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BRIEF COMMUNICATIONS

Synthesis of Glycoconjugates of Physiologically Active Compounds

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Abstract—Synthesis of *N*-glycosylamines derived from *D*-glucose and *D*-galactose (glycoconjugates of aniline derivatives and of *d*-pseudoephedrine and cytisine alkaloids) was studied with the aim to develop new pharmaceuticals.

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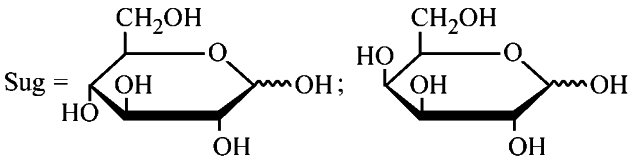
N-Glycosylamines find growing use for preparing natural glycopeptides, their analogs, and glycoconjugates used for various biological studies. *N*-Glycosylamines, the reaction products of carbohydrates with alkyl- and arylamines, attract attention of chemists, biochemists, and biologists. *N*-Glycosylamines can also be used for preparing new pharmaceuticals [2].

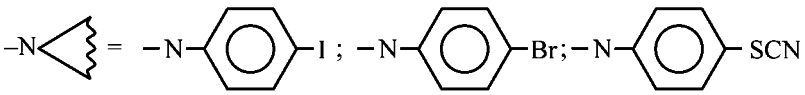
It is known than aniline is an antipyretic. However, it is too toxic to be used as a pharmaceutical. Introduction of various substituents into the benzene ring or the amino groups yields compounds with a wide range of pharmacological properties. Halogenation increases the lipophilicity of pharmaceuticals and facilitates their penetration through biomembranes [2]. For example, *p*-thiocyanatoaniline is a strong insecticide [3], and *p*-bromoaniline is a precursor for preparing Fenazepam, which is a tranquilizer with hypnotic and anticonvulsant effect [4].

N-Glycosylamines were prepared by condensation of *p*-substituted anilines and *D*-glucose (**1, 3, 5**) or *D*-galactose (**2, 4, 6**). Their biological activity was studied. The condensation was performed in an alcoholic solution on heating by the procedure described in [5]:

1–6



1, 3, 5 **2, 4, 6**



1, 2 **3, 4** **5, 6**

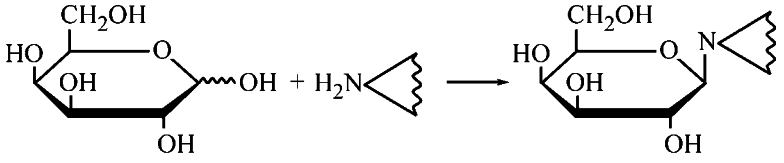
N-Glycosylamines **1**–**6** are white crystalline compounds readily soluble in water, ethanol, and DMF.

The presence of the band at 891 ± 7 cm^{-1} in the IR spectra of compounds **1**–**6** suggests the β-confor-

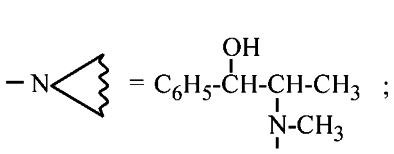
mation at the anomeric center. The bands in the range 1010–1090 cm^{-1} are assigned to the pyranose form of the glycoside residue. The bands in the range 2130–2160 cm^{-1} in the IR spectrum of compound **5** are due to the –S–C≡N group. The C–Hal and C–N stretching bands of compounds **1**–**4** are observed in the ranges 500–700 and 1280–1330 cm^{-1}, respectively.

New biologically active compounds can be prepared by functionalization of monosaccharide with phramacophore groups and physiologically active alkaloid fragments. In addition, it is known that introduction of carbohydrate residues into the structure of biologically active molecules increases their solubility in water, decreases their toxicity, and increases their target transport and penetrability into a cell.

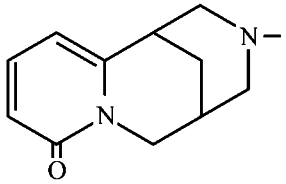
To prepare biologically active compounds and to increase the solubility and decrease the toxicity of alkaloid derivatives, we used commercial *D*-galactose as a substituent at the nitrogen atom. Condensation of *D*-galactose with an alkaloid, *d*-pseudoephedrine or cytisine, in a small volume of ethanol containing catalytic amounts of acetic acid yields *N*-galactosylamines **7** and **8**:



7, 8



7



8

Galactosylamines **7** and **8** are white crystalline compounds; their composition and structure were confirmed by elemental analysis and by ^1H NMR and IR spectroscopy. The absence of the band at 844 ± 8 cm^{-1} in the IR spectra of these compounds suggests their β-conformation. According to data of [6], absorption in the range 1120–1170 cm^{-1} is typical for cyclic sugars, and open-chain sugars do not absorb in this range. The strong band of the amide group (N–C=O) of the alkaloid at 1640–1650 cm^{-1} is present, along with bands of the carbohydrate fragment, in the IR spectrum of compound **8**.

