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Organic Chemistry

N-Nitrosation of N-Xylosylamines and Study of their Potential Biological Activity

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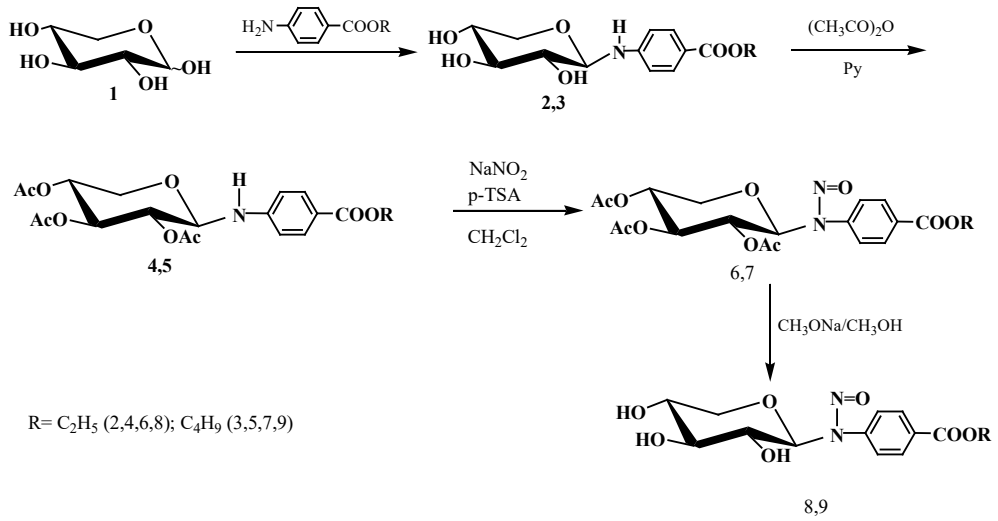
Nitroso compounds, as nitric oxide generators, play a prominent role in organic chemistry and are actively assayed in search for biologically active substances. The synthesis and study of new types of nitroso compounds represent a promising and rational approach to discovering new potential biologically active compounds. By condensation of D-xylose with anesthesin and butamben in ethanol, the corresponding N-β-xylosylamines were synthesized. Through acetylation and subsequent nitrosation of N-β-xylosylamines with sodium nitrite in the presence of p-toluenesulfonic acid in dichloromethane, at room temperature a new type of nitroso group containing N-β-D-xylosylamines was obtained. With the help of computer program PASS Onlain is based on the analysis of structure activity-relationships wide range of possible biological activity and toxic/side effects for synthesized N-xylosylamines were determined. *© 2024 Bull. Georg. Natl. Acad. Sci.*

nitric oxide, N-β-xylosylamines, biologically activity, quantum-chemical calculations

Nitric oxide (NO) is a pivotal biological mediator and intracellular regulator of metabolism in organisms, participating in various physiological and pathophysiological processes. Its unique nature and mechanism of action involve regulation of blood vessel tone, inhibition of platelet aggregation and adhesion to vascular walls, modulation of respiratory, gastrointestinal, and urinary functions, crucial roles in immune regulation, and defense against bacterial damage. Nitroso compounds, acting as nitric oxide generators, play an important role in organic chemistry and are actively researched for their potential as biologically active substances.

Literature data [1-3] indicate that the synthesis and study of nitroso compounds is a promising strategy for discovering potential biologically active compounds. This necessitates a more in-depth and thorough study of these compounds. Therefore, the aim of our work was to synthesize N-nitroso derivatives of N-β-Anesthesin- and N-β-butamben-D-xylosylamines and to assess their potential biological activity.

β-anesthesin- and N-β-butamben-D-xylosylamines (2,3) were synthesized by condensation of D-xylose (1) with anesthesin and Butamben in ethanol using glacial acetic acid as a catalyst. By acetylation



Scheme. Synthesis and N-Nitrosation of N-β-Anesthesin- and N-β-Butamben-Xylosylamines.

and father N-nitrozation of synthesized compounds 2 and 3 corresponding N-β-anesthesin-2,3,4-tri-O-acetyl-D-xylosylamine (4) and N-β-butamben-2,3,4-tri-O-acetyl-D-xylosylamine (5) wera obtained. Final N-nitroso-N-β-anesthesin- and N-nitroso-N-β-Butamben-D-xylosylamines (8,9) were obtained from N-nitroso acetylated xylosylamines (6,7) by de-acetylation using the Zemplen procedure in which sodium methoxide was used in a catalytic amount in methanolic solution according to the Scheme.

