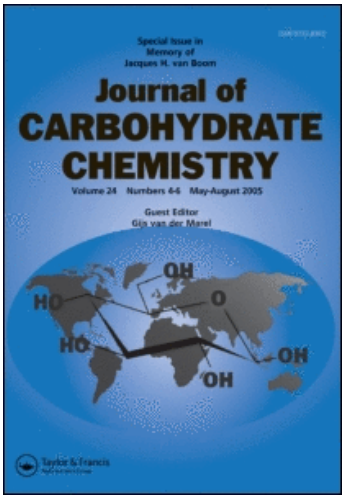

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SYNTHESIS OF THE BIS-TETRAHYDROPYRANO[2,3-*b*:2',3'-*e*] PIPERAZINE RING SYSTEM: A NEW TRICYCLIC HETEROCYCLE FROM D-GLUCOSAMINE

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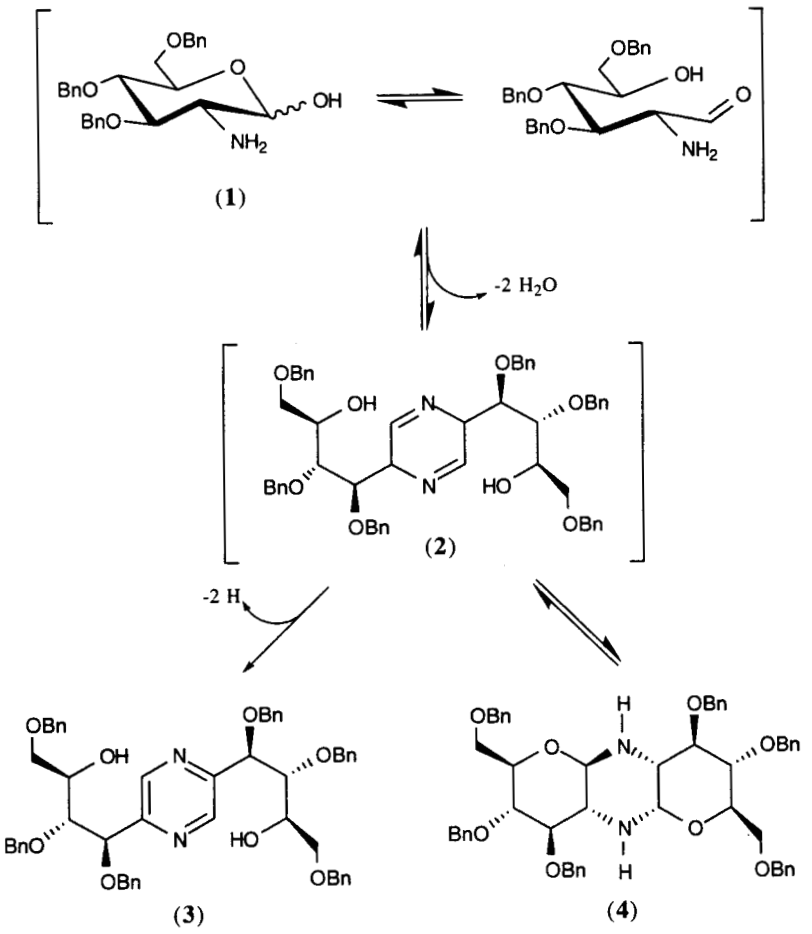
ABSTRACT

2-Amino-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose was transformed into its bis(tetrahydropyranyl)piperazine dimer (**4**) by reaction with 1,1'-thionyldiimidazole or 1,1'-sulfonyldiimidazole. This dimeric form of glucosamine is the first representative of this previously unknown heterocyclic ring system.

INTRODUCTION

The preparation of nitrogen heterocycles from saccharide derivatives has been of interest for over a century.[1] In recent years aza sugars, amino sugars, glycosyl amines, and other saccharide based nitrogen heterocycles have received much attention due to their apparent utility including inhibition of glycosidases,[2] involvement in DNA strand breakage,[3] chelation of metals,[4] and as synthetic intermediates.[5] While it is generally known that 2-amino-2-deoxy-D-glucopyranose and its derivatives can form 2,5-bis (tetrahydroxybutyl)pyrazines under alkaline conditions[6] (Scheme 1, **3**) or undergo typical rearrangements associated with amino carbonyl compounds[7] (*i.e.* Amadori rearrangement), we find no reports in the literature for their direct conversion to fully saturated piperazine containing tricyclic heterocycles. The synthesis and full ^{1}H NMR structural determination of the bis(tetrahydropyranyl)piperazine glucosamine dimer (**4**) are presented.



