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Synthesis and Biological Activity of New N-aminoglycosides with a Pyrazole Fragment

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Abstract

New aminoglycosides obtained by the interaction of (1,3,5-trimethyl-1-H-pyrazol-4-yl)methanamine with *D*-glucose and *D*-galactose have been characterized. The structure of the class of monosaccharide derivatives studied and their probable stereochemical (anomeric) composition have been established using modern physicochemical research methods (^{1}HNMR and IR spectroscopy). A high growth promoting activity of N-aminoglycoside synthesized has been shown on the example of root formation of common bean.

Key words: N-aminoglycosides, glycosylation, monosaccharides

INTRODUCTION

Compounds containing heterocyclic fragments including nitrogen containing parts [1] in their structure are known to lead in the arsenal of drugs. A special place among them is occupied by pyrazole derivatives because of a good preparative availability [1–3]. At the same time, numerous drugs, in particular, pyrazole derivatives show some toxicity and have a number of side effects, which hinders their wide use in medical practice. The introduction into the structure of physiologically active compounds of carbohydrate fragments not only increases their water solubility but also decreases considerably their toxicity. Thanking to this, the method of glycosylation of a physiologically active compound (or its individual fragment) at the glycosidic centre can be recommended for the preparation of low-toxic drugs [4]. N-glycosylamines (N-glycosides) attract an attention of chemists, biochemists and biologists, since they are formed under biological conditions at the interaction of carbohydrates with alkyl- and arylamines. Pharmacologists consider N-glycosylamines as a potential source of new drugs [5].

We have earlier studied the reaction of glycosylation of not only physiologically active natural alkaloids, (–)-cytisine [6] and ***d??***-pseudoephedrine [7], but also many primary functionally substituted aliphatic unsaturated (vinyl ether of monoethanolamine) [8] and aromatic amines including halogen containing amines and pyridine [9], phenylenediamines, aminophenols [10]. The biological activity and possible anomeric effect of aminoglycosides [6–10], their spatial structure [11], and the influ-

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ence of the basicity of amines and their spatial factors [10] on the reaction have been defined.

RESULTS AND DISCUSSION

Aminoglycoside derivatives containing pyrazole fragments as aglycones have not been described in the literature. In this regard, we attempted to synthesize corresponding N-aminoglycosides on the ground of pyrazole and its amino-derivative, *viz.*, (1,3,5-trimethyl-1-H-pyrazole-4-yl)methanamine **1**.

The direct glycosylation of 3,5-dimethylpyrazole or 4-bromo-3,5-dimethylpyrazole did not lead to the preparation of N-aminoglycoside even at long boiling of alcoholic solutions of a substituted pyrazole and monosaccharide in the presence of catalytic amounts of acetic acid. This is associated with a quite low basicity of the amine fragment as a result of the conjugacy of the unshared pair of electrons of the nitrogen with the pyrazole ring.

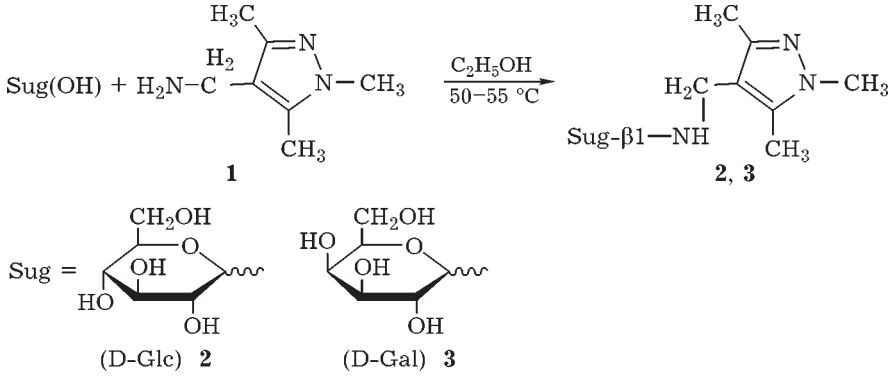
Unlike 3,5-dimethylpyrazole the condensation of monosaccharides of *D*-glucose and *D*-galactose with primary (1,3,5-1-H-pyrazole-4-yl)methanamine occurs under relatively mild conditions at the temperature of 50–55 °C in the alcoholic medium without the addition of an acidic catalyst, which is due to a high basicity of the initial amine.

