cose-6-phosphate dehydrogenase (20 units). As a control an identical incubation was performed with liver homogenate which had been heated previously for 15 min in boiling water. The incubations were terminated after 30 min by the addition of 3 ml of water and freezing. Water obtained from each incubation by lyophilization was counted in Diotol as three 1-ml aliquots. The total tritium water content of the brain and liver incubations was 0.15 and 0.13% of the substrate, while the control incubation contained 0.07%. Therefore, the release of tritium from morphine-6-^3H in the presence of brain and liver homogenates was only 0.08 and 0.06% of the material incubated.

Isotopic Stability of Morphine-6-^3H in Man. A volunteer 27-year-old male subject weighing 74 kg was given an intravenous injection of morphine-6-^3H (100 μg, 7.2×10^6 cpm). A blood sample was obtained at 6 hr after injection and urine was collected for 72 hr at intervals. The blood and aliquots of the urine collections were frozen and lyophilized and the water thus obtained was counted. Both plasma and urinary water had a maximum specific activity of 2 cpm/ml. Since the estimated total body water of a 74-kg man is 48 l., the total body water tritium content is 96,000 cpm or 1.3% of the dose. When corrected for the control, the total exchange amounts to 0.3% of the injected material.

Isotope Stability of Morphine-6-^3H under Acid Hydrolysis Conditions. Morphine-6-^3H (0.25 mg, 612,000 cpm) was dissolved in 10 ml of 10% hydrochloric acid and heated at 121–124° at 18 atm of pressure for 60 min.[17] The solution was cooled, the pH adjusted to 9.0 with base, and the basic solution extracted four times with chloroform–2-propanol (3:1). An identical experiment was performed with morphine-N-$^{14}CH_3$ (0.25 mg, 153,000 cpm).

The recovery of radioactivity in the organic extract was 39.8% for morphine-6-^3H and 38.7% for morphine-N-$^{14}CH_3$. The similar recoveries demonstrate that the acid conditions did not lead to selective isotope loss from morphine-6-^3H.

Urinary Excretion of Morphine-6-^3H in Men after iv and im Injection. Morphine-6-^3H (7.16×10^6 cpm, 0.1 mg) in redistilled propylene glycol was administered intravenously to a 27-year-old volunteer male subject. Urines were collected at intervals for 72 hr. Aliquots of each urine collection were diluted with water and counted in Diotol on a Packard liquid scintillation counter with suitable quenching corrections. Other aliquots of each urine collection were lyophilized to obtain water which was counted.

In the second study morphine-6-^3H (7.4×10^6 cpm, 10 mg) in propylene glycol was administered intramuscularly to a 24-year-old male volunteer subject. The urine collection and counting were then carried out precisely as in the previous study.

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Synthesis and Some Pharmacological Properties of 8-L-Homoarginine-vasopressin and of 1-Deamino-8-L-homoarginine-vasopressin

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Syntheses of 8-L-homolysine-vasopressin[1] and its 1-deamino derivative[2] were reported from these laboratories. The high biological activity† of the homolysine analogs in the rat prompted the preparation of the corresponding cyclic peptides with L-homoarginine in position 8. It seemed to be reasonable to expect that again potent compounds can be obtained. Indeed, both homoarginine analogs are highly active by several biological assays (Table I). 8-L-Homoarginine-vasopressin has somewhat greater antidiuretic activity[4] but slightly lower vasopressor activity[5] than does 8-L-arginine-vasopressin. 1-Deamino-8-L-homoarginine-vasopressin also has greater antidiuretic activity than 8-L-arginine-vasopressin but considerably less than 1-deamino-8-L-arginine-vasopressin. Its vasopressor activity is also lower than that of the L-arginine analogs. The oxytocic (isolated rat uterus) activities[6] of the L-homoarginine analogs are quite similar to those of the corresponding L-arginine analogs.

The pharmacological properties of the new vasopressin analogs demonstrate that the precise length of the side chain in position 8 is not critical to antidiuretic and vasopressor activities, as shown by the ornithine-lysine-homolysine series[2] and the arginine-homoarginine pair. The basic character of this side chain is more important.

