Chemistry of Natural Compounds, Vol. 45, No. 4, 2009

SYNTHESIS OF NEW *N*-AMINOGLYCOSIDES BASED ON HALO-SUBSTITUTED *p*-PHENYLENEDIAMINES AND *p*-AMINOPHENOLS

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UDC 547.455.6;547.917;547.551.51

Condensation of the monosaccharides D-glucose and D-galactose with synthesized halo-substituted p-*phenylenediamines and 4-amino-2,6-dibromophenol was studied. It was found that glycosylation occurred only at the 4-amino group that was sterically unhindered by the halogen atom. The position of the aglycon in the glycoside was established by PMR spectroscopy.*

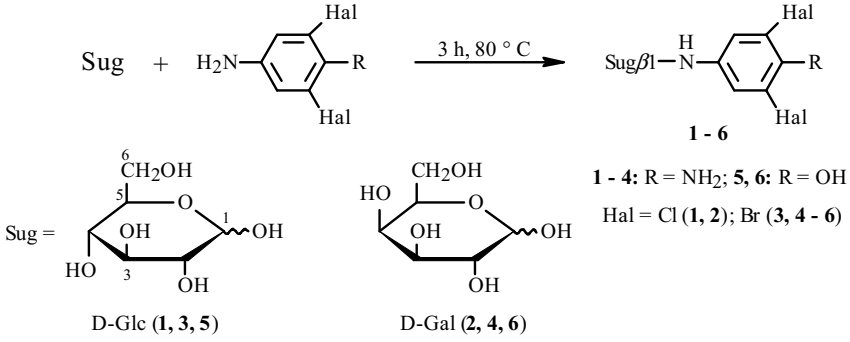
Key words: *N*-glycosylamines, D-glucose, D-galactose, phenylenediamines, aminophenol, PMR spectroscopy.

Monosaccharide derivatives are of great scientific and practical interest because many of them exhibit pronounced biological activity over a broad spectrum including effective anticancer and antiviral drugs [1, 2].

We have previously synthesized *N*-aminoglycosides of D-glucose and D-galactose from 4-bromo- and 4-iodoaniline, 4-bromo-3-methylaniline, and 2-amino-5-bromopyridine, for which the bioprognosis computed by the PASS (Prediction of Activity Spectra for Substances) program revealed high probability coefficients for the presence of antiviral and antibacterial activity [3, 4]. Furthermore, it was shown [5] that *N*-aminoglycosides based on 2-amino-5-bromopyridine had pronounced anti-oxidant activity.

We performed the following transformations in order to synthesize new polyfunctional derivatives of *N*-aminoglycosides. 2,6-Dibromo-4-nitroaniline and 2,6-dichloro-4-nitroaniline were synthesized by known methods [6, 7] and reduced by $SnCl_2$ in HCl [7] to give the corresponding 2,6-dibromo-1,4-phenylenediamine and 2,6-dichloro-1,4-phenylenediamine.

Condensation of these with monosaccharides (D-glucose and D-galactose) in EtOH (95%) gave in about 70% yields the corresponding *N*-(4-amino-3,5-dihalophenyl)-*β*-D-glucopyranosylamines (**1** and **3**) and *N*-(4-amino-3,5-dihalophenyl)-*β*-D-galactopyranosylamines (**2** and **4**). The reactions took on average 2.5-3 h and did not require an acid catalyst as for preparation of *N*-aminoglycosides of 4-bromo-3-methylaniline and 2-amino-5-bromopyridine [3]. It was found that condensation of the monosaccharides with 2,6-dihalo-1,4-phenylenediamine occurred at the sterically unhindered and more basic 4-amino group whereas access to the 1-amino group was sterically hindered by the two halogen atoms located in the *o*-positions.



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 0009-3130/09/4504-0522

The resulting *N*-aminoglycosides **1**–**4** were rather stable. They could be recrystallized in alcohols with heating and were not only very promising compounds for biological tests but also convenient synthons for further chemical transformations because they contained a free primary amino group.

IR spectra of **1**–**4** exhibited absorption bands at 898 cm^{-1}. This was indicative of the β-conformation of the anomeric center. Several bands at 1070–1015 were consistent with the pyranose form of the glycoside [8]. The C–Hal bond appeared at 700–600; C–N, 1330–1245. Stretching vibrations of OH and NH appeared as a broad strong band at 3450–3100. An analysis of IR spectra of **1**–**4** showed that they did not contain a C=N bond, i.e., were not Schiff bases.

PMR spectra of **1**–**4** confirmed that they had the pyranose form as the β-anomer. This was indicated by the resonance of anomeric H(1) in the axial position with chemical shift 4.20 ppm and SSCC J ~ 7.2-7.8 Hz.

