SYNTHESIS AND BIOLOGICAL PROPERTIES OF BRADYKININ-POTENTIATING PEPTIDES FROM SNAKE VENOM

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Among compounds capable of enhancing the action of bradykinin, particular interest is presented by the peptides isolated from snake venom [1-6]. The bradykinin-potentiating peptides (BPPs) of this group contain from five to thirteen amino acid residues and have a number of common structural features, which include a high content of proline, the same sequences of three or four amino acid residues for the majority of the peptides, and also the presence in all the peptides of N-terminal pyroglutamic acid and C-terminal proline.

The results of a study of the biological action of the BPPs has shown that they increase the contraction of smooth-muscle preparations caused by bradykinin in in vitro experiments and enhance the hypotensive effect of the hormone in in vivo experiments. An increase is observed not only in the intensity but also in the duration of the action of bradykinin [1, 3-10]. It has also been established that BPPs inhibit the enzyme (or enzymes) cleaving the kinin and converting the inactive decapeptide angiotensin I into the octapeptide angiotensin II, one of the functions of which in the organism is raising the blood pressure [2, 7-11].

The capacity of the BPPs for changing the metabolism of two highly active endopeptides that affect hemodynamics makes them a valuable tool for investigating the mechanism of the most important physiological processes taking place in the organism. The possibility is not excluded, either, of the practical use of BPPs for regulating these processes in various pathological states. In view of this, we have performed the synthesis and a biological study of some BPPs from snake venoms and their analogs.

The present paper describes the synthesis of the pentapeptide (I) and the undecapeptide (II),* isolated from the venoms of the snakes *Bothrops jararaca* [1] and *Agkistrodon halis blomhoffii* [3, 5], respectively, and also give the results of their comparative pharmacological investigation.

Glu-Lys-Trp-Ala-Pro (I)†

Glu-Gly-Leu-Pro-Pro-Arg-Pro-Lys-Ile-Pro-Pro. (II)

*In the literature, the symbol BPP_{5a} or SQ 20, 475 [8] is used for the pentapeptide (1) and B [3] for the undecapeptide (II).

†The abbreviations of the amino acids and their derivatives are given in accordance with the rules recommended by the IUPAC Commission [12]. Additional abbreviations: CDI) N,N'-dicyclohexylcarbidiimide; DCU) N,N'-dicyclohexylurea; TEA) triethylamine; THF) tetrahydrofuran; DMFA) dimethylformanide; TFA) trifluoroacetic acid.

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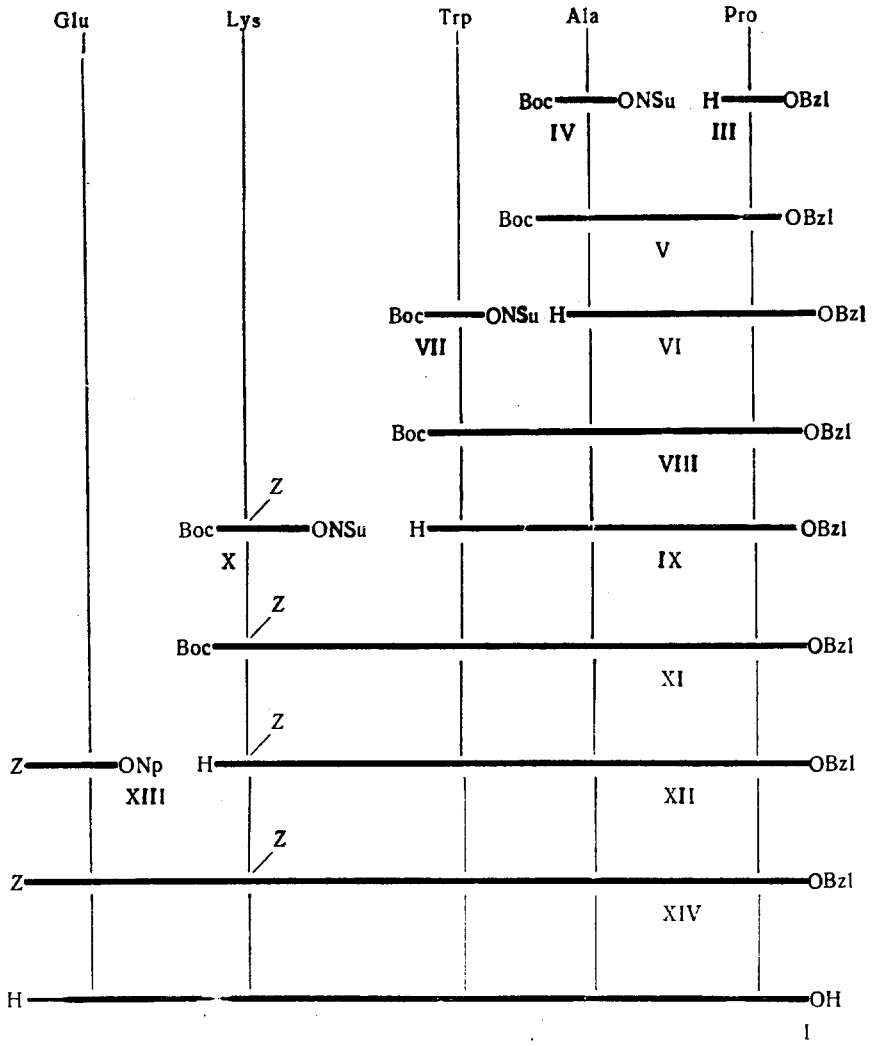
SCHEME I



