posited 45-50 mg of maleylated 11S-globulin. The rate of elution was 15 ml/h and the volume of the fractions was 1.6 ml.

The CD spectra were obtained on a Jasco J = 20 spectropolarimeter. The thickness of the cell was 0.01 cm. Protein was dissolved in 0.1 M phosphate buffer containing 7.2% of NaCl, pH 7.75. The protein concentration was 1 mg/ml.

SUMMARY

1. It has been shown that a decisive role in the formation and stabilization of the quaternary structure of the native 11S-globulin is that of hydrophobic interactions.

2. It has been established that the ε-NH_2 groups of the lysine residues take part in the stabilization of the quaternary structure of the 11S-globulin.

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A STUDY OF THE PROPERTIES OF SYNTHETIC ANALOGS OF THE TRYPTOPHAN-CONTAINING FRAGMENT 113-121 OF THE BASIC PROTEIN OF MYELIN

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New analogs of fragment 113-121 of the basic protein of myelin were synthesized: Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Arg, in which the phenylalanine in the first position has been replaced by L-alanine (V) and by D-phenylalanine (IX), and also a shortened analog with the deletion of the serine in the second position (XIII) and a lengthened analog with the insertion of glycine between the phenylalanine and tryptophan (XVII). In experiments on guinea pigs, one of the compounds obtained exhibited encephalitogenic activity. The circular dichroism spectra of compounds (I) and (IX), and also of some model compounds, have been studied in order to analyze the contribution of the aromatic amino acid residues to the dichroic absorption.

In preceding papers [1-3] devoted to the synthesis and study of the physicochemical and encephalitogenic properties of analogs of the tryptophan-containing fragment 113-121, Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Arg (I), of the basic protein of human myelin, we have shown that replacement of the glutamic acid residue in the sixth position of glycine and also the acetylation of the N-terminal amino groups of the nonapeptide (I) have no effect on encephalitogenic activity. However, the introduction of glycine in place of the alanine-5 or phenylalanine-1 residue leads to the complete loss of EAE activity; the same effect is observed with an increase or decrease by one amino acid residue of the length of the encephalitogenic determinant.

We have continued the study of the relationship between the biological properties of analogs of the peptides (I) and their primary structure and conformation. In particular, we have investigated the role of the N-terminal phenylalanine residue and its position relative to the tryptophan residue for the induction of experimental allergic encephalomyelitis

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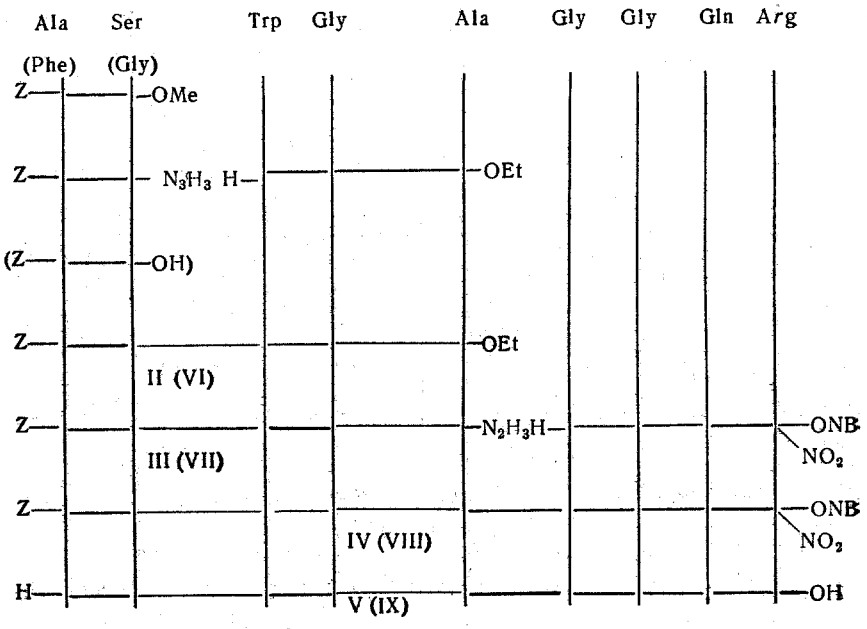


Scheme 1. Synthesis of the analogs (V) and (IX) of the encephalitogenic nonapeptide.