Scheme 1

RESULTS AND DISCUSSION

Current efforts in our laboratory include studies aimed at the synthesis of 1,2-cyclic sulfamidates of D-glucosamine derivatives utilizing *bis*-reactive thionyl and sulfonyl reagents. During the course of these investigations, the reaction of 2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (**1**) with 1,1'-sulfonyldiimidazole or 1,1'-thionyl diimidazole resulted in formation of the hexabenzylated fructosazine derivative (**3**) and the previously unknown tricyclic dimer of D-glucosamine (**4**) (Scheme 1).

Table 1. Conditions for reaction of **2** to give products **3** and **4**

Reaction	Reagent	Solvent	Temperature	Time, h	% Yield[a] 3	4
1	$SOIm_2$ 1.5 equiv	THF	-15 °C to RT	48	13	66[b]
2	$SOIm_2$ 1.5 equiv	THF	-15 °C to RT	36	12	52[b]
3	SO_2Im_2 2.5 equiv	DMF	RT	12	no reaction	
4	SO_2Im_2 2.8 equiv	Toluene-DMF (8:1)	50 °C	16[c]	32	25
5	SO_2Im_2 1.1 equiv	DMF sieves	60 °C	34[c]	< 5	0
6	SO_2Im_2 5 equiv	DMF	60 °C	5 days	15	0
7	none	Toluene-DMF (6:1)	60 °C	16	no reaction	
8	Im 11 equiv	Toluene-DMF (7:1)	60 °C	16	no reaction	
9	$MgSO_4$	CH_2Cl_2	RT	8	0	0
10	$CaSO_4$ Et_3N	THF	RT	24[c]	0	trace
11	$CaSO_4/MgSO_4$ iPr_2EtN	DMF	55 °C	18[c]	trace	trace

a. Values indicate isolated yields after chromatography
b. Reaction 1 (100 mg scale), Reaction 2 (gram scale)
c. Staring material (**2**) remained after stopping reaction at time given.

The formation of 2,5-bis(tetrahydroxybutyl)pyrazines (such as fructosazine derivative **3**) from 2-amino-2-deoxy-D-glucopyranose has been observed in reactions containing aqueous ammonia,[8] phosphate buffered lysine,[9] NaOMe in MeOH,[6,10] aqueous $NaHCO_3$,[12] and phosphate buffer (pH 7.4).[13] The mechanism for this pyrazine pathway involves an initial *bis*-Schiff base intermediate (dihydrofructosazine derivative **2**, Scheme 1). The formation of **4** presented here, probably results from intramolecular addition of the C-5 hydroxyl groups to the imine carbons of intermediate **2**. This condensation is analogous to glycosyl amine formation from reducing sugars and amines. Pfleiderer *et al.* have reported similar cyclization of a glucosamine derivative providing the *N,O*-acetal heterocycle.[11]

To determine the role of reagents in this transformation, a number of reaction conditions were investigated (Table 1).

Reactions 1 and 2 (Table 1) show higher yields of **4** with the more reactive 1,1'-thionyldiimidazole reagent. Product **4** appears in these reaction mixtures before **3**. If the reactions are allowed to proceed after the disappearance of **2**, the ratio of product **3** to **4** increases. This suggests product **4** is in equilibrium with **2** and that this equilibrium allows **3** to predominate under thermodynamic conditions. This is consistent with the higher temperature required for the reaction with 1,1'-sulfonyldiimidazole providing **3** but little **4** (Table 1, reactions 3-6). Additional evidence for this equilibrium was obtained by dissolving **4** in DMF containing 1,1'-sulfonyldiimidazole and heating to 55 °C. Product **3** was produced in nearly quantitative yield after three hours. The 1,1'-thionyldiimidazole reagent used in reactions 1 and 2 contains imidazole,[17] suggesting the preferential formation of **4** might be simply ascribed to the presence of this base. To test the effect of imidazole, it was added to a variety of reactions and produced no effect. Reactions 7-8 (Table 1) show no reaction occurs with heating alone or with heating in the presence of imidazole.

Reactions 9-11 (Table 1) show the formation of **4** does not occur simply by altering the dehydration equilibrium between **1** and **2** (Scheme 1). This result is somewhat surprising since the condensation of (*R*)-*N*-methylphenylglycinol with aliphatic carbaldehydes affords oxazolidines in high yield under conditions of reaction 9.[14] The precise role of the 1,1'-thionyl and 1,1'-sulfonyldiimidazole in this reaction is still not completely clear. The results presented suggest that these reagents are directly involved in altering the equilibrium between **2** and **4** (Scheme 1) and are not acting as simple dehydrating agents. This apparent alteration of the fructosazine pathway may have gone previously undetected since reactions of 2-amino-2-deoxy-D-glucopyranose and its derivatives containing the unprotected amine and anomeric position that form the fructosazine byproducts are typically performed in alkaline alcoholic or aqueous solvents.

