-1

resonance appears as doublet. Likewise, NMR data of the analogous complex generated by reaction of **2** plus $HgCl_2$ and a large excess of triethylamine, are coincidental with those of compound **16**. The detection of triethylamine hydrochloride by ^{1}H-NMR, in quantitative amount, evidences that NH proton is lacking. Both observations agree with coordination of mercury with the thioimidate group and support the release of water as by-product in the presence of HgO.

The bidentate coordination of thioimidates has been previously documented,[20] and further evidences arise from spectroscopic data. Thus, the IR spectrum of complex **16** shows a strong absorption at 1604 cm^{-1}, that cannot be attributed[20a] to the band I of thioamides,[22] at 1560 cm^{-1} in thioamide **2**. We assume that the absorption at 1604 cm^{-1} correlates likely with the C=N double bond, being metal ion coordinated to both sulfur and nitrogen atoms. The latter is also supported by the fact that H-1 resonates to chemical shifts quite similar to those of structurally related glycoamidines,[19] in which the carbohydrate moiety is linked to an imine, not amine, group.

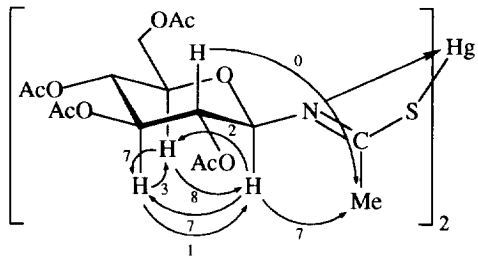


Figure 2. Nuclear Overhauser interactions of complex **16**.

In addition, NOE experiments (Figure 2), particularly the intensification of CH_3 signal upon irradiation of H-1, in stark contrast to the situation with H-2, are in agreement with a *s-cis* conformation between H-1 and N=C at the glycosidic bond and support the *E*-configuration for the double bond as well. At this stage, it is worth pointing out that, despite the fact that the conformation of the *s-cis* form is identical to that of thioamide **2**, *N*-monosubstituted thioamides do not adopt freely an *E*-configuration.[12b] This anchored geometry should therefore be necessary for the simultaneous coordination of nitrogen and sulfur atoms. Furthermore, *s-cis* and *E* dispositions are also consistent with the chemical shift of H-1, as this proton resonates to higher field ($\Delta\delta$ = 1.32 ppm) than its analogous signal in compound **2**, which undergoes the deshielding effect[12b] of the thiocarbonyl group.

In the absence of base, the reaction of mono- or disubstituted thioamides with increasing amounts of HgO modify neither the NMR spectra nor the solubility of the oxide, suggesting that the kind of coordination should be different. Reaction of thioamide **3** with HgO yields glycosylamide **12**. As previously mentioned HgO also promotes the reaction of **3** with amines to give amidines. These neutral thioamides, however, act likely as monodentate ligands coordinated by the sulfur atom[20] in weak equilibria (Figure 3).

The formation of coordination compounds such as **16**, coming from *N*-substituted thioamides should therefore proceed *via* the intermediacy of thioimidate ions,[20] according to equilibria postulated in Equations 1-2.

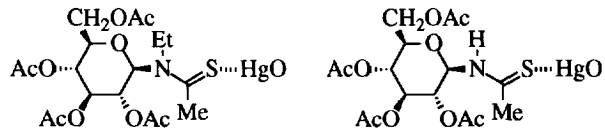
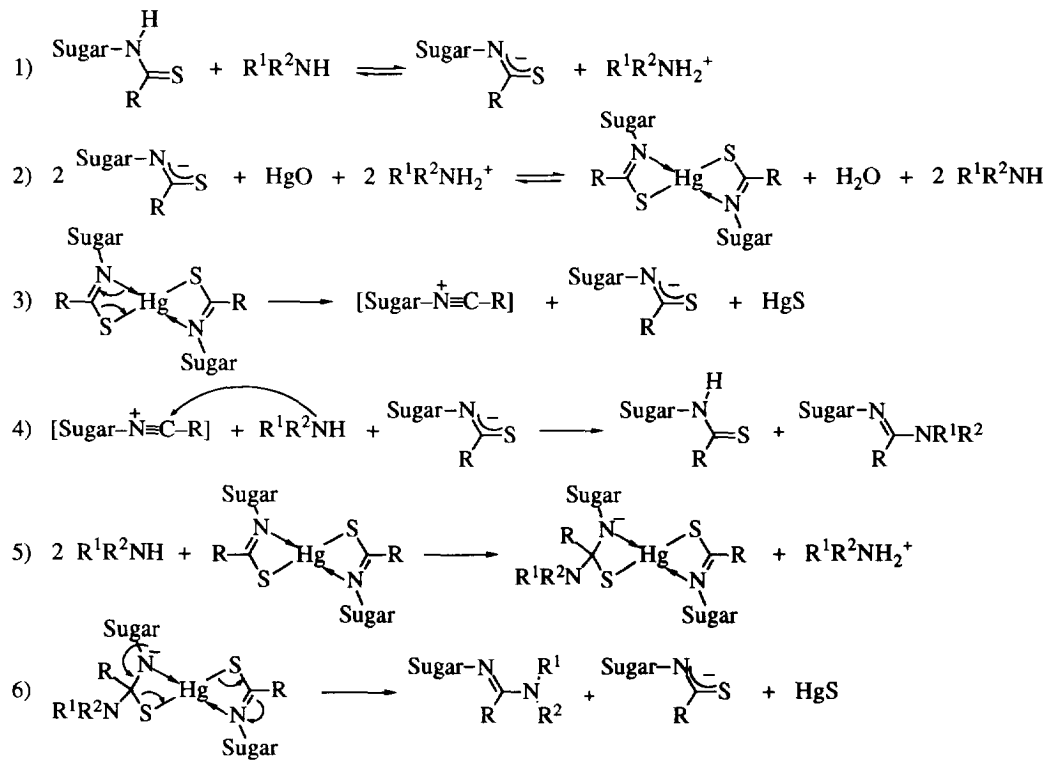