(EAE). As in the preceding communications, the 6-glutamic acid in the peptide is replaced by glycine. In some cases, glycine was also introduced in place of the serine-2, since this substitution does not affect the EAS activity of the peptides [7].

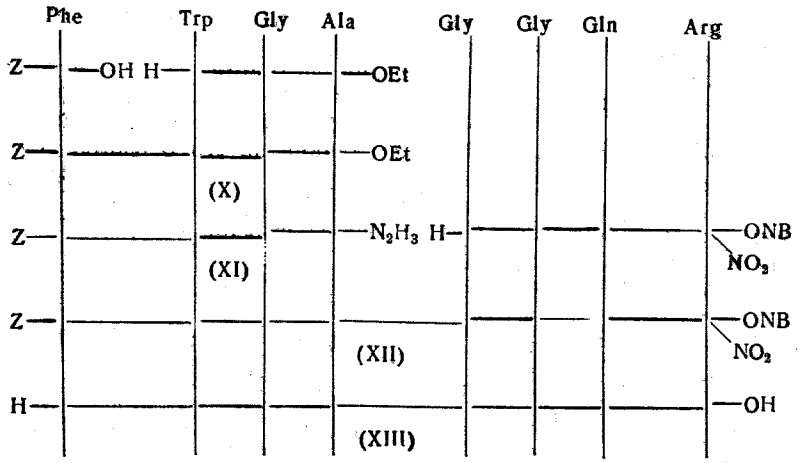
The present paper describes the synthesis of the following four analogs of the monopeptide (I): the L-Ala[1] analog (V), i.e., a peptide containing the less hydrophobic amino acid analine in place of phenylalanine; the D-analog (IX); the des-Ser[2] analog (XIII); and the homo-2[1]-Gly analog (XVII). In the last two compounds, the distance between the terminal phenylalanine and the tryptophan residue has been changed.

The synthesis of the above-mentioned peptides was effected by the classical method of condensing fragments (Schemes 1-3). All the protective groups of the completely protected peptides were eliminated in one stage by hydrogenation over a palladium catalyst.

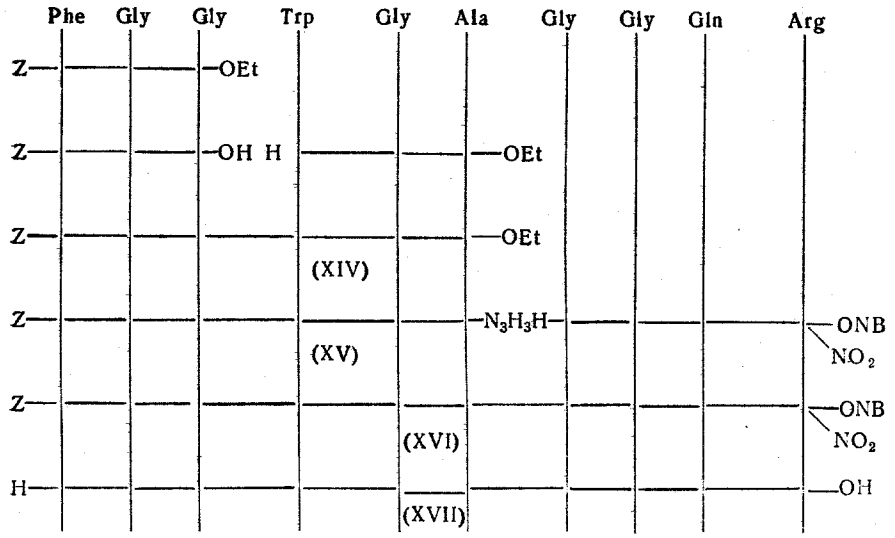
Below we give the results of a study of the EAE activities of the peptides on guinea pigs. The procedure for the biological tests has been described previously [8]. The encephalitogenic activity is expressed by the ratio of the number of diseased guinea pigs to the total number of animals taken in the tests:

Formula of the peptide	Dose, μg	EAE activity
I. HPhe-Ser-Trp-Gly-Ala-Gly-Gly-Gln-Arg-OH	50	3/4
V. HAla-Ser-Trp-Gly-Ala-Gly-Gly-Gln-Arg-OH	50	0/4
IX. H-D-Phe-Ser-Trp-Gly-Ala-Gly-Gly-Gln-Arg-OH	50	0/4
XIII. HPhe-□-Trp-Gly-Ala-Gly-Gly-Gln-Arg-OH	50	0/4
XVII. HPhe-Gly-Gly-Trp-Gly-Ala-Gly-Gly-Gln-Arg-OH	50	0/4