We performed the synthesis of the peptide (I), which has been obtained previously by the solid-phase method [7], in accordance with Scheme I by the successive addition of N-protected amino acids to the benzyl ester of proline by the activated-ester method. Crystallization from a mixture of methanol and ether of the product obtained after the hydrogenation of the protected pentapeptide (XIV) gave the chromatographically and electrophoretically pure pentapeptide (I).

The undecapeptide (II) was obtained by Scheme II, which envisages the stepwise synthesis of the N-terminal heptapeptide and the C-terminal tetrapeptide, followed by the joining up of these fragments.* As the initial compound for obtaining the heptapeptide (XXXVIII) we used the dipeptide Arg^{+}-Pro^{-}, in which the protection of the ω-amino group of the arginine and of the carboxy group of the proline is effected by the formation of a strong intramolecular ionic bond. The use of the p-nitrophenyl esters of N-protected amino acids for the growth of the peptides chain led to high yields of pure substances at all the stages of the synthesis. The C-terminal fragment (XXIII) was obtained by the successive addition to the benzyl ester of proline of the Boc derivatives of proline and leucine with the aid of CDI and of N^{α}-Boc-N^{ε}-Z-lysine by the p-nitrophenyl ester method. The undecapeptide (II) obtained by the condensation of the fragments (XXXVIII and XXIII) in the presence of CDI

*After we had completed this part of the work, a paper by Japanese authors appeared which reported, without description, an experiment on the synthesis of the undecapeptide (II) performed by a different scheme [13].

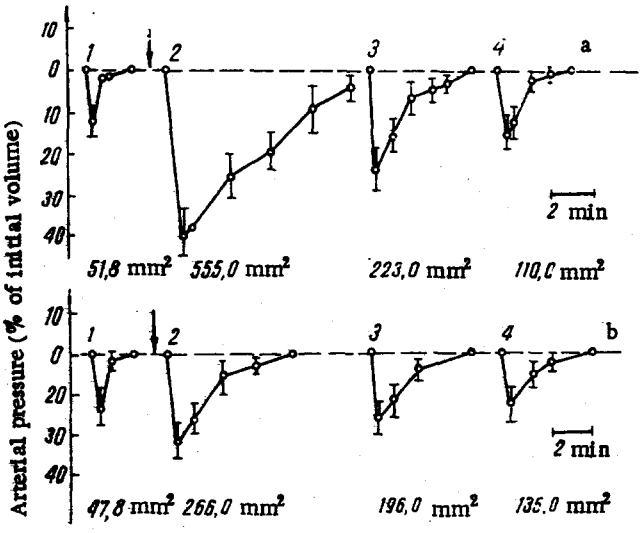


Fig. 1. Influence of the undecapeptide (II) (a) and of the pentapeptide (I) (b) on the hypotensive effect of bradykinin on decerebrated cats (the arrows denote the moment of introduction of the peptide): 1) control introduction of bradykinin; 2, 3, 4) injection 5, 15, and 30 min after the administration of the peptides (the figures below give the "areas of the hypotensive effect").

TABLE 1. Bradykin-Potentiating Activity of Peptides (I) and (II)

Tissue investigated	Number of the substances	Mean value of the "potentiating units" [1], μmole/ml	
		peptide (I)	peptide (II)
Guinea-pig intestine	19	0,06±0,021	0,02±0,012
Horn of the rat uterus	15	0,12±0,070	0,13±0,050

followed by the hydrogenation of the protected undecapeptide (XXXIX) was purified by crystallization from a mixture of methanol and ether.

