SYNTHESIS OF [8-GLUTAMINE]-VASOPRESSIN

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We have previously shown [1] that a characteristic feature common to a series of physiologically active peptides is the presence of the fragment Pro/Val–Arg/Lys–Gly–, which contains a basic amino acid adjacent to proline or valine. The necessity for a basic amino acid for the exhibition of the vasopressor and antidiuretic activity of the neurohypophyseal hormones was one of the first conclusions drawn on the basis of a comparison of the structures and functions of [Arg^8]-, [His^8]-, and [Leu^8]-vasopressins [2]. However, the value of basicity (positive charge) for the exhibition of the functions of other peptides of similar structure such as angiotensin is disputed [3]. The question is of fundamental importance for the elucidation of the mechanism of the action of these compounds. The low activity of analogs of vasopressin with histidine, leucine, and formyllysine [4] can be explained by steric factors rather than by the absence of a positive charge. For a further study of this question, we have synthesized an analog of vasopressin with glutamine in position 8. The lateral functional group of glutamine differs sterically only very slightly from that of ornithine, but at the same time at physiological pH values it is practically free from positive charge.

The study of the biological properties of [8-glutamine]-vasopressin (glumipressin) (I) is, moreover, of great interest because this substance is a possible product of the molecular evolution of the neurohypophyseal hormones [5].

According to preliminary results of biological testing, (I) has 2 MU/mg of vasopressor activity, i.e., it is 180 times less active than [8-ornithine]-vasopressin [6]. Thus, the necessity for a positive charge in position 8 to ensure the high pressor activity of vasopressin is confirmed.

We obtained the protected nonapeptide Tos-Cys–(Bzl)-Tyr–Phe–Gln–Asn–Cys–(Bzl)-Pro–Gln–Gly-NH_2 (II) by the azide method, coupling the appropriate tosylhexapeptide [7] with the amide of prolylglutamyl-glycine [8]; composition $C_{66}H_{81}N_{13}O_{15}S_3 \cdot 2H_2O$, yield 67%, mp 207-210° C (dimethylformamide–water), $[\alpha]_D^{20} - 9.8°$ (c 1; dimethylformamide), R_f 0.66 [thin-layer chromatography on plates of the Silufol type in system 1) butan-1-ol–acetic acid–water (4 : 1 : 1)] and 0.72 [system 2) propan-2-ol–25% aqueous ammonia (7 : 3)].

After the splitting off of the protective groups from the nonapeptide (II) with sodium in liquid ammonia, oxidation of the product with atmospheric oxygen at pH 6.9, and purification on Sephadex G-15, first with 50% and then with 0.2 N acetic acid, a chromatographically and electrophoretically pure preparation of (I) was obtained: $C_{45}H_{61}N_{12}O_{13}S_2 \cdot C_2H_4O_2 \cdot H_2O$, $[\alpha]_D^{20} - 43.6°$ (c 0.39; 0.5 N acetic acid); R_f 0.15 (1), 0.60 (2); E^{Gly} 0.6; E^{His} 0.4 (electrolyte 1 N acetic acid, pH 2.4, potential difference 50 V/cm, 1.5 h).

Amino-acid composition: cystine 1.06, tyrosine 0.92, phenylalanine 1.00, glutamic acid 2.15, aspartic acid 1.11, proline 0.82, and glycine 1.00.

The pharmacological tests were performed by Z. P. Aune, and the amino acid composition of the new compound was determined by R. F. Platnietse.

LITERATURE CITED

1. G. I. Chipens, Second All-Union Symposium on Peptide Chemistry; Abstracts of Lectures [in Russian],

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 543-544, July-August, 1971. Original article submitted March 12, 1971.

Dushanbe (1967), p. 7; G. I. Chipens, O. S. Papsuevich, A. Yu. Krikis, and Z. P. Auna, 7th International Symposium on the Chemistry of Natural Compounds; Abstracts of Lectures [in Russian], Riga (1970), p. 29.
2. P. G. Katsoyannis and V. du Vigneaud, Arch. Biochem. Biophys., 78, 555 (1958).
3. E. Havinga, C. Schattenkerk, G. H. Wisser, and K. E. T. Kerling, Rec. Trav. Chim., 83, 672 (1964).
4. A. Boissonnas, St. Guttmann, R. L. Huguenin, P.-A. Jaquenoud, and E. Sandrin, Helv. Chim. Acta, 46, 2347 (1963).
5. W. H. Sawyer, T. C. Wuu, J. W. M. Baxter, and M. Manning, Endocrinology, 85, 385 (1969).
6. R. L. Huguenin and R. A. Boissonnas, Helv. Chim. Acta, 46, 1669 (1963).
7. M. Zaoral, Coll. Czech. Chem. Commun., 30, 1853 (1965).
8. E. Klieger, Exper., 24, 13 (1968).