LITERATURE CITED

1. K. P. Balitskii and I. G. Veksler, Reactivity of the Body and the Chemotherapy of Tumors[in Russian], Kiev (1975).
2. I. G. Veksler, Oncology [in Russian], Kiev (1977), No. 8, pp. 24-28.
3. I. G. Veksler, Byull. Eksp. Biol., No. 7, 64-66 (1980).
4. V. A. Kabanov, R. V. Petrov, and R. M. Khaitov, Zh. Vses. Khim. Obshch. im. D. I. Mendeleeva, 27, No. 4, 57-68 (1982).
5. R. E. Kavetskii, K. P. Balitskii, I. G. Veksler, et al., Vopr. Onkol., 23, No. 11, 88-93 (1977).
6. A. F. Nikolaev, V. M. Bondarenko, and N. K. Shakalova, Vysokomol. Soedin., 15B, No. 10, 737-740 (1973).
7. R. V. Petrov, R. M. Khaitov, and R. I. Ataullakhanov, Immunogenetics and Artificial Antigens [in Russian], Moscow (1983).
8. J. S. Haskill, B. Elliott, and R. Kerber, J. Exp. Med., 135, No. 6, 1410-1415 (1972).
9. N. K. Jerne and A. A. Nordin, Science, 140, 405-407 (1963).
10. P. U. LaGrange, G. D. Mackaness, and T. E. Miller, J. Exp. Med., 139, 528-542 (1974).

SYNTHESIS OF STRUCTURAL ANALOGS OF THE 13-16 FRAGMENT OF GASTRIN, AND THEIR EFFECTS ON GASTRIC SECRETION

Yu. M. Taskaeva, G. A. Korshunova, L. S. Vasilevskaya, and Yu. P. Shvachkin

UDC 615.357:577.175.322].012.1.07

In a study of the relationships between structure and activity in gastrin derivatives, we have previously synthesized and examined the properties of the novel peptides (II-VIII), which are structural analogs of the 13-16 fragment (I) of human gastrin [5].

Compounds (II-V) are tetrapeptidamides, which differ from natural gastrin fragment I in the replacement of the L-methionine residue at position 15 by L-leucine, and modification or substitution of the glycine residue in position 13. Compound (II) contains an N-tert-Butoxycarbonylglycine residue, and in (III-V) the glycine residue at 13 is replaced by γ-aminobutyric, δ-aminovaleric, or ε-aminocaproic acid respectively.

	13 14 15 16	
H —	Gly — Trp — Met — Asp — NH_2	I
Boc—	Gly—Trp—Leu—Asp—NH_2	II
Boc—	γ—Abu—Trp—Leu—Asp—NH_2	III
Boc—	δApe—Trp—Leu—Asp—NH_2	IV
Boc—	ε—Ahx—Trp—Leu—Asp—NH_2	V
Boc—	Trp—γ—Abu—Asp—NH_2	VI
Boc—	Trp—δ—Ape—Asp—NH_2	VII
Boc—	Trp—ε—Ahx—Asp—NH_2	VIII

Boc is tert-butoxycarbonyl, γ-Abu is the γ-aminobutyric acid residue, δ-Ape is the δ-aminovaleric acid residue, and ε-Ahx is the ε-aminocaproic acid residue [3].

Compounds (VI-VIII) form a tripeptidamide subgroup in which the N-terminal group is N-tert-butoxycarbonyl-L-tryptophan, and the central unit is one of the above-mentioned nonproteinogenic aminoacids.

In planning the synthesis of these compounds, it was borne in mind that the smallest fragment to show the full spectrum of biological activity of gastrin is its C-terminal tetrapeptide [5], and that removal of the C-terminal L-phenylalanine residue results in the appearance of antisecretor activity in gastrin derivatives [4]. It was also taken into account that replacement of the L-methionine residue in position 15 by L-leucine has no effect on the activity of gastrin peptides [4] while at the same time giving more stable compounds.

M. V. Lomonosov Moscow State University. Institute of Nutrition, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 2, pp. 124-127, February, 1990. Original article submitted February 22, 1989.