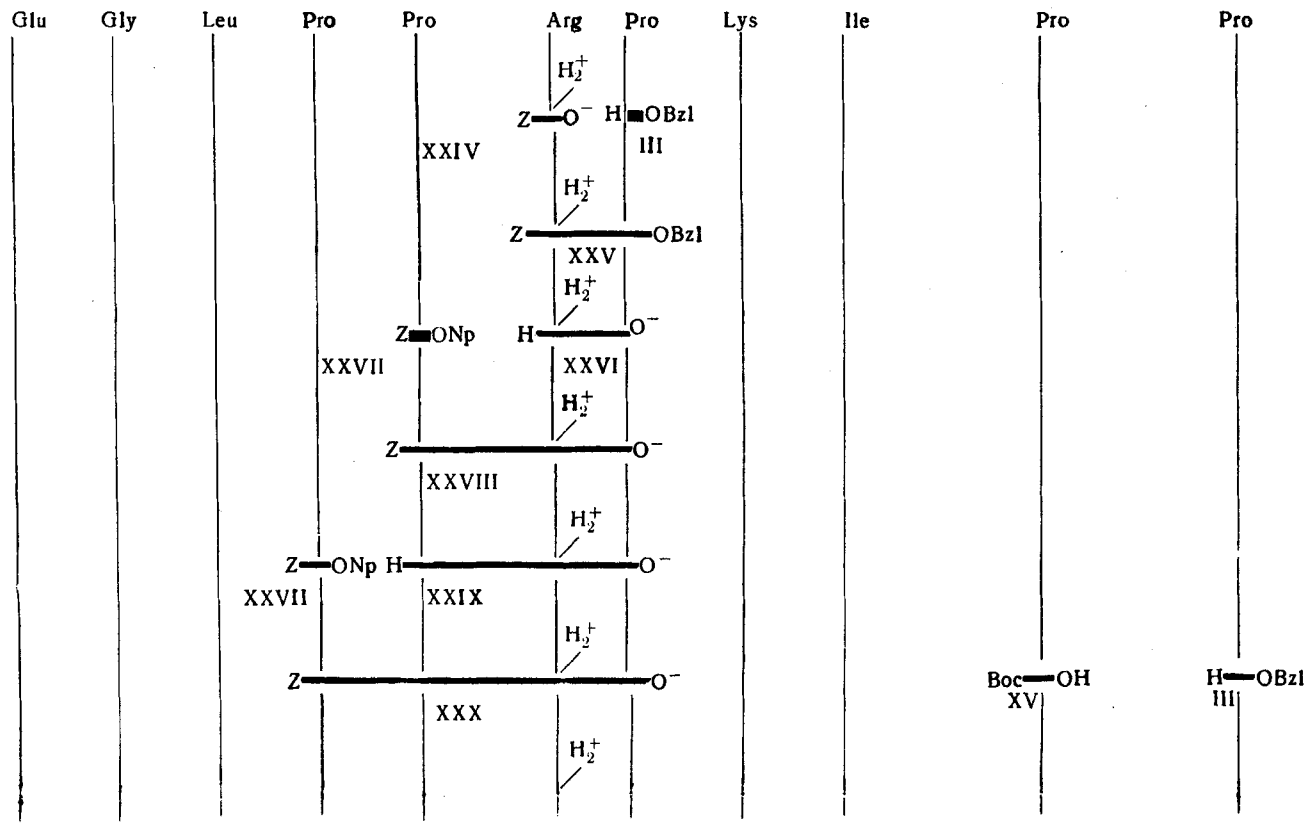
The pharmacological properties of the pentapeptide (I) have been studied in fairly great detail by Stewart et al. [7] in experiments on isolated organs of the smooth musculature (contractile action) and on the intact animal (hypotensive action and capillary permeability). So far as concerns the undecapeptide (II), its pharmacological investigation is limited to a determination of the contractile action on the rat uterus and on an isolated segment of the small intestine of the guinea pig [6, 9, 13]. On comparing the results obtained by the last test, Stewart came to the conclusion that the activity of the pentapeptide (I) was five times greater than that of the undecapeptide (II) [14].

The bradykinin-potentiating action of the peptides (I) and (II) that we synthesized were studied in in vivo experiments from their capacity for increasing the hypotensive effect of bradykinin on decerebrated cats and increasing the permeability of the vessels of the skin in rats. In addition, the influence of the peptides on the contractile action of bradykinin was checked in in vitro experiments on preparations of the guinea-pig intestine and rat uterus.

The depths of hypotension and also the "areas of the hypotensive effect" [15] caused by the administration of bradykinin before and after the injection of the potentiating peptides (I) and (II) are shown in Fig. 1. As can be seen from this, the undecapeptide (II) increases the hypotensive effect of bradykinin more than the pentapeptide (I).