Figure 3. Coordination for *N,N*-disubstituted thioamides and *N*-monosubstituted thioamides in the absence of base.



Scheme 2. Proposed mechanism for the formation of sugar amidines

The transformation of the coordinated intermediate into the corresponding amidine should follow either a pathway of a) elimination-addition or b) addition-elimination. The mechanism of elimination-addition (Equations 3-4) involves the participation of a nitrilium ion. These species have been previously proposed as intermediates in the reaction of Mumm.[23] We have also suggested[15] that the formation of imides by reaction of thioamides with Ag(I) carboxylates occurs presumably *via* such nitrilium ions.

The alternative mechanism of addition-elimination, however, cannot be ruled out in these reactions of thioamides promoted by metal ions (Equations 5-6). Thus, this could be applied to *N,N*-disubstituted thioamides, for which nitrilium ions cannot be generated. Moreover, the reaction of cyclic thioamides, such as thiocaprolactam, with metal carboxylates affords a mixture of the corresponding imide and amide derivatives,

and the formation of a cyclic nitrilium ion is unlikely owing to geometric considerations.[19]

The behavior of aromatic amines deserves further considerations. The ineffectiveness of aniline in the synthesis of amidine **15** may be attributed to one of these reasons or both of them: (a) its lower basicity, thus avoiding the formation of complex **16**; (b) its lower nucleophilicity, disfavoring the transformation of the complex into amidine **15**. To ascertain whether these properties affect the reactivity of aromatic amines, we performed several transformations which were monitored by NMR measurements. After adding aniline to a solution of **2** in $CDCl_3$, the coupling between H-1 and NH protons is not lost, in contrast to alkylamines. Addition of HgO did not result in the formation of mercury complex either. However, the reaction of **2** with aniline and HgO in the presence of catalytic amounts of triethylamine afforded the glycoamidine **15**. This supports the fact that the reactivity of aniline towards *N*-substituted thioamides is greatly influenced by its basicity, rather than by its nucleophilicity. Moreover, the *N,N*-disubstituted thioamide **3**, without exchangeable protons, reacts with aniline; and basic catalysis is now unnecessary due to the formation of a monodentate complex coordinated with the sulfur atom.

In conclusion, a general methodology has been developed for the rapid preparation of glycoamidine templates. These substances are not only versatile chirons in the synthesis of some glycoconjugates, but also potential glycosidase inhibitors and precursors of carbohydrate hosts having nitrogen binding sites. Our route is a facile and valuable protocol that expands the utility and explores the scope and limitations of the mercury-promoted reaction of thioamides, which should provide further applications.

Experimental

Melting points were determined on a Electrothermal 8100 apparatus and are uncorrected. Optical rotations were measured at 20±5 °C on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a FT-MIDAC spectrophotomer and UV spectra on a Milton Roy Spectronic 120. The ^{1}H- (200 MHz) and ^{13}C-NMR (50.3 MHz) spectra were recorded on a Bruker AC 200-E spectrometer. The Job plot was determined on a Bruker 400 AC/PC spectrometer. Analytical thin layer chromatography (TLC) was performed with silica gel (Kieselgel 60 GF_{254}) and flash column chromatography with silica gel (Kieselgel 60, 230-400 mesh), using the following eluents: (a) toluene:acetone 7:3; (b) toluene:acetone:dichloromethane 3:1:1; (c) toluene:acetone:dichloromethane 7:1:2; (d) toluene:acetone:dichloromethane 8:1:1; and (e) toluene:dichloromethane 7:3.