It was found that none of the peptides synthesized induced EAE in guinea pigs. The absence of activity in the case of peptide (V) shows that to induce the disease the presence of the residue of a hydrophobic amino acid in the first position is necessary, since the replacement of the hydrophobic phenylalanine by the less hydrophobic alanine led to an inactive peptide. The replacement of the L-phenylalanine by its D-isomer in analog (IX) caused loss of activity, which agrees well with the high stereospecificity of immunochemical reactions [9]. The absence of EAE activity in the analogs (XIII) and (XVII) permits the assumption that the presence of a hydrophobic amino acid at the N-end of the peptide is necessary for the de-



Scheme 2. Synthesis of the octapeptide (XIII).



Scheme 3. Synthesis of the decapeptide (XVII).

velopment of the disease. Therefore, a definitely fixed arrangement of the phenylalanine and tryptophan residues relative to one another is necessary. In other words, it is the primary structure of the peptide and not any particular conformation of it that is of first-degree importance for the induction of EAE.

In the study of the biological activities of peptides and the investigation of their interactions with various micromolecules, the question frequently arises of whether a low-molecular-weight peptide possesses a definite unique spatial structure before its interaction with a macromolecule or whether it is "structured" on the surface of the latter. Thus, for the correct interpretation of the experimental results it is necessary to establish what is responsible for the specificity of the interaction: the linear arrangement of the functional groups of the peptide, i.e., its primary structure, or a definite confirmation of the peptide molecule as a whole. The available information indicates that the conformation of cyclic peptides is of prime importance for their functioning [10]. At the same time, the biological effect of linear peptides does not always correlate unambigousuly with features of their secondary structure. Sometimes, e.g., in spite of the difference in the spatial structures of analogs of linear peptides they nevertheless possess biological activity and act on one and the same receptor system [11]. In this case, the activity of the peptide is apparently determined by the primary structure and not by its conformation in aqueous solution. It is possible that such a situation is involved in the case of peptides inducing EAE.

According to the literature [2, 3, 5-7], the dichloric absorption of the encephalitogenic peptides in the 200-250 nm region does not change with a variation of the pH or the temperature or in the presence of detergents, and the CD curve shows the absence of regular structures of the α-helix and β-structure type. We have previously [3] put forward the hypothesis

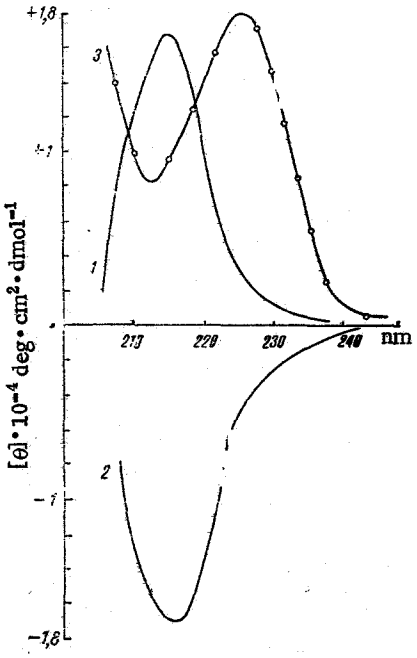


Fig. 1

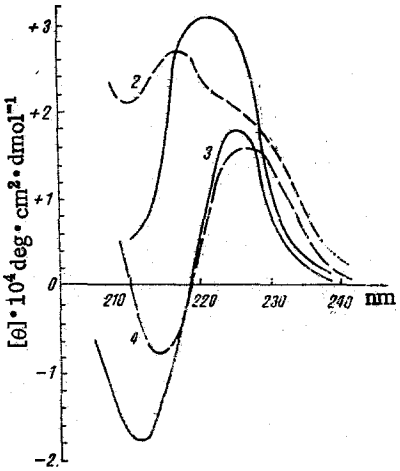


Fig. 2

Fig. 1. CD spectra of the methyl esters of L- and D-phenylalanines and of glycyl-L-tryptophanylglycine: 1) L-PheOMe; 2) D-PheOMe; 3) Gly-L-Trp-Gly.

