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SYNTHESIS OF β-GLYCOSIDES OF N-ACETYLGLUCOSAMINE IN THE PRESENCE OF HgI_2

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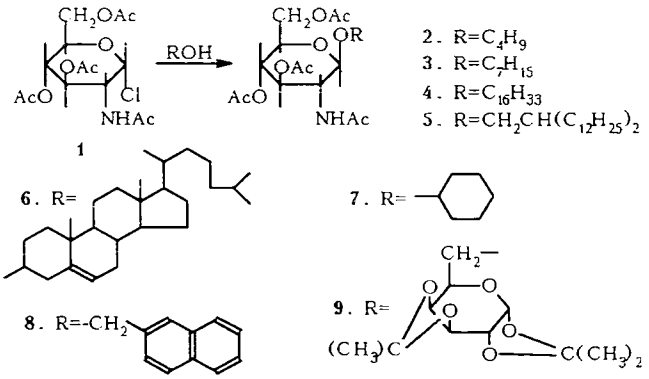
The use of HgI_2 as catalyst in the synthesis of trans-*glycosides of N-acetylglucosamine is described. Using this catalyst, β-glycosides of N-acetylglucosamine with aglycons of different structures and lyophilicities have been synthesized. The possibility of performing oligosaccharide synthesis has been demonstrated.*

The use of $HgBr_2$ as catalyst for glycosylation reactions in the series both of neutral sugars [1] and of aminosugars is known. In the second case, either azidosugars or phthalimide derivatives of aminosugars are usually used as glycosyl donors. At the same time, HgI_2 has been used only for the *trans*-glycosylation of *D*-mannose derivatives [3].

The key stage in the synthesis of glycosides of N-acetylmuramoyldipeptide is the preparation of glycosides of N-acetylglucosamine. We have established that HgI_2 is a highly effective catalyst for the synthesis of *trans*-glycosides of N-acetylglucosamine. This approach permits the use of the simplest and most accessible glycosyl donor — 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-*D*-glucopyranosyl chloride (**1**) [4]. Its reaction with equimolar amounts of primary aliphatic alcohols takes place in 24-36 h at room temperature. The yields of butyl, heptyl and heptadecyl β-glycosides (**2-4**) have amounted to 56-80%, which are higher than by the oxazoline method and are comparable with those obtained by the use as catalysts of mercury(II) bromide and cyanide (Table 1). During the reaction, only the *trans*-glycosides are formed. The structures of glycosides (**2-4**) were confirmed by comparison with compounds obtained previously [5, 6] and by their PMR spectra (Table 2). Thus, the presence of one-proton doublets with a CS of 4.68 ppm and a splitting constant of 8.5 Hz in each case witnessed the β-configuration of the anomeric center. We must mention the nonequivalence of the protons of the α-methylene groups of the aglycons, identified in the form of two doublets of triplets in the 3.40-3.86 ppm region.



The reactions with other lipophilic alcohols took place analogously: 2-dodecyltetradecan-1-ol (yield of glycoside (**5**) 72%) and 2-naphthylmethanol (yield of glycoside (**8**) 65%). The IR spectrum and constants of compound (**5**) agreed with those of the glycoside synthesized previously [7]. The structure of glycoside (**8**) was shown by PMR spectroscopy. The signals of

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TABLE 1. Yields of Glycosides in Glycosylation Reactions of Compound (**1**), %

	2	3	4	5	6*	7	8	9
HgI_2	80	56	61	72	57	71	65	56
$Hg(Cn)_2$, $HgBr_2$	82	82	63		35			
$Hg(OAc)_2$, $HgBr_2$	59	49	59					
HgO, $HgBr_2$	61	62						

*Yields are given for the deacetylated derivative.