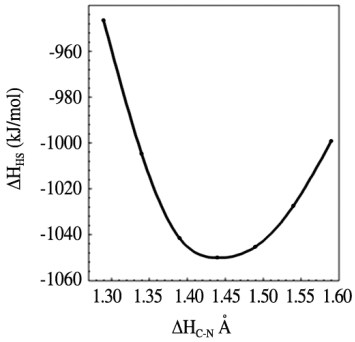
Quantum-chemical calculations. With the purpose of theoretical substantiation of the direction of the reactions of synthesis of some derivatives of sugars containing nitroso (N=O) groups, quantum-chemical calculations were carried out using the semi-empirical AM1 method. The calculations were performed using CS MOPAC (Chem 3D Ultra-version 8.03). Prior to each calculation by the AM1 (Austin Model 1) method, the compound was optimized – energy minimization, using both the molecular mechanics (MM) method and the quantum chemical method. It is established that the reactions proceed with the formation of 1,2-trans-glycosides. In the framework of the quasi-ANS-matrices method, a mathematical and chemical study of the synthesized compounds was carried out. It turned out that the correlation is satisfactory.

The AM1 method revealed that reactions forming 1,2-trans-glycosides were obtained. Heats of formation were analyzed in relation to C-N bond lengths, demonstrating stability up to 1.60 Å. Graphs depicting the heats of formation of glycosylamines (ΔH) as a function of bond length (RC-N) are presented in Figs. 1 and 2.

Probable biological activity of synthesized substances. Study of the spectrum activity. The spectrum of potential biological activity of the synthesized substances was investigated using the computer program PASS Online [4-7]. This investigation includes the analysis of their biological activity, encompassing pharmacological actions, mechanisms of action, toxicity and side effects.

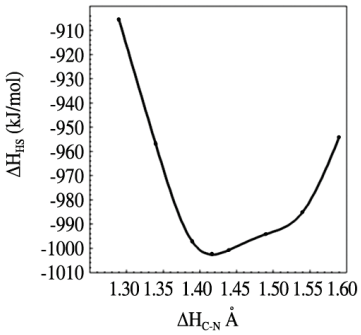
Materials and Methods

Reagents. Analytical grade D-xylose, 4-aminobenzoic acid ethyl ester, butamben, pyridine, acetic anhydride, dichloromethane, sodium nitrite, and p-toluenesulfonic acid were used. The purity of products and Rf values were determined on Silufol UV-254 using solvent system benzene: ethanol (9:1). IR spectra were recorded using a "NICOLETis5" spectrometer. C^{13}NMR spectra were recorded on Ascend^{TM}400 in $CDCI_3$. We used only freshly prepared solvents for the experiment.



RC-N	ΔH (kJ/mol)
1.29	-946.97357
1.34	-1005.11707
1.39	-1041.97204
1.44	**-1050.5264**
1.49	-1045.68673
1.54	-1027.8425
1.59	-999.64737

Fig. 1. Heat of substance 2 (ΔH). Dependence on RC-N bond length.



RC-N	ΔH (kJ/mol)
1.29	-905.23382
1.34	-956.66936
1.39	-997.0221
1.44	**-1000.42696**
1.49	-993.88204
1.54	-984.86349
1.59	-953.91748

Fig. 2. Heat of substance formation 4 (ΔH). Dependence on RC-N bond length.

Synthesis. N-β-anesthesin-2,3,4-tri-O-acetyl-D-xylosylamine (4). Dissolved 0.005 mol of 3 ml in pyridine, added acetic anhydride, and stirred at 0°C. After filtration and drying, yield (91%), mp: 90°C, R_f 0,68.

IR spectrum (ν, cm^{-1}) 3368-3400 (NH); 2959-2873 (CH_3); 1740 (C=O);1600-1690 (C=C_arom.); 1180 (C1-N); 842-770 (pyranose ring).

C^{13} NMR spectrum (δ, ppm), $CDCI_3$: 96.76 (C-1); 75.02 (C-2); 78.57 (C-3); 73.20 (C-4); 77.45 (C-5); 58.72 (C-6). Aromatic nucleus: 151.48 (C-1); 113.45 (C-2); 133.22 (C-3); 118.70 (C-4); 131.20 (C-5); 112.33 (C-6); 165.5-170.0 (C=O); 62.5-65.00 (CH_2 of ethyl group).

β-Butamben-2,3,4,6-Tetra-O-acetyl-D-xylosylamine (5) was prepared analogously. Yield (60%); mp: 52-55°C. R_f 0.51.