0091-150X/90/2402-0117$12.50

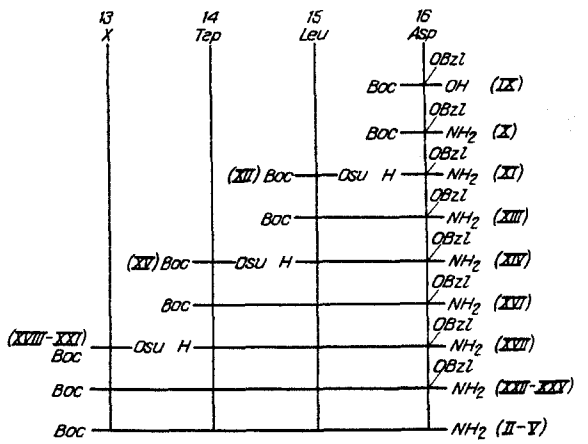
The introduction of hydrophobic groups into the N-terminal region of the peptides should facilitate the bonding of these compounds to the appropriate receptors [4, 5]. The use of three homologous ω-amino acids (γ-aminobutyric, δ-aminovaleric, and ε-aminocaproic) at positions 13 and 15 of the tetrapeptidamide (I) makes it possible to determine experimentally the effects of the distance between the terminal amino-group and the L-tryptophan residue (in III-V) and the L-tryptophan and L-asparaginic acid residues (in VI-VIII) on the biological activity of the new structural analogs of the tetrapeptidamide (I).

Compounds (II-V) were synthesized in solution by stepwise extention of the peptide chain, commencing with the C-terminus (Scheme 1).

The amino-components used in the peptide syntheses were L-asparaginic acid α-amide β-benzyl ester (XI) and the amides of the appropriate intermediate peptides. The carboxyl components for the peptide syntheses were the N-hydroxysuccinimide esters of the appropriate protected aminoacids. As will be seen from Scheme 1, the starting materials for these syntheses were N-tert-butoxycarbonyl-L-asparaginic acid β-benzyl ester (IX), N-tert-butoxycarbonyl-L-leucine N-hydroxysuccinimide ester (XII), N^{α}-tert-butoxycarbonyl-L-tryptophan N-hydroxysuccinimide ester (XV), and the N-hydroxysuccinimide esters of N-tert-butoxycarbonylglycine (XVIII), N-tertbutoxycarbonyl-γ-aminobutyric acid (XX), and N-tert-butoxycarbonyl-ε-aminocaproic acid (XXI).

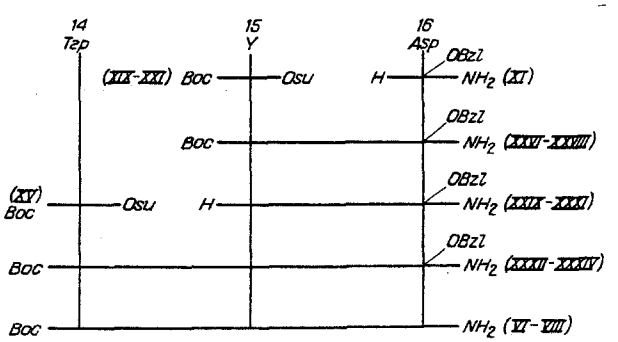
The intermediates were N-tert-butoxycarbonyl-L-asparaginic acid α-amide β-benzyl ester (X) the abovementioned amide (XI), N-tert-butoxycarbonyl-L-leucyl-β-benzyl-L-asparaginamide (XIII), L-leucyl-β-benzyl-L-asparaginamide (XIV), N-tert-butoxycarbonyl-L-tryptophyl-L-leucyl-β-benzyl-L-asparaginamide (XVI), L-tryptophyl-L-leucyl-β-benzyl-L-asparaginamide (XVII), N^{α}-tert-butoxycarbonylglycyl-L-tryptophyl-L-leucyl-β-benzyl-L-asparaginamide (XXII), N-tert-butoxycarbonyl-γ-aminobutyryl-L-tryptophyl-L-leucyl-β-benzyl-L-asparaginamide (XXIII),

SCHEME 1



Here and in Scheme 2: X = Gly, γ-Abu, δ-Ape, and ε-Ahx; and OSu is the N-hydroxysuccinimide ester.

