Synthesis of β-D-glucopyranosyl- and β-D-galactopyranosylamines from 4-bromo-3-methylaniline and 2-amino-5-bromopyridine

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The possibility of coupling of D-glucose and D-galactose with 4-bromo-3-methylaniline, 2,4,6-tribromoaniline, and 2-amino-5-bromopyridine was studied. The substituent in the aromatic ring was found to influence the conditions and possibility of the reaction. The yields of β-D-glucopyranosyl- and β-D-galactopyranosylamines from 4-bromo-3-methylaniline and 2-amino-5-bromopyridine were 50—65%; 2,4,6-tribromoaniline did not react at all.

Key words: *N*-glycosylamines, D-glucose, D-galactose, 4-bromo-3-methylaniline, 2,4,6-tribromoaniline, 2-amino-5-bromopyridine.

Permanent development and application to clinical practice of novel drugs, especially antibacterial and antiviral ones, are prompted by not only a seriously deteriorated environmental situation favoring the progressive growth of some diseases, but also the so-called drug resistance of many pathogenic bacteria and viruses.[1,2] It is known that the development of drug resistance to almost all currently existing drugs reflects the natural adaptation of species to the environment.

Functionalization of monosaccharides by way of introducing active pharmacophore groups into their molecules can serve as a tool for the design of new biologically active compounds. In addition, carbohydrate-containing biologically active compounds are known to be more soluble in water, less toxic, and more convenient for targeted drug delivery and penetration into cells.[3,4]

N-Glycosylamines are coming into ever increasing use for the synthesis of natural glycopeptides, their analogs, and glycoconjugates to be employed in various biological investigations.[5—7] Much attention given by chemists, biochemists, and biologists to *N*-glycosylamines is due to their formation under biological conditions from carbohydrates and alkyl- and arylamines. Pharmacologists consider *N*-glycosylamines to be potential sources of new drugs.[8]

The antipyretic properties of aniline are also known; however, this compound is too toxic to be used for medical purposes. By introducing various substituents (*e.g.*, acetyl) into the benzene ring and the amino group, one can appreciably reduce the toxicity and obtain derivatives with a broad spectrum of pharmacological activities.[9] The presence of halogen atoms in drug molecules strongly influences the physiological activity by way of enhancing the lipophilicity of drugs, which facilitates their penetration through biomembranes.[10] In addition, halogen derivatives of pyrimidine-based glycosides are widely used in medical practice as potent antiviral drugs (*e.g.*, 5-iodo-2´-deoxyuridine, or idoxuridine, is employed in the chemotherapy of herpes[11]).

In connection with this, we tried to obtain new halogen-containing *N*-glycosylamines from haloaniline and halopyridine derivatives.

Earlier,[12] we have synthesized *N*-glycosylamines from D-glucose and D-galactose and 4-bromo- and 4-iodoanilines. Noncatalytic coupling of D-glucose or D-galactose with 4-iodoaniline or 4-bromoaniline proceeds rather smoothly in 95% ethanol at 60—70 °C and is completed in 4—5 h.

To extend the range of halogen-containing *N*-glycosylamines, we studied this coupling reaction with 4-bromo-3-methylaniline, 2,4,6-tribromoaniline, and 2-amino-5-bromopyridine as the amine components. Glycosylation of 4-bromo-3-methylaniline was catalyzed by AcOH (Scheme 1). The yields of glycosides **1** and **2** were 60%.

As for 2,4,6-tribromoaniline, the corresponding *N*-glycosylamines could not be obtained even upon prolonged (for many hours) reflux in the presence of AcOH.

