SYNTHESIS OF LIPOPHILIC α-ALKYLAMIDES OF N-ACETYLMURAMOYL-L-ALANYL-D-GLUTAMIC ACID

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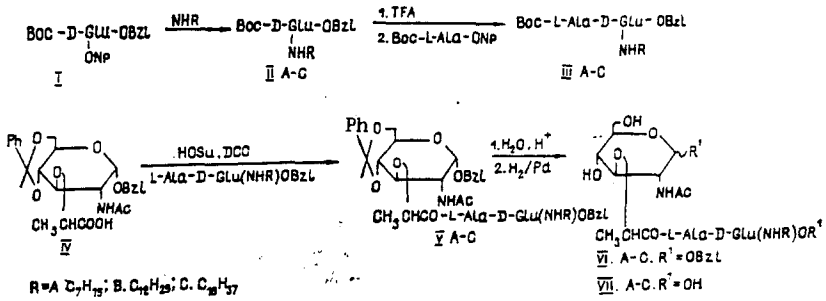
The synthesis of α-alkylamides of N-acetylmuramoyl-L-alanyl-D-glutamic acid has been performed.

Lipophilic derivatives of N-acetylmuramoyl-L-alanyl-D-isoglutamine (muramoyldipeptide, MDP) possess a high immunoadjuvant, antitumoral, anti-infection activity [1, 2]. Furthermore, lipophilic glycopeptides are necessary for obtaining liposomes containing adjuvants [2]. One of the convenient centers for the introduction of lipophilic components into the MDP molecule is the glutamine fragment. In the literature, modifications of muramoyldipeptide containing lipophilic α-alkyl esters of glutamine [3], γ-alkyl esters and γ-alkylamides of isoglutamine [4, 5], and α-methyl γ-alkyl diesters of glutamic acid [4] have been described. Hasegawa's group has synthesized methyl esters of 1-deoxy-N-acetylmuramoyl-L-alanyl-N'-acyl-D-isoglutamines [6] using higher carboxylic acids as the lipophilic components.

Continuing investigations of glycopeptides with different methods of attaching lipophilic components to the MDP molecules [7, 8], we have synthesized α-alkylamides of N-acetylmuramoyl-L-alanyl-D-glutamic acid (VII A-C) differing by the length of the aliphatic chain. The synthesis of the compounds was effected with the aim both of studying the interrelationship between the structure of muramoyldipeptide derivatives and their biological activity and also of seeking biologically active substances among MDP analogues.



The treatment of the diester (I) [9] with heptyl-, dodecyl-, and octadecylamines gave the corresponding α-alkylamides (II A-C). The IR spectra of these compounds showed strong absorption bands of methylene groups (Table 1). From the amides (II A-C) were obtained the dipeptide derivatives (III A-C). Then the protected muramic acid (IV), obtained by a modified procedure [10], was activated with N-hydroxysuccinimide (HOSu) and N,N'-dicyclohexylcarbodiimide (DCC). The activated ester was condensed with the dipeptides (the Boc protection was eliminated by treatment with trifluoroacetic acid) in the presence of N-methylmorpholine. Glycopeptides (V A-C) were isolated with 80-89% yields. The structures of these compounds were confirmed by their PMR spectra (Table 2), in which, together with the protons of the carbohydrate moiety, signals of the dipeptide fragment were observed. Two-stage deblocking (acid hydrolysis of the benzylidene protective groups and subsequent catalytic hydrogenolysis of the benzyl ester and benzyl glycoside groups) led to the final compounds (VII A-C). The absence of protective groups from them was confirmed by their IR spectra.

EXPERIMENTAL

For general observations, see [7].

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TABLE 1. Yields, Physicochemical Constants, and Characteristic IR Frequencies of the Compounds Synthesized