General procedure for the synthesis of amidines 4-10 and 13. To a vigorously stirred solution of thioamides (**1-3**) in dichloromethane at room temperature, HgO and the corresponding amine were added. The reaction was monitored by TLC (eluent a) and/or NMR and, after the disappearance of the thioamide and the complex initially formed[24], the mixture was filtered through $BaSO_4$ or celite to remove HgS, which was washed with dichloromethane. The solvent was evaporated to give an oil that was crystallized from ether or ether/petroleum ether. According to this general protocol, with slight modifications when appropriate, the following compounds were prepared.

***N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*,*N'*-pentamethylenformamidine (4).** Prepared by reaction of **1** (0.12 g, 0.31 mmol), HgO (0.10 g, 0.46 mmol), and piperidine (0.05 g, 0.60 mmol) in dichloromethane (5 mL) for 90 min. Work-up and crystallization from ether afforded **4** (0.045 g, 33 %); mp 110-112 °C; $[\alpha]_{589}$ -28°, $[\alpha]_{578}$ -29°, $[\alpha]_{546}$ -35°, $[\alpha]_{436}$ -76°, $[\alpha]_{365}$ -165° (*c* 0.5, CH_2Cl_2); lit[10]. mp 107-108 °C; $[\alpha]_{589}$ -2.3° (*c* 2.4, $CHCl_3$).

***N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*-isopropylformamidine (5).** Prepared by reaction of **1** (0.49 g, 1.25 mmol), HgO (0.35 g, 1.62 mmol), and isopropylamine (0.07 g, 1.25 mmol) in dichloromethane (20 mL) for 30 min. Work-up and crystallization from ether gave **5** (0.21 g, 40 %); mp 104-105 °C; $[\alpha]_{589}$ -15°, $[\alpha]_{578}$ -16°, $[\alpha]_{546}$ -17°, $[\alpha]_{436}$ -39°, $[\alpha]_{365}$ -89° (*c* 0.54, CH_2Cl_2); λ_{max} 226 nm (log ε 3.67); IR (KBr) 3413, 1753, 1652, 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.16 (d, *J* = 6.0 Hz, 6H, $CH(CH_3)_2$), 2.07, 2.03, 2.01, 1.99 (4 s, 12H, $COCH_3$), 3.79 (ddd, $J_{4,5}$ = 9.4, $J_{5,6}$ = 4.4, $J_{5,6'}$ = 2.1 Hz, 1H, H-5), 4.3-4.0 (m, 1H, $CH(CH_3)_2$), 4.13 (dd, $J_{6,6'}$ = 12.3 Hz, 1H, H-6'), 4.25 (dd, 1H, H-6), 4.39 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.63 (bs, 1H, NH), 5.01 (t, $J_{2,3}$ ~ 9.0 Hz, 1H, H-2), 5.13 (t, $J_{3,4}$ = 9.4 Hz, 1H, H-4), 5.25 (t, 1H, H-3), 7.48 (s, 1H, N=CH). ^{13}C-NMR ($CDCl_3$) δ 20.39, 20.44, 20.54, 22.21, 23.76, 41.97, 47.00, 62.17 (C-6), 68.48 (C-4), 72.64 (C-2), 73.06 (C-5), 73.24 (C-3), 94.39 (C-1), 152.29 (N=CH), 168.88, 169.21, 170.18, 170.57. Calcd. for $C_{18}H_{28}N_2O_9$: C, 51.92 ; H, 6.78 ; N, 6.73. Found: C, 51.73; H, 6.76; N, 6.52.

