1a) ranged from 2.00×10^5 dpm/mg to 1.06×10^6 dpm/mg. The animals were housed in all glass metabolism cages which allowed for the separate collection of urine and feces, and expiratory CO_2-^{14}C in 10 N NaOH. For the experiment which lasted 48 hr, the mouse was transferred to a clean metabolism cage at the end of 24 hr. Urine and CO_2-^{14}C (as Na_2CO_3-^{14}C) were counted in Diotol;[24] feces and blood were combusted in an O_2 flask, and the CO_2-^{14}C absorbed in 1 M Hyamine hydroxide and counted. Organs were homogenized in 9 vols of H_2O and aliquots were counted as a thixotropic gel suspension.[25] Proteins were precipitated by addition of an equal vol of 10% TCA, heated at 90° for 15 min, and the protein precipitates collected, washed successively with 5% TCA, boiling 95% EtOH-Et_2O (3:1), and Me_2CO and dried.

The 3.5-hr urine sample from mouse 1 was examined as follows: 5.0 mg each of unlabeled 1a and carrier L-proline were added, mixed thoroughly, and the urine charged on a column of Bio-Rad AG2-X10 (200–400 mesh, ¯OH) anion-exchange resin. The column was eluted successively with 20 ml of H_2O (fractions 1 and 2, 15% of the urinary radioactivity), 35 ml of 1 N HOAc (fractions 3–5, 30%) and 20 ml of 2 N NaOH (35%) for a recovery of 80%. The carriers were eluted with the HOAc. Fractions 1 and 3 were concentrated and chromatographed on silica gel HF_{254} with MeOH-HOAc-H_2O (46:1:3), and contiguous sections of the plate (0.5 cm) were scraped and counted. Two unidentified radioactive peaks were detected in fraction 1, while fraction 3 contained one major radioactive peak coincident with carrier 1a (TPT-NaOH test), and two minor peaks, one of which with an R_f close to that of carrier proline.

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Synthesis and Certain Pharmacological Properties of Lysine-vasopressinoic Acid Methylamide and Lysine-vasopressinoic Acid Dimethylamide†

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Lysine-vasopressinoic acid methylamide and lysine-vasopressinoic acid dimethylamide, analogs in which Me groups formally replace the amide hydrogens of the glycinamide residue of lysine-vasopressin, have been prepd by solid-phase peptide synthesis, and certain pharmacological properties of these neurohypophyseal hormone analogs have been detd. Lysine-vasopressinoic acid methylamide exhibits approx 1.5 units/mg of rat pressor activity, 0.4 unit/mg of oxytocic activity, and less than 0.1 unit/mg of avian vasodepressor (AVD) activity. Lysine-vasopressinoic acid dimethylamide exhibits approx 0.06 unit/mg of rat pressor, 0.4 unit/mg of oxytocic, and less than 0.1 unit/mg of AVD activity. Lysine-vasopressin possesses approx 266 units/mg of rat pressor, 7 units/mg of oxytocic, and 50 units/mg of AVD activity.

In connection with conformational studies on lysine-vasopressin (LVP), the methylamide and dimethylamide of lysine-vasopressinoic acid were desired (Figure 1). A suitable precursor of both LVP analogs, Z-Cys(Bzl)-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Lys(Tos)-Gly resin (I), was synthesized by the general procedure of the Merrifield solid-phase method[1-3] as applied by Meienhofer and Sano[4] to the synthesis of the corresponding 1-N-tosyl polypeptide resin, with modifications described in the Experimental Section. Cleavage of the protected polypeptide resin I with $MeNH_2$ and Me_2NH[5,6] gave the methylamide and dimethylamide, respectively, of the protected nonapeptide. Removal of the protecting groups with Na in boiling NH_3[7] followed by air oxidn of the resulting disulfhydryl compds in dil aqueous soln yielded lysine-vasopressinoic acid methyl- and dimethylamide. Both analogs were purified by ion-exchange chromatog on IRC-50 resin.[8]

Lysine-vasopressinoic acid methylamide possesses approx 1.5 units/mg of rat pressor activity, 0.4 unit/mg of oxytocic activity, and less than 0.1 unit/mg of avian vasodepressor
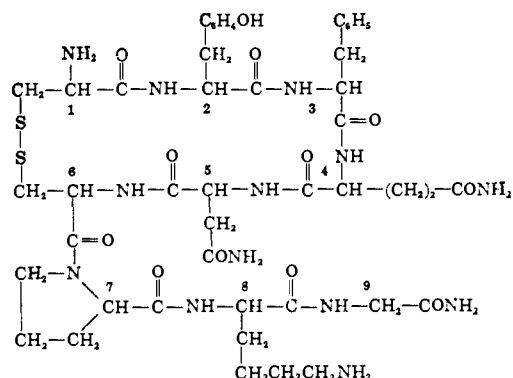
Figure 1. The structure of lysine-vasopressin, with numbers indicating the position of the individual amino acid residues. In lysine-vasopressinoic acid methylamide, the glycinamide at position 9 is replaced with glycine methylamide. In lysine-vasopressinoic acid dimethylamide, the glycine residue at position 9 is replaced with glycine dimethylamide.