SCHEME 2



N-tert-butoxycarbonyl-δ-aminovaleryl-L-tryptophyl-L-leucyl-β-benzyl-L-asparaginamide (XXIV), and N-tert-butoxycarbonyl-ε-aminocaproyl-L-tryptophyl-L-leucyl-β-benzyl-L-asparaginamide (XXV).

In order to remove the tert-butoxycarbonyl protection from the intermediate amides, they were subjected to acidolysis (treatment with CF_3COOH or HCl in an organic solvent). Removal of the ester protection (β-benzyl esters of the L-asparaginic acid residues) was effected by catalytic hydrogenolysis.

In accordance with Scheme 1, there were obtained N-tert-butoxycarbonyl-glycyl-L-tryptophyl-L-leucyl-L-asparaginic acid α-amide (II), N-tert-butoxy-carbonyl-γ-aminobutyryl-L-tryptophyl-L-leucyl-L-asparaginic acid α-amide (III), N-tert-butoxycarbonyl-δ-aminovaleryl-L-tryptophyl-L-leucyl-L-asparaginic acid α-amide (IV), and N-tert-butoxycarbonyl-ε-aminocaproyl-L-tryptophyl-L-leucyl-L-asparaginic acid α-amide (V).

Compounds (VI-VIII) were synthesized as in Scheme 2. The starting materials used were the amide (XI), and N-hydroxysuccinimide esters of the N-tert-butoxy-carbonyl-ω-aminoacids (XIX-XXI), and the N-hydroxysuccinimide ester of N-tert-butoxycarbonyl-L-tryptophan (XV). The intermediate compounds were N-tert-butoxycarbonyl-γ-aminobutyryl-β-benzyl-L-asparaginamide (XXVI), N-tert-butoxycarbonyl-δ-aminovaleryl-β-benzyl-L-asparaginamide (XXVII), N-tert-butoxycarbonyl-ε-aminoacaproyl-β-benzyl-L-asparaginamide (XXVIII), the dipeptidamides with a free ω-amino-group (XXIX-XXXI), N-tert-butoxycarbonyl-L-tryptophyl-γ-aminobutyryl-β-benzyl-L-asparaginamide (XXXII), N-tertbutoxycarbonyl-L-tryptophyl-δ-aminovaleryl-β-benzyl-L-asparaginamide (XXXIII), and N-tert-butoxycarbonyl-L-tryptophyl-ε-aminocaproyl-β-benzyl-L-asparaginamide (XXXIV).

Removal of the protecting ester (benzyl) groups from the protected tripeptidamides (XXXII-XXXIV) gave N-tert-butoxycarbonyl-L-tryptophyl-γ-aminobutyryl-L-asparaginic acid α-amide (VI), N-tert-butoxycarbonyl-L-tryptophyl-δ-aminovaleryl-L-asparaginic acid α-amide (VII), and N-tert-butoxycarbonyl-L-tryptophyl-ε-aminocaproyl-L-asparaginic acid β-amide (VIII).

The effects of these compounds on gastric secretion were assessed in dogs.

EXPERIMENTAL (CHEMISTRY)

Thin layer chromatography (TLC) was carried out on Silufol UV-254 plates (Czech SSR) in the following solvent systems: chloroform–methanol, 4:1 (A), 2-propanol–25% ammonia-water, 14:1:5 (B), butanol-acetic acid-water, 4:1:1 (C), benzene–acetone–acetic acid, 50:25:2 (D), acetone–hexane, 7:3 (E) ethyl acetate–methanol–acetic acid, 95:5:1 (F), and chloroform–ethanol–acetic acid, 17:2:1 (G). The eluent used for several of the compounds was ethyl acetate (H).