The synthesis of the two new hormone analogs was carried out in solution according to the stepwise strategy.[7,8] The guanidine group in the side chain of the homoarginine residue was protected by tosylation.[9,10] For the coupling steps, the dicyclohexylcarbodiimide method[11] and *p*-nitrophenyl esters of the protected amino acids[7] were used. After completion of the chain elongation, the protecting groups were removed by reduction with sodium in liquid ammonia and the cyclic disulfides were formed by oxidation with air[12] or potassium ferricyanide. The new analogs were obtained in homogeneous form by a combination of gel filtration, ion-exchange chromatography, and partition chromatography.

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†A reexamination of the activities of 1-deamino-8-L-homolysine-vasopressin confirmed that it is a potent analog of the parent hormone but also showed that the previously reported (ref 2) values require considerable corrections (*cf.* Table I and ref 3).

Table I. Some Pharmacological Activities of Lysine-, Homolysine-, Arginine-, and Homoarginine-vasopressins and Their 1-Deamino Analogs

Analog	Activities (in units/mg ± S.E. of the assays)			Ref
	Oxytocic	Antidiuretic	Vasopressor	
8-Lysine-vasopressin	4.8 ± 0.3	203 ± 7	243 ± 3	*c*
1-Deamino-8-lysine-vasopressin	12 ± 0.5	301 ± 11	126 ± 2	*c*
8-Homolysine-vasopressin		159 ± 18[a]	267 ± 13	
1-Deamino-8-homolysine-vasopressin		634 ± 54[b]	153 ± 4[b]	
8-Arginine-vasopressin	15 ± 1	332 ± 20	376 ± 6	*d*
1-Deamino-8-arginine-vasopressin	47 ± 2	1390 ± 140	370 ± 20	*d*
8-Homoarginine-vasopressin	13 ± 1	427 ± 49	250 ± 9	
1-Deamino-8-homoarginine-vasopressin	20 ± 1	460 ± 41	96 ± 4	

[a] At doses of 8×10^{-8} mg and 16×10^{-8} mg. [b] Unreported assays on preparation synthesized by Lindeberg, *et al.*[2] [c] R. D. Kimbrough, Jr., W. D. Cash, L. A. Branda, W. Y. Chan, and V. du Vigneaud, *J. Biol. Chem.*, **238,** 1411 (1963). [d] M. Manning, L. Balaspiri, M. Acosta, and W. H. Sawyer, *J. Med. Chem.*, **16,** 975 (1973).

Experimental Section

Capillary melting points were taken and are uncorrected. Unless otherwise stated, tlc was performed on precoated silica gel plates with the following solvent systems: A, *n*-BuOH–AcOH–H_2O (3:1:1); B, *n*-PrOH–H_2O (7:3); C, *n*-BuOH–AcOH–H_2O (4:1:5), upper phase; D, *n*-BuOH–pyridine–AcOH–H_2O (30:20:6:24). In tlc and paper electrophoresis, peptides were detected by use of the uv, ninhydrin, and chlorination techniques and, in the case of peptides containing free homoarginine, by treatment with phenanthrenequinone.[13] For quantitative amino acid analysis, samples were hydrolyzed with constant boiling HCl containing 20% (wt/v) of phenol in evacuated, sealed tubes at 110° for 24 hr and analyzed according to the method of Spackman, *et al.*[14] The following abbreviations were used: tlc (thin-layer chromatography), DCHA (dicyclohexylamine), DCC (dicyclohexylcarbodiimide), ONP (*p*-nitrophenyl ester). Where analyses are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values.

N^{α}-Benzyloxycarbonyl-N^{G}-tosyl-L-homoarginine was prepared from L-homoarginine (Calbiochem) in 71% yield according to procedures published for the corresponding arginine derivative.[9,10] The amorphous product was obtained chromatographically pure: mp 55–65°; R_f(A) 0.67, R_f(B) 0.57; $[\alpha]^{25}D$ −2.3° (*c* 2, MeOH). A sample was converted into the DCHA salt: mp 155–157°; $[\alpha]^{25}D$ +4.6° (*c* 4, MeOH). *Anal.* ($C_{34}H_{51}N_5O_6S$) C, H, N, S.