***N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*,*N'*-diethylacetamidine (6).** (a) Prepared by reaction of **2** (1.94 g, 4.80 mmol), HgO (1.36 g, 6.30 mmol), and diethylamine (0.60 g, 8.24 mmol) in dichloromethane (50 mL) for 5 days. Work-up gave **6** after crystallization from ether (1.31 g, 61 %); mp 130-131 °C; $[\alpha]_{589}$ -3°, $[\alpha]_{578}$ -3°, $[\alpha]_{546}$ +4°, $[\alpha]_{436}$ +13° (*c* 0.5, CH_2Cl_2); λ_{max} 236 nm (log ε 4.19); IR (KBr) 2970, 1745, 1640, 1370, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.08 (t, *J* = 7.0 Hz, 6H, CH_2CH_3), 1.99 (s, 3H, N=C(CH_3)), 1.97, 2.01, 2.03, 2.06 (4 s, 12H, $COCH_3$), 3.13 (dq, *J* = 14.1 Hz, 2H, CH_2CH_3), 3.4-3.6 (m, 2H, CH_2CH_3), 3.82 (ddd, $J_{4,5}$ = 9.4, $J_{5,6}$ = 5.2, $J_{5,6'}$ = 2.2 Hz, H-5), 4.11 (dd, $J_{6,6'}$ = 12.0 Hz, 1H, H-6'), 4.25 (dd, 1H, H-6), 4.68 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1), 5.09 (t, $J_{2,3}$ = 9.6 Hz, 1H, H-2), 5.11 (t, $J_{3,4}$ = 9.6 Hz, 1H, H-4), 5.28 (t, 1H, H-3); ^{13}C-NMR ($CDCl_3$) δ 13.45, 13.47, 20.58, 20.65, 20.72, 42.27, 62.70 (C-6), 69.12 (C-4), 73.04 (C-5), 73.70 (C-2, C-3), 88.33 (C-1), 161.55 (N=C), 169.10, 169.44, 170.48, 170.71. Calcd. for $C_{20}H_{32}N_2O_9$: C, 54.04 ; H, 7.26 ; N, 6.30. Found: C, 53.97 ; H, 7.38 ; N, 6.26.

(b) To a magnetically stirred solution of **2** (1.00 g, 2.5 mmol) in dichloromethane (40 mL) was added $HgCl_2$ (0.56 g, 2.6 mmol) and diethylamine (0.5 g, 7.25 mmol). After 6 days at room temperature, the reaction mixture was filtered through celite, washed with dichloromethane, and the solvent evaporated. The residue was crystallized from ether to give **6** impurified with diethyl ammonium chloride, which could not be separated.

***N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*-benzyl-*N'*-methyl acetamidine (7).** Prepared by reaction of **2** (0.48 g, 1.20 mmol), HgO (0.37 g, 1.7 mmol), and *N*-methylbenzylamine (0.40 g,

3.3 mmol) in dichloromethane (20 mL) for 4 days. Work-up and crystallization from ether gave **7** (0.52 g, 87 %); mp 138-139 °C ; $[\alpha]_{589}$ +30°, $[\alpha]_{578}$ +32°, $[\alpha]_{546}$ +38°, $[\alpha]_{436}$ +73°, $[\alpha]_{365}$ +145° (*c* 0.53, CH_2Cl_2); λ_{max} 233, 273 nm (log ε 4.22, 4.25); IR (KBr) 1745, 1595, 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.88 (bs, 3H, N=C(CH_3)), 2.0-2.1 (m, 12H, $COCH_3$), 2.94 (s, 1H, *N*-CH_3), 3.82 (ddd, $J_{4,5}$ = 9.8, $J_{5,6}$ = 5.1, $J_{5,6'}$ = 2.4 Hz, 1H, 5H), 4.0-4.4 (m, 1H, *N*-CH_2), 4.13 (dd, $J_{6,6'}$ = 12.2 Hz, 1H, H-6'), 4.26 (dd, 1H, H-6), 4.71 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.8-5.2 (m, 1H, *N*-CH_2), 5.14 (t, $J_{2,3}$ = 9.6, $J_{3,4}$ = 9.0 Hz, 2H, H-2 H-4), 5.29 (t, 1H, H-3), 7.1-7.4 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$) δ 13.75, 20.46, 20.52, 20.60, 36.13, 52.75, 62.53 (C-6), 69.94 (C-4), 73.00 (C-5), 73.55, 73.59 (C-2, C-3), 88.24 (C-1), 162.92 (N=C), 168.96, 169.28, 170.30, 170.53. Calcd. for $C_{24}H_{32}N_2O_9$: C, 58.53 ; H, 6.55 ; N, 5.69. Found: C, 58.12; H, 6.56; N, 5.57.