Compound	Yield, %	mp, °C	$[\alpha]_{546}$, deg (c; solvent)	ν, cm^{-1}					R_f (system)
				OH, NH	$(CH_2)_n$	C=O	amide	Ph	
II A	79	75—76	+10 (1,0; $CHCl_3$)	3320	2940; 2870	1740; 1700	1660, 1530	750, 700	0,45 (1)
II B	81	73—75	+8 (1,0; $CHCl_3$)	3320	2930; 2860	1740; 1700	1660, 1530	740, 650	0,51 (1)
II C	87	80—81	+7 (1,0; $CHCl_3$)	3320	2910; 2850	1730; 1690	1660, 1530	750, 700	0,58 (1)
III A	75	103—104	+14 (1,0; $CHCl_3$)	3310	2940; 2870	1730; 1700	1660, 1540	750, 700	0,29 (1)
III B	78	101—102	+12 (1,0; $CHCl_3$)	3315	2915; 2835	1740; 1700	1660, 1555	755, 700	0,32 (1)
III C	81	100—102	+9 (1,0; $CHCl_3$)	3330	2940; 2870	1740; 1690	1660, 1540	750, 700	0,33 (1)
V A	89	—	+60 (1,0; DMFA)	3290	2940; 2870	1740	1650, 1560	740, 700	0,55 (2)
V B	88	—	+80 (1,0; DMFA)	3320	2950; 2880		1660, 1570	730, 700	0,60 (2)
V C	83	—	+84 (1,0; DMFA)	3270	2920; 2860	1730	1630, 1540	730, 690	0,63 (2)
VI A	84	—	+148 (1,0; AcOH)	3450—3320	2950; 2880	1760	1660, 1560	740, 700	0,16 (2)
VI B	86	—	+100 (1,0; AcOH)	3450—3320	2940; 2870	1740	1660, 1560	740, 700	0,16 (2)
VI C	76	—	+86 (1,0; AcOH)	3450—3320	2950; 2880	1750	1650, 1560	730, 700	0,20 (2)
VII A	52	—	+48 (1,0; EtOH)	3450—3270	2940; 2880		1660, 1560		0,57 (3)
VII B	50	—	+44 (1,0; EtOH)	3450—3310	2930; 2870		1650, 1560		0,60 (3)
VII C	62	—	+34 (1,0; EtOH)	3450—3280	2940; 2870		1660, 1550		0,61 (3)

TABLE 2. PMR Spectrum of Compounds (V A-C)

Group	V A	V B	V C
$\underline{CH_3}CH_3$	0,84t	0,84t	0,84t
$(\underline{CH_2})_n$, $\underline{CH_3}CH$	1,22m	1,22m	1,22m
NAc	1,79s	1,78s	1,79s
γ-$\underline{CH_2}$—Glu	2,32t	2,15t	2,16t
H-1 ($J_{1,2}$, Hz)	4,85d(3,5)	4,77d(3,3)	4,86d(3,5)
$\underline{OCH_2}Ph$ (J_{gem} Hz)	4,49d, 4,70d(12)	4,42d, 4,66d(12)	4,50d, 4,71d(12)
$COO\underline{CH_2}Ph$	5,05s	5,04s	5,05s
$\underline{CH}Ph$	5,69s	5,68s	5,69s
Ph	7,33m	7,36m	7,33m
NH	7,51d, 8,12d, 8,17d	7,62d, 8,13d, 8,16d	7,51d, 8,12d, 8,16d
$\underline{NH}CH_3$	7,81t	7,88t	7,80t

PMR spectra were obtained on a Varian XL-200 (200 MHz) spectrometer with DMSO-d_6 as solvent.* The analyses of all the compounds corresponded to the calculated figures.

For TLC we used the following solvent systems: 1) benzene—ethanol (10:1); 2) chloroform—ethanol (10:1); and 3) butanol—acetic acid—water (3:1:1). The yields, physicochemical constants, and IR spectra of the compounds synthesized are given in Table 1.

α-Octadecylamide of γ-Benzyl tert-Butoxycarbonyl-D-glutamate (II C). A solution of 1.0 g (2.2 mmole) of the α-p-nitrophenyl γ-benzyl diester of Boc-D-glutamic acid [9] in 15 ml of dry dioxane was treated with 0.59 g (2.2 mmole) of octadecylamine and 0.33 ml of triethylamine. The solution was stirred at room temperature for 24 h. The solvent was evaporated off in a rotary evaporator. The residue was dissolved in 100 ml of ethyl acetate and the solution was washed free from p-nitrophenol with 1 N aqueous ammonia until it had become colorless. The organic layer was dried with Na_2SO_4 and evaporated, giving 1.131 g of the amide (II C). The dodecyl- and heptylamides (II A, B) were synthesized similarly.