Z-L-Pro-L-Har(Tos)-Gly-NH_2. Z-L-Har(Tos)-OH and H-Gly-OEt were condensed by the DCC method[11] as described for the arginine derivative.[9,10] The amorphous product, R_f(A) 0.66, R_f(B) 0.67, $[\alpha]^{25}D$ −6.8° (*c* 2, 95% AcOH), which was obtained in 87% yield, was deprotected by hydrogenation in a 9:1 mixture of 95% EtOH and AcOH in the presence of a 5% Pd/C catalyst and then acylated with Z-L-Pro-ONP[15] as described in the synthesis of lysine-vasopressin:[16] yield 87%. The amorphous protected tripeptide ester, R_f(A) 0.68, R_f(B) 0.69, $[\alpha]^{25}D$ −47.4° (*c* 2, 95% AcOH), was converted with 70% yield into the amide by treatment with methanolic NH_3: mp 155–157°; R_f(A) 0.61, R_f(B) 0.62; $[\alpha]^{25}D$ −45.3° (*c* 1, 95% AcOH); amino acid analysis, Pro 0.97, Har 1.01, Gly 1.02, NH_3 1.00.

Z-L-Cys(Bzl)-L-Pro-L-Har(Tos)-Gly-NH_2. The Z group was removed from the protected tripeptide amide with HBr in AcOH, and the chain was lengthened by the addition of Z-L-Cys(Bzl)-ONP[15,17] in the presence of diisopropylethylamine[18] as described in the synthesis of 8-L-homolysine-vasopressin,[1] yielding 87% of the protected tetrapeptide amide: mp 143–145°; R_f(A) 0.63, R_f(B) 0.64; $[\alpha]^{25}D$ −38.8° (*c* 1, DMF); amino acid analysis, Cys(Bzl) 1.05, Pro 0.98, Har 1.00, Gly 1.00, NH_3 1.02.

Z-L-Asn-L-Cys(Bzl)-L-Pro-L-Har(Tos)-Gly-NH_2. The tetrapeptide amide was deprotected and acylated, as described above, with Z-Asn-ONP.[9,10,19] The product was secured in 75% yield: mp 156–158°; R_f(A) 0.59, R_f(B) 0.61; $[\alpha]^{25}D$ −39.2° (*c* 1, DMF); amino acid analysis, Asp 0.98, Cys(Bzl) 1.01, Pro 0.99, Har 1.01, Gly 1.01, NH_3 1.96.

Z-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-Har(Tos)-Gly-NH_2. After deprotection with HBr in AcOH, the pentapeptide amide was converted into the protected hexapeptide derivative by reaction with Z-L-Gln-ONP.[15,17] The product was precipitated by the addition of 95% EtOH, filtered, and washed extensively with hot 95% EtOH, hot EtOAc, and hot MeOH: yield 83%; mp 183–185°; R_f(A) 0.58, R_f(B) 0.58; $[\alpha]^{25}D$ −41.2° (*c* 1, DMF). On thin-layer chromatograms, a small amount of impurity was detected: R_f(A) 0.37, R_f(B) 0.51. It could not be removed by reprecipitation from DMF–EtOH or AcOH–EtOH, but its amount was substantially decreased by washing with hot MeOH. Amino acid analysis gave Glu 1.01, Asp 0.99, Cys(Bzl) 0.84, Cys 0.13, Pro 1.03, Har 1.00, Gly 0.99, NH_3 2.85.

Z-L-Phe-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-Har(Tos)-Gly-NH_2. The lengthening of the chain from the hexapeptide derivative to the protected heptapeptide followed the procedure in ref 16. The product was obtained in 84% yield by precipitation with 95% EtOH: mp 222–227°; R_f(A) 0.59, 0.42 (trace), R_f(B) 0.58; $[\alpha]^{25}D$ −44.2° (*c* 1, DMF); amino acid analysis, Phe 0.96, Glu 1.04, Asp 0.97, Cys(Bzl) 0.42, Cys 0.35, Pro 1.05, Har 1.01, Gly 0.97, NH_3 3.11.

Z-L-Tyr(Bzl)-L-Phe-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-Har(Tos)-Gly-NH_2. The protected octapeptide was prepared in 84% yield by the procedure described above: mp 234–237°; R_f(A) 0.61, 0.36 (trace), R_f(B) 0.64, 0.41 (trace); $[\alpha]^{25}D$ −46.3° (*c* 1, DMF); amino acid analysis, Tyr 0.85, Tyr(Bzl) + Cys(Bzl) 0.5, Phe 1.00, Glu 1.03, Asp 1.02, Cys 0.44, Pro 1.04, Har 0.99, Gly 1.00, NH_3 2.94.