***N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*-benzylacetamidine (8).** Prepared by reaction of **2** (3.24 g, 8.0 mmol), HgO (2.24 g, 10.3 mmol), and benzylamine (0.86 g, 8.00 mmol) in dichloromethane (100 mL) for 4 days. Conventional work-up gave **8** (2.3 g, 59 %); mp 80-82 °C ; $[\alpha]_{578}$ -7°, $[\alpha]_{546}$ -7°, (*c* 0.13, CH_2Cl_2); λ_{max} 273 nm (log ε 4.31); IR (KBr) 3410, 1755, 1630, 1540, 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.9-2.1 (m, 15H, $COCH_3$, N=C(CH_3)), 3.81 (d, $J_{4,5}$ = 9.9, $J_{5,6}$ = 5.0, $J_{5,6'}$ = 2.3 Hz, 1H, H-5), 4.0-4.3 (m, 1H, *N*-CH_2), 4.13 (dd, $J_{6,6'}$ = 12.0, 1H, H-6'), 4.25 (dd, 1H, H-6), 4.4-4.8 (m, 3H, H-1, NH, *N*-CH_2), 5.10 (t, $J_{1,2}$ ~ 8.5, $J_{2,3}$ = 9.9 Hz, 1H, H-2), 5.14 (t, $J_{3,4}$ = 9.1 Hz, 1H, H-4), 5.28 (t, 1H, H-3), 7.2-7.4 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$) δ 17.30, 20.41, 20.61, 45.08, 62.41 (C-6), 68.76 (C-4), 73.11 (C-5), 73.47 (C-2, C-3), 88.09 (C-1), 160.34 (N=C), 169.14, 169.27, 170.32, 170.64. Calcd. for $C_{23}H_{30}N_2O_9$: C, 57.73; H, 6.32; N, 5.85. Found: C, 57.42; H, 6.60; N, 5.83.

***N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*-propyl-*N'*-isopropyl acetamidine (9).** Obtained by reaction of **3** (0.45 g, 1.0 mmol), HgO (0.28 g, 1.30 mmol), and isopropylamine (0.08 g, 1.35 mmol) in dichloromethane (10 mL) for 30 h. After work-up compound **9** was obtained (0.30 g, 63 %); mp 91-92 °C ; $[\alpha]_{589}$ +23°, $[\alpha]_{578}$ +25°, $[\alpha]_{546}$ +28° (*c* 0.57, CH_2Cl_2); λ_{max} 273 nm (log ε 4.22); IR (KBr) 2973, 1745, 1629, 1374, 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.82 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.02 (d, *J* = 6.2 Hz, 3H, $CH(CH_3)_2$), 1.03 (d, *J* 6.2, 3H, $CH(CH_3)_2$), 1.3-1.7 (m, *J* = 9.5, *J* = 5.0 Hz, 2H, $CH_2CH_2CH_3$), 1.88 (s, 3H, N=C(CH_3)), 1.95, 2.01, 2.03, 2.06 (4 s, 12H, $COCH_3$), 3.00 (ddd, *J* = 15.0 Hz, 1H, $CH_2CH_2CH_3$), 3.22 (ddd, 1H, $CH_2CH_2CH_3$), 3.49 (dq, 1H, $CH(CH_3)_2$), 3.74 (dt, $J_{4,5}$ = 10.1, $J_{5,6}$ ~ 3, $J_{5,6'}$ ~ 3 Hz, 1H, H-5), 4.1-4.3 (m, 2H, H-6, H-6'), 5.08 (t, $J_{3,4}$ = 8.9 Hz, 1H, H-4), 5.18 (t, $J_{1,2}$ = 8.9, $J_{2,3}$ = 9.3 Hz, 1H, H-2), 5.29 (t, 1H, H-3), 5.62 (d, 1H, H-1); ^{13}C-NMR ($CDCl_3$) δ 11.36, 12.20, 20.48, 23.27, 24.49, 24.58, 44.76, 48.71, 62.00 (C-6), 68.46 (C-4), 69.02 (C-2), 73.16 (C-5), 74.03 (C-3), 83.42 (C-1), 153.11 (N=C), 169.39, 169.39, 170.12, 170.51. Calcd. for $C_{22}H_{36}N_2O_9$: C, 55.92; H, 7.68; N, 5.93. Found: C, 55.60; H, 7.84; N, 5.62.

***N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*,*N'*-dipropylacetamidine (10).** Obtained by reaction of **3** (0.45 g, 1.0 mmol), HgO (0.28 g, 1.30 mmol), and *n*-propylamine (0.06 g, 1.0 mmol) in