Attempts to acetylate **4** at the piperazine ring nitrogens with pyridine/acetic anhydride were unsuccessful. The primary products obtained contained the pyrazine ring (^{1}H NMR singlet 8 to 9 ppm). The addition of acetic anhydride in the absence of added base showed no reaction after 12 h demonstrating the unreactive nature of the ring nitrogens in this system

NMR Studies. ^{1}H NMR of **4** in $CDCl_3$ resulted in rapid decomposition of material if this solvent contained any acid. Even in $CDCl_3$ free of acid, the ^{1}H NMR spectrum was difficult to interpret owing to the presence of overlapping signals (Table 2). Two separate seven proton spin systems were assigned in the COSY and TOCSY spectra. The significant signal overlap along with broad and shallow signals for the amine protons were expected to adversely affect further NMR experiments. The use of CD_3CN as the solvent (Table 2 & Figure 1) provided reduced signal overlap, sharpened the NH peaks and allowed ring connectivity to be assigned.

TABLE 2. ^{1}H NMR shifts[a] for product **4**

	α-ring							β-ring						
Solvent	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
$CDCl_3$	4.73	2.98	3.95	3.60	3.95	3.60	3.71	3.00	2.45	3.29	3.60	3.12	3.60	3.71
CD_3CN	4.57	2.81	3.95	3.55	3.89	3.60 - 3.73		3.24	2.34	3.37	3.51	3.18	3.60 - 3.73	
Splitting	d	dd	dd	dd	m	m		d	dd	dd	dd	m	m	
J value (Hz)	$J_{1,2}$ (4)	$J_{2,3}$ (10)	$J_{3,4}$ (10)	$J_{4,5}$ (10)				$J_{1,2}$ (8)	$J_{2,3}$ (10)	$J_{3,4}$ (10)	$J_{4,5}$ (10)			

a. Recorded with TMS as standard, underlined values indicate overlapping signals

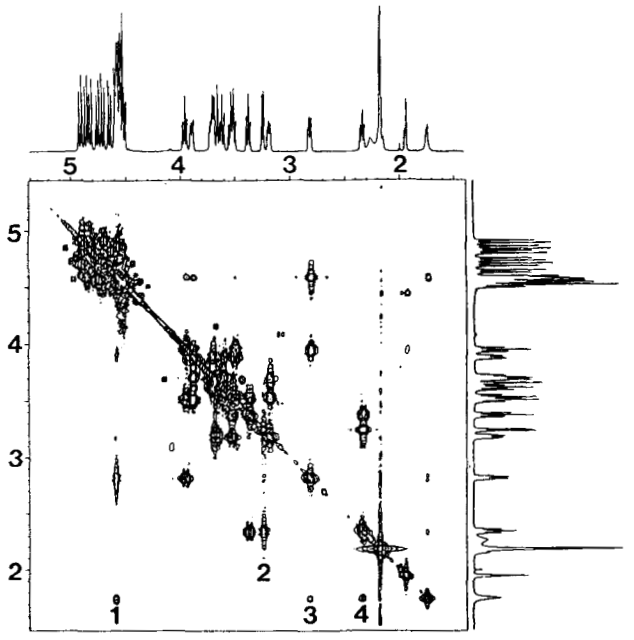


Figure 1. Two dimensional COSY spectrum of **4** in CD_3CN (10 mM). *Cross peaks*: 1, α-H-1/β-NH; 2, β-H-1/α-NH; 3, α-H-2/β-NH (long range coupling); 4, β-H-2/β-NH.

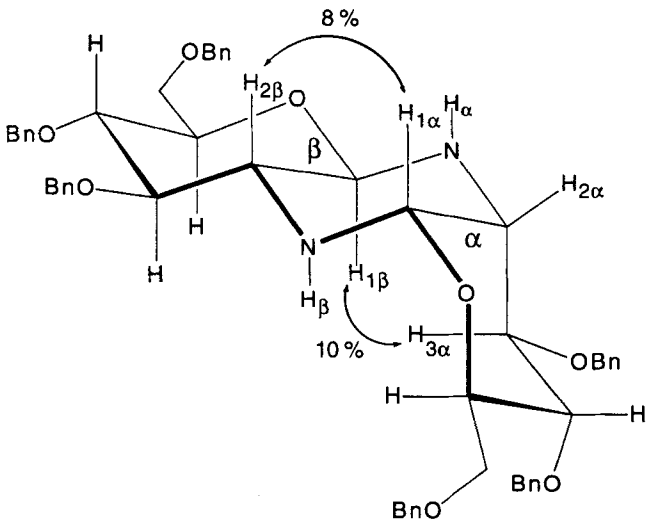


Figure 2. Configuration and NOE of **4**.

