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SYNTHESIS OF GLYCOSIDIC ANALOGUES OF N-ACETYLNEURAMOYL-L-ALANYL-D-ISOGLUTAMINE

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β-Heptyl and β-hexadecyl glycosides of N-acetylglucosamine have been obtained by the oxazoline method followed by deacetylation. Via a benzylidenation stage, the glycosides have been converted into the corresponding N-acetylmuramic acid derivatives and from these compounds glycosidic analogues of N-acetylmuramoyl-L-alanyl-D-isoglutamine have been synthesized.

N-Acetylmuramoyl-L-alananyl-D-isoglutamine (muramoyldipeptides, MDP), being the minimum fragment of the peptidoglycan of the cell walls of bacteria that is responsible for their immunoadjuvant activity, has attracted wide attention. MDP is a convenient object for the study of the interrelationship between chemical structure and biological activity. Syntheses of a large number of peptide and carbohydrate analogues of muramoyldipeptide have been described (see the reviews [1, 2]). An important group of carbohydrate derivatives of MDP is formed by its glycosides. Reports have been published in the literature on the synthesis of of methyl α- and β-glycosides [3], benzyl α- and β-glycosides [1, 2], and p-aminophenyl β-glycoside [3] of N-acetylmuramoyl-L-alanyl-D-isoglutamine, and also information on their biological activities [2, 4]. The synthesis of the methyl β-glycoside of a furanose analogue of MDP has been reported [5]. No syntheses of higher aliphatic glycosides of MDP have been described in the literature.

Continuing investigations of carbohydrate analogues of muramoyldipeptide [6], we have synthesized the heptyl and hexadecyl β-glycosides of N-acetylmuramoyl-L-alanyl-D-isoglutamine (XI, XII). The study of these compounds will permit a judgement of the influence of the chain length of the aliphatic aglycon on biological activity among MDP glycosides.

The initial compounds in the synthesis of the glycopeptides (XI) and (XII) were peracetylated heptyl and hexadecyl N-acetyl-β-glucosaminides (I) and (II), which were obtained by treating 2-methyl-(3,4,6-tri-O-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-d]-2-oxazoline with heptanol and cetyl alcohol, respectively, in dichloroethane. Subsequent Zemplen deacetylation led to the alkyl N-acetyl-β-glucosaminides (III) and (IV). The benzylidenation of these compounds with benzaldehyde dimethyl acetal, using the minimum amount of solvent, permitted the rapid synthesis in good yields of the benzylidene derivatives (V) and (VI).

The alkylation of the hydroxy group at C_3 with L-α-chloropropionic acid led to protected N-acetylmuramic acids with yields exceeding 90%. The acids obtained, (VII) and (VIII), were activated with N-hydroxysuccinimide (HOSu) and with N,N'-dicyclohexylcarbidiimide (DCC) and were then condensed with the γ-benzyl ether of L-alanyl-D-isoglucamine. The dipeptide derivatives (IX) and (X) were isolated by column chromatography with yields of 75 and 72%, respectively.

In the PMR spectra of the glycopeptides (IX) and (X) it was possible to identify: the singlets of N-acetyl groups and of the methylene protons of benzyl groups; the triplets of

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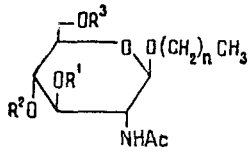
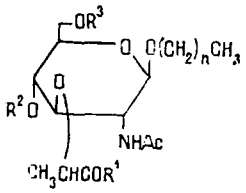
the methyl groups of the aglycons and of the γ-methylene groups of the isoglutamine residue; and the multiplets of the methylene protons of the aglycon and of the phenol groups, which confirmed their structure. The elimination of the protective groups was carried out in steps; first the benzylidene protection was removed by acid hydrolysis, and then the benzyl ether group in the isoglutamine residue was subjected to catalytic hydrogenolysis. This gave the desired compounds: O-(heptyl and hexadecyl 2-acetamido-2-deoxy-β-D-glucopyranosid-3-yl)-D-lactoyl-L-analyl-D-isoglutamines. The IR spectra of compounds (I-II) agreed with their structures.

Glycopeptides (XI) and (XII) acted on complementary rosette formation (EAC-RFC) on the activation of leucocyte migration, and in the nitro-BT test in a similar manner to muramoyl dipeptide.*

Detailed results of the biological trials will be published in a separate communication.