dichloromethane (10 mL) for 30 h. After work-up **10** was obtained (0.23 g, 47 %); mp 74-76 °C; $[\alpha]_{589}$ +25°, $[\alpha]_{578}$ +26°, $[\alpha]_{546}$ +29°, $[\alpha]_{436}$ +50°, $[\alpha]_{365}$ +77° (*c* 0.5, CH_2Cl_2); λ_{max} 229 nm (log ε 4.28); IR (KBr) 2975, 1745, 1632, 1380, 1245 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.83 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 0.91 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.4-1.7 (m, *J* = 5.1, *J* = 6.9 Hz, 4H, $CH_2CH_2CH_3$), 1.8-2.1 (m, 15H, $COCH_3$, $N{=}C(CH_3)_2$), 2.9-3.4 (m, 2H, $CH_2CH_2CH_3$), 3.14 (t, 2H, $CH_2CH_2CH_3$), 3.75 (dt, $J_{4,5}$ = 9.3, $J_{5,6}$ = $J_{5,6'}$ = 5.0 Hz, 1H, H-5), 4.1-4.2 (m, 2H, H-6, H-6'), 5.09 (t, $J_{3,4}$ = 9.3 Hz, 1H, H-4), 5.19 (t, $J_{1,2}$ = 8.8, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 5.25 (t, 1H, H-3), 5.67 (d, 1H, H-1); ^{13}C-NMR ($CDCl_3$) δ 11.28, 11.79, 12.54, 20.40, 23.32, 24.74, 44.89, 51.08, 61.93 (C-6), 68.57, 68.89 (C-2, C-4), 73.14 (C-5), 73.96 (C-3), 83.24 (C-1), 155.74 (N=C), 169.33, 169.97, 170.39. Calcd. for $C_{22}H_{36}N_2O_9$: C, 55.92 ; H, 7.68; N, 5.93. Found: C, 55.63; H, 7.79; N, 5.77.

***N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*-(4-methoxyphenyl)acetamidine (13).** Prepared by reaction of **2** (0.45 g, 1.0 mmol), HgO (0.24 g, 1.1 mmol), and 4-methoxyaniline (0.25 g, 2.0 mmol) in dichloromethane (20 mL) for 4 days. After work-up, the residue was purified by preparative TLC (eluent a) to give **13** that was crystallized from ether (0.25 g, 50 %); mp 130-131 °C; $[\alpha]_{589}$ +22°, $[\alpha]_{578}$ +23°, $[\alpha]_{546}$ +27°, $[\alpha]_{436}$ +50° (*c* 0.5, CH_2Cl_2); λ_{max} 272 nm (log ε 4.42); IR (KBr) 3390, 2965, 1745, 1660, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.77 (s, 3H, $N{=}C(CH_3)$), 2.03, 2.04, 2.09, 2.10 (4 s, 12H, $COCH_3$), 3.78 (s, 3H, OCH_3), 3.8-3.9 (m, $J_{4,5}$ = 9.6, $J_{5,6}$ = 4.4, $J_{5,6'}$ = 2.0 Hz, 1H, H-5), 4.11 (dd, $J_{6,6'}$ = 12.3 Hz, 1H, H-6'), 4.32 (dd, 1H, H-6), 4.8-5.2 (bs, 1H, NH), 4.97 (t, $J_{1,2}$ ~ 9.5, $J_{2,3}$ = 9.5 Hz, 1H, H-2), 5.09 (t, $J_{3,4}$ = 9.5 Hz, 1H, H-4), 5.34 (t, 1H, H-3), 5.50 (bs, 1H, H-1), 6.67 (d, *J* = 8.7 Hz, 2H, Ph), 6.82 (d, 2H, Ph); ^{13}C-NMR ($CDCl_3$) δ 17.24, 20.50, 20.66, 55.31, 61.78 (C-6), 68.27 (C-4), 70.97 (C-2), 72.9 (C-3, C-5), 79.48 (C-1), 143.24 (N=C), 169.50, 169.83, 170.56, 170.90. Calcd. for $C_{23}H_{30}N_2O_{10}$: C, 55.87 ; H, 6.11 ; N, 5.67. Found: C, 56.00; H, 6.20; N, 5.58.

***N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*-phenylacetamidine (15).** A mixture of **2** (0.22 g, 0.5 mmol), triethylamine (0.02 ml, 0.10 mmol), HgO (0.11 g, 0.50 mmol), and aniline (0.09 g, 1.0 mmol) in dichloromethane (10 mL), was stirred for 5 days. The reaction mixture was filtered through celite, washed with dichloromethane, and the solvent evaporated. The residue was purified by colum chromatography (eluents b, c) and **15** crystallized from ether/petroleum ether (0.13 g, 58 %); mp 122-123 °C ; $[\alpha]_{589}$ +33°, $[\alpha]_{578}$ +35°, $[\alpha]_{546}$ +42° (*c*, 0.5 in CH_2Cl_2); λ_{max} 250, 226 nm (log ε 3.65, 3.75); IR (KBr) 3430, 2960, 1745, 1665, 1380 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.76 (s, 3H, $N{=}C(CH_3)$), 2.03, 2.08, 2.09 (3 s, 12H, $COCH_3$), 3.8-3.9 (m, $J_{4,5}$ = 10.0, $J_{5,6}$ = 4.4, $J_{5,6'}$ = 1.9 Hz, 1H, H-5), 4.12 (dd, *J* = 12.5 Hz, 1H, H-6'), 4.32 (dd, 1H, H-6), 4.98 (t, $J_{1,2}$ ~ 8, $J_{2,3}$ ~ 9.5 Hz, 1H, H-2), 5.09 (t, $J_{3,4}$ ~ 9.5 Hz, 1H, H-4), 5.2-5.4 (m, 1H, NH), 5.35 (t, 1H, H-3), 5.52 (bs, 1H, H-1), 6.73 (d, *J* = 7.6 Hz, 2H, Ph), 6.99 (t, *J* = 7.6 Hz, 1H, Ph), 7.25 (t, 2H, Ph); ^{13}C-NMR ($CDCl_3$) δ 17.00, 20.36, 20.51, 61.69 (C-6), 68.18 (C-4), 70.83 (C-2), 72.80 (C-3, C-5), 79.29 (C-1), 150.00 (N=C), 169.36, 169.67, 170.39, 170.66. Anal. Calcd. for $C_{22}H_{28}N_2O_9$: C, 56.89 ; H, 6.08 ; N, 6.03. Found: C, 56.99; H, 6.09; N, 6.00.