Fig. 2. CD spectra of peptide (I) and its D-phenylalanine analog (IX), and the sum of the spectra of the methyl esters of L- and D-phenylalanines and of glycyl-L-tryptophanylglycine: 1) the nonapeptide (I); 2) L-PheOMe + Gly-L-Trp-Gly; 3) the peptide (IX); 4) D-PheOMe + Gly-L-Trp-Gly.

that the ellipticity of analogs of the encephalitogenic peptide (I) in the 200-250 nm region is determined mainly by the contribution of the aromatic chromophores and not by $n\rightarrow\pi^*$-transitions in the peptide bonds. Additional evidence confirming this opinion has been obtained. Figures 1 and 2 show the CD spectra of the nonapeptide (I) and its D-Phe[1] analog, and also the spectra of model compounds: hydrochlorides of the methyl esters of L- and D-phenylalanines and also glycyl-L-tryptophanylglycine. The first two stereoisomers model the dichloric absorption of the N-terminal phenylalanine in the nonapeptide (I) and its D-Phe[1] analog, respectively; the tripeptide Gly-Trp-Gly models the contribution of tryptophan to the ellipticity of the peptides investigated. As can be seen from Fig. 2, the CD of the monopeptide (I) correlates satisfactorily with curve 2, which represents the sum of the dichroic absorptions of the methyl ester of L-phenylalanine and the tripeptide Gly-Trp-Gly, and the CD of the D-Phe[1] analog correlates well with curve 4, which represents the summed dichroism of the two model compounds D-PheOMe and Gly-Trp-Gly. This coincidence indicates that the CD spectrum of the monopeptide and its analogs in the 200-250 nm region is determined mainly by the contributions of the aromatic chromophores of phenylalanine and tryptophan, and the peptide chromophores make a considerably smaller contribution.

EXPERIMENTAL

All the amino acids used (with the exception of the D-phenylalanine in the analog (IX)) were L isomers (Reanal, Hungary). The melting points of the compounds synthesized were determined in open capillaries; their uncorrected values are given. The homogeneity of the protected peptides was determined by TLC on Silufol plates (Kavalier, Czechoslovakia) in the following solvent systems: 1) butan-1-ol—acetic acid—water (4:1:1); and 2) butan-1-ol—acetic acid—pyridine—water (30:20:6:10). The spots on the chromatograms were revealed with iodide or the Ehrlich reagent. The homogeneity of the free peptides was investigated by paper chromatography in the following systems: 3) butan-1-ol—acetic acid—water (4:1:5) or 4) isoamyl alcohol—pyridine—water (35:35:30). The spots on the chromatograms were revealed with ninhydrin or the Ehrlich or the Sakaguchi reagent.

For high-voltage paper electrophoresis we used Filtrak FN-17 paper (GDR). The amino acid compositions of the peptides were determined on an AAA-881 amino acid analyzer (Mikrotekhnika, Czechoslovakia). he angles of rotation and the ORD and CD spectra were recorded on a Spectropol-1 spectropolarimeter (Sofica, France) fitted with an attachment for recording CD spectra. The measurements were carried out at a peptide concentration of 0.5 mg/ml in a thermostated (25°C) cell with an optical path length of 0.1 cm. The curves were recorded two or three times at the rate of 5-10 nm/min. The CD results are given in the form of molecular ellipticities. The results of elementary analyses agreed with the calculated figures.

Hydrazide of Benzyloxycarbonylalanylserine (I). A solution of 5.0 g (15.4 mmole) of the methyl ester of benzyloxycarbonylalanylserine [12] in 30 ml of methanol and 2 ml of hydrazine hydrate was kept at 20°C for 20 h. The precipitate of hydrazide that had deposited was filtered off, washed successively with methanol and ether, and dried in a vacuum desiccator over sulfuric acid. Yield 4.2 g (84%), mp 224°C, $[\alpha]_D^{25}$ +8.0° (c 1, DMFA). According to the literature [12], mp 223-224°C.