Initial inspection of the 1D ^{1}H and 2D-COSY (Figure 1) show two typical D-glucopyranoside rings, one with C-1-α and one with C-1-β configuration. The spectroscopic data shows H-2 of the β-pyranose and H-1 of the α-pyranose coupled with the same NH proton (1.74 ppm). The second NH proton shows unusual behavior. At low concentrations it shows a single exchangeable signal at 2.14 ppm and no coupling to other protons is observed. At higher concentrations the intensity of this signal is reduced and an additional exchangeable singlet appears at 2.26 ppm maintaining combined integration as one proton (3 mM 6:1, 10 mM 1:1). This NH signal, observed at higher concentrations (> 3 mM), shows coupling to β-H-1 suggesting a concentration dependence on its axial/equatorial orientation.

Evidence for the configuration of **4**, obtained by 1D-differential NOE experiments (Figure 2), clearly shows through space proximity of the α and β pyranose rings. The dramatic upfield shift of β-H-1 and β-H-2 compared to the chemical shift of the α-H-1 and α-H-2 is typical of that seen in glycosylamines, diglycosylamines, and in carbohydrates containing ring nitrogens. This is expected as H-1 and H-2 of the β-sugar are axial with respect to both the pyranose and piperazine ring while H-1 and H-2 of the α-sugar are equatorial to the pyranose and piperazine ring, respectively.

The spectroscopic data and proposed mechanism for the formation of **4** show that no stereochemical changes occur in the pyranose rings during cyclization. The configuration of **4** (Figure 2) is extremely rigid with no flexibility about the energetically

favored, all chair, core tricyclic system. Modeling studies show that formation of the α,α and β,β dimers would require the piperazine ring to exist in the higher energy boat conformation or the pyranose rings to maintain high energy $^1C_4$ conformations. The α,α dimer would also exhibit unfavorable steric interactions additionally favoring formation of the α,β dimer (**4**).

CONCLUSIONS

The synthesis of the previously unknown dimer of glucosamine (**4**) reported here represents an interesting new carbohydrate-derived tricyclic ring system. This new ring system may display chemical utility or interesting biological activities. Excellent chelation properties of such compounds having rigid, defined *exo* and *endo* faces are anticipated based on previous reports of amino sugars[4,15] and other 1,4-diamino polyhydroxylated tricyclic heterocycles.[16] The biological activities of **4**, or more stable derivatives, in a deprotected form require exploration. It is also likely that this reaction may have general synthetic utility and be applicable to other 2-amino sugars.

EXPERIMENTAL

General methods. 1,1'-Thionyldiimidazole was prepared as previously reported.[17] 1,1'-Sulfonyldiimidazole was purchased (Aldrich). All other reagents and solvents were of reagent grade and were dried using standard procedures.

Melting points are uncorrected. Optical rotations were measured with a Perkin Elmer 141 polarimeter at 22 °C. Mass spectra were obtained using a VG ZAB-HF instrument (VG Analytical, Inc.) in the fast atom bombardment (FAB) ionization mode using a Xenon beam. Triethanolamine was used as the matrix. All reactions were monitored by thin layer chromatography on aluminum sheets, silica gel 60 F_{254} (Merck); detection under short wavelength UV light (254 nm) or by dipping the plates into staining solution (1.0 g ceric ammonium sulfate and 24.0 g ammonium molybdate in 31 mL sulfuric acid 470 mL water) then heating. Flash chromatography was performed using 230-400 mesh silica gel 60 (Aldrich).

^{1}H NMR analysis -For ^{1}H NMR spectroscopy, the thoroughly dried sample was redissolved in 0.7 mL of the fully deuterated solvents and transferred to the NMR tube (5.0 mm o.d. x 25 cm, PP-528; Wilmad Glass Co., Buena, NJ). All spectra were performed using a UNITY-500 spectrometer equipped with a VXR 5000 computer system at the operating frequency of 500 MHz. The operating conditions for one-dimensional (1D) spectra were as follows: frequency, 500 MHz; sweep width, 6 kHz; flip angle, 90 (7.1 μs);

sampling point, 48k; accumulation, 32 pulses; temperature, 298 K. Differential NOE experiments were performed for 700 times accumulations with a pulse delay 3 times the longest T_1 (13 s), estimated from an inversion-recovery experiment. Chemical shifts were indicated by ppm from the signal of tetramethylsilane as an internal standard.