The compounds were detected on the chromatograms with ninhydrin, the tryptophan-containing peptides also being detected by UV. UV spectra were obtained on a Varian Cary-219 spectrophotometer (Switzerland), using ethanol as solvent. The amino acids present in the hydrolyzates were determined quantitatively using an automated Hitachi KLA-3B amino acid analyzer (Japan). Acid hydrolysis of the peptides was effected under standard conditions (6N HCl, 105°C, 24 h) in sealed and previously evacuated ampuls. The optical rotations of the compounds were measured on a DIP 360 polarimeter (Jasco, Japan). The concentrations of the solutions and the solvents used are given for each compound. Melting points were determined on a Boetius VEB analytic apparatus (East Germany).

N-tert-Butoxycarbonyl-β-benzyl-L-asparaginic Acid β-Amide (X). To a solution of 8 g (24.6 mmole) of β-benzyl N-tert-butoxycarbonyl-L-asparaginate (IX) in 20 ml o f DMF was added 5 g (27.2 mmole) of pentafluorophen ol, the mixture cooled to 0°C, and a solution of 5.6 g (27.2 mmole) of N,N'-dicylohexyl-carbodiimide (DCHC) in 5 ml of DMF added. the mixture was stirred for 1 h at 0°C and 16 h at 20°C, cooled to 0°C, and filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue reprecipitated from ethyl acetate with hexane. To 9.3 g (19 mmole) of the resulting α-pentafluorophenyl N-tert-butoxycarbonyl-β-benzyl-L-asparaginate was added 30 ml of dioxane and 7 ml of 12.5% aqueous ammonia. The mixture was stirred for 1 h at 20°C, evaporated under reduced pressure, the residue triturated with 50 ml of water, and the solid filtered off, washed with water, and dried in vacuo over P_2O_5 to give 5.1 g (63%) of (X), mp 160-161°C, R_f 0.89 (A), 0.86 (B).

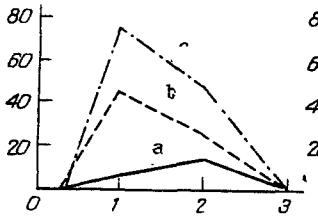


Fig. 1

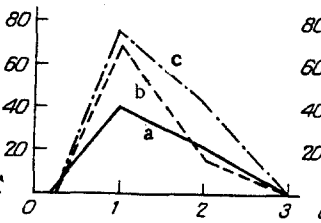


Fig. 2

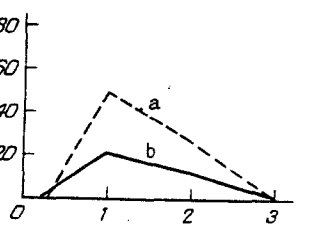


Fig. 3

Fig. 1. Increased gastric secretion induced by pentagastrin in the presence of (II). a) effect of (II) (5 mg); b) effect of pentagastrin (50 μg); c) effect of (II) (5 mg) in the presence of pentagastrin (50 μg). Here and in Figs. 2 and 3, the horizontal axis represents the time in hours, and the vertical axis the volume of gastric juice in ml.

Fig. 2. Dose-dependent effect of (II) on gastric secretion. a) effect of pentagastrin (50 μg); b) effect of (II) (2.5 mg) in the presence of pentagastrin (50 μg); c) effect of (II) (5 mg) in the presence of pentagastrin (50 μg).

Fig. 3. Inhibition of gastric secretion induced by pentagastrin on treatment with (II). a) effect of pentagastrin (50 μg); b) effect of (II) (60 mg) in the presence of pentagastrin (50 μg).

L-Asparaginic Acid β-Benzyl Ester α-Amid (XI). To 2.5 g (7.8 mmole) of (X) was added 10 ml of a 79% solution of CF_3COOH in dichloromethane, and the mixture kept for 30 min at 20°C. It was then evaporated to dryness under reduced pressure, the oily residue triturated with diethyl ether, and the crystalline solid filtered off and dried in vacuo to give 2.5 g (96%) of (XI) as its trifluoroacetate, mp 172-174°C, R_f 0.30 (A).