Ethyl Ester of Benzyloxycarbonylalanylseryltryptophanylglycylalanine (II). With stirring, 8 ml (32 mmole) of a 4.08 N solution of hydrogen chloride in tetrahydrofuran and then 0.97 ml (8.1 mmole) of tert-butyl nitrite were added to a solution of 2.62 g (8.1 mmole) of the hydrazide (I) in 10 ml of DMFA cooled to −30°C; the mixture was stirred at −30°C for 30 min and was then neutralized with 4.9 ml (32 mmole) of triethylamine and was added to a cold solution of the amino component previously obtained by the hydrogenation of 4 g (8.1 mmole) of the ethyl ester of benzyloxycarbonyltryptophanylglycylalanine [2]. The solution was stirred at −10°C for 1 h and was left at 10°C for 20 h. The triethylammonium chloride was eliminated by filtration, and the dimethylformamide was distilled off in vacuum in a rotary evaporator. The oil formed was dissolved in ethyl acetate and was washed successively with 1 N hydrochloric acid, water, 1 N sodium bicarbonate solution, and water again and was dried over magnesium sulfate. The organic solvent was distilled off in vacuum and the residue was crystallized from a mixture of ethyl acetate and petroleum ether. Yield 3.2 g (60%), mp 123-125°C, $[\alpha]_D^{25}$ −21.0° (c 1; DMFA), R_f 0.60 (system 1), 0.55 (system 2). $C_{32}H_{40}O_9N_6$.

The hydrazide of benzyloxycarbonylalanylseryltryptophanylglycylalanine (III) was obtained from 3 g (4.6 mmole) of the protected peptide (II) in the same way as compound (I). Yield 2.5 g (85%), mp 208-210°C, $[\alpha]_D^{25}$ −12.0° (c 1; DMFA), R_f 0.43 (system 1), 0.50 (system 2). $C_{30}H_{38}O_8N_8$.

The p-nitrobenzyl ester of benzyloxycarbonylalanylseryltryptophanylglycylalanylglycylglycylglutaminylnitroarginine (IV) was obtained in a similar manner to peptide (II) from 0.6 g (0.94 mmole) of the hydrazide (III) and 0.75 g (1 mmole) of the p-nitrobenzyl ester of benzyloxycarbonylglycylglycylgutaminylnitroarginine [2] previously deblocked with hydrogen bromide in acetic acid.

After the DMFA had been distilled off, the residue oil was triturated with ether. The amorphous product formed was triturated on the filter and washed successively with 1 N hydrochloride acid, water, 1 N sodium bicarbonate solution, and water again, and was dried in a vacuum desiccator over phosphorus pentoxide. After crystallization from ethanol, the yield was 0.5 g (50%), mp 140-144°C, $[\alpha]_D^{25}$ −18.0° (c 1; acetic acid), R_f 0.51 (system 1), 0.61 (system 2). $C_{52}H_{66}O_{18}N_{16}$.

Alanylseryltryptophanylglycylalanylglycylglycylglutaminylarginine (V). The completely protected nonapeptide (IV) (0.2 g) was hydrogenated over a palladium catalyst in ethanol-acetic acid-water (6:1:1) for 16 h. After the solvent had been distilled off, the residue was dissolved in methanol and was reprecipitated with ether. The yield of slightly colored product was 150 mg (75%). Its subsequent purification was carried out by ion-exchange chromatography at pH 6.0 with a concentration gradient of ammonium acetate buffer from 0.05 to 0.5 M, as described previously [1]. The optical densities of the fractions were measured at 280 nm; fractions containing the required material were combined and freeze-dried to constant weight. Yield 72%, mp 132-140°C, R_f 0.36 (system 3), 0.21 (system 4), E_{Lys} 0.33 (pH 6.5), $[\alpha]_D^{25}$ −12.3° (c 1; H_2O). Amino acid composition: Ala 2.1; Ser 0.9; Gly 3.3; Glu 1.0; Arg 0.95.

