30 sec and changing the order of the oxidation and capping stages. Capping was carried out first and then oxidation by the corresponding solutions: a 1 M solution of acetic anhydride in diisopropylethylamine–N methylimidazole–acetonitrile (4.5:1:30) (capping agent), and a 0.2 M solution of I_2 in pyridine–acetic acid (9:1) (oxidizing agent) without intermediate washing. This change in the conditions led to a shortening of the time of growth of the oligonucleotide chain by one unit to 9.5 min without lowering the yields of final products, which were obtained in an amount of 3 OU_{260} for d and 4.5 OU_{260} for e.

The synthesis on paper disks was carried out in the Viktoriya-2 automatic synthesizer with a modified hydraulic scheme [3], and on the CPG support in the Viktoriya-4M synthesizer.

The oligonucleotides (a-e) were isolated on ion-exchange and reversed-phase high-performance liquid chromatography (HPLC, Fig. 1). The nucleotide sequence was determined by the Maxam–Gilbert method.

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INTERACTION OF THE ANTIBIOTIC FERVENULIN WITH INDOLE

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UDC 547.874

3-Substituted analogs of the antibiotic fervenulin (I) are transformed into derivatives of xanthine [1] or of 6-azapurine [2] as the result of the nucleophilic attack of their pyrimidotriazine nucleus by formamide at the C_{8a} atom and by the OH^- ion at the C_5 atom, respectively.

We have studied the interaction of (I) with indole (II). When equimolar amounts of saturated butanol solutions of compounds (I) and (II) were mixed, the crystalline molecular complex (III) with a 1:1 composition of the components was obtained with a yield of 65-70%. The frequency of absorption, ν_{NH}, of the electron-donating indole component of the crystals of compound (III) was 92 cm^{-1} lower than for free indole (3405 cm^{-1}). Such a change in the stretching vibrations of a N–H bond in primary and secondary amines indicates the participation of the nitrogen atom in coordination [3].

The peak intensities of the absorption bands at 1586 and 1542 cm^{-1} (C=C and C=N) in the IR spectrum of (III) (tablets with KBr) were, respectively, 45 and 23% lower than those for the antibiotic (I). This shows a decrease in the polarity of the C=C and C=N bonds in (III) because of some transfer of the charge of the indole nitrogen atom to the triazine moiety of the fervenulin molecule.

When compounds (I) and (II) were heated in boiling butanol (3-4 h), no products other than (III) were obtained. At the same time, in the presence of hydrochloric acid indole (II) and 2-methylindole (IV) add to (I) after only 15 minutes' heating in ethanol with the formation of the hydrochlorides of the 4a-indole derivatives of 6,8-dimethyl-2,4,5,6 7,8-hexahydropyrimidol[5,4-e1][1,2,4]triazine-5,7-dione (V and VI). By treating aqueous solutions of the hydrochlorides obtained with sodium acetate, the bases (V) and (VI) were isolated in the free state. The yield of (V) was 75%, mp 225-226°C, and that of (VI) 55%, mp 240-241°C (scheme).

A doublet signal of the C_{4a} atom of compound (I) in the high-resolution ^{13}C NMR spectrum ($^3J_{C_{4a}H-3}$ = 8.6 Hz) was observed at 133.10 ppm, while the sp^3-hybridized C_{4a} atom of compound (VI) gave a signal at 56.31 ppm with retention of doublet splitting ($^3J_{C_{4a}H-3}$ = 10 Hz). The

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Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 155-156, January-February, 1987. Original article submitted September 1, 1986.

0009-3130/87/2301-0133$12.50

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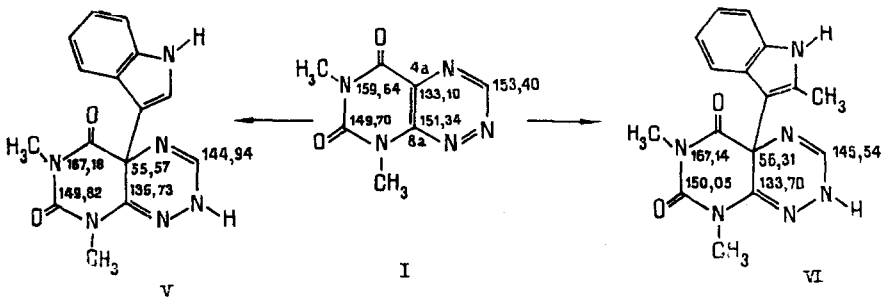

V I VI

presence of a proton on the N_2 (and not the N_4) atom of compound (VI) was shown by the doublet splitting of the C_3 signal with the small SSCC of $^2J_{C_3H-2}$ = 3.7 Hz in addition to $^1J_{C_3H-3}$ = 196.2 Hz and the absence of it for C_{4a}. Compound (V) had an analogous structure, as was confirmed by the closeness of the values of the ^{13}C chemical shifts of the pyrimidotriazine nucleus for compounds (V) and (VI).

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SYNTHESIS OF NEW STRUCTURAL ANALOGS OF TETRAGASTRIN

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UDC 547.964.4

In connection with a study of the structural-functional organization of peptide hormones, we have performed the synthesis of new structural analogs of tetragastrin (synonym: fragment 14-17 of gastrin; fragment 30-33 of cholecystokinin, trimafam, CCK-4)[1-3], which consists of a tetrapeptide with the structure (I). It was the previously unknown analogs (II-IV) differing from natural tetragastrin (I) by the replacement of the L-tryptophan residue in position 1 by L-ornithine, D-ornithine, and L-alanine residues, respectively, that were synthesized.

$$H-\overset{1}{X}-L\cdot\overset{2}{Met}-L\cdot\overset{3}{Asp}-L\cdot\overset{4}{Phe}-NH_2$$

I. X = L·Trp III. X = D·Orn
II. X = L·Orn IV. X = L·Ala.

Compounds (II-IV) were synthesized by a scheme providing for the stepwise growth of the peptide chain in solution using as the amino components the amides of the C-terminal amino acid (V) and of the intermediate peptides (VIII) and (XI), and as the activated carboxy components the pentafluorophenyl esters of the protected amino acids (VI), (IX), and (XII-XIV) [4]. As can be seen from the scheme, the intermediate compounds were the protected dipeptide (VII), tripeptide (X), and tetrapeptides (XV-XVII). (Scheme, top, following page.)

The structures of the new tetragastin analogs were determined unambiguously by the scheme of synthesis, and their individuality was confirmed by the results of analytical determinations.

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Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 156-158, January-February, 1987. Original article submitted August 10, 1986.

0009-3130/87/2301-0134$12.50

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