IR spectrum (ν, cm^{-1}) 3370-3400 (NH); 2959-2873 (CH_3); 1738 (C=O);1607-1690 (C=C_arom.); 1180 (C1-N); 842-770 (pyranose ring).

C ^{13} NMR spectrum (δ, ppm), $CDCI_3$: 93.7 (C-1); 78.2 (C-2); 77.54 (C-3); 75.0 (C-4); 65.6 (C-5); 62.5 (C-6). Aromatic nucleus: 149.40(C-1); 117.50 (C-2); 128.00 (C-3); 116.80 (C-4); 132.20 (C-5); 110.30 (C-6); 166.0-169.5 (C=O); The acetyl group (C=O) appears at about 172.5 and the (CH_3) group appears at about 22.3; 32.3-35.00 (Butamben Group CH_2 group).

β-N-Nitroso-anesthesin-tri-O-acetyl-D-xylosylamine (6). Reacted 0.0018 mol of 2 with sodium nitrite and p-toluenesulfonic acid in dichloromethane. The product after filtration and concentration, yielded a yellow substance. Yield: (77%), mp:127-129°C, R_f 0.71 IR spectrum (ν, cm^{-1}): 2978 (CH_3); 1367-1416 (CH); 1584 (C=C_arom.); 1735-1750 (C=O); 1496 (N-N=O);

C ^{13} NMR spectrum (δ, ppm), $CDCI_3$**:** 97.8 (C-1); 77.35 (C-2); 76.7 (C-3); 69..20 (C-4); 75.4 (C-5); 60.72 (C-6); Aromatic Nucleus: 150.48 (C-1); 113.45 (C-2); 130.00 (C-3); 117.65 (C-4); 132.20

(C-5); 112.33 (C-6); N-nitroso Group: 147.00-152.00; 165.5-170.0 (C=O); 62,5-65.00 (CH_2);

N-Nitroso-N-β-Butamben-2,3,4-tri-O-acety-D-xylosylamine (7) was prepared analogously. Yield (89%). mp: 85-87°C. R_f 0,64.

IR spectrum (ν, cm^{-1}): 2978 (CH_3); 1367-1416 (CH); 1584 (C=C_arom.); 1700-1750 (C=O); 1496 (N-N=O);

C^{13} NMR spectrum (δ, ppm), $CDCI_3$: 97.76 (C-1); 77.02 (C-2); 76.57 (C-3); 70.25 (C-4); 76.45 (C-5); 59.72 (C-6); Aromatic Nucleus: **1**51.00 (C-1); 113.45 (C-2); 131.22 (C-3); 118.70 (C-4); 131.20 (C-5); 112.33 (C-6) N-nitroso Group: 146.00-151.00; 165.5-170.0 (C=O); 30-35 (CH_2).

ორგანული ქიმია

N-ქსილოზილამინების N-ნიტროზირება და მათი პოტენციური ბიოლოგიური აქტივობის შესწავლა

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** აკადემიის წევრი, ივანე ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, თბილისი, საქართველო*

*** ივანე ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, ქიმიის დეპარტამენტი, ზუსტ და საბუნებისმეტყველო მეცნიერებათა ფაკულტეტი, თბილისი, საქართველო*

ნიტროზო ნაერთები, როგორც აზოტის ოქსიდის დონორი ნაერთები, მნიშვნელოვან როლს ასრულებს ორგანულ ქიმიაში და აქტიურად განიხილება ბიოლოგიურად აქტიური ნივთიერებების ძიებაში. ახალი ტიპის ნიტროზო ნაერთების სინთეზი და კვლევა პერსპექტიული და რაციონალური მიდგომაა ახალი, პოტენციური, ბიოლოგიურად აქტიური ნაერთების გამოსავლენად. D-ქსილოზის ანესთეზინსა და ბუტამბენთან კონდენსაციით ეთანოლის არეში სინთეზირდა შესაბამისი N-β-ქსილოზილამინები, რომელთა აცეტილირებითა და შემდგომი ნიტროზირებით, ნატრიუმის ნიტრიტითა და P-ტოლუოლ სულფონილის მჟავას დამატებით დიქლორმეთანის არეში, ოთახის ტემპერატურაზე, მივიღეთ N-ქსილოზილამინების ახალი ტიპის ნიტროზოწარმოებულები. კომპიუტერული პროგრამის Pass Online გამოყენებით, სინთეზირებული N–ქსილოზილამინებისთვის დადგინდა შესაძლო ბიოლოგიური აქტივობისა და ტოქსიკური/გვერდითი ეფექტების ფართო სპექტრი.

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