α-Octadecylamide of γ-Benzyl tert-Butoxycarbonyl-L-alanyl-D-glutamate (III C). Compound (II C) (1.02 g; 1.7 mmole) was dissolved in 4 ml of trifluoroacetic acid and the solution was left for 30 min. Then it was evaporated to dryness and the last traces of the acid were eliminated by distillation with toluene. The residue was dissolved in 4 ml of DMFA, and 0.53 g (1.7 mmole) of the p-nitrophenol ester of tert-butoxycarbonyl-L-alanine (II) and 0.38 ml (3.4 mmole) of N-methylmorpholine were added. The reaction mixture was stirred at 40°C for 48 h. Then it was diluted with 100 ml of ethyl acetate and the p-nitrophenol was washed out with 1 N aqueous ammonia. The organic layer was dried with Na_2SO_4 and evaporated. The yield of the dipeptide (III C) was 0.93 g. Dipeptides (III A and B) were synthesized by the same method.

α-Octadecylamide of γ-Benzyl 2-Acetamido-1-O-benzyl-4,6-O-benzylidene-2-deoxy-α-D-glucopyranosyl-(3→O)-D-lactoyl-L-alanyl-D-glutamate (V C). A solution of 0.24 g (0.5 mmole) of benzyl 2-acetamido-4,6-O-benzylidene-3-O-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside (IV) [10] in 5 ml of THF was treated with 0.06 g (0.55 mmole) of HOSu and 0.11 g (0.55 mmole) of DCC. The reaction mixture was stirred for 3 h and the precipitate of dicyclohexylurea was filtered off and was washed with 2 ml of THF. To the combined filtrate was added the deblocked dipeptide (obtained by treating 0.33 g of the derivative (III C) with 3 ml of trifluoroacetic acid followed by evaporation to dryness) and 0.11 ml of N-methylmorpholine. After 24 h the precipitate was filtered off; reprecipitation with ether from chloroform—ethanol (5:1) gave 0.42 g of compound (V C). The glycopeptides (V A and B) were obtained similarly.

α-Octadecylamide of γ-Benzyl 2-Acetamido-1-O-benzyl-2-deoxy-α-D-glucopyranosyl-(3→O)-D-lactoyl-L-alanyl-D-glutamate (VI C). With heating in the boiling water bath, glycopeptide (V C) (0.39 g; 0.38 mmole) was dissolved in 4 ml of 80% acetic acid and the solution was heated for 30 min. Then it was evaporated, and by column chromatography [chloroform—ethanol (50:1)→chloroform—ethanol (10:1)], 0.27 g of the diol (VI C) was isolated. Compounds (VI A and B) were obtained similarly.

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α-Octadecylamide of 2-Acetamido-2-deoxy-D-glucopyranosyl-(3→O)-D-lactoyl-L-alanyl-D-glutamic Acid (VII C). The diol (VI C) (0.15 g; 0.16 mmole) was dissolved in 12 ml of THF–ethanol–water (10:1:1) and was subjected to hydrogenolysis at room temperature over 0.2 g of 10% Pd/C. After 72 h, the catalyst was filtered off and was washed with 5 ml of ethanol. The filtrate was evaporated, and the addition of 25 ml of ether precipitated 0.075 g of compound (VII C). Glycopeptides (VII A and B) were synthesized similarly.

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OXIDATION OF HEXADEC-11Z-EN-1-OL BY Cr(VI) REAGENTS ON POLYMERIC SUPPORTS

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A method is proposed for the oxidation of hexadec-11Z-en-1-ol to hexadec-11Z-enal by Cr(VI) reagents on polymeric supports.

Recently, pyridinium chlorochromate, proposed by Corey [1], has been widely used as a mild oxidizing agent for converting alcohols into the corresponding carbonyl compounds. A disadvantage of this reagent is the necessity for the careful purification of the reaction mixture to eliminate compounds of low-valence chromium from the desired carbonyl compound.

The use of a polymeric analogue of pyridinium chlorochromate for the oxidation of a number of alcohols is known [2]. An advantage of polymeric reagents is the easy purification of the final product by filtration, and also the possibility of their repeated use after regeneration.

We have studied the oxidation of hexadec-11Z-en-1-ol to hexadec-11Z-enal – the main component of the pheromone of the cotton bollworm – by chromium(VI) reagents on polymeric supports.

As the polymeric supports we have used graft copolymers of polypropylene and Ftorlon [a polyfluoroethylene] with 4-vinylpyridine (Kh-53 and Kh-54, respectively) and also of polyacrylonitrile with 2-methyl-5-vinylpyridine (Kh-52) [3, 4].

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