$R^1=R^2=R^3=Ac$ I. $n=6$, II. $n=15$
$R^1=R^2=R^3=H$ III. $n=6$, IV. $n=15$
$R^1=H$, R^2, $R^3=>CHPh$ V. $n=6$, VI. $n=15$



$R^1=OH$, R^2, $R^3=>CHPh$ VII. $n=6$, VIII. $n=15$
$R^1=L$-Ala-D-iGln-OBn, R^2, $R^3=>CHPh$ IX. $n=6$, X. $n=15$
$R^1=L$-Ala-D-iGln, $R^2=R^3=H$ XI. $n=6$, XII. $n=15$

EXPERIMENTAL

Melting points were determined on a PTP instrument and optical rotations at 20-22°C on a Polamat A polarimeter (GDR). PMR spectra were obtained on a Varian XL-100 spectrometer (100 MHz, USA) with Me_4Si as internal standard and DMSO-d_6 as solvent. IR spectra were recorded on a Specord IR-75 spectrophotometer (GDR, KBr tablets). TLC was performed on Silufol UV-254 plates (Czechoslovakia), the zones being revealed by carbonization at 400°C. The following solvent systems were used: chloroform–ethanol (20:1) (1); (15:1)(2); (10:1) (3); (5:1) (4); and ether–ethanol (20:1) (5). Column chromatography was performed on washed silica gel L 100-250 μ (Czechoslovakia). The results of elementary analysis for all the compounds corresponded to the calculated values.

Heptyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (I). A solution of 1.40 g (4.26 mmole) of 2-methyl(3,4,6-tri-O-acetyl-1,2-dideoxy-α-D-glucopyrano)[1,1-d]-2-oxazoline [7] in 10 ml of dry dichloroethane was treated with 1.0 ml (7.06 mmole) of freshly distilled heptan-1-ol and 20 mg of anhydrous p-toluenesulfonic acid. The reaction was performed at 85-90°C (bath temperature) until the oxazoline had decomposed completely (monitoring by TLC in system 2). The reaction mixture was neutralized with pyridine and evaporated. Column chromatography (benzene–ether) led to the isolation of 1.60 g (85%) of product (I).

An analytical sample was recrystallized from ether–hexane: mp 123-124°C, $[\alpha]_{546}$ −16° (c 1.1; chloroform) R_{fI} 0.41; R_f (oxazoline) 0.50 (system 2). ν_{max}^{KBr} (cm^{-1}): 3310 (NH); 2960, 2930, 2870 (CH_3, CH_2); 1760, 1230 (ester), 1670, 1540 (amide).

Hexadecyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (II). Hexadecan-1-ol (0.75 g, 3.10 mmole) was glycosylated with 1.50 g (4.56 mole) of the oxazoline derivative in 15 ml of dichloroethane in the presence of 30 mg of p-toluenesulfonic acid as described for the preparation of compound (I).

Yield 1.24 g (70%), mp 120-121°C (ether, $[\alpha]_{546}$ −14° (c 0.87; chloroform), R_{fII} 0.76; R_f (oxazoline) 0.48 (system 5). ν_{max}^{KBr} (cm^{-1}): 3300 (NH); 2910, 2840 (CH_3, CH_2); 1730, 1230 (ester); 1660, 1540 (amide).

*The biological trials were performed by S. S. Obernikhin (Simferol' State University) under the direction of A. M. Bratchik (Crimean Medical Institute).

Heptyl 2-Acetamido-2-deoxy-β-D-glucopyranoside (III). A solution of 1.35 g (3.03 mmole) of acetate (I) in 15 ml of methanol was treated with 1 ml of 1 N sodium methanolate in methanol. After the end of deacetylation (monitoring by TLC in system 2), the solution was neutralized with the cation-exchanger KU-2 (H^+). The resin was filtered off and was washed with 10 ml of methanol, and the filtrate was evaporated. The residue was crystallized from ether.

The yield of compound (III) was 0.81 g (84%) mp 187-188°C, $[\alpha]_{546}$ −30°C (c 0.73; ethanol), R_f 0.17 (system 2). ν_{max}^{KBr} (cm^{-1}): 3250-3400 (NH,OH); 2950, 2930, 2850 (CH_3, CH_2); 1650, 1560 (amide).

Hexadecyl 2-Acetamido-2-deoxy-β-D-glucopyranoside (IV). A solution of 1.01 g (1.77 mmole) of derivative (II) in a mixture of 20 ml of methanol and 3 ml of dichloromethane was treated with 1 ml of 1 N sodium methanolate in methanol. After 1 h, the precipitate that had deposited was filtered off and was washed with 10 ml of cold methanol. The filtrate was neutralized with cation-exchanger KU-2 (H^+). The resin was filtered off and washed with 10 ml of methanol, and the mother solution was evaporated. The total yield of glycoside (IV) was 0.77 g (98%). An analytical sample was recrystallized from methanol: mp 189-192°C $[\alpha]_{546}$ −18° (c 0.88; dimethylformamide), R_f 0.24 (4). ν_{max}^{KBr} (cm^{-1}): 3250-3380 (NH, OH): 2900, 2830 (CH_3, CH_2); 1640, 1550 (amide).