In average, the reaction is complete in 3–4 h, at that, products of the condensation are isolated from the alcoholic medium as a small white crystalline precipitate. The duration of the reaction in case of *D*-galactose increases somewhat because of its low solubility in the alcoholic media. A slight excess of aminopyrazole **1** was used for a more complete progress of the reaction and increase of the yield.

N-aminoglycosides (Scheme 1) obtained on the ground of (1,3,5-trimethyl-1-H-pyrasazole-4-yl)methanamine are crystalline compounds that are well soluble in water, stable at normal conditions, they saponify partially at a long heating of their alcoholic solutions.

In IR spectra of compounds **2**, **3** obtained there is an absorption band in the field of 885 cm^{-1}, which indicates the β-conformation at the anomeric centre. The presence of several peaks in the field of 1010–1090 cm^{-1} indicates the pyranose form of the glycoside residue. Stretching vibrations of OH and NH groups appear as a broad intensive band in the field of 3295–3400 cm^{-1}. The analysis of IR spectra of compounds **2** and **3** has shown that they do not contain the bond C=N, therefore, they are not compounds of the type of Shiff bases.

At the analysis of the ^1H NMR spectrum of compound **2** it has been established that signals of protons of groups CH, CH_2 (H-2–H-6) of the carbohydrate part of the molecule appear in the field of 2.85–3.70 ppm as complex multiplets. The anomeric proton of the carbohydrate residue appears as a triplet (the interaction with the neighbouring proton of the pyranose ring and N–H proton amine group) at 4.38 ppm with constant of spin-spin interaction (CSSI) is equal to 5.71 Hz typical for the β-anomer. Protons of hydroxyl groups of the pyranose rings in the field of 4.30–4.80 ppm appear as a triplet and three doublets. Methyl groups of the pyrazole cycle appear as sharp singlets at 2.06



Scheme 1.

TABLE 1

Influence of growth regulators on the root formation of beans

Compounds	Concentration, mg/L	Length of the root zone, cm	Quantity, piece			Length of all roots, cm
			Growth point	Tubercle	Roots	
Water (control)	–	5.7	27	6	21	32.0
Akpinol						
(reference compound)	10	5.3	19	8	11	79.4
	50	4.7	16	5	11	62.6
	100	5.4	22	13	9	56.0
N-(1,3,5-1-H-pyrazolyl-	10	6.4	27	6	22	101.9
4-methyl)-β-*D*-gluco-	50	7.5	30	10	20	125.3
pyranosylamine	100	6.0	27	8	19	83.0

ppm (C–CH_3), 2.14 ppm (C–CH_3) and 3.6 ppm (N–CH_3), respectively. The integral curve corresponds to the total number of protons.

To determine the possible biological activity of the derivatives synthesized compound **2** was investigated for the growth promoting activity. Tests were conducted at the Kazakh Research Institute of Fruit Growing and Viticulture (Almaty) at the Laboratory of Agroecology and Mass Analysis.

Water-soluble compound, N-(1,3,5-trimethyl-1-H-pyrazolyl-4-methyl)-β-*D*-glucopyranosylamine **2**, has been used. Water served as the control, Akpinol (Table 1) was applied as a comparison standard. Tests were conducted on the shoots of common bean: concentrations of the rhizogenesis regulator were 10, 50 and 100 mg/L. The root formation was determined by the following parameters: the length of the root zone, amount of growth points, tubercle, roots, and the total length of all roots.