Thus, the PMR spectrum (DMSO-d_6, 500 MHz) of **3** showed resonances for CH– and CH_2–groups of the carbohydrate at 3.05–3.64 ppm as a complex multiplet. The anomeric proton of the carbohydrate appeared as a triplet (coupling with the neighboring proton of the pyranose ring and the N–H proton of the amine) at 4.20 ppm with SSCC = 7.8 Hz, characteristic of the β-anomer [9]. Protons of secondary hydroxyls of the pyranose ring were recorded at 4.81–4.94 ppm as doublets; of the primary hydroxyl, at 4.43 ppm as a triplet. Resonances of the two aromatic protons were recorded as a narrow singlet at 6.86 ppm; of the N–H proton at the glycoside center, a doublet at 5.98 ppm; of the free protons of the NH_2 group on the aromatic ring, a singlet at 4.51 ppm.

The mass spectrum of **3** had a peak for the molecular ion of relative intensity 10%. Products of decomposition at the C–N glycoside bond were mainly detected.

N-Aminoglycosides **5** and **6** were synthesized analogously from 4-amino-2,6-dibromophenol. They contained the structurally similar bromophenol pharmacophore that is characteristic of certain antiviral drugs (tebrophen and arbidol) [10].

Bioscreening for antioxidant activity by a complex study of the oxidant and test compound at the common level of peroxide oxidation of lipids (POL) was carried out *in vitro* in order to establish the assumed biological activity of **1**–**4**. The experiment used POL modeling by yolk lipoproteide. The test results established that **1**–**4** did not exhibit antioxidant activity in *in vitro* tests.

Antimicrobial activity of **3** and **5** was studied against test strains *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and yeast fungus *Candida albicans* by agar diffusion. The reference drugs were gentamicin for bacteria and nystatin for fungi. The antimicrobial activity of **3** and **5** were estimated from the diameter (mm) of the growth-inhibition zones of the test strains.

Bioscreening of **5** found moderate antibacterial activity only against Gram-positive strain *S. aureus* and moderate antifungal activity against *C. albicans*. Compound **3** had practically the same moderate activity against Gram-positive strains (*S. aureus* and *B. subtilis*) and the Gram-negative strain (*E. coli*) and antifungal activity against *C. albicans*. Therefore, **3** had a broader spectrum of antimicrobial activity.

EXPERIMENTAL

IR spectra were recorded in KBr disks on a Fourier-transform Avatar-320 spectrometer (Nicolet). PMR spectra were recorded in DMSO-d_6 on a Bruker DRX500 spectrometer at 500 MHz relative to TMS internal standard. Mass spectra were recorded on a Finnigan MAT.Incos 50 instrument with direct sample introduction and ionizing energy 70 eV. Melting points were determined on a Boetius apparatus. The course of reactions and purity of products were monitored by TLC on Sorbfil plates with elution by 2-propanol:benzene:NH_4OH (25%) (10:5:2). Spots were detected by iodine vapor.

***N*-(4-Amino-3,5-dichlorophenyl)-β-D-glucopyranosylamine (1).** A solution of D-glucose (0.90 g, 5 mmol) in EtOH (10 mL) was stirred, treated with 2,6-dichloro-1,4-phenylenediamine (0.89 g, 5 mmol), and stirred for 3 h at 75–80°C. The solution with a crystalline precipitate was cooled (−10°C) and filtered. The precipitate was wahsed with cold 2-propanol and recrystallized from EtOH to afford **1** (1.48 g, 70%), mp 160–162°C (dec.). $C_{12}H_{16}Cl_2N_2O_5$. PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.04 (2H, m, H-4, H-2), 3.22 (2H, m, H-6), 3.40 (1H, m, H-5), 3.64 (1H, dd, $J_{3,2}$ = 6.0, H-3), 4.21 (1H, t, J = 7.6, H_β-1), 4.42 (1H, t, OH-6), 4.59 (2H, s, Ar–NH_2), 4.80 (1H, d, OH-4), 4.86 (1H, d, OH-2), 4.95 (1H, d, OH-3), 5.98 (1H, d, J = 7.6, NH), 6.67 (2H, s, H–Ar).