The two peptides scarcely differ in their capacity for enhancing the actions of bradykinin on the rat uterus, but in experiments on a segment of the small intestine of the guinea pig the undecapeptide (II) is more active (Table 1). The divergence from information in the literature [14] is apparently due to the fact that this was based on the results of the

SCHEME II


Glu
Gly
Leu
Pro
Pro
Arg
Pro
Lys
Ile
Pro
Pro
H_2^+
Z—O⁻
H—OBzl
III
XXIV
Z—OBzl
XXV
Z—ONp
H—O⁻
XXVII
XXVI
Z—O⁻
XXVIII
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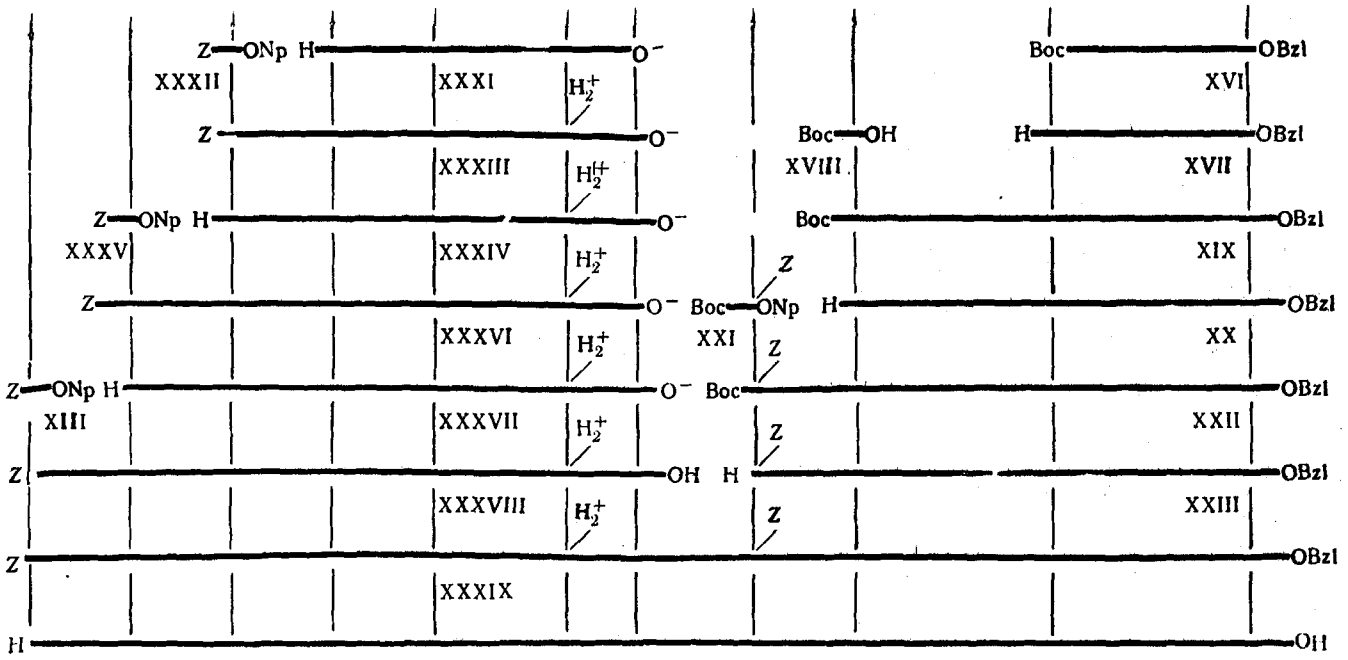
XXVII
XXIX
Z—O⁻
XXX
Boc—OH
XV
H—OBzl
III


Z—ONp H—O⁻
XXXII
XXXI
H₂⁺
Z—O⁻
XXXIII
H₂⁺
Z—ONp H—O⁻
XXXV
XXXIV
H₂⁺
Z—O⁻
XXXVI
H₂⁺
Z—ONp H—O⁻
XIII
XXXVII
H₂⁺
Z—OH
XXXVIII
H₂⁺
Z
XXXIX
H
Boc—OH
XVIII
Z
Boc—ONp
XXI
Z
Z
Z
H
Boc—OBzl
XVI
H—OBzl
XVII
Boc—OBzl
XIX
H—OBzl
XX
Boc—OBzl
XXII
H—OBzl
XXIII
OBzl
OH

II

testing of peptides performed under different conditions.