Z-L-Cys(Bzl)-L-Tyr-L-Phe-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-Har(Tos)-Gly-NH_2. The preparation of this protected nonapeptide closely followed the procedure used in ref 17. The product was obtained in 93% yield: mp 235–237°; R_f(A) 0.59, R_f(B) 0.62; $[\alpha]^{25}D$ −52.2° (*c* 1, DMF); amino acid analysis, Cys 0.60, Cys(Bzl) + Tyr(Bzl) 1.9, Tyr 0.37, Phe 1.01, Glu 1.04, Asp 0.99, Pro 1.05, Har 0.98, Gly 1.00, NH_3 2.94.

8-L-Homoarginine-vasopressin. A sample (0.20 g) of the protected nonapeptide was dissolved in boiling liquid NH_3 (*ca.* 0.2 l.) and treated with small pieces of Na until the blue color persisted for 3 min. The reaction was terminated by the addition of a few drops of AcOH; the solution was evaporated to *ca.* 25 ml and then lyophilized. The residue was dissolved in O_2-free H_2O (0.25 l.), washed with Et_2O (50 ml), and aerated at pH 6.6 for 4 hr. AcOH was added to pH 5.0 and the solution was concentrated *in vacuo* and lyophilized, yielding 400 mg of semisolid material. A part of this (200 mg) was dissolved in 0.1 *M* AcOH (5 ml) and applied to a column (1.4 × 86 cm) of Sephadex G-15 and eluted with the same solvent at a flow rate of 29 ml/hr. Fractions of 7.5 ml were collected. The material in the main peak (preceded by three smaller ones) was collected in fractions 15–19. These were lyophilized to give 140 mg of partially purified product. When this material was subjected to ion-exchange chromatography on Whatman CM-52 carboxymethylcellulose with a linear gradient of 0.025–0.25 *M* NH_4OAc, pH 6.9, the hormone analog was eluted at a concentration of 0.095 *M*, yielding 48 mg of freeze-dried product which was further purified by rechromatography on Sephadex G-15 as described above. A single symmetrical peak was obtained. After lyophilization and drying *in vacuo* over NaOH and P_2O_5, the recovery was 41 mg. The peptide was homogeneous on tlc on cellulose: R_f(C) 0.41, R_f(D) 0.57. On paper electrophoresis at pH 6.46 (1.24 *M* pyridine–0.069 *M* AcOH) at 42 V/cm, 8-L-homoarginine-vasopressin moved toward the cathode as a single spot, 8.0 cm in 1.5 hr (E_{arg} 0.47): $[\alpha]^{25}D$ −19.1° (*c* 0.5, 1 *M* AcOH); amino acid analysis, Cys (as cysteic acid) 1.97, Tyr 0.96, Phe 0.98, Glu 1.02, Asp 1.01, Pro 1.04, Har 0.96, Gly 1.00, NH_3 3.29.

β-Benzylmercaptopropionyl-L-Tyr-L-Phe-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-Har(Tos)-Gly-NH_2. This protected peptide was

synthesized in 83% yield as described for the corresponding L-homolysine analog:[2] mp 229–231°; R_f(A) 0.60, R_f(B) 0.63; $[\alpha]^{25}D$ −45.3° (c 1, DMF).