N-tert-Butoxycarbonyl-L-leucyl-β-benzyl-L-asparaginic Acid α-Amide (XIII). To a solution of 1.1 g (3 mmole) of (XI) in 4 ml of DMF was added 0.42 ml (3 mmole) of Et_3N, and the mixture stirred for 20 min at 20°C. It was then cooled to 0°C, 0.89 g (2.7 mmole) of N-tert-butoxycarbonyl-L-leucine N-hydroxy-succinimide ester (XII) [2] added, and stirred for 1 h at 0°C and 1 day at 20°C. The mixture was then evaporated to dryness, dissolved in 100 ml of ethyl acetate, washed with 0.1 N HCl and water, and dried over $MgSO_4$. The solution was evaporated to dryness, to give 0.81 f (72%) of (XIII) as a colorless, crystalline powder, mp 105-107°C, R_f 0.76 (A), 0.77 (H).

L-Leucyl-β-benzyl-L-asparaginic Acid α-Amide (XIV). Obtained as for (XI), from 1.4 g (3.34 mmole) of (XIII) and 10 ml of 70% CF_3COOH in dichloromethane. Yield 1.2 g (86%) of (XIV) as its trifluoroacetate, mp 61-63°C, R_f 0.35 (A), 083 (B).

N-tert-Butoxycarbonyl-L-tryptophyl-L-leucyl-β-benzyl-L-asparaginic Acid α-Amide (XVI). Obtained as for (XIII), from 1.3 g (3.2 mmole) of (XV) [2], 1.6 g (3.6 mmole) of (XIV), and 0.5 ml (3.6 mmole) of Et_3N. The product was reprecipitated from methanol with ether, to give 1.8 g (97%) of product, mp 142-144°C, R_f 0.69 (E), 0.53 (H).

L-Tryptophyl-L-leucyl-β-benzyl-L-asparaginic Acid α-Amide (XVII). To 10 ml of 6.3 N HCl in dioxane was added 0.35 ml of anisole, and argon passed through the solution. Compound (XVI) (600 mg, 1 mmole) was added, and the mixture kept for 2 h at 20°C under argon. It was then concentrated, and resulting oil washed with ether. The compound (0.54 g, 100%) was obtained as its hydrochloride, mp 175-177°C, R_f 0.46 (A), 0.87 (B), 0.45 (D).

N-tert-Butoxycarbonylglycyl-L-tryptophyl-L-leucyl-β-benzyl-L-asparaginic Acid α-Amide (XXII). Obtained as for (XIII), from 0.2 g (0.37 mmole) of (XVII), 0.091 g (0.33 mmole) of N-tert-butoxycarbonylglycine N-hydroxy-succinimide ester (XVIII) [2], and 0.05 ml (0.37 mmole) of Et_3N. The product was reprecipitated from methanol with ether, to give 0.12 g (60%) of material, mp 118-120°C, R_f 0.70 (A), 0.82 (B), 0.91 (C).

N^{γ}-tert-Butoxycarbonylaminobutyryl-L-tryptophyl-L-leucyl-β-benzyl-L-asparaginic Acid α-Amide (XXIII). Obtained as for (XII), from 0.30 g (0.55 mmole) of (XVIII), 0.17 g (0.55 mmole) of N^{γ}-tert-butoxycarbonylaminobutyric acid N-hydroxysuccinimide ester (XIX) [2], and 0.08 ml (0.55 mmole) of Et_3N. The product was reprecipitated from methanol with ether, to give 0.18 g (52%) of material, mp 141-143°C, R_f 0.72 (A), 0.79 (G).

N^{δ}-tert-Butoxycarbonylaminovaleryl-L-tryptophyl-L-leucyl-β-benzyl-L-asparaginic Acid α-Amide (XXIV). Obtained as for (XIII), from 0.30 g (0.55 mmole) of (XVIII), 0.16 g (0.49 mmole) of N^{δ}-tert-butoxycarbonylaminovaleric acid N-hydroxysuccinimide ester (XX) [2], and 0.08 ml (0.55 mmole) of Et_3N. The product was purified on a column of silica gel, to give 0.25 g (64%) of an oil, R_f 0.9 (A), 0.94 (B), 0.89 (C), 0.29 (H).