***N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*-propyl-*N'*-phenyl acetamidine (14).** A mixture of **3** (0.45 g, 1.0 mmol), triethylamine (0.02 g, 0.20 mmol), HgO (0.24 g, 1.1 mmol), and aniline (0.19 g, 2.0 mmol) in dichloromethane (25 mL), was stirred for 20 days. The reaction mixture was filtered through celite, washed with dichloromethane, and the solvent evaporated. The residue was purified by colum chromatography (eluents d, e) and **14** crystallized from ether/petroleum ether (0.07 g, 13 %); mp 107-108 °C; $[\alpha]_{589}$ +32°, $[\alpha]_{578}$ +33°, $[\alpha]_{546}$ +37°, $[\alpha]_{436}$ +43° (*c* 0.5, CH_2Cl_2); IR (KBr) 2920, 1720, 1600, 1425, 1355 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.63 (m, 2H, $CH_2CH_2CH_3$), 1.89, 2.02, 2.04, 2.09 (4 s, 15H, $COCH_3$, $N{=}C(CH_3)$), 3.13 (ddd, *J* = 5.4, *J* = 10.0 Hz, 1H, $CH_2CH_2CH_3$), 3.38 (ddd, 1H, $CH_2CH_2CH_3$), 3.78 (dt, $J_{4,5}$ = 9.9, $J_{5,6}$ = $J_{5,6'}$ = 3.3 Hz, 1H, H-5), 4.21 (d, 2H, H-6, H-6'), 5.13 (t, $J_{3,4}$ = 9.3 Hz, 1H, H-4), 5.29 (t, $J_{1,2}$ = 8.9, $J_{2,3}$ = 9.1 Hz, 1H, H-2), 5.33 (t, 1H, H-3), 5.71 (bs, 1H, H-1), 6.67 (d, *J* = 7.2 Hz, 2H, Ph), 6.96 (t, *J* = 7.4 Hz, 1H, Ph), 7.24 (t, 2H, Ph); ^{13}C-NMR ($CDCl_3$) δ 11.41, 14.90, 20.52, 23.17, 45.14, 61.82 (C-6), 68.21, 69.06, 73.51, 73.68 (C-2, C-3, C-4, C-5), 83.37 (C-1), 155.51 (N=C), 169.40, 169.40, 169.99, 170.47. Calcd. for $C_{25}H_{34}N_2O_9$: C, 59.26 ; H, 6.77 ; N, 5.53. Found: C, 59.09; H, 6.73; N, 5.47.

An alternative experiment in the absence of triethylamine, at reflux for 15 days, gave a very small amount of **14**, as evidenced by NMR analysis.

Bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthioacetamide)mercury(II) (16). (a) To a vigorously stirred solution of **2** (3.03 g, 7.50 mmol) in dichloromethane (50 mL) at room temperature, HgO (2.10 g, 9.72 mmol) and triethylamine (0.01 g, 0.10 mmol) were added, and the reaction was monitored by TLC (eluent a). After 6 h., the mixture was filtered through celite to remove the HgO, which was washed with dichloromethane, and the filtrate was evaporated. The resulting residue was dissolved in toluene to give a yellowish gel, which solidified with ether, then filtered, washed with ether, and dried to an amorphous solid (3.27 g). NMR analyses of a $CDCl_3$ solution of this solid revealed a 1.5:1 mixture of **16** and **2**. Spectroscopic data for **16**: IR (KBr) 2970, 1760, 1610, 1440, 1380, 1230, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.00, 2.03, 2.10 (3 s, 12H, $COCH_3$), 2.27 (s, 3H, $CSCH_3$), 3.77 (ddd, $J_{4,5}$ = 10.2, $J_{5,6}$ = 4.8, $J_{5,6'}$ = 2.5 Hz, 1H, H-5), 4.12 (dd, 1H, $J_{6,6'}$ = 12.5 Hz, H-6), 4.22 (dd, 1H, H-6'), 4.58 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-1), 5.02 (t, $J_{2,3}$ = 9.9 Hz, 1H, H-2), 5.07 (t, $J_{3,4}$ = 9.0 Hz, 1H, H-4), 5.24 (t, 1H, H-3); ^{13}C-NMR ($CDCl_3$) δ 20.25, 20.36, 20.45, 22.53, 61.80 (C-6), 68.15, 72.28, 72.58, 73.70 (C-2, C-3, C-4, C-5), 86.70 (C-1), 168.87, 169.03, 169.90, 170.31, 182.37 (C=S).