TABLE 2. PMR Spectra of Compounds (**2-5**), (**7**), and (**8**) (solutions in C^2HCl_3, J, Hz)

	2	3	4	5	7	8
NAS	1.95 s	1.95 s	1.88 s	1.93 s	1.83 s	1.81 s
OAc	2.03 s 2.04 s, 2.08 s	2.02 s, 2.03 s, 2.08 s	1.96 s, 1.97 s, 2.02 s	2.03 s, 2.04 s, 2.09 s	1.91 s, 1.92 s, 1.97 s	1.97 s, 2.01 s (6H)
H-1	4.68 d	4.69 d	4.62 d	4.63 d	4.76 d	4.57 d
$J_{1,2}$	8.5	8.5	8.5	8.5	8.4	8.0
H-2	3.82 ddd	3.80 ddd	3.75 ddd	3.85 ddd	3.56 ddd	3.91 ddd
$J_{2,3}$	10.5	10.5	10.3	10.3	10.6	10.4
H-3	5.31 dd	5.32 dd	5.25 dd	5.29 dd	5.29 dd	5.08 dd
$J_{3,4}$	9.5	9.5	9.6	9.5	9.3	9.2
H-4	5.06 dd	5.07 dd	5.00 dd	5.08 dd	4.93 dd	5.00 dd
$J_{4,5}$	9.5	9.5	9.6	9.5	9.5	9.2
H-5	3.70 ddd	3.69 ddd	3.64 m	3.68 m	3.59 ddd	3.57 ddd
$J_{5,6}$	4.5, 2.5	4.5, 2.5	4.8, 2.2	4.5, 2.5	5.2, 2.6	4.8, 2.5
H-6	4.13 dd, 4.26 dd	4.12 dd, 4.27 dd	4.05 dd, 4.21 dd	4.14 dd, 4.27 dd	4.00 dd, 4.16 dd	4.08 dd, 4.20 dd
$J_{6a,6b}$	12.0	12.0	12.5	12.0	12.2	12.0
NH	5.59 d	5.55 d	5.47 d	5.46 d	5.48 d	5.34 d
$J_{2,NH}$	8.5	8.8	8.8	8.5	8.4	8.8
C_1-OCH_2	3.48 dt, 3.86 dt	3.46 dt, 3.86 dt	3.40 dt, 3.79 dt	3.29 dd, 3.79 dd		4.66 d, 4.95 d
$(CH_2)_n$	1.34 m, 1.55 m	1.25 m, 1.55 m	1.20 m, 1.50 m	1.24 m, 1.60 m	1.15 m, 1.61 m	
CH_3CH_2	0.90 t	0.87 t	0.81 t	0.89 t		
Working frequency, MHz	500	200	200	500	200	200

the protons of the glycoside residue, close to the signals of the other glycosides (see Table 2), and of the aglycon were interpreted: two doublets of an *AB* system of methylene protons with CSs of 4.66 and 4.95 ppm and multiplets of aromatic protons with CSs of 7.35 and 7.71 ppm. The doublet of the anomeric proton with a CS of 4.57 ppm and a splitting constant of 8.0 Hz showed the formation of a β-glycosidic bond.

When less reactive secondary alcohols — cholesterol and cyclohexanol — were used as the aglycons the reaction took place more slowly: 7 days in the first case and 4 days in the second. The yields of glycosides (**6**) and (**7**) were 57 and 71%, respectively, which were considerably higher than on the use of a catalytic system of mercury(II) cyanide and bromide in the synthesis of compound (**6**). The PMR spectrum of the cyclohexyl β-glycoside (**7**) corresponded to its structure. The methylene protons of the cyclohexyl residue were observed in the form of two multiplets with CSs of 1.15 and 1.61 ppm. The β-configuration of the glycosidic bond was shown by the presence in the spectrum of a doublet of the glycosidic proton with a CS of 4.75 ppm and a SSCC of 8.4 Hz. The assignment of the signals of the other protons was analogous to that of β-glycosides described previously (see Table 2).

The possibility has been shown of performing oligosaccharide synthesis in the presence of HgI_2. Glycosylation of the primary hydroxyl in 1,2:3,4-di-O-isopropylidene-α-*D*-galactopyranose for 7 days led to the disaccharide (**9**). The presence in its PMR spectrum of a doublet of the anomeric proton with a CS of 4.60 ppm and a splitting constant of 8.4 Hz showed the presence of a β-glycosidic bond. We also determined the signals of the skeletal protons and of the protective groups, including four singlets of O- and N-acetates in the 1.85-1.97 ppm region and singlets of the methyl groups of the protective isopropylidene residues in the 1.21-1.40 region.