In a study of the influence of the peptides on the capacity of bradykinin for increasing the permeability of the vessels of the skin, we established that the combined injection of bradykinin and peptide (I) or (II) was accompanied by a considerable increase in the coloring of the skin (up to 15-20 mm in diameter as compared with 5 mm in the control). On comparing the activities of peptides (I) and (II) in this test, we found no fundamental difference between them, but in a number of cases we observed a somewhat greater intensity of the spot at the position of injection of the undecapeptide (II).

Our subsequent investigations were directed to determining the structural and conformational features of the BPPs responsible for their biological action.

EXPERIMENTAL

Synthesis of the Bradykinin-Potentiating Peptides (I) and (II). The melting points were determined on a heated block; they are given without correction. The purity of the compounds was checked by thin-layer chromatography on neutral alumina (activity grade II), and also by paper electrophoresis in a vertical instrument at 900 V, pH 2.4. The substances were revealed with the Sakaguchi reagent, ninhydrin, chlorine–iodine, and iodine. The amino acid compositions of the hydrolyzates obtained by boiling the peptides in sealed tubes with 6 N HCl for 48 h were determined on an automatic analyzer. Solutions of the substances in organic solvents were dried with $MgSO_4$ and evaporated in vacuum at a temperature not exceeding 40°C.

The yields and constants of the compounds obtained are given in Table 2. The elementary analyses of the compounds for which melting points are given in the table corresponded to the calculated values for the C, H, N, and Cl contents.

Hydrochloride of the Benzyl Ester of L-Alanyl-L-proline (VI). A solution of 0.4 g of the N-hydroxysuccinimide ester of Boc-L-alanine (IV) [16] in 3 ml of THF was added to a suspension of 0.37 g of the hydrochloride of the benzyl ester of L-proline (III) and 0.22 ml of TEA in 4 ml of DMFA, the mixture was stirred at room temperature for 20 h, the precipitate was filtered off, and the filtrate was evaporated. The residue was dissolved in ethyl acetate, and the solution was washed with 1 N NH_4OH, water, 1 N HCl, and water again, and was

TABLE 2. Constants and Yields of the Peptides

Compound	Empirical formula	mp, °C	$[\alpha]_D^{20}$, deg (c, solvent)	Electrophoretic mobility, E_{Leu}	Yield, %
I	$C_{28}H_{36}N_7O_7$	175—180	−8,1 (0,1; w*)		66
II	$C_{56}H_{81}N_{15}O_{13}$	203—206	−162 (0,05; w)	0,61	80
VI	$C_{15}H_{20}N_2O_3 \cdot HCl$	178—179	−78 (0,2; m†)		95
VIII	$C_{31}H_{38}N_4O_6 \cdot 1/2H_2O$	97—102	−65 (0,2; m)		84
IX	$C_{29}H_{36}N_4O_4 \cdot HCl \cdot H_2O$	138—140	−72 (0,2; m)		97
XI	$C_{44}H_{54}N_6O_9 \cdot H_2O$	126—129	−58 (0,23; m)		72
XII	$C_{39}H_{46}N_6O_7 \cdot HCl \cdot H_2O$	93—96	−66 (0,2; m)		60
XIV	$C_{52}H_{57}N_7O_{11}$	107—110	−61 (0,2; m)		62
XVII	$C_{16}H_{21}N_3O_3 \cdot HCl$	188—189	−156 (0,18; w)	2,4	93
XX	$C_{23}H_{33}N_3O_4 \cdot HCl \cdot H_2O$	138—140	−93 (0,2; m)	1,2	83
XXIII	$C_{37}H_{51}N_5O_7 \cdot HCl \cdot 3H_2O$	103—107	−58 (0,23; m)	0,91	87
XXV	$C_{20}H_{33}N_3O_5 \cdot HCl$	175—176	−57 (0,076; m)		55
XXVI	$C_{11}H_{21}N_3O_3$	Oil	−7,5 (0,6; w)		91
XXVIII	$C_{24}H_{34}N_8O_8$	165—167	−94 (0,3; w)	1,6	84
XXIX	$C_{16}H_{28}N_4O_4$	Oil	−85 (0,8; w)	2,4	90
XXX	$C_{29}H_{41}N_7O_7$	158—160	−137 (0,09; w)	1,15	79
XXXI	$C_{21}H_{35}N_7O_5$	Oil	−143 (0,1; w)	2,1	95
XXXIII	$C_{35}H_{52}N_8O_8$	152—153	−122 (0,05; w)	0,94	93
XXXIV	$C_{27}H_{46}N_8O_6$	Oil	−120 (0,035; w)	1,96	96
XXXVI	$C_{37}H_{55}N_9O_9 \cdot 4H_2O$	161—163	−121 (0,08; w)	0,85	76
XXXVII	$H_{29}H_{49}N_9O_7$	Oil	−168 (0,12; w)	1,45	96
XXXVIII	$C_{42}H_{60}N_{10}O_{11} \cdot 3H_2O$	185—187	−204 (0,03; w)	0,61	79
XXXIX	$C_{79}H_{107}N_{15}O_{17} \cdot HCl$	—	—	0,76	91