The properties of compounds **1**–**8** are presented in the table.

The IR spectra of all the compounds presented in the table are characterized by strong stretching bands of the OH and NH groups in the range 3250–3400 cm^{-1}.

The ^1H NMR spectrum of compound **7** contains the signals of the protons of the alkaloid and carbohydrates moieties. The doublet of the CH_3–C group is observed at 1.14 ppm (J = 5.75 Hz), and the intense singlet of the *N*-methyl group, at 2.53 ppm. The signal of the methine proton of the CH–N group appears in the form of complex multiplet at 2.64–2.85 ppm. The doublet at 4.55 ppm is assigned to the methine proton of the CHO group (J = 3.5 Hz). The doublet of the anomeric proton H(1) of the carbohydrate residue is observed at 4.48 ppm (J = 9.2 Hz), which confirms the β-conformation of the reaction product.

EXPERIMENTAL

The ^1H NMR spectra of solutions in DMF–d_7 were recorded on a Varian XL-100 spectrometer operating at 100 MHz. The IR spectra of the samples in KBr pellets were recorded on an Avatar-320 spectrometer. Melting points were determined on a Boetius apparatus. The reaction course was monitored and the purity of the condensation products was determined by thin-layer chromatography on Sorbfil plates using isopropanol : benzene : ammonia = 10 : 5 : 2 system

Physicochemical constants and elemental analyses of the compounds

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
1	75.5	118–119	38.25	4.04	3.93	$C_{12}H_{16}INO_5$	37.81	4.21	3.67
2	65.2	181–182	38.19	4.01	3.99	$C_{12}H_{16}INO_5$	37.81	4.21	3.67
3	72.5	117–118	43.46	4.61	4.47	$C_{12}H_{16}BrNO_5$	43.13	4.83	4.19
4	64.9	119–120	43.50	4.56	4.42	$C_{12}H_{16}BrNO_5$	43.13	4.83	4.19
5	87.6	171–172	50.43	4.89	9.23	$C_{13}H_{16}N_2O_5S$	49.99	5.16	8.97
6	70.1	179–180	50.41	4.91	9.25	$C_{13}H_{16}N_2O_5S$	49.99	5.16	8.97
7	55.4	146–147	59.12	7.46	4.55	$C_{16}H_{25}NO_6$	58.70	7.70	4.28
8	71.6	188–189	58.41	6.59	8.29	$C_{17}H_{24}N_2O_6$	57.94	6.86	7.95

as the eluent. The chromatograms were developed with iodine vapor.

Glucosyl-*p*-iodoaniline (1). To a solution of glucose (0.02 mol) in ethanol (20 ml), *p*-iodoaniline (0.02 mol) was added. The mixture was stirred at 50–55°C for 4 h. Excess solvent was removed on a water bath. White crystals that precipitated on slight cooling were filtered off and washed with cold isopropanol. The product was recrystallized from an ethanol: isopropanol (5 : 1) mixture. Galactosyl-*p*-iodoaniline (**2**) was prepared similarly.

Glucosyl-*p*-bromoaniline (3). To a solution of glucose (0.02 mol) in ethanol (20 ml), *p*-bromoaniline (0.02 mol) was added with stirring. The mixture was stirred at 55–60°C for 5 h. Excess solvent was removed on a water bath. White crystals that precipitated on slight cooling were filtered off and washed with cold isopropanol. The product was recrystallized from ethanol. Galactosyl-*p*-bromoaniline was prepared similarly.

Glucosyl-*p*-thiocyanatoaniline (5). To a solution of glucose (0.01 mol) in ethanol (15 ml), *p*-thiocyanatoaniline (0.01 mol) was added. The mixture was stirred at 60–65°C for 6 h. Crystals that precipitated on cooling were filtered off and washed with cold isopropanol. The product was recrystallized from an ethanol : isopropanol (2 : 1) mixture. Galactosyl-*p*-thiocyanatoaniline (**6**) was prepared similarly.

Galactosyl-*d*-pseudoephedrine (7). To a solution of galactose (0.01 mol) in ethanol (15 ml), *d*-pseudoephedrine (0.01 mol) was added. The mixture was stirred at 55–60°C for 24 h in the presence of 1–2 drops of glacial acetic acid. White crystals that precipitated on cooling were washed with cold isopropanol and then with absolute ether. The product was recrystallized from isopropanol.

Galactosylcytisine (8). To a solution of galactose (0.01 mol) in ethanol (15 ml), cytisine (0.01 mol) was added. The mixture was stirred at 55–60°C for 24 h in the presence of 1–2 drops of glacial acetic acid. White crystals that precipitated on cooling were washed with absolute ether. The product was recrystallized from an isopropanol : benzene : ethanol (3 : 2 : 1) mixture.

CONCLUSIONS

(1) The carbohydrates were condensed with biologically active amines (*p*-iodoaniline, *p*-bromoaniline, and *p*-thiocyanatoaniline) and with alkaloids (*d*-pseudoephedrine and cytisine).

(2) The physicochemical constants, compositions, and structures of the condensation products were determined.

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