1-Deamino-8-L-homoarginine-vasopressin. The protected nonapeptide (150 mg) was reduced with Na in liquid NH_3 and oxidized in dilute solution with 0.01 *M* $K_3Fe(CN)_6$ according to the procedure in ref 2. After passage through a short column (1 × 3.5 cm) of Dowex 1-X2 (200–400 mesh, acetate form), the solution was lyophilized; the residue (244 mg) was dissolved in 0.1 *M* AcOH (5 ml), applied to a column (1.4 × 86 cm) of Sephadex G-15, and eluted with the same solvent. The fractions corresponding to the main peak (104–153 ml) were freeze-dried to give 83 mg of impure product. After ion-exchange chromatography on SE-Sephadex C-25 using a linear gradient of 0.025–0.25 *M* NH_4OAc, pH 6.9, the main component, which was eluted at a concentration of 0.06 *M*, R_f(C) 0.51 (cellulose), was still accompanied by trace amounts of two impurities, R_f(C) 0.47 and 0.37. The lyophilized material (69 mg) was dissolved in 5 ml of the lower phase of the solvent system 0.2 *M* AcOH–pyridine–95% EtOH–*n*-BuOH (7:1:1:4)[20] and applied to a column (2.5 × 70 cm) of Sephadex G-25 (superfine) equilibrated with the lower phase. Elution was performed with the upper phase at a flow rate of 9.3 ml/hr. The fractions from 198 to 229 ml were combined, thus discarding a shoulder on the front edge of the main peak, and evaporated to dryness *in vacuo* at 25°. The evaporation was repeated twice after addition of absolute EtOH and the residue was dissolved in 0.2 *M* AcOH (3 ml) and chromatographed on Sephadex G-25 (superfine) (1.4 × 88 cm) in the same solvent. After lyophilization and drying *in vacuo*, the purified product weighed 22 mg. Rechromatography under the same conditions of the front part of the main peak in the partition purification and subsequent gel filtration on Sephadex G-25 afforded a further 19 mg of the same product. Single spots were obtained on thin-layer chromatograms on cellulose, R_f(C) 0.51, R_f(D) 0.68, and silica gel, R_f(D) 0.41. On paper electrophoresis at pH 6.46 (1.24 *M* pyridine–0.069 *M* AcOH) at 42 V/cm, 1-deamino-8-L-homoarginine-vasopressin moved toward the cathode as a single spot, 6.8 cm in 1.5 hr (E_{arg} 0.32): $[\alpha]^{25}D$ −87.9° (c 0.5, 1 *M* AcOH); amino acid analysis, Tyr 0.96, Phe 1.01, Glu 1.00, Asp 0.99, Cys (as cysteic acid) 0.97, Pro 1.00, Har 1.01, Gly 0.99, NH_3 3.05.

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Book Reviews

The Biological Role of the Clot Stabilizing Enzymes: Transglutaminase and Factor XIII. Volume 202. Edited by K. Laki with 30 contributors. New York Academy of Sciences [*Ann. N. Y. Acad. Sci.*, **202**, 1 (1972)], New York, N. Y. 1972. 348 pp. 14.9 × 22.7 cm. $26.00.

The New York Academy of Sciences has published a monograph of the proceedings of a conference held by the Academy on November 18–19, 1971. The 30 papers presented cover the field of the clot-stabilizing enzymes as it stood at the end of 1971; both laboratory and clinical aspects have been considered. The term "transglutaminase" is used to describe all of the enzymes involved in clot stabilization. The 30 presentations are recorded under eight general headings. These include Part I, Clot-Stabilizing Enzymes and Their Precursors (fibrin-stabilizing factor system of blood plasma; synthesis site of factor XII); Part II, Mode of Transglutaminase Action (factor XIII biosynthesis and function; hepatic transglutaminase properties); Part III, Fibrin Cross-Linking Plasma Enzyme (fibrinogen molecular structure; structure in normal and factor XIII-deficient individuals; effects of stabilizing factor); Part IV, Structural Aspects of Fibrin Cross-Linking (factor XIII free human fibrinogen; acceptor cross-linking site titration; transglutaminase precursor structure; cross-links and heredity); Part V, Pathological Aspects of Cross-Link Enzymes (hereditary aspects of cross-linking and hemorrhagic disease; cross-link inhibitors); Part VI, Fibrin Cross-Linkage, Thrombosis and Atherosclerosis (effects of oral contraceptives, thrombosis, pregnancy and atherosclerosis on cross-linkage and stabilization); Part VII, Fibrin Cross-Linking Enzymes in Tissues (tissue comparisons of molecular properties and activities of enzymes from different sources); Part VIII, Tumor Growth, Fibrinolysis and Fibrin Stabilization (stabilizing factor inhibitors; evolutionary consideration of clotting factors; mammalian fibrin and fibrinogen carboxy terminal structure; clot degradation studies; polypeptide organization in cross-linking; inhibition of factor XIII: tumor growth/transglutaminase considerations). A short editor's introduction precedes the contents of the book.

All of the papers represent scholarly research presentations of clinical, chemical, and biochemical studies on the clot-stabilizing enzymes. The individual papers vary in length from 3 to 22 pages, are generally well documented, and contain graphic presentations of the current status of the knowledge of each enzyme or factor discussed. The papers have been written by researchers active in the particular field of review and contain considerable material of interest for those scientists concerned with specific biochemical or metabolic studies of these enzyme systems. Medicinal chemists intrigued with specific structural or biochemical considerations of the clot-stabilizing factors in normal and selected disease states should find many papers of interest in this monograph.

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