*w) water; †m) ethanol.

evaporated. This gave 0.45 g (85%) of the Boc-dipeptide (V) in the form of a chromatographically homogeneous oil. The substance was dissolved in 3 ml of methanol, and 1.5 ml of 5 N HCl was added, and after 30 min the solution was evaporated and the residue crystallized from a mixture of methanol and ether.

Benzyl Ester of tert-Butoxycarbonyl-L-tryptophyl-L-alanyl-L-proline (VIII). A solution of 0.3 g of the N-hydroxysuccinimide ester of Boc-L-tryptophan (VII) [16] in 5 ml of THF was added to a solution of 0.26 g of the hydrochloride of the ester (VI) and 0.12 ml of TEA in 2 ml of DMFA. The mixture was stirred at room temperature for 20 h, the precipitate was filtered off, and the filtrate was evaporated. The residue was dissolved in ethyl acetate, and the solution was washed with 1 N NH_4OH, water, 5% citric acid, and water again, and was evaporated. The residue was reprecipitated from ethanol with water.

Hydrochloride of the Benzyl Ester of L-Tryptophyl-L-alanyl-L-proline (IX). A solution of 0.35 g of the protected tripeptide (VIII) in 3 ml of methanol was treated with 1.5 ml of 5 N HCl in ether, and after 30 min the mixture was evaporated. The residue was crystallized from a mixture of methanol and ether.

Benzyl Ester of N^{α}-tert-Butoxycarbonyl-N^{ϵ}-benzyloxycarbonyl-L-lysyl-L-tryptophyl-L-alanyl-L-proline (XI). To a suspension of 0.35 g of the hydrochloride of the ester of the tripeptide (IX) in 2 ml of DMFA was added 0.1 ml of TEA and a solution of 0.3 g of the N-hydroxysuccinimide ester of N^{α}-Boc-N^{ϵ}-Z-L-lysine (X)* in 5 ml of THF. The reaction mixture was kept at room temperature for 20 h and was filtered, and the filtrate was evaporated. The residue was dissolved in ethyl acetate, and the solution was washed with 1 N NH_4OH, water, 5% citric acid, and water again, and was evaporated. The residue was triturated with dry ether and the precipitate obtained was reprecipitated from ethanol with water.

Hydrochloride of the Benzyl Ester of N^{ϵ}-Benzyloxycarbonyl-L-lysyl-L-tryptophyl-L-alanyl-L-proline (XII). A solution of 0.18 g of the protected tetrapeptide (XI) in 2 ml of methanol was treated with 1 ml of a 5 N solution of HCl in ether. After 30 min, the solution was evaporated and the residue was crystallized from a mixture of methanol and ether.

Benzyl Ester of Benzyloxycarbonyl-L-pyroglutamyl-N^{ϵ}-benzyloxycarbonyl-L-lysyl-L-tryptophyl-L-alanyl-L-proline (XIV). To a solution of 0.1 g of the hydrochloride of the tetrapeptide ester (XII) in 0.5 ml of DMFA were added 0.02 ml of TEA and 0.42 g of the p-nitrophenyl ester of Z-L-pyroglutamic acid (XIII) [17]. After 48 h, the solvent was distilled off, the residue was distilled in ethyl acetate, and the solution was washed with 1 N NH_4OH, water, 1 N HCl, and water again, and was evaporated. The residue was triturated with dry ether, and the precipitate was filtered off.

L-Pyroglutamyl-L-lysyl-L-tryptophyl-L-alanyl-L-proline (I). The protected pentapeptide (XIV) (0.07 g) was hydrogenated with Pd black in methanol. The catalyst was filtered off, the solution was evaporated, and the residue was crystallized from a mixture of methanol and ether.

Amino acid analysis: Glu 1.00, Lys 1.09, Ala 1.02, Pro 0.96, Trp (determined spectrophotometrically, λ_{max} 274 nm in water), 99.8%.