***N*-(4-Amino-3,5-dichlorophenyl)-β-D-galactopyranosylamine (2)** was synthesized analogously to **1** from D-galactose (0.90 g, 5 mmol) and 2,6-dichloro-1,4-phenylenediamine (0.89 g, 5 mmol) to afford **2** (1.27 g, 78%), mp 164–

166°C (dec.). $C_{12}H_{16}Cl_2N_2O_5$. PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.40 (2H, m, H-4, H-2), 3.50 (1H, m, H-5), 3.66 (2H, m, H-6), 3.75 (1H, m, H-3), 4.18 (1H, t, J = 7.2, H_β-1), 4.55 (1H, t, OH-6), 4.60 (2H, s, Ar–NH_2), 4.62 (1H, d, OH-4), 4.68 (1H, d, OH-2), 4.75 (1H, d, OH-3), 5.98 (1H, d, J = 7.2, NH), 6.67 (2H, s, H–Ar).

***N*-(4-Amino-3,5-dibromophenyl)-β-D-glucopyranosylamine (3)** was synthesized analogously to **1** from D-glucose (0.90 g, 5 mmol) and 2,6-dibromo-1,4-phenylenediamine (1.33 g, 5 mmol) to afford **3** (1.54 g, 72%), mp 188–190°C (dec.). $C_{12}H_{16}Br_2N_2O_5$. PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.05 (2H, m, H-4, H-2), 3.20 (2H, m, H-6), 3.41 (1H, m, H-5), 3.64 (1H, dd, $J_{3,2}$ = 6.0, H-3), 4.20 (1H, t, J = 7.8, H_β-1), 4.43 (1H, t, OH-6), 4.51 (2H, s, Ar–NH_2), 4.81 (1H, d, OH-4), 4.86 (1H, d, OH-2), 4.94 (1H, d, OH-3), 5.98 (1H, d, J = 7.8, NH), 6.86 (2H, s, H–Ar). Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 428 (10) $[M]^+$, 308 (38), 279 (100), 266 (62), 60 (60), 43 (52).

***N*-(4-Amino-3,5-dibromophenyl)-β-D-galactopyranosylamine (4)** was synthesized analogously to **1** from D-galactose (0.90 g, 5 mmol) and 2,6-dibromo-1,4-phenylenediamine (1.33 g, 5 mmol) to afford **4** (1.48 g, 70%), mp 155–157°C (dec.). $C_{12}H_{16}Br_2N_2O_5$. PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.42 (2H, m, H-4, H-2), 3.52 (1H, m, H-5), 3.60 (2H, m, H-6), 3.70 (1H, m, H-3), 4.18 (1H, t, J = 7.2, H_β-1), 4.52 (1H, t, OH-6), 4.58 (2H, s, Ar–NH_2), 4.61 (1H, d, OH-4), 4.68 (1H, d, OH-2), 4.75 (1H, d, OH-3), 5.97 (1H, d, J = 7.2, NH), 6.85 (2H, s, H–Ar).

***N*-(4-Hydroxy-3,5-dibromophenyl)-β-D-glucopyranosylamine (5)** was synthesized analogously to **1** from D-glucose (0.36 g, 2 mmol) and 4-amino-2,6-dibromophenol (0.54 g, 2 mmol) to afford **5** (0.55 g, 64%), mp 172–174°C (dec.). $C_{12}H_{15}Br_2NO_6$. PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.10 (2H, m, H-4, H-2), 3.22 (2H, m, H-6), 3.41 (1H, m, H-5), 3.62 (1H, dd, $J_{3,2}$ = 6.0, H-3), 4.25 (1H, t, J = 7.7, H_β-1), 4.75 (1H, t, OH-6), 4.82 (1H, d, OH-4), 4.86 (1H, d, OH-2), 4.96 (1H, d, OH-3), 5.98 (1H, d, J = 7.7, NH), 6.88 (2H, s, H–Ar), 8.90 (1H, s, Ar–OH).

***N*-(4-Hydroxy-3,5-dibromophenyl)-β-D-galactopyranosylamine (6)** was synthesized analogously to **1** from D-galactose (0.18 g, 1 mmol) and 4-amino-2,6-dibromophenol (0.27 g, 1 mmol) to afford **6** (0.28 g, 65%), mp 160–161°C (dec.). $C_{12}H_{15}Br_2NO_6$. PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.40 (2H, m, H-4, H-2), 3.52 (1H, m, H-5), 3.62 (2H, m, H-6), 3.72 (1H, m, H-3), 4.20 (1H, t, J = 7.4, H_β-1), 4.46 (1H, t, OH-6), 4.50 (1H, d, OH-4), 4.56 (1H, d, OH-2), 4.62 (1H, d, OH-3), 5.97 (1H, d, J = 7.4, NH), 6.89 (2H, s, H–Ar), 8.90 (1H, s, Ar–OH).

ACKNOWLEDGMENT

We thank Candidate of Medical Sciences S. B. Akhmetova, Head of the Bioscreening Laboratory, AO SPC Fitokhimiya and Candidate of Medical Sciences R. B. Seidakhmetova, Scientist, for the biological tests.

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