The analysis of the data showed that compound **2** studied at concentrations selected contributed to a better rooting of beans, in comparison with water and a comparison standard Akpinol. The greatest two-fold effect on root formation compared with Akpinol is observed when the concentration of compound **2**, equal to 50 mg/L. At concentrations of 10 and 100 mg/L the effect of compound **2** is minimal.

Therefore, new N-aminoglycosides prepared for the first time by the condensation of monosaccharides (*D*-glucose and *D*-galactose) with (1,3,5-trimethyl-1-H-pyrazol-4-yl)methanamine have been synthesized and characterized. The structure and composition of aminoglycosides synthesized have been confirmed by data of the elemental analysis, IR, ^{1}H NMR spectroscopy.

EXPERIMENTAL

IR spectra are recorded on a Nicolet AVATAR-320 FT-IR spectrometer in tablets with KBr. ^{1}H NMR spectra are registered using a Bruker DRX500 spectrometer with the frequency of 500 MHz in a solution of DMSO-d_6, relatively to the internal standard TMS (the measurement error is ±0.05 ppm). Melting points have been defined on the device Boetius (the measurement error is ±0.1 °C). The TLC analysis has been done on plates Sorbfil, the manifestation with iodine steam.

N-(1,3,5-trimethyl-1-H-pyrazolyl-4-methyl-β-*D*-glycopyranosylamine (2). A mixture of 1.8 g (0.01 mol) of *D*-glucose, 1.39 g (0.01 mmol) of (1,3,5-trimethyl-1-H-pyrazol-4-yl)methanamine **1** in 15 mL of absolute ethanol was stirred at 50–60 °C for 4 h. A white precipitate fallen out was filtered off, washed with acetonitrile. It was recrystallized from isopropyl alcohol. A portion of 2.5 g (83 %) of a white crystalline compound 2 with m. p. of 130–132 °C was obtained. Found, %: C 52.11, H 8.02, N 14.28. $C_{13}H_{23}N_3O_5$. Calculated, %: C 51.82, H 7.69, N 13.94. ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, *J*, Hz): 2.06 (3H, s, CH_3), 2.14 (3H, s, CH_3), 2.87 (1H, td, N–H, J = 3.74, 8.57), 2.97–3.11 (3H, m, H-4, H-2, H-3), 3.25–3.70 (3H, m, H-6, H-5), 3.55 (2H, m, CH_2), 3.59 (3H, s, N–CH_3), 4.38 (1H, t, $H_β$-1, J = 5.71), 4.31 (1H, t, OH-6, J = 5.22), 4.77 (1H, d, OH-2, J = 4.47), 4.79 (1H, d, OH-3, J = 3.88).

N-(1,3,5-trimethyl-1-H-pyrazolyl-4-methyl-β-*D*-galactopyranosylamine (3). A mixture of 0.9 g (0.005 mol) of *D*-galactose, 0.7 g (0.005 mol) of (1,3,5-trimethyl-1-H-pyrazol-4-yl)methanamine in 20 mL of ethanol was stirred at the temperature of 45–50 °C for 5 h. A white residue precipitated was filtered off, washed with acetonitrile. The yield is 1.09 g, m. p. is 165–167 °C. Found, %: C 52.01, H 7.34, N 14.37. $C_{13}H_{23}N_3O_5$. Calculated, %: C 51.82, H 7.69, N 13.94. ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, *J*, Hz): 2.05 (3H, s, CH_3), 2.14 (3H, s, CH_3), 3.16–3.75 (7H, m, N–H, H-2–H-6), 3.56 (2H, m, CH_2), 3.59 (3H, s, N–CH_3), 4.16 (1H, dd, $H_β$-1, J = 4.61, 11.7), 4.47 (1H, t, OH-6, J = 5.7), 4.53 (1H, d, OH-4, J = 5.25), 5.07 (1H, d, OH-2, J = 6.15), 5.13, (1H, d, OH-3, J = 4.62).

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