Ethyl Ester of Benzyloxycarbonyl-D-phenylalanylglycyltryptophanylglycylalanine (VI). At 0°C, 1.2 g (7.3 mmole) of N-hydroxysuccinimide and 1.5 g (7.3 mmole) of DCHC were added to a solution of 2.6 g (7.3 mmole) of benzyloxycarbonyl-D-phenylalanylglycine [13] in 25 ml

of a mixture of DMFA and methylene chloride (1:1), and the mixture was stirred at this temperature for 1 h. Then the amino component obtained from 3.6 g (7.3 mmole) of the ethyl ester of benzyloxycarbonyltryptophanylglycylalanine [1] previously deblocked by catalytic hydrogenation was added. The reaction mixture was kept at room temperature for 20 h and then the dicyclohexylurea was removed and the solvent was distilled off and the residue was dissolved in ethyl acetate and subjected to further purification as described for the synthesis of compound (II). Yield 3 g (79%), mp 135-140°C, $[\alpha]_D^{25}$ −2.2° (c 1; DMFA); R_f 0.67 (system 1), 0.70 (system 2). $C_{37}H_{42}O_8N_6$.

The hydrazide of benzyloxycarbonyl-D-phenylalanylglycyltryptophanylglycylalanine (VII) was obtained from 2.5 g of the protected peptide (VI) in the same way as compound (I). After crystallization from ethanol, the yield was 1.8 g (75%), mp 197-200°C $[\alpha]_D^{25}$ +1.5° (c 1; DMFA), R_f 0.56 (system 1), 0.58 (system 2). $C_{35}H_{40}O_7N_8$.

The p-nitrobenzyl ester of benzyloxycarbonyl-D-phenylalanylglycyltryptophanylglycylalanylglycylglycylglutaminylnitroarginine (VIII) was obtained from 1.2 g (2.3 mmole) of the hydrazide (VII) and 1.8 g (2.5 mmole) of the p-nitrobenzyl ester of benzyloxycarbonylglycylglycylglutaminylnitroarginine [2] previously deblocked with hydrogen bromide in acetic acid in a similar manner to the peptide (IV). After crystallization from ethanol the yield was 1.1 g (62%), mp 162-174°C, $[\alpha]_D^{25}$ −4.3° (c 1; DMFA); R_f 0.40 (system 1), 0.25 (system 2). $C_{57}H_{68}O_{17}N_{16}$.

D-Phenylalanylglycyltroptophanylglycylalanylglycylglycylglutaminylarginine (IX). The protected peptide (VIII) (0.5 g) was hydrogenated in the same way as described for compound (V). Yield 61%. After purification of CM-cellulose at pH 6.0 the yield was 75%, mp 148-160°C, R_f 0.40 (system 3), 0.36 (system 4); E_{Lys} 0.35 (pH 6.5); $[\alpha]_D^{25}$ −30° (c 0.5; H_2O). Amino acid composition: Phe 1.0; Ser 0.89; Gly 3.7; Ala 1.2; Glu 1.1; Arg 0.95.

The ethyl ester of benzyloxycarbonylphenylalanyltryptophanylglycylalanine (X) was synthesized in a similar manner to peptide (VI) from 2.9 g (9.7 mmole) of benzyloxycarbonylphenylalanine and the amino component obtained by hydrogenating 4.95 g (10 mmole) of the ethyl ester of benzyloxycarbonyltryptophanylglycylalanine [2]. Yield 4.5 g (70%), mp 78-80°C, $[\alpha]_D^{25}$ −12.4° (c 1; ethanol); R_f 0.62 (system 1), 0.64 (system 2). $C_{35}H_{39}O_7N_5$.

The hydrazide of benzyloxycarbonylphenylalanyltryptophanylglycylalanine (XI) was obtained in a similar manner to the hydrazide (I) from 4.2 g (6.5 mmole) of the protected peptide (X). After crystallization from ethanol, the yield was 2.8 g (67%), mp 215-217°C, $[\alpha]_D^{25}$ −9.5° (c 1; DMFA); R_f 0.56 (system 1), 0.58 (system 2). $C_{33}H_{37}O_6N_7 \cdot H_2O$.

The p-nitrophenyl ester of benzyloxycarbonylphenylalanyltryptophanylglycylalanylglycylglycylglutaminylnitroarginine (XII) was synthesized in a similar manner to peptide (IV) from 1.66 g (2.64 mmole) of the hydrazide (XI) and 2.5 g (3.5 mmole) of the p-nitrobenzyl ester of benzyloxycarbonylglycylglycylglutaminylnitroarginine previously deblocked with hydrogen bromide in glacial acetic acid.