N^{ε}-tert-Butoxycarbonylaminocaproyl-L-tryptophyl-L-leucyl-β-benzyl-L-asparaginic Acid α-Amide (XXV). Obtained as for (XIII), from 0.35 g (0.65 mmole) of (XVIII), 0.28 g (0.72 mmole) of N-tert-butoxycarbonylaminocaproic acid N-hydroxysuccinimide ester (XXI) [2], and 0.091 ml (0.65 mmole) of Et_3 N. The product was reprecipitated from methanol with ether, to give 0.35 g (75%) of an oil, R_f 0.76 (A), 0.90 (C), 0.33 (H).

N-tert-Butoxycarbonylglycyl-L-tryptophyl-L-leucyl-L-asparaginic Acid α-Amide (II). A solution of 0.12 g (0.20 mmole) of (XXII) in 80% methanol was subjected to hydrogenolysis in the presence of 10% Pd/C for 4 h. The mixture was then filtered and concentrated, and the residue reprecipitated from methanol with ether, to give 0.064 g (35%) of material, mp 199-201°C, R_f 0.56 (A), 0.75 (B), $[\alpha]_D^{20}$ - 28° (c 1.0, DMF), UV spectrum: λ_{min} 250 mnm, ε 1520; λ_{max} 284 nm, ε 4740; λ_{max} 293 nm, ε 3960. Amino acid analysis: Gly 1.00 (1), Asp 0.98 (1), Leu 1.16 (1).

N^{γ}-tert-Butoxycarbonylaminobutyryl-L-tryptophyl-L-leucyl-L-aspraginic Acid α-Amide (III). Obtained as for (II), from 0.12 g (0.17 mmole) of (XXIII). The product was reprecipitated from methanol with water, to give 0.098 g (97%) of materialm mp 232-234°C, R_f 0.59 (A), 0.74 (B), 0.94 (C), $[\alpha]_D^{20}$ -11.2° (c 1, DMF). UV spectrum: λ_{min} 248 nm, ε 2930; λ_{max} 289 nm, ε 5560; λ_{max} 280 nm, ε 6160. Amino acid analysis: Asp 0.97 (1), Leu 1.00 (1), Abu 0.96 (1).

N^{δ}-tert-Butoxycarbonylaminovaleryl-L-tryptophyl-L-leucyl-L-asparaginic Acid α-Amide (IV). Obtained as for (II), from 0.20 g (0.28 mmole) of (XXIV). Yield 0.075 g (43%), mp 199-202°C, R_f 0.83 (A), 0.88 (B), 0.89 (C), $[\alpha]_D^{20}$ -22.8° (c 1, DMF). UV spectrum: λ_{min} 248 nm, ε 2720; λ_{max} 290 nm, ε 4970; λ_{max} 282 nm, ε 5620. Amino acid analysis: Asp 0.93 (1), Leu 1.00 (1), Ape 1.18 (1).

N^{ε}-tert-Butoxycarbonylcaproyl-L-tryptophyl-L-leucyl-L-asparaginic Acid α-Amide (V). Obtained as for (II), from 0.35 g (0.49 mmole) of (XXV). Yield 0.14 g (44%), mp 206-208°C, R_f 0.68 (A), 0.79 (B), 0.88 (C), $[\alpha]_D^{20}$ -23° (c 1, DMF). UV spectrum: λ_{min} 250 nm, ε 1390; λ_{max} 284 nm, ε 4260; λ_{max} 293 nm, ε 3570. Amino acid analysis: Asp 1.00 (1), Leu 1.00 (1), Ahx 0.81 (1).

