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SYNTHESIS OF *N*-AMINOGLYCOSIDES OF THE ALKALOID CYTISINE

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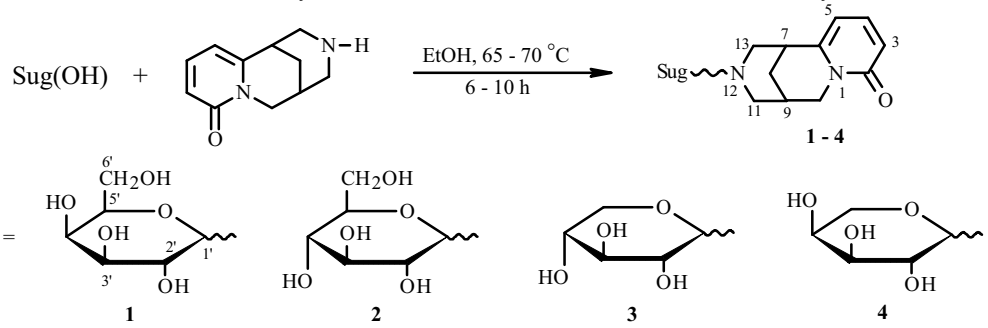
A series of new N*-aminoglycosides of the alkaloid cytisine based on industrially available monosaccharides D-glucose, D-galactose, D-xylose, and L-arabinose was synthesized and characterized. The optimal methods for condensing and isolating the products were found. The structures and position of cytisine in the glycosides were proved by PMR spectroscopy.*

Key words: cytisine, *N*-aminoglycosides, monosaccharides D-glucose, D-galactose, D-xylose, L-arabinose.

It is well-known that introducing carbohydrates into the structure of physiologically active compounds not only increases their water-solubility and decreases substantially their toxicity [1-3] but also sometimes enhances targeted transport of the drug to the required part of the living cell. Modified sugar derivatives are highly interesting scientifically and practically because many of them possess a broad spectrum of distinct biological activity [4] and are used in medicine, for example, as effective antiviral and anticancer preparations [5, 6]. One of the main and simplest methods of modifying monosaccharides is the synthesis of *N*-glycosylamines, which are attractive to chemists, biochemists, and biologists because they can occur under biological and plant conditions and are reaction products of carbohydrates and alkyl- and arylamines.

Herein 1-glycopyranosylamines **1-4** were prepared and characterized by condensation of D-galactose, D-glucose, D-xylose, and L-arabinose with the alkaloid cytisine in a small amount of ethanol with a catalytic amount of acetic acid.



Condensation and, more importantly, subsequent isolation of the products are significantly improved by using anhydrous ethanol because the synthesized glycosides are very soluble in water, even minute amounts of which hinder crystallization of the products. Using catalytic amounts of acetic acid in the reaction had a substantial effect on the rate of formation of the aminoglycosides but noticeably decreased the yields and isolation of the final products.

The resulting *N*-cytisinoglycosides could be very promising replacements for drugs based on cytisine that are already in use (respiratory analeptic "cytiton" and anti-smoking agent "lobesil") because they will surely be less toxic and have a longer duration of action because of their gradual hydrolysis in the organism.

The structures of **1-4** were determined using IR and PMR spectroscopy.

The conformation of the cytisine aglycon on the glycoside C1 atom could be established from the position of the anomeric proton in the PMR spectrum. It is known [1] that the α-anomer typically lies at weaker field in the PMR spectrum by about 4.5-5.5 ppm and has a small SSCC (2.5-5.0 Hz). The *trans*-axial proton of β-anomers occurs at stronger field with a SSCC of about 6.0-10.0 Hz.

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PMR spectra of the synthesized *N*-cytisinoglycosides showed that glycosides **1**-**4** occurred as a 1:1 mixture of the α- and β-anomers despite the bulky cytisine group and the stability of the β-anomers in DMSO solution. The integrated intensities and specific location of doublets for the anomeric proton, for example, at 4.08 ppm for **1** with H1-β SSCC J = 8.8 Hz and at 4.25 ppm with H1-α SSCC J = 4.5 Hz, were consistent with this.

EXPERIMENTAL

IR spectra in KBr disks were recorded on an Avitar-320 spectrometer; PMR spectra in DMSO-d_6, on a Bruker DRX 500 spectrometer at 500 MHz with TMS internal standard. TLC was performed on Sorbfil plates using isopropanol:benzene:ammonia (10:5:2) with development by iodine vapor.

***N*-Cytisino-β-D-galactopyranosylamine (1).** Cytisine (1.90 g, 0.01 mol) was added to a stirred solution of D-galactose (1.80 g, 0.01 mol) in anhydrous ethanol (15 mL) and stirred for 8 h at 65-70°C. Cooling (-10°C) precipitated white crystals that were filtered off and washed with acetone. Yield 2.62 g (74%), mp 188-189°C (isopropanol:ethanol), $C_{17}H_{24}N_2O_6$. IR spectrum (KBr, ν, cm^{-1}): 3410 (OH), 1642 (N–C=O). PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.75 (2H, dd, $J_{8,7}$ = 12.2, $J_{8,9}$ = 12.5, H-8), 2.40 (1H, br.d, H-9), 2.65 (2H, dd, $J_{11a,11e}$ = 10.2, $J_{11a,9}$ = 9.4, H-11), 2.80 (2H, m, H-2′), 3.02 (2H, m, H-13), 3.09 (1H, br.d, H-7), 3.20 (1H, m, H-4′), 3.39 (1H, m, H-5′), 3.48 (2H, m, H-6′), 3.72 (1H, m, H-3′), 3.80 (1H, m, H-10a), 3.85 (1H, d, $J_{10a,10e}$ = 15.5, H-10e), 4.08 (1H, d, $J_{1',2'}$ = 8.8, H-1′β), 4.25 (1H, d, $J_{1',2'}$ = 4.5, H-1′α), 6.06 (1H, d, $J_{5,4}$ = 6.8, H-5), 6.18 (1H, d, $J_{3,4}$ = 9.0, H-3), 7.30 (1H, dd, $J_{4,5}$ = 6.8, $J_{4,3}$ = 9.0, H-4).