Heptyl 2-Acetamido-4,6-O-benzylidene-2-deoxy-β-D-glucopyranoside (V). A mixture of 0.70 g (2.19 mole) of glycoside (III), 1 ml of dioxane, 1 ml of benzaldehyde dimethyl acetal, and 5 drops of 10% sulfuric acid in methanol was heated in a beaker with careful stirring in an oil bath (90°C), 5 min. The reaction mixture was treated with 50 ml of hexane and cooled and the precipitate that deposited was filtered off. Column chromatography (chloroform→chloroform–methanol (10:1)) yielded the benzylidene derivative (V), which was recrystallized from chloroform–ethanol–hexane.

Yield 0.67 g (75%), mp 243-245°C, $[\alpha]_{546}$ −70° (c 0.77; dimethylformamide), r_f 0.90 (system 2). ν_{max}^{KBr} (cm^{-1}): 3410, 3260 (OH, NH): 2960, 2930, 2870 (CH_3, CH_2); 1630, 1550 (amide); 750, 695 (Ph).

Hexadecyl 2-Acetamido-4,6-O-benzylidene-2-deoxy-β-D-glucopyranoside (VI). Glycoside (IV) (0.75 g; 1.69 mmole) was benzylidenated in a similar manner to compound (III). The yield of compound (VI) was 0.66 g (73%). An analytical sample was crystallized from chloroform–ethanol: mp 222-223°C, $[\alpha]_{546}$ −56°, (c 0.8; chloroform), R_f 0.41 (system 2). ν_{max}^{KBr} (cm^{-1}): 3410, 3300 (OH, NH): 2920, 2840 (CH_3, CH_2); 1630, 1560 (amide); 740, 690 (Ph).

Heptyl 2-Acetamido-4,6-O-benzylidene-3-O-(D-1-carboxyethyl)-2-deoxy-β-D-glucopyranoside (VII) A solution of 0.55 g (1.35 mmole) of product (V) in 12 ml of dry dioxane was treated with 020 g (6.67 mmole) of sodium hydride (80%, in oil). The reaction mixture was heated to 90°C, was kept at this temperature for 1 h, and was cooled to 65°C, and 0.3 ml (3.27 mmole) of L-α-chloropropionic acid was added. The reaction was carried out at 60-65°C for 3 h, and then the mixture was cooled, and 1 ml of water was added dropwise. The solution was poured into 300 ml of cold water and, with stirring, the resulting mixture was acidified with 1 N hydrochloric acid to pH 2-3. The acid that floated to the top was extracted with chloroform (3 × 100 ml), and the extract was washed with 50 ml of water, dried with sodium sulfate, and evaporated. This residue was recrystallized from chloroform.

Yield 0.59 g (91%), mp 236-237°C (decomp), $[\alpha]_{546}$ −30° (c 1.07; dimethylformamide); R_f 0.58 (system 1). ν_{max}^{KBr} (cm^{-1}): 3280 (NH); 2960, 2930, 2850 (CH_3 CH_2); 1740 (C=O); 1660, 1580 (amide); 760, 700 (Ph).

Hexadecyl 2-Acetamido-4,6,O-benzylidene-3-O-(D-1-carboxyethyl)-2-deoxy-β-D-glucopyranoside (VIII). A solution of 0.44 g (0.83 mmole) of compound (VI) in 9 ml of dry dioxane was treated with 0.10 g (3.33 mole) of sodium hydride and 0.15 ml (1.63 mmole) of L-α-chloropropionic acid by the procedure described for the preparation of the acid (VII).

Yield: 0.48 g (96%), mp 202-204°C, $[\alpha]_{546}$ −23° (c 1.01; chloroform), R_f 0.45 (system 2). ν_{max}^{KBr} (cm^{-1}): 3290 (NH); 2930, 2870 (CH_3, CH_2); 1770 (C=O); 1680, 1580 (amide); 760, 700 (Ph).