(AVD) activity.‡ The dimethylamide possesses approx 0.06 unit/mg of rat pressor, 0.4 unit/mg of oxytocic, and 0.1 unit/mg of AVD activity. LVP possesses approx 266 units/mg[15] of rat pressor, 7 units/mg[16] of oxytocic, and 50 units/mg[16] of AVD activity. Thus these three activities of LVP are drastically reduced by formal substitution of Me groups for the amide hydrogens of the glycinamide residue.

These results are very similar to those obtained with the corresponding methylamide and dimethylamide compds[6] related to deamino-oxytocin, a highly potent analog of the hormone oxytocin. In this case the substituted amide compds were devoid of AVD activity and had oxytocic activity that was only 2–3% of that of the parent compd.

Experimental Section§

Z-Cys(Bzl)-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Lys(Tos)-Gly Resin (I). Boc-Gly resin (Merrifield polystyrene-*co*-2% divinylbenzene resin) (10 g) contg 0.76 mmole of Gly/g of resin was washed 3 times with 50 ml of AcOH and then treated with 50 ml of 1 *N* HCl in AcOH for 25 min. The resin was washed with 3 × 50 ml each of AcOH, EtOH, and *N,N*-dimethylformamide (DMF) and then treated with 1.5 ml of Et₃N in 50 ml of DMF for 10 min. The neutralized Gly resin was washed with 3 × 50 ml of DMF.

The Gly resin was suspended in 50 ml of DMF contg 5.25 mmoles of *p*-nitrophenyl Boc-Lys(Tos) and the suspension was shaken for 16 hr at room temp. An aliquot of the resin-bath soln was examd by tlc on silica gel layers in the solvent system EtOAc–PhH (1:1). Since tlc showed a small amt of residual nitrophenyl ester in the reaction mixt, 0.5 g of 1-hydroxybenzotriazole[17] was added and shaking was contd overnight. No nitrophenyl ester was detected in the reaction mixt by tlc. The peptide resin was washed successively with 3 × 50 ml of DMF, 3 × 50 ml of EtOH, and 2 × 50 ml of DMF, then treated with 1.5 g of 3-nitrophthalic anhydride[18] and 1.5 ml of Et₃N in 50 ml of DMF for 30 min at room temp to acylate excess amino groups. The Boc-Lys(Tos)-Gly resin was washed with 3 × 50 ml of DMF, 3 × 50 ml of dioxane, and 3 × 50 ml of EtOH. The ninhydrin test of Kaiser, *et al.*, for free amino groups of the resin[19] was neg.

For the further extension of the peptide resin chain, the cycle of deprotection and neutralization described for Boc-Gly resin pre-

‡The 4-point assay design of Schild[9] was used for measurement of pharmacological activities against the U. S. P. Posterior Pituitary Reference Standard. The oxytocic assays were performed on isolated uteri from Sherman albino rats in natural estrus by the method of Holton,[10] as modified by Munsick,[11] with the use of Mg-free van Dyke-Hastings soln as the bathing fluid. Pressor assays were carried out on anesthetized male rats as described in ref 12. Avian vasodepressor responses were measured on conscious roosters as described in ref 13, as modified by Munsick, *et al.*[14]

§Melting points were done in capillary tubes and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for the elements were within ±0.4% of the theoretical values.

ceded the introduction of each new protected amino acid residue, except that the hexapeptide resin terminating in Boc-Gln was washed with 50 ml of F₃CCO₂H and deprotected by treatment with an additional 50 ml of this reagent instead of with HCl in AcOH. The Boc derivs (10.4 mmoles) of Pro, Cys(Bzl), Phe, and Tyr(Bzl) were coupled to the growing chain by the action of 10.4 mmoles of dicyclohexylcarbodiimide[20] (DCI) in the presence of 10.4 mmoles of 1-hydroxybenzotriazole. The appropriate Boc amino acid was dissolved with the triazole deriv in 30 ml of DMF at −20°. DCI was added to this mixt in 10 ml of DMF. The soln was allowed to come to room temp, then transferred to the resin vessel for shaking overnight with the peptide resin.