Coupling of D-glucose and D-galactose with 2-amino-5-bromopyridine in ethanol in the presence of AcOH

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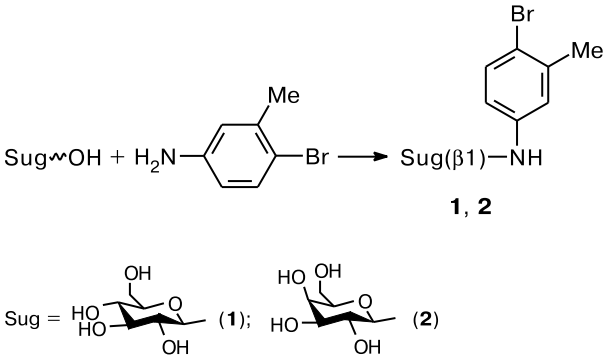
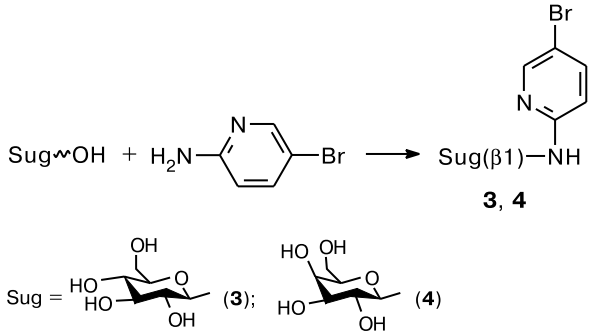
Scheme 1



gave *N*-(5-bromopyridin-2-yl)-β-D-glucopyranosylamine (**3**) and *N*-(5-bromopyridin-2-yl)-β-D-galactopyranosylamine (**4**), respectively, in 50—56% yields (Scheme 2).

Scheme 2



Unlike compounds **1** and **2**, *N*-glycosylamines **3** and **4** are fairly stable and can easily be recrystallized.

The IR spectra of *N*-glycosylamines **1**—**4** show an absorption band at 891±8 cm^{-1}, which suggests the β-configuration of the anomeric carbon.[13] The presence of several peaks at 1010—1090 cm^{-1} is due to the pyranose form of the glycoside residue. The spectra also exhibit bands at 600—700 cm^{-1} (C—Hal) and 1280—1330 cm^{-1} (C—N stretching) and an intense band at 3260—3380 cm^{-1} (OH and NH stretching). According to the IR spectra, compounds **1**—**4** contain no C=N bond (*i.e.*, they are not Schiff bases).

^{1}H NMR data for compounds **1**—**4**, *viz.*, the presence of a signal at δ 4.30—4.50 ($J_{1,2}$ = 7.8—8.2 Hz) for the anomeric H(1) proton in the axial position, confirm that these compounds exist in the pyranose form as β-anomers.

The mass spectra of compounds **1**—**4** contain peaks of molecular (I_{rel} = 10—35%) and fragmentation ions.

According to computer-assisted biological prediction performed with the PASS (Prediction of Activity Spectra for Substances) program,[14] *N*-aminoglycosides **1**—**4** can be very promising antibacterial or antiviral drugs.

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX-500 instrument (500 MHz) in DMSO-d_6 with Me_4Si as the internal standard. IR spectra were recorded on an AVATAR-320 FTIR spectrometer (KBr pellets). Mass spectra were recorded on a Finnigan MATINCOS 50 instrument (EI, 70 eV, direct inlet probe). The melting point was determined with a Boetius instrument. The course of the reaction was monitored and the purity of the products was checked by TLC on Sorbfil plates in Pr^iOH—benzene—25% NH_3 (10 : 5 : 2). Spots were visualized with the iodine vapor. 4-Bromo-3-methylaniline and 2-amino-5-bromopyridine (Aldrich) were used as purchased. 2,4,6-Tribromoaniline was prepared according to a known procedure.

