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LETTERS TO THE EDITOR

Synthesis and Biological Activity of *N*-Methylglycosamine Derivatives of Thiourea

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The development and introduction into the medical practice of the new highly effective drugs, antibacterial and antiviral especially, is necessary not only due to an appreciable environment degradation, causing a progressive growth of variety of diseases, but also to the presence of the known medicinal resistance of many pathogenic bacteria and viruses toward the drugs used for treatment [1, 2].

With respect to probable formation of the new effective and low-toxic drugs the modification of natural carbohydrates and their derivatives is of great interest. Carbohydrate residues incorporated into the structure of biologically active compounds lead to a sharp decrease in their toxicity, increase the solubility of drugs in water, improve the purposeful transport to certain organism cells, and elongate their lifetime [3, 4].

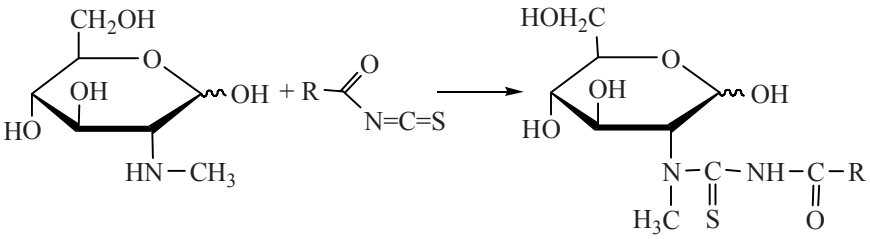
At present a variety of monosaccharide derivatives already is widely used in medicine as effective antibacterial, antiviral, and anticancer drugs [5–8].

Among the monosaccharide *N*-glycosylamines, *N*-methylglycosamine involving a free secondary amino group at the carbohydrate atom C^2 is a very promising synthon for further transformations. Thus, compounds were synthesized [9] possessing a high immunostimulating activity, starting from *N*-methylglycolsamine and 6-chloropurine, 8-bromohypoxanthine, and 8-bromoinosine.

In this work we carried out incorporation of thiourea fragment into the structure of *N*-methylglycosamine. Thioureal derivatives possess also a variety of valuable and useful properties and are widely used not only in organic synthesis, but in industry, agriculture, and also inmedicine [6, 10, 11].

Isothiocyanate method is one of the convenient preparative ways to include thiourea fragments into aromatic, cyclic, and heterocyclic amines. For this purpose we carried out the reaction of benzoyl isothiocyanates with *N*-methylglycosamine. Synthesis of initial benzoyl isothiocyanates was performed *in situ* by heating the corresponding acid chloride with potassium thiocyanate in acetone.

The following reaction of *N*-methylglycosamine with benzoyl isothiocyanates gives rise to N-substituted glycosylthioureas **I–III**.



I–III

I, R = C_6H_5; **II**, 4-$CH_3C_6H_4$; **III**, 4-BrC_6H_4.

Reaction was carried out in alcohol medium at the temperature from 25 to 50ºC. Compounds **I–III** obtained are white crystalline substances, well soluble in water and alcohol. Amines addition to isothiocyanates proceeds by the well known mechanism.

Composition, structure and individuality of compounds synthesized **I–III** were proved by elemental analysis, IR and ^{1}H NMR spectroscopic data, and TLC.

In the IR spectra of these compounds broad strong absorption bandswere observed in the range of 3470–3270 cm^{-1} originating from stretching vibrations of OH and NH groups and from stretching vibrations of aromatic CH-fragments. The absorption bands in the ranges of 1540–1520 and 1670–1660 cm^{-1} belong to thiocarbonyl (C=S) and carbonyl (C=O) groups respectively.

The presence of the protons of both carbohydrate fragment and aromatic ring was established by the analysis of the ^{1}H NMR spectrum of compound **II** (DMSO-d_6, 500 MHz). Signals of carbohydrate CH- and CH_2-groups protons are observed at 3.40–4.00 ppm as a complex multiplet. Doublets and a triplet in the region of 4.40–4.60 ppm belong to the protons of pyranose ring hydroxy groups. A narrow singlet at 2.37 ppm is characteristic of methyl protons of aromatic ring. Singlet signal of N–CH_3 group protons is registered at 3.37 ppm. Aromatic protons give two doublets at 7.78 and 7.30 ppm (*J* 8.1 Hz). Analysis of the ^{1}H NMR spectrum of **II** showed also that anomeric proton H^1 of carbohydrate residue appears as two doublets at 5.55 (*J* 4.65 Hz) and 4.84 ppm (*J* 5.00 Hz) characteristic for the mixture (1:1 ratio) of α- and β-anomers respectively.