Hydrochloride of the Benzyl Ester of L-Prolyl-L-proline (XVII). At 0°C, a solution of 1.48 ml of TEA in 3 ml of methylene chloride was added to a suspension of 2.0 g of the hydrochloride of the benzyl ester of L-proline (III) in 8 ml of methylene chloride, and the mixture was stirred at 0°C for 15 min. Then it was cooled to −5°C and solutions of 1.78 g of Boc-L-proline (XV) in 4 ml of methylene chloride and of 1.76 g of CDI in 2 ml of methylene chloride were added successively, and after being stirred at −5°C for 1 h the mixture was left at room temperature for 12 h. The precipitate of DCU was filtered off, the solvent was distilled off, the residue was dissolved in 50 ml of ethyl acetate, and the solution was washed with 5% $NaHCO_3$, water, 5% citric acid, and water again, and was evaporated. The yield of the protected dipeptide (XVI) was 2.57 g (77%). A solution of 2.57 g of this peptide (XVI) in 6 ml of glacial acetic acid was treated with 20 ml of 1 N HCl in glacial acetic acid and the mixture was kept at room temperature for 30 min. Then the solvent was distilled off and the residue was triturated with dry ether, filtered off, and dried.

*Obtained by the method of Anderson et al. [16]. Yield 70%, mp 53-54°C (from ether).

The benzyl ester of tert-butoxycarbonyl-L-isoleucyl-L-prolyl-L-proline (XIX) was obtained from 2.0 g of the hydrochloride of the dipeptide ester (XVII) in a similar manner to (XVI). Yield 2.52 g (69%).

The hydrochloride of the benzyl ester of L-isoleucyl-L-prolyl-L-proline (XX) was obtained from 2.52 g of the protected tripeptide (XIX) similary to compound (XVII).

Benzyl Ester of N^{α}-tert-Butoxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysyl-L-isoleucyl-L-prolyl-L-proline (XXII). A solution of 1.53 g of the hydrochloride of the ester (XX) in 10 ml of water was passed through a column of IRA-410 ion-exchange resin in the OH^- form. The eluate was evaporated in vacuum. The residue was dissolved in 1.5 ml of DMFA, a solution of 1.7 g of the p-nitrophenyl ester (XXI) [18] in 1.5 ml of DMFA was added, and the mixture was left at 40°C for 12 h. The solvent was distilled off, the residue was dissolved in 100 ml of ethyl acetate, and the solution was washed with a 1 N solution of NH_4OH, water, a 5% solution of citric acid, and water again, and was evaporated.

Hydrochloride of the Benzyl Ester of N^{ε}-Benzyloxycarbonyl-L-lysyl-L-isoleucyl-L-prolyl-L-proline (XXIII). Substance (XXIII) was obtained from 2.08 g of the protected tetrapeptide (XXII) in a similar manner to compound (XVII).

Amino acid analysis: Ile 0.98, Pro 2.16, Lys 0.90.

Hydrochloride of the Benzyl Ester of N^{α}-Benzyloxycarbonyl-L-arginyl-L-proline (XXV). With stirring, 0.34 g of CDI in 0.05 ml of DMFA was added to a solution of 0.5 g of N^{α}-Z-L-arginine (XXIV) and 0.39 g of the hydrochloride of the benzyl ester of L-proline (III) in 1.5 ml of DMFA cooled to −10°C, and the mixture was left at room temperature for 12 h. The precipitate was filtered off, and from the filtrate ethyl acetate precipitated the hydrochloride of the dipeptide (XXV), which was then recrystallized from a mixture of ethanol and ether.

L-Arginyl-L-proline (XXVI). A solution of 0.73 g of the protected dipeptide (XXV) in 7 ml of methanol was hydrogenated with Pd black. The catalyst was filtered off, the solution was evaporated, the residual oil (0.42 g) was dissolved in 4 ml of water, and the solution was passed through a column of IRA-410 ion-exchange resin in the OH^- form. The eluate was evaporated in vacuum.

Benzyloxycarbonyl-L-prolyl-L-arginyl-L-proline (XXVIII). A solution of 0.22 g of the dipeptide (XXVI) in 0.5 ml of water was treated with 0.39 g of the p-nitrophenyl ester of Z-L-proline (XXVII) in 0.5 ml of dioxane. The reaction mixture was left at 45°C for 2 h, the solvent was distilled off, the residue was dissolved in 1 ml of dry DMFA, and the solution was left at 40°C for 12 h. Then dry ethyl acetate precipitated the N-substituted tripeptide (XXVIII).