Boc-Gln and Boc-Asn, as well as Z-Cys(Bzl) for the N-terminal position, were introduced through their cryst nitrophenyl esters. In each case the requisite deblocked, neutralized peptide resin was treated with 7.9 mmoles of the appropriate nitrophenyl ester in 50 ml of DMF and the mixt was shaken for 8 hr. After addn of 0.1 g of 1-hydroxybenzotriazole the shaking was continued for an addl 7 hr. The resin was washed with 2 × 50 ml of DMF, treated with 2.0 ml of Et₃N in 50 ml of DMF, washed again with 3 × 50 ml of DMF, and finally treated overnight with a second portion (2.6 mmoles) of the appropriate nitrophenyl ester.

After each coupling reaction the peptide resin was checked for unreacted amino groups by the Kaiser ninhydrin procedure.[19] In the 2 cases where a faint reaction was obsd (after the addns of Boc-Pro and Boc-Tyr(Bzl)), the residual amino groups were acylated with 3-nitrophthalic anhydride in the manner described for acylation of excess Gly resin after the addn of Boc-Lys(Tos).

After the addn of the Z-Cys(Bzl) residue to the peptide chain, the protected peptide resin was washed successively with 3 × 50 ml of DMF, 3 × 50 ml of AcOH, 3 × 50 ml of EtOH, and 3 × 50 ml of Et₂O. The protected nonapeptide resin I was dried first in the air, then *in vacuo*; yield 16.7 g.

Z-Cys(Bzl)-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Lys(Tos)-Gly-NHMe. The protected nonapeptide resin I (2.0 g) was suspended in 10 ml of anhyd MeOH and approximately 20 ml of dry MeNH₂ was condensed into the suspension at −70°. The mixt was stirred in a sealed flask for 24 hr at 0°. The flask was vented through a NaOH-filled drying tube and most of the MeNH₂ was allowed to escape at room temp. The remaining suspension was dild with DMF. MeOH and residual MeNH₂ were removed by rotary evapn. Resin particles were removed from the resulting suspension by filtration and washed well with DMF. The combined filtrate and DMF washings were evapd under reduced pressure to a heavy gum which was redissolved in 7 ml of DMF and added dropwise through a glass wool filter to 100 ml of H₂O with stirring. The pptd product was collected by filtration, washed on the filter with H₂O and EtOH, then air-dried on the filter. The air-dried solid was dissolved in about 10 ml of AcOH and added dropwise with stirring to 100 ml of hot EtOH to form a clear soln from which a ppt sepd on cooling. The ppt was collected by filtration, washed on the filter with EtOH and Et₂O, then air-dried on the filter. The product was dissolved in AcOH and recovered as a light powder by lyophilization; yield 447 mg, mp 216–219°, [α]²³D −36° (*c* 0.5, AcOH). *Anal.* (C₈₃H₉₉N₁₃O₁₆S₃) C, H, N.

Lysine-vasopressinoic Acid Methylamide. Z-Cys(Bzl)-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Lys(Tos)-Gly-NHMe (215 mg) was dissolved in about 200 ml of boiling anhyd NH₃, freshly distd from Na. A fresh Na stick was introduced intermittently into the soln until a blue color persisted for 20 sec. Excess Na was discharged with AcOH. The NH₃ was evapd to a vol of about 20 ml, and the remainder of the NH₃ was removed by lyophilization at the water aspirator. The residue was dissolved in 200 ml of deionized H₂O, the pH adjusted to 6.8, and the soln was aerated until the Ellman test[21] was neg. After being adjusted to pH 4.0 with AcOH, the soln was passed through a column of Amberlite IRC-50 (XE-64) (H⁺ form) for desalting[22,5] of the product. The col was washed with 0.2 *N* AcOH and H₂O, the product was eluted with 30% pyridine in 4% aqueous AcOH, and the eluate was dild 1:1 with H₂O and lyophilized to yield 155 mg of crude product.