N^{γ}-tert-Butoxycarbonylbutyryl-β-benzyl-L-asparaginic Acid α-Amide (XXVI). Obtained as for (XIII), from 0.50 g (1.5 mmole) of (XI), 0.51 g (1.7 mmole) of (XIX), and 0.21 ml (1.5 mmolw) of Et_3N. The product was reprecipitated from methanol with ether, to give 0.30 g (50%) of material, mp 94-96°C, R_f 0.63 (A), 0.45 (B), 0.88 (C).

N^{δ}-tert-Butoxycarbonylaminovaleryl-β-benzyl-L-asparaginic Acid α-Amide (XXVII). Obtained as for (XIII), from 0.40 g (1.2 mmole) of (XI), 0.34 g (1.1 mmole) of (XX), and 0.17 ml (0.2 mmole) of Et_3N. The product was reprecipitated from methanol with ether, to give 0.27 g (61%) of material, mp 87-89°C, R_f 0.93 (A), 0.92 (B), 0.79 (C).

N^{ε}-tert-Butoxycarbonylamincaproyl-β-benzyl-L-asparaginic Acid α-Amide (XXVIII). Obtained as for (XIII), from 0.35 g (1.1 mmole) of (XI), 0.41 g (1.2 mmole) of (XI), and 0.12 ml (1.1 mmole) of N-methylmorpholine. The product was reprecipitated from methanol with ether, to give 0.25 g (70%) of material, mp 81-82°C, R_f 0.30 (D), 0.23 (H).

N-tert-Butoxycarbonyl-L-tryptophyl-λ-aminobutyryl-β-benzyl-L-asparaginic Acid α-Amide (XXXII). To 0.30 g (0.71 mmole) of (XXVI) was added 3 ml of 70% CF_3COOH in dichloromethane. The mixture was kept for 30 min at 20°C, then evaporated to dryness under reduced pressure. The residul oil was washed with ether, to give 0.31 g (0.71 mmole) of γ-butyryl-β-benzyl-L-asparaginic acid α-amide as its trifluoroacetate (XXIX). This was dissolved in 3 ml of DMF, 0.10 ml (0.71 mmole) of Et_3N added, and the mixture stirred for 20 min at 20°C. It was then cooled to 0°C, 0.32 g (0.80 mmole) of (XV) added, and the mixture stirred for 1 h at 0°C and 1 day at 20°C. It was then evaporated to dryness, dissolved in 50 ml of ethyl acetate, washed with 0.1 N HCl, water, 5% $NaHCO_3$, and water, and dried over $MgSO_4$. The solution was evaporated to dryness, and the product reprecipitated from methanol with ether, to give 0.27 g (64%) of material, mp 126-128°C, R_f 0.86 (B), 0.24 (D), 0.12 (H).

N-tert-Butoxycarbonyl-L-tryptophyl-γ-aminovaleryl-β-benzyl-L-asparaginic Acid α-Amide (XXXIII). Obtained as for (XXXII), from 0.27 g (0.64 mmole) of (XXVII) and 3 ml of 70% CF_3COOH in dichloromethane [this afforded 0.25 g (0.57 mmole) of δ-aminovaleryl-β-benzyl-L-asparaginic acid α-amide as its trifluoroacetate (XXX)], 0.20 g (0.50 mmole) of (XV), and 0.08 ml (0.57 mmole) of Et_3N. The product was reprecipitated from methanol with ether, to give 0.23 g (76%) of material, mp 104-106°C, R_f 0.81 (A), 0.82 (B), 0.91 (C).

N-tert-Butoxycarbonyl-L-tryptophyl-ε-aminocarpoyl-β-benzyl-L-asparaginic Acid α-Amide (XXXIV). Obtained as for (XXXII), from 0.25 g (0.58 mmole) of (XXVIII), 4 ml of 70% CF_3COOH in dichloromethane [this afforded 0.25 g (0.56 mmole) of ε-aminocaproyl-β-benzyl-L-asparaginic acid α-amide as its trifluoroacetate (XXXI)], 0.24 g (0.6 mmole) of (XV), and 0.06 ml (0.56 mmole) of N-methylmorpholine. the product was reprecipitated from methanol with ether, to give 0.24 g (63%) of material, mp 107-108°C, R_f 0.89 (A), 0.22 (H).