***N*-Cytisino-β-D-glucopyranosylamine (2)** was prepared analogously to **1** but in 5 h. Compound **2** was isolated and crystallized after drying for 3 d in a desiccator over P_2O_5. The solid was crystalized from CH_3CN. Yield 90%, mp 183-184°C, $C_{17}H_{24}N_2O_6$. IR spectrum (KBr, ν, cm^{-1}): 3406 (OH), 1648 (N–C=O). PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.75 (2H, dd, $J_{8,7}$ = 12.4, $J_{8,9}$ = 12.5, H-8), 2.36 (1H, br.s, H-9), 2.65 (2H, dd, $J_{11a,11e}$ = 10.8, $J_{11a,9}$ = 10.4, H-11), 2.95 (2H, m, H-4′, H-2′), 3.02 (2H, m H-13), 3.06 (1H, m, H-7), 3.14 (2H, m, H-6′), 3.38 (1H, m, H-5′), 3.51 (1H, d, $J_{1',2'}$ = 9.0, H-1′β), 3.62 (1H, dd, $J_{3',2'}$ = 6.0, H-3′), 3.72 (1H, dd, $J_{10a,9}$ = 7.2, H-10a), 3.85 (1H, d, $J_{10a,10e}$ = 15.0, H-10e), 3.98 (1H, d, $J_{1',2'}$ = 5.1, H-1′α), 6.07 (1H, d, $J_{5,4}$ = 6.8, H-5), 6.18 (1H, d, $J_{3,4}$ = 9.0, H-3), 7.30 (1H, dd, $J_{4,5}$ = 6.8, $J_{4,5}$ = 9.0, H-4).

***N*-Cytisino-β-D-xylopyranosylamine (3)** was prepared analogously to **2**. Yield 77%, mp 162-164°C, $C_{16}H_{22}N_2O_5$. IR spectrum (KBr, ν, cm^{-1}): 3390 (OH), 1642 (N–C=O). PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.73 (2H, dd, $J_{8,7}$ = 12.5, $J_{8,9}$ = 12.6, H-8), 2.35 (1H, br.s, H-9), 2.55 (2H, dd, $J_{11a,11e}$ = 10.9, $J_{11a,9}$ = 10.4, H-11), 2.72 (1H, br.d, H-7), 2.89 (1H, t, $J_{2,3}$ = 10.9, H-2′), 3.02 (3H, m, H-4′, H-13), 3.16 (2H, m, H-5′), 3.46 (1H, d, $J_{1',2'}$ = 9.1, H-1′β), 3.64 (1H, dd, $J_{3',2'}$ = 5.5, H-3′), 3.71 (1H, dd, $J_{10a,9}$ = 6.9, H-10a), 3.84 (1H, d, $J_{10a,10e}$ = 15.3, H-10e), 3.93 (1H, br.s, H-1′α), 6.04 (1H, d, $J_{5,4}$ = 6.8, H-5), 6.17 (1H, d, $J_{3,4}$ = 8.9, H-3), 7.30 (1H, dd, $J_{4,5}$ = 6.8, $J_{4,3}$ = 8.9, H-4).

***N*-Cytisino-β-L-arabinopyranosylamine (4)** was prepared analogously to **2**. Yield 62%, mp 175-177°C, $C_{16}H_{22}N_2O_5$. IR spectrum (KBr, ν, cm^{-1}): 3390 (OH), 1646 (N–C=O). PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.75 (2H, dd, $J_{8,7}$ = 12.3, $J_{8,9}$ = 12.5, H-8), 2.40 (1H, br.d, H-9), 2.66 (2H, dd, $J_{11a,11e}$ = 10.5, $J_{11a,9}$ = 9.8, H-11), 2.80 (1H, t, $J_{2,3}$ = 9.7, H-2′), 3.04 (2H, m, H-13), 3.21 (1H, m, H-7), 3.30 (1H, m, H-4′), 3.50 (2H, m, H-5′), 3.63 (1H, d, $J_{1',2'}$ = 7.2, H-1′β), 3.73 (1H, m, H-3′), 3.81 (1H, dd, $J_{10a,9}$ = 6.4, H-10a), 3.85 (1H, d, $J_{10a,10e}$ = 15.2, H-10e), 4.05 (1H, d, $J_{1',2'}$ = 5.6, H-1′α), 6.07 (1H, d, $J_{5,4}$ = 6.7, H-5), 6.18 (1H, d, $J_{3,4}$ = 8.5, H-3), 7.31 (1H, dd, $J_{4,5}$ = 6.7, $J_{4,3}$ = 8.5, H-4).

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