Biological screening of compound **III** on antibacterial and antifungal activities showed that it possesses moderately expressed broad spectrum activity relative to gram-positive strains *(Staphylococcus aureus, Bacillus subtilis)* as well as to gram-negative strains *(Escherichia coli)* in comparison with references used, gentamycin (for bacteria) and nystatin (for fungi).

Thus, the corresponding N-substituted glycosylcarbonothioyl benzamides **I–III** were obtained starting from *N*-methylglycosamine; among them substance **III** possess moderately expressed antibacterial and antifungal activities.

EXPERIMENTAL

The ^{1}H NMR spectra were registered on a Bruker DRX500 spectrometer (500 MHz) in DMSO-d_6 relative to internal TMS. The IR spectra were recorded on an AVATAR-320 spectrometer from KBr. The reaction progress was monitored with TLC on Sorbfil plates, using 2-propanol–benzene–25% ammonia (10:5:2) system as an eluent.

(*N*-Methylglycosamino-1-carbonothioyl)benzamide (I). To a solution of 1.4 g (10 mmol) of benzoyl chloride in 10 ml of acetone was added under stirring 0.97 g (10 mmol) of potassium thiocyanate. The reaction mixture was refluxed for 2 h under stirring and filtered off through a paper filter into a suspension of 1.89 g (9.8 mmol) of *N*-methylglycosamine in 10 ml of 2-propanol. This mixture was heated under stirring at 40–50ºC for 5 h to full dissolution of *N*-methylglycosamine and kept for 24 h at room temperature. The solvent excess was distilled off. The oily residue was dried over P_2O_5 and crystallized from acetonitrile–hexane mixture. Yield 2.13 g (81%), white crystalline substance, mp 140–143ºC (2-propanol). Found, %: C 50.87; H 6.03; N 8.12. $C_{15}H_{20}N_2O_6S$. Calculated, %: C 50.55; H 5.66; N 7.86. ^{1}H NMR spectrum, δ, ppm: 3.37 s (3H, N–CH_3), 3.40–3.95 m (6H, H^2–H^6), 4.88 d (1H, $H_β$-1, *J* 5.25 Hz), 5.56 d (1H, $H_α$-1, *J* 4.6 Hz), 7.35–7.62 m (5H, H–Ar).

(*N*-Methylglycosamino-1-carbonothioyl)-4-methylbenzamide (II) was prepared similarly from 1.54 g (10 mmol) of 4-methylbenzoyl chloride, 0.97 g (10 mmol) of potassium thiocyanate and 1.89 g (9.8 mmol) of *N*-methylglycosamine. Yield 1.56 g (43%), mp 108–110ºC (2-propanol). Found, %: C 52.11; H 6.38; N 7.87. $C_{16}H_{22}N_2O_6S$. Calculated, %: C 51.88; H 5.99; N 7.56. ^{1}H NMR spectrum, δ, ppm: 2.37 s (3H, CH_3–Ar), 3.37 s (3H, N–CH_3), 3.40–4.00 m (6H, H^2–H^6), 4.84 d (1H, $H_β$-1, *J* 5.0 Hz), 5.55 d (1H, $H_α$-1, *J* 4.6 Hz), 7.30 and 7.78 d. d (4H, H–Ar, *J* 8.1 Hz).

(*N*-Methylglycosamino-1-carbonothioyl)-4-bromobenzamide (III) was prepared similarly from 2.20 g (10 mmol) of 4-bromobenzoyl chloride, 0.97 g (10 mmol) of potassium thiocyanate and 1.89 g (9.8 mmol) of *N*-methylglycosamine. Yield 2.46 g (57%), mp 130–131ºC (2-propanol). Found, %: C 41.82; H 4.63; N 6.75. $C_{15}H_{19}BrN_2O_6S$. Calculated, %: C 41.39; H 4.40; N 6.44. ^{1}H NMR spectrum, δ, ppm: 3.31 s (3H, N–CH_3), 3.42–3.90 m (6H, H^2–H^6), 4.93 d (1H, $H_β$-1, *J* 6.3 Hz), 7.80 and 7.86 d. d (4H, H–Ar, *J* 8.31 Hz).

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