***N*-(4-Bromo-3-methylphenyl)-β-D-glucopyranosylamine (1).** One to two drops of glacial AcOH were added to a solution of D-glucose (3.60 g, 0.02 mol) and 4-bromo-3-methylaniline (3.72 g, 0.02 mol) in ethanol (20 mL). The resulting solution was stirred at 60—65 °C for 6 h and concentrated to one third of its volume. The white crystalline precipitate that formed upon cooling was filtered off, washed with cold isopropyl alcohol, and recrystallized from 95% ethanol. The yield of compound **1** was 4.55 g (65.4%), m.p. 118—120 °C, $[\alpha]_D^{20}$ −76 (*c* 1, DMSO). Found (%): C, 45.17; H, 5.56; N, 4.33. $C_{13}H_{18}BrNO_5$. Calculated (%): C, 44.84; H, 5.21; N, 4.02. ^{1}H NMR, δ: 2.25 (s, 3 H, CH_3—Ar); 3.08—3.67 (m, 6 H, H(2)—H(6)); 4.31 (t, 1 H, H(1), J = 7.9 Hz); 6.32 (d, 1 H, NH, J = 7.9 Hz); 6.48 (d, 1 H, H(6′), J = 7.6 Hz); 6.67 (s, 1 H, H(2′)); 7.23 (d, 1 H, H(5′)). MS, *m/z* (I_{rel} (%)): 349 $[M]^+$ (33), 347 $[M]^+$ (35), 227 (40), 214 (75), 198 (67), 185 (100), 60 (76).

***N*-(4-Bromo-3-methylphenyl)-β-D-galactopyranosylamine (2)** was obtained as described for compound **1**. The yield was 60%, m.p. 130—131 °C, $[\alpha]_D^{20}$ −33.5 (*c* 1, DMSO). Found (%): C, 45.02; H, 5.44; N, 4.21. $C_{13}H_{18}BrNO_5$. Calculated (%): C, 44.84; H, 5.21; N, 4.02. ^{1}H NMR, δ: 2.25 (s, 3 H, CH_3—Ar); 3.08—3.67 (m, 6 H, H(2)—H(6)); 4.31 (t, 1 H, H(1), J = 7.8 Hz); 6.32 (d, 1 H, NH, J = 7.8 Hz); 6.48 (d, 1 H, H(6′), J = 7.6 Hz); 6.67 (s, 1 H, H(2′)); 7.23 (d, 1 H, H(5′)).

***N*-(5-Bromopyridin-2-yl)-β-D-glucopyranosylamine (3).** A solution of D-glucose (1.80 g, 0.01 mol), 2-amino-5-bromopyridine (1.73 g, 0.01 mol), and two to three drops of glacial AcOH in ethanol (10 mL) was stirred at 65—75 °C for 8 h. The solution was concentrated by half. The white crystalline precipitate that formed was filtered off, washed with cold isopropyl alcohol, and recrystallized from 95% ethanol. The yield of compound **3** was 1.65 g (50%), m.p. 197—198 °C, $[\alpha]_D^{20}$ −34.5 (*c* 1, DMSO). Found (%): C, 39.87; H, 4.24; N, 8.11. $C_{11}H_{15}BrN_2O_5$. Calculated (%): C, 39.42; H, 4.51; N, 8.36; ^{1}H NMR, δ: 3.05—3.62 (m, 6 H, H(2)—H(6)); 4.41 (t, 1 H, H(1), J = 8.2 Hz); 6.55 (d, 1 H, H—Ar—N, J = 8.4 Hz); 7.23 (d, 1 H, NH, J = 8.2 Hz); 7.60 (d, 1 H, H—Ar—Br); 8.08 (s, 1 H, N—HAr—Br). MS, *m/z* (I_{rel} (%)): 336 $[M]^+$ (10), 334 $[M]^+$ (10), 201 (100), 172 (30), 158 (22), 60 (40).

***N*-(5-Bromopyridin-2-yl)-β-D-galactopyranosylamine (4)** was obtained as described for compound **3**. The yield was 56%, m.p. 180—181 °C, $[\alpha]_D^{20}$ −6.2 (*c* 1, DMSO). Found (%): C, 39.60; H, 4.74; N, 8.23. $C_{11}H_{15}BrN_2O_5$. Calculated (%): C, 39.42; H, 4.51; N, 8.36. ^{1}H NMR, δ: 3.35—3.80 (m, 6 H, H(2)—H(6)); 4.50 (t, 1 H, H(1), J = 7.9 Hz); 6.58 (d, 1 H, H(3′), J = 8.4 Hz); 7.20 (d, 1 H, NH, J = 7.9 Hz); 7.62 (d, 1 H, H(4′)); 8.10 (s, 1 H, H(6′)).

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