Crystallization from ethanol gave 1.35 g (43%) of the protected octapeptide with mp 167-170°C, $[\alpha]_D^{25}$ −12.1° (c 1; DMFA); R_f 0.55 (system 1), 0.65 (system 2). $C_{55}H_{65}O_{16}N_5$.

Phenylalanyltryptophanylglycylalanylglycylglycylglutaminylarginine (XIII). A solution of 1 g of the protected peptide (XII) was hydrogenated over palladium black for 16 h, and the product was isolated as described above for compound (V). The yield after purification on CM-cellulose was 0.7 g (75%), mp 128-134°C, $[\alpha]_D^{25}$ −26.3° (c 1; H_2O) R_f 0.37 (system 3), 0.20 (system 4); E_{Lys} 0.40 (pH 6.5). Amino acid composition: Phe 1.0; Ala 1.1; Gly 2.9; Glu 0.93; Arg 1.2.

The ethyl ester of benzyloxycarbonylphenylalanylglycylglycyltryptophanylglycylalanine (XIV) was obtained similarly to compound (VI) from 3 g (7.2 mmole) of benzyloxycarbonylphenylalanylglycylglycine [14] and 3.6 g of the ethyl ester of benzyloxycarbonyltryptophanylglycylalanine [2] previously deblocked by hydrogenation over a palladium catalyst. The yield was 3 g (68%), mp 148-152°C, $[\alpha]_D^{25}$ −22.6° (c 1; DMFA); R_f 0.65 (system 1), 0.68 (system 2). $C_{39}H_{45}O_9N_7$.

Hydrazide of Benzyloxycarbonylphenylalanylglycylglycyltryptophanylalanine (XV). The protected hexapeptide (XIV) (2.5 g) was treated with hydrazine hydrate in methanol as described in the synthesis of the hydrazide (I). Crystallization from ethanol gave 2 g (80%) of the desired compound with mp 190-192°C, $[\alpha]_D^{25}$ −20.3° (c 1; DMFA), R_f 0.49 (system 1), 0.51 (system 2). $C_{37}H_{43}O_8N_9$.

The p-nitrobenzyl ester of benzyloxycarbonylphenylalanylglycylglycyltryptophanylglycylalanylglycylglycylglutaminylnitroarginine (XVI) was synthesized in a similar manner to peptide (IV) from 1 g (1.7 mmole) of the hydrazide (XV) and an amino component obtained by deblocking 1.3 g (1.7 mmole) of the p-nitrobenzyl ester of benzyloxycarbonylglycylglycylglutaminylnitroarginine [2]. Yield 1.41 g (70%), mp 167-175°C, $[\alpha]_D^{25}$ −15.4° (c 1; DMFA); R_f 0.58 (system 1), 0.60 (system 2). $C_{59}H_{71}O_{18}N_{17}$.

Phenylalanylglycylglycyltryptophanylglycylalanylglycylglycylglutaminylarginine (XVII) was obtained by the hydrogenation of 1 g of the protected decapeptide (XVI) as for the case of compound (V). Yield 0.8 g (82%). After purification from CM-cellulose, the yield was 75%, mp 130-133°C, $[\alpha]_D^{25}$ −23.5° (c 1; H_2O), E_{Lys} 0.38 (pH 6.5), R_f 0.35 (system 3), 0.33 (system 4). Amino acid composition: Phe 1.1; Ala 0.9; Gly 4.4; Glu 1.2; Arg 1.15.

SUMMARY

1. Four new analogs of the encephalitogenic nonapeptide corresponding to fragment 113-121 of the basic protein of human myelin have been synthesized by the block method.

2. It has been shown that the replacement of the N-terminal phenylalanine by L-alanine or by D-phenylalanine leads to the loss of EAE activity. A change in the distance between the phenylalanine and tryptophan residues by one amino acid residue also gives an inactive compound.

3. The CD spectra of the D-Phe[1] analog of the monopeptide (I) and of a series of model compounds have been investigated. It has been shown that the dichroic absorption of the peptides investigated in the 200-250 nm region is determined mainly by the contributions of the aromatic chromophores of phenylalanine and tryptophan residues.

4. It has been concluded that for the induction of EAE there must be hydrophobic residues (Phe, Trp), at the N-end of the nonapeptide (I), amino acids with small radicals (Gly, Ala) in the central part of the molecule, and residues having positive charges (Lys or Arg) as the C-terminal groups.

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