γ-Benzyl Ester of O-(Heptyl 2-acetamido-4,6-O-benzylidene-2-deoxy-β-D-glucopyranosid-3-yl)-D-lactoyl-L-alanyl-D-isoglutamine (IX). With cooling and stirring, 0.16 g (1.39 mmole) of HOSu and 0.30 g (1.45 mmole) of DCC were added to a solution of 0.56 g (1.17 mmole) of the acid (VII) in 12 ml of dry tetrahdryfuran and 6 ml of dimethylformamide. After 2 h, the precipitate of N,N'-dicyclohexylurea was filtered off and it was washed with 10 ml of tetrahydro-

furan–dimethylformamide (2:1). The reaction mixture was treated with 0.18 ml of triethylamine and a solution of 0.54 g (1.28 mmole) of the γ-benzyl ester of the trifluoroacetate of L-alanyl-D-isoglutamine [8] in 6 ml of tetrahydrofuran. After a day, the gel that had precipitated was filtered off and was washed with 10 ml tetrahydrofuran and 30 ml of ether. The filtrate was evaporated and the residue was diluted with 50 ml of water, after which an additional portion of the peptide derivative (IX) was extracted with chloroform (3 × 50 ml).

The yield after purification by column chromatography (chloroform→chloroform–ethanol (10:1)) amounted to 0.67 g (75%), mp 248-250°C. $[\alpha]_{546}$ −3° (c 0.73; dimethylformamide), R_f 0.55 (system 1). ν_{max}^{KBr} (cm^{-1}): 3390, 3280 (NH_2, NH); 2950, 2920, 2850 (CH_3, CH_2): 1730 (ester); 1650, 1540 (amide): 740, 680 (Ph).

PMR (ppm, δ): 0.75 t (3H; CH_3CH_2); 1.05-1.34 m (CH_2, $2CH_3CH$); 1.68 s (3H; NAc); 2.23 t (2H; γ CH_2); 4.94 s (2H; $COOCH_2Ph$); 5.54 s (1H, CHPh); 7.18 m (10H; 2pH).

γ-Benzyl Ester of O-(Hexadecyl 2-Acetamino-4,6-O-benzylidene-2-deoxy-β-D-glucopyranosid-3-yl)-D-lactoyl-L-alanyl-D-isoglutamine (X). By analogy with the method for obtaining compound (IX), 0.46 g (0.76 mmole) of the acid (VIII) in 23 ml of tetrahydrofuran was activated under the action of 0.11 g (0.96 mmole) of HOSu and 0.20 g (0.98 mmole) of DCC. The activated ester was condensed with 0.35 g (0.94 mmole) of the γ- benzyl ester of the trifluoroacetate of L-alanyl-D-isoglutamine in the presence of 0.12 ml of triethylamine.

The yield of derivative (X) was 0.49 g (72%), mp 213-216°C, $[\alpha]_{546}$ −6° (c 0.63; chloroform), R_f 0.33 (system 2). ν_{max}^{BKr} (cm^{-1}): 3400, 3270 (NH_2, NH); 2920, 2840 (CH_3, CH_2); 1720 (ether); 1660, 1540 (amide); 730, 690 (Ph). PMR (ppm, δ): 0.74 t (3H;CH_3CH_2); 1.02-1.16 m (CH_2, CH_3CH); 1.38 d (3H, J_{CH_3CH} = 7 Hz; CH_3CH); 1.68 s (3H; NAc); 2.24 t (2H; γ CH_2); 4.94 s (2H; $COOCH_2Ph$); 5.54 s (1H; CHPh); 7.23 m (10H; 2Ph).

O-(Heptyl 2-Acetamido-2-deoxy-β-D-glucopyranosid-3-yl)-D-lactoyl-L-alanyl-D-isoglutamine (XI). With heating on the boiling water bath, 0.54 g (1.70 mmole) of compound (IX) was dissolved in 10 ml of 80% acetic acid. After the end of the hydrolysis of the benzylidene protection (monitoring by TLC in system 3), the reaction mixture was evaporated, and the γ-benzyl ester of O-(heptyl 2-acetamido-2-deoxy-β-D-glucopyranosid-3-yl)-D-lactoyl-L-alanyl-D-isoglutamine was precipitated with 70 ml of ether. The precipitate was filtered off, dried, and dissolved in 16 ml of a mixture of tetrahydrofuran and water (15:1). The solution was subjected to hydrogenolysis over 0.1 g of 10% Pd/C for 4 h. The catalyst was filtered off and was washed with 5 ml of tetrahydrofuran and 5 ml of water. The filtrate was evaporated and the residue was dissolved in 3 ml of ethanol, and the addition of 50 ml of ether precipitated 0.34 g (82%) of the amorphous glycopeptide (XI), $[\alpha]_{546}$ +9° (c 0.93; ethanol), R_f 0.15 (system 3). ν_{max}^{KBr} (cm^{-1}): 3380, 3290 (OH, NH); 2960, 2930, 2850 (CH_3, CH_2); 1660, 1540 (amide).