Two-dimensional (2D) COSY spectra, and homonuclear Hartman-Hahn total correlation spectra (TOCSY) were recorded using the phase-sensitive mode. All 2D spectra were recorded with 512 x 2048 data points and a spectral width of 5000 Hz. TOCSY(MLEV-17) spectra were recorded with a mixing time of 100 ms. A total of from 8 to 16 scans were accumulated for each t_1, with a relaxation delay of 3 s. The digital resolution was 2.5 Hz/point in both dimensions with zero-filling in the t_1 dimension. A phase-shifted sine function was applied for both t_1 and t_2 dimensions in all other cases.

2-Amino-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (1). 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose[18] (4.5 g, 9.6 mmol) was dissolved in pyridine-water, 3:1 (100 mL). H_2S gas was bubbled through the stirring solution for 8 min. The flask was sealed with a rubber septum and stirred at room temperature. After 48 h the dark brown reaction mixture was repeatedly evaporated with toluene azeotrope until a crude yellow mass remained. Flash chromatography (ethyl acetate/hexanes v/v 1:1 → 2:1 → chloroform/methanol v/v 40:1) afforded **1** (2.0 g). Additional impure fractions were combined and evaporated and re-chromatographed (chloroform/methanol v/v 36:1) to give combined yield **1** (3.1 g, 72%) as a white solid.[19] $[\alpha]_D$ = +75° (*c* 1, $CHCl_3$); HRMS: Calcd for $C_{27}H_{31}N_1O_5$ [m+Li^+]$^+$ 456.2362: Found 456.2368. FABMS required LiI in matrix for stability.

Anal. Calcd for $C_{27}H_{31}N_1O_5$ (449.5) C 72.14 H 6.95 N 3.12; Found C 71.84 H 7.22 N 3.01.

Preparation of 2,5-bis(1,2,3-tri-*O*-phenylmethyltetrahydroxybutyl) pyrazine (3) and bis(4,5-diphenylmethoxy-6-phenylmethoxymethyl)tetra hydropyrano[2,3-*b*:2',3'-*e*]piperazine (4).

1,1'-Thionyldiimidazole method. Imidazole (1.5 g, 22 mmol) was dissolved in 40 mL dry THF under N_2 gas. The solution was cooled to 0 °C and thionyl chloride (0.4 mL, 5.4 mmol) was added dropwise with stirring. This mixture was filtered directly into a stirring solution of 40 mL THF containing 2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (**1**) (1.61 g, 3.6 mmol) at -15 °C. The reaction was placed in an ice bath after 10 min and allowed to gradually warm to RT. After 36 h, the reaction was placed in the refrigerator for 12 h, filtered, and evaporated. Purification by flash chromatography (column packed with 0.1% triethylamine) ethyl acetate-hexanes, v/v 1:2, afforded **3** (0.19 g, 12%) as a colorless glass: ^{1}H NMR ($CDCl_3$) δ 2.5 (br s, 1H, OH), 3.57 (dd, 1H, $J_{5,6b}$

= 3 Hz, H-6b), 3.67 (dd, 1H, $J_{5,6a}$ = 5 Hz, $J_{6a,6b}$ = 10 Hz, H-6a), 3.86 (dd, 1H, $J_{4,5}$ = 8 Hz, H-4), 3.98 (dd, 2H, 1 OCH_2Ph), 4.00 (m, 1H, H-5), 4.43-4.65 (m, 4H, 2 OCH_2Ph), 5.03 (d, 1H, $J_{3,4}$ = 3 Hz, H-3), 6.90-7.33 (m, 15H, 3 C_6H_5), 8.83 (s, 1H, H-1). FABMS: 861 $[M + H^+]^+$ and **4** (0.80 g, 52%) as a white solid. $[\alpha]_D$ = +142.2 (*c* 0.69, CH_3CN), mp 139-140 (CH_3CN), FABMS: 863 $[M+H^+]^+$.

Anal. Calcd for $C_{54}H_{58}N_2O_8$ (862.4) C, 75.14; H, 6.78; N, 3.25. Found: C, 75.02; H, 6.94; N, 3.27.

1,1'-Sulfonyldiimidazole method. (see Table 1 for specific solvents, conditions and reagents) To a solution of 2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (**1**) in solvent stirring at RT under an inert atmosphere in a flask fitted with a reflux condenser was added 1,1'-sulfonyldiimidazole and the reaction heated for the time and temperature reported. The reaction was allowed to cool, repeatedly azeotroped with heptane and purified by flash chromatography as reported in the previous procedure providing yields reported in Table 1.

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