EXPERIMENTAL

Melting points were determined on a PTP instrument, and optical rotations at 20-22°C on a Polamat-A polarimeter. PMR spectra were obtained on Bruker WP-200 (200 MHz) and Bruker WM-500 (500 MHz) instruments, with tetramethylsilane as internal standard; chemical shifts are given in ppm, δ scale. IR spectra were recorded on a Specord 75-IR spectrophotometer (KBr tablets). TLC was conducted on Silufol UV-254 plates (Kavalier). The substances were detected by carbonization at 300°C. Column chromatography was performed on washed silica gel L 100-250 μm. The elementary analyses of the compounds synthesized agreed with their calculated values.

2-Dodecyltetradecan-1-ol (B26-OH) was obtained by the $LiAlH_4$ reduction of methyl 2-dodecyltetradecanoate, which was synthesized via malonic ester. 2-Naphthylmethanol was synthesized by the $LiAlH_4$ reduction of 2-naphthoic acid.

General Glycosylation Procedure. A solution of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-*D*-glucopyranosyl chloride [4] in dry dichloroethane (25 ml/g) was treated with 1.16 equiv. of the catalyst mercury(II) bromide (50 mg/g) and with the alcohol (2 equiv. for low-molecular-mass and 1.1 equiv. for high-molecular-mass alcohols; when mercury(II) iodide was used, 1 equiv. both for low- and for high-molecular-mass alcohols). The reaction mixture was stirred in the presence of 3 Å molecular sieves until the glycosyl donor had disappeared (TLC monitoring in the benzene–ethanol (10:1) and (5:1) systems). The molecular sieves and the undissolved catalyst were filtered off, and the filtrate was diluted with chloroform and washed with water. When mercury(II) iodide was used, the extract was first washed with a solution of potassium iodide. The organic layer was separated off, dried with anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography (eluent: benzene→benzene–ethanol (50:1)).

Butyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranoside (2). The glycosylation of 182 mg (2.46 mmole) of butan-1-ol in the presence of HgI_2 yielded 259 mg (80%) of the butyl β-glycoside (**2**). Glycoside (**2**) was also obtained by glycosylation using the Zemplen–Helferich and Schroeder methods (see Table 1), mp 144-145°C, $[\alpha]_{546}$ −17.3° (*c* 0.77, chloroform). Literature [5]: mp 144°C, $[\alpha]_{546}$ −17.6° (chloroform).

Heptyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranoside (3). The glycosylation of 95 mg (0.8 mmole) of heptan-1-ol in the presence of HgI_2 gave 204 mg (56%) of the heptyl β-glycoside (**3**). Glycoside (**3**) was also obtained by the glycosylation of 156 mg (1.34 mmole) of heptan-1-ol by the Zemplen–Helferich and Schroeder methods (see Table 1), mp 122-124°C, $[\alpha]_{546}$ −18.9° (*c* 0.77; chloroform). Literature [6]: mp 123-124°C, $[\alpha]_{546}$ −16° (*c* 1.1; chloroform).

Hexadecyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranoside (4). The glycosylation of 199 mg (0.8 mmole) of hexadecan-1-ol in the presence of HgI_2 yielded 278 mg (61%) of the hexadecyl β-glycoside (**4**). Hexadecan-1-ol (301 mg) was also glycosylated by the Zemplen–Helferich method to glycoside (**4**) (see Table 1); mp 119-120°C, $[\alpha]_{546}$ −13.5° (*c* 0.87; chloroform). Literature [6]: mp 120-121°C, $[\alpha]_{546}$ −14.0° (chloroform).

2-Dodecyltetradecyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranoside (5). The glycosylation of 259 mg (1.04 mmole) of 2-dodecyltetradecan-1-ol in the presence of HgI_2 gave 278 mg (72%) of the 2-dodecyltetradecyl β-glycoside (**5**); mp 88-89°C, $[\alpha]_{546}$ −18.0° (*c* 0.77; chloroform). Literature [7]: mp 88-90°C, $[\alpha]_{546}$ −18.4° (chloroform).