O-(Hexadecyl 2-Acetamido-2-deoxy-β-D-glucopyranosid-3-yl)-D-lactoyl-L-alanyl-D-isoglutamine (XII). The elimination of the benzylidene protection and the hydrogenolysis of the benzyl ether in compound (X) (0.46 g, 0.52 mmole) were performed by the method described above. After purification of the reaction product by column chromatography (chloroform→chloroform–ethanol (5:1)), 0.25 g (68%) of the amorphous glycopeptide (XII) was isolated with $[\alpha]_{546}$ −2° (c 0.67; ethanol), R_f 0.25 (system 4). ν_{max}^{KBr} (cm^{-1}): 3400-3300 (OH, NH); 2920, 2860 (CH_3, CH_2); 1660 1540 (amide).

CONCLUSIONS

A method has been developed for the synthesis of the heptyl and hexadecyl β-glycosides of N-acetylmuramoyl-L-alanyl-D-isoglutamine.

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POTENTIOMETRIC DIFFERENTIATED TITRATION OF THE COMPONENTS OF NUCLEIC ACIDS AND THEIR DERIVATIVES.

VII. ACIDIMETRIC DETERMINATION OF SOME N-ACYL-2'-DEOXYRIBONUCLEOSIDES AND THEIR 5'-TRITYLATED DERIVATIVES

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The conditions have been investigated for the potentiometric titration of N-acyl-2'-deoxyribonucleotides and of trityl carbinol derivatives and their two-component mixtures with a nitromethane solution of perchloric acid. The influence of water, acetone, chloroform, and acetic acid on the conditions for the acidimetric analysis of tri-p-methyltrityl carbinol, p-monomethoxytrityl carbinol, and di-p-methoxy trityl carbinol in nitromethane have been shown. Procedures have been developed for the quantitative determination of N^6-benzoyl-5'-di-p-methoxytrityl-2'-deoxyriboadenosine, the 5'-tri-p-methyltrityl and 5'-p-monomethoxytrityl derivatives of N^4-benzoyl-2'-deoxyribocytidine, of N^6-benzoyl-2'-deoxyriboadenosine, and of N^2-isobutyryl-2'-deoxyriboguanosine by differentiated potentiometric titration. For the determination of the 5'-di-p-methoxy derivatives of N^4-benzoyl-2'-deoxyribocytidine and of N^6-benozyl-2'-deoxyriboadenosine a procedure is proposed which includes the use of two parallel titrations. Methods have been developed for the use of milligram amounts of substance.

In preceding papers [1-6], methods have been proposed for the potentiometric acidimetric titration of ribo- and 2'-deoxyribonucleotides, and of di-p-methoxytrityl carbinol and 5'-di-p-methoxytritylthymidine in nonaqueous solutions. The aim of the present work was to investigate the conditions for the potentiometric acidometric titration and the development of a procedure for the quantitative determination of N^6-benzoyl-2'-deoxyriboadenosine (dA^{Bz}), N^4-benzoyl-2'-deoxyribocytidine (dC^{Bz}), and N^2-isobutyryl-2'-deoxyriboguanosine (dG^{iBu}) and their 5'-di-p-methoxytrityl, 5'-monomethoxytrityl, and 5'-trimethyltrityl derivatives, preparations of which find wide use of oligonucleotide synthesis. Existing spectrophotometric and chromatographic methods for the quantitative determination of N-acyl-2'-deoxyribonucleosides and their 5'-tritylated derivatives possess inadequate accuracy and require for their performance the presence of standard samples of the substances to be analyzed, and therefore investigations directed to improving the analytical quality control are of practical interest.

Nitromethane (NM) was selected as the titration medium. Characteristic for this solvent is the wide extent of the absolute scale of acidity and a differentiation capacity with respect to weak bases [7, 8]. Furthermore, NM, like other nitroalkanes, is capable of ionizing trityl carbinol and its derivatives [9].

Figure 1 shows the most characteristic potentiometric titration curves. It can be seen that each of the curves for the titration of N-acyl-2'-deoxyribonucleosides has one potential jump which corresponds to the end of the quantitative protonation of the purine heterocycle (curves 1 and 3) or the pyrimidine heterocycle (curve 2). A comparison of these curves permits the conclusion that dA^{Bz} in NM posssesses a higher proton-accepting capacity than dC^{Bz}

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