N-tert-Butoxycarbonyl-L-tryptophyl-γ-aminobutyryl-L-asparaginic Acid α-Amide (VI). Obtained as for (II), from 0.25 g (0.42 mmole) of (XXXII). Yield 0.20 g (97%), mp 90-92°C, R_f 0.59 (A), 0.80 (B), 0.77 (C), $[\alpha]_D^{20}$ −22.6° (c 1, DMF). UV spectrum: λ_{min} 244, ε 1740; λ_{max} 290 nm, ε 4710; λ_{max} 281 nm, ε 5540. Amino acid analysis: Asp 1.00 (1), Abu 1.00 (1).

N-tert-Butoxycarbonyl-L-tryptophyl-δ-aminovaleryl-L-asparaginic Acid α-Amide (VII). Obtained as for (II), from 0.22 g (0.36 mmole) of (XXXIII). Yield 0.14 g (76%), mp 130-132°C, R_f 0.51 (A), 0.64 (B), 0.73 (C). $[\alpha]_D^{20}$ −19.4°(c 1, DMF). UV spectrum: λ_{min} 245 nm, ε 1690; λ_{max} 289 nm, ε 4090; λ_{max} 281 nm, ε 4780. Amino acid analysis: Asp 1.00 (1), Ape 1.14 (1).

N-tert-Butoxycarbonyl-β-tryptophyl-ε-aminocaproyl-L-asparaginic Acid α-Amide (VIII). Obtained as for (II), from 0.21 g (0.34 mmole) of (XXXIV). Yield 0.14 g (78%), mp 115-117°C, R_f 0.42 (A), 0.72 (B), 0.85 (C). UV spectrum: λ_{min} 244 nm, ε 2130; λ_{max} 289 nm, ε 3900; λ_{max} 280 nm, ε 4410. $[\alpha]_D^{20}$ −24.09° (c 1, DMF). Amino acid analysis: Asp 1.0 (1), Ahx 0.82 (1).

EXPERIMENTAL (BIOLOGY)

The effects of the test compounds on gastric secretion were studied in dogs with Vasov chronic fistula [1], and in dogs which had been subjected to subdiaphragmic vagotomy. The test compounds were administered to the dogs intravenously over a period of 2 min in doses of 2.5 mg, 5 mg, and 60 mg. After 15 min, pentagastrin was given subcutaneously in a dose of 50 μg. The controls received pentagastrin only. All the tests were carried out 18 h following the last meal of the animals, when the gastric secretion was neutral. The changes in the rates of secretion in the animals were recorded.

The tetrapeptides (II-V) have been found to be similar in respect of the type and magnitude of their effects on gastric secretion. When administered intravenously in doses of 5 mg, compounds (II-V) induce weak gastric secretion. In the presence of pentagastrin, they have a definite modifying effect, gastric secretion being increased by 1.5-2 times over that induced by pentagastrin alone.

When (II-V) are given in doses of 60 mg/kg, they give rise to an antagonistic effect, gastric secretion being reduced by a fator of 2-2.5 times as compared with that caused by pentagastrin.

Quantitative data showing the enhancement of gastric secretion, dose dependency, and inhibition of gastric secretion by (II), are shown in Figs. 1-3. The plots for the compounds (III-V) were similar in appearance.

Compounds (VI-VIII) showed no effects whatsoever on gastric secretion.

LITERATURE CITED

1. E. N. Speranskaya, Methodology of Operations on the Digestive Tract [in Russian], Moscow (1952), pp. 18-28.
2. G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, J. Am. Chem. Soc., 86, 1839-1842 (1964).
3. IUPAC-IUB, Eur. J. Biochem., 138, 9-37 (1984).
4. J. Martinez, R. Magous, M.-F. Lignon, et al., J. Med. Chem., 27, 1597-1601 (1984).
5. J. S. Morley, Proc. R. Soc., B, 170, 97-111 (1968).