(b) The reaction was performed as described in the procedure (a) with **2** (1.94 g, 4.80 mmol), HgO (0.68 g, 3.1 mmol) and diethylamine (0.30 g, 4.1 mmol) in dichloromethane (40 mL). After 2 h, TLC showed **16** as major compound and traces of amidine **6** only. The reaction mixture was filtered through celite to remove HgO, which was washed with dichloromethane, and the filtrate was evaporated. The resulting residue was treated with benzene-ether to give and amorphous solid (0.99 g), showing similar NMR and IR data to those of compound described in the aforementioned procedure.

Reaction of complex 16 with *N*-methylbenzylamine. To a magnetically stirred solution of crude complex **16** (0.33 g) in dichloromethane (15 mL) at room temperature, was added *N*-methylbenzylamine (0.24 g, 2.0 mmol), and the process was controlled by TLC (eluent a). After 8 h., the reaction mixture was filtered through celite, washed with dichloromethane, the solvent was evaporated and the resulting residue purified by colum chromatography (eluent a) to give amidine **7** (0.05 g).

Reaction of thioamide 2 with HgO. To a magnetically stirred solution of **2** (0.20 g, 0.50 mmol) in dichloromethane (10 mL) at room temperature, was added HgO (0.28 g, 1.30 mmol). After 1 month, the mixture was filtered through celite, the solution was evaporated and the resulting residue crystallized from ethanol to give amide **11** (0.12 g, 64%), which was characterized[12b] by physical and spectroscopic data. Alternatively, ^{1}H-NMR monitoring of this reaction in $CDCl_3$ for a week did not reveal the formation of complex **16**.

Reaction of thioamide 2 with aniline and HgO. To a vigorously stirred solution of **2** (0.22 g, 0.5 mmol) in $CDCl_3$ (2 mL) at room temperature, was added HgO (0.11 g, 0.50 mmol) and aniline (0.09 mL, 1.0 mmol). NMR analysis evidenced the formation of amide **11** after 24 h. Neither coordination complex **16** nor the amidine **15** could be detected.

Reaction of thioamide 3 with HgO. A suspension of **3** (0.22 g, 0.5 mmol) and HgO (0.14 g, 0.65 mmol) in $CDCl_3$ (3 mL), was magnetically stirred for a week. Formation of amide **12** was detected by NMR analysis, but coordination between **3** and HgO could not be detected.

Titration of thioamide 2 with HgO in the presence of triethylamine. To a solution of **2** (220 mg, 0.50 mmol, 0.25 M) in $CDCl_3$ (2 mL) was added triethylamine (12 mg, 0.12 mmol), benzene (47 mg, 0.60 mmol) as internal reference and, successively, HgO (13 portions of 5.4 mg each, 0.025 mmol, and 2 portions of 10.8 mg each, 0.050 mmol). Each sample was stirred for 12 h and ^{1}H-NMR spectra were recorded after each addition of HgO. This remained insoluble after the addition of ~54 mg (0.25 mmol).

Job plot. Eleven reaction mixtures of thioamide **2** (134.4, 121.0, 114.1, 107.4, 100.7, 94.0, 87.3, 80.6, 73.9, 67.2, 53.8 mg), and HgO (0.0, 6.5, 9.7, 13.0, 16.2, 19.4, 22.6, 26.0, 29.2, 32.4, 38.9 mg) in a solution of triethylamine in $CDCl_3$ (0.165 M, 2 mL) were stirred at room temperature for 24 h. Each sample was monitorized by ^{1}H-NMR spectroscopy and X_c (complexed sugar / free + complexed sugar) was determined by integration of H-1, H-3, H-5, H-6, H-6', N=C(CH_3) signals.

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24. If the reaction is incomplete, additional portions of mercury(II) oxide and amine may be added and the method allowed to proceed further.

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