L-Prolyl-L-arginyl-L-proline (XXIX). A solution of 0.35 g of the benzyloxycarbonyltripeptide (XXVIII) in 3 ml of a 36% solution of HBr in glacial acetic acid was left at room temperature for 1 h. Then the solution was evaporated in vacuum and the residue was triturated with dry ether. The precipitate was filtered off and dissolved in 5 ml of water, the solution was passed through a column of IRA-410 ion-exchange resin in the OH^- form, and the eluate was evaporated.

The benzyloxycarbonylpeptides (XXX), (XXXIII), (XXXVI), and (XXXVIII) were obtained in a similar manner to compound (XXVIII).

Amino acid analysis of the Z-heptapeptide (XXXVIII): Glu 0.95, Gly 1.08, Leu 1.00, Arg 0.96, Pro 3.09.

The peptides (XXXI), (XXXIV), and (XXXVII) were obtained in the same way as compound (XXIX) from the benzyloxycarbonylpeptides (XXX), (XXXIII), and (XXXVI), respectively.

Pyroglutamylglycyl-L-leucyl-L-prolyl-L-prolyl-L-arginyl-L-prolyl-L-lysyl-L-isoleucyl-L-prolyl-L-proline (II). A solution of 0.39 g of the heptapeptide (XXXVII) and 0.316 g of the hydrochloride of the tetrapeptide ester (XXIII) in 1.5 ml of dry DMFA was cooled to −10°C, and a solution of 0.09 g of CDI in 0.5 ml of DMFA was added. The reaction mixture was stirred at 0°C for 1.5 h and was left to stand for 12 h. The precipitate was filtered off, and the addition of ethyl acetate to the filtrate yielded 0.62 g (91%) of the hydrochloride of the substituted undecapeptide (XXXIX).

Amino acid analysis: Glu 0.91, Gly 0.90, Pro 5.14, Leu 1.16, Ile 1.04, Arg 1.01, Lys 0.96.

The substance obtained (0.5 g) was dissolved in 10 ml of methanol and was hydrogenated with Pd black. The catalyst was filtered off, the solvent was distilled off in vacuum, the residue was dissolved in 10 ml of water, and the solution was passed through a column of IRA-410 ion-exchange resin in the OH^- form. The eluate was evaporated, and the undecapeptide (II) was crystallized from a mixture of methanol and ether.

Pharmacological Tests of the Peptides (I) and (II). The way in which the hypotensive action of bradykinin changed under the influence of the peptides (I) and (II) was investigated on decerebrated cats. The bradykinin* was injected intravenously in doses causing a considerable hypotensive effect (2-4 μg/kg). The depressor reaction in response to the bradykinin was recorded before the administration of the peptides and 5, 15, and 30 min after the intravenous injection (3 μmole/kg). The average results of five experiments are shown in Fig. 1.

The influence of the peptides (I) and (II) on the capacity of bradykinin for increasing the pearmeability of the vessels of the skin was studied on 20 albino rats to which Evans Blue (100 mg/kg) had been administered 5 min before the injection of the substances under investigation [15] (sic). The bradykinin (1 μg in 0.05 ml) was injected subcutaneously alone or in combination with the 0.02 μmole of the peptide under investigation. Control injections of all the substances investigated in the same amounts were made in other parts of the skin of the experimental rat. The rats were sacrificed 20 min after the injection of the preparation. The diameters of the colored sections on the inner surface of the skin were measured and the comparative intensities of the colorations of the tissue were estimated visually.

The potentiating action of the peptides (I) and (II) in in vitro experiments were compared on isolated rat uterus and a section of the small intestine of the guinea pig. The preparations of the uterus and the intestine were placed in a bath with a volume of 5 ml and were kept in nutrient solution at constant temperature (30°C for the isolated uterus, Jelon's solution, and 36°C for the isolated intestine, Tyrode's solution) with aeration by a mixture of 95% O_2 + 5% CO_2. The surfaces in contact with the solutions had previously been coated with a layer of paraffin wax. In both cases, for each peptide the "potentiating unit" [1], i.e., the concentration of potentiating peptide that would increase the effect of the concentration of bradykinin taken to the value observed with the action of twice the dose of hormone. On each preparation, after the appropriate washing out, the "potentiating unit" was determined a minimum of three times, and the mean value was used for calculation. The working concentrations of bradykinin were selected in such a way that the ratio of the magnitudes of the effects of an ordinary and a double dose of bradykinin was 1:2.

SUMMARY

A pentapeptide and undecapeptide possessing bradykinin-potentiating action have been synthesized, and they have been subjected to comparative pharmacological investigation.

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*The work was performed with bradykinin (triacetate) synthesized in the laboratory of peptide synthesis of the M. M. Shemyakin Institute of the Chemistry of Natural Compounds of the Academy of Sciences of the USSR [19].

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