Cholesterol 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranoside (6). Cholesterol (1.0 g; 2.58 mmole) was glycosylated with 0.86 g (2.36 mmole) of the chloride (I) in the presence of mercury(II) cyanide and bromide for 10 days. The residue obtained after working up was deacetylated by Zemplén's method, and 0.5 g (35%) of glycoside (**6**) was isolated by column chromatography (eluent: chloroform→chloroform–ethanol (5:1)). The glycosylation of 127 mg (0.33 mmole) of cholesterol in the presence of HgI_2, followed by deacetylation of the full acetate so obtained yielded 92 mg (57%) of the cholesterol β-glycoside (**6**); mp 172-174°C, $[\alpha]_{546}$ −31.0° (*c* 0.77; dimethyl sulfoxide). PMR spectrum (500 MHz, C^2HCl_3-$C^2H_3O^2H$): 0.44 (Me-18, s), 0.75 (Me-19, s), 0.62 (2Me-26/27, d), 0.68 (Me-21, d), 1.75 (NAc, s), 3.03 (H-5′, m, $J_{5.6a}$ 5 Hz, $J_{5.6b}$ 2.5 Hz), 3.11 (H-3, m), 3.16 (H-4′, t, $J_{4.5}$ 9 Hz), 3.27 (H-2′ and H-3′, m, $J_{3.4}$ 9 Hz), 3.50 (H-6′a, dd), 3.61 (H-6′b, dd, $J_{6a.6b}$ 12 Hz), 4.34 (H-1′, d, $J_{1.2}$ 8 Hz), 5.10 (H-6, d).

Cyclohexyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranoside (7). The glycosylation of 55 mg (0.8 mmole) of cyclohexanol in the presence of HgI_2 yielded 166 mg (71%) of the cyclohexyl β-glycoside (**7**); mp 179°C (decomp.), $[\alpha]_{546}$ −17.6° (*c* 0.77; chloroform). IR spectrum (KBr, ν, cm^{-1}): 3280 (NH), 2900, 2830 (CH_2, CH_3), 1720 (ester), 1640, 1520 (amide).

2-Naphthylmethyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranoside (8). The glycosylation of 88 mg (0.8 mmole) of 2-naphthylmethanol in the presence of HgI_2 led to 174 mg (65%) of the 2-naphthylmethyl β-glycoside (**8**); mp 175-178°C, $[\alpha]_{546}$ −36.9° (*c* 0.62; chloroform). IR spectrum (KBr, ν, cm^{-1}): 3300 (NH), 2940, 2840 (CH_2, CH_3), 1720 (ester), 1640, 1520 (amide), 730, 690 (arom.).

6-O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranosyl)-1,2;3,4-di-O-isopropylidene-α-*D*-galactopyranose (9). The glycosylation of 108 mg (0.42 mmole) of diacetonegalactose in the presence of HgI_2 led to the isolation of 180 mg (56%) of the disaccharide (**9**), mp 84-86°C, $[\alpha]_{546}$ −60.5° (*c* 0.62; chloroform). IR spectrum (cm^{-1}): 3300 (NH), 2960, 2910 (CH_2, CH_3), 1720 (ester), 1640, 1520 (amide), 850 (Me_2C). PMR spectrum (C^2HCl_3, 200 MHz): 1.21 (Me_2C, s), 1.33 and 1.40 (Me_2C, s), 1.85 (NAc, s), 1.90, 1.91, 1.97 (3 OAc, s), 4.20 and 4.47 (2H-6-GlcNAc, dd, $J_{5.6a}$ 2.5 Hz, $J_{5.6b}$ 4.8 Hz), 4.60 (H-1-GlcNAc, d, $J_{1.2}$ 8.4 Hz), 4.98 (H-4-GlcNAc, dd, $J_{4.5}$ 9.2 Hz), 5.06 (H-3-GlcNAc, dd, $J_{3.4}$ 9.2 Hz), 5.42 (H-1-Gal, d, $J_{1.2}$ 5 Hz), 5.67 (NH, d).

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