The crude hormone analog (140 mg in 2.5 ml of 0.5 *M* NH₄OAc, pH 6.38) was purified by chromatog on a column (0.9 × 55.5 cm) of Amberlite IRC-50 (XE-64) equilibrated with the same buffer at 4°. The eluate was collected in 4.2-ml fractions. The chromatogram obtained by plotting Folin–Lowry color values[23] of the fractions showed a major peak centered at fraction 16. The fractions corresponding to the center portion of this peak were pooled, desalted, and lyophilized to yield 81.5 mg of purified product. The fractions corresponding to the sides of the major chromatog peak were pooled, desalted, lyophilized, and subjected to rechromatog on IRC-50 (XE-64) to yield an addnl 16.5 mg of purified product; [α]²⁵D −24.7°

(*c* 0.5, 1 *N* AcOH). *Anal.* ($C_{47}H_{67}N_{13}O_{12}S_2 \cdot C_2H_4O_2 \cdot H_2O$) C, H, N. A sample was hydrolyzed in 6 *N* HCl at 110° for 24 hr and analyzed in the Beckman-Spinco amino acid analyzer.[24] The following molar ratios were found: Asp 1.1, Glu 1.1, Pro 1.1, Gly 1.0, Cys 2.0, Phe 1.0, Tyr 1.0, Lys 1.0, NH_3 1.9, and $MeNH_2$ 1.1.

Z-Cys(Bzl)-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Lys(Tos)-Gly-NMe_2. The nonapeptide resin I (2.0 g) was suspended in 10 ml of anhyd MeOH and about 20 ml of dry Me_2NH was condensed into the suspension at -70°. The reaction mixt was stirred in a sealed flask at room temp for 24 hr. Further treatment of the reaction mixt was analogous to that described for the monomethyl analog, except that the pptn from AcOH–hot EtOH was repeated a second time; yield 320 mg, mp 204-208°, $[\alpha]^{23}D$ -40° (*c* 0.6, AcOH). *Anal.* ($C_{84}H_{101}N_{13}O_{16}S_3$) C, H, N.

Lysine-vasopressinoic Acid Dimethylamide. Z-Cys(Bzl)-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Lys(Tos)-Gly-N(Me)$_2$ (104 mg) was reduced with Na in NH_3, the resulting disulfhydryl compd was oxidized, and the product was desalted as described above to yield 67.4 mg of crude product. Chromatog on IRC-50 in 0.5 *M* NH_4OAc as described above, followed by development of Folin-Lowry color, revealed a major peak centered at fraction 21. The fractions corresponding to the center portion of this peak were pooled, desalted, and lyophilized to yield 28.5 mg of purified lysine-vasopressinoic acid dimethylamide; $[\alpha]^{25}D$ -28.2° (*c* 0.5, 1 *N* AcOH). *Anal.* ($C_{48}H_{69}N_{13}O_{12}S_2 \cdot C_2H_4O_2 \cdot 2.5H_2O$) C, H, N. A sample was hydrolyzed in 6 *N* HCl at 110° for 24 hr and analyzed in the Beckman-Spinco amino acid analyzer. The following molar ratios were found: Asp 1.1, Glu 1.1, Pro 0.9, Gly 1.0, Cys 1.7, Phe 1.0, Tyr 1.0, Lys 1.0, and NH_3 1.9. The Me_2NH content of the hydrolysate was detd by chromatog analysis of dinitrophenyl derivs according to a method described earlier.[6] By this method Me_2NH was found to be present in the hydrolysate in a molar ratio of 1.0 mole of Me_2NH per mole of analog.

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Immunochemical Studies on Linear Antigenic Polypeptides with a Known Primary Structure. Specificity of Antibodies to Poly(L-tyrosyl-L-glutamyl-L-alanylglycyl)glycine-*1*-14C Ethyl Ester[†]

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The synthesis of poly(Trp-Glu-Ala-Gly)Gly Me ester is described. The specificity of antibodies formed by rabbits in response to the antigenic challenge of poly(Tyr-Glu-Ala-Gly)Gly-*1*-14C Et ester (1) has been studied with respect to the role of the tyrosyl residue. For this purpose a series of polypeptides was used in which the tyrosyl residue was replaced by one of the following: OMe-Tyr, Phe, Trp, and Ala. Using these polypeptides and antisera to 1 it has been found by cross-reaction studies that all of these polymers have the same conformation. Further, absorption studies have shown that antibodies to the antigen 1 possess specificities for the phenolic OH and also for the aromatic system of the tyrosyl residue.

The specificity of antibody formed in response to an antigen is dependent on both the antigenic determinants present in the antigen and also on the genetic capacity of the animal to differentiate between and respond to those determinants. Neither the mechanisms of specific antigen recognition nor the nature of its genetic control is well understood. With respect to antibody specificity we have been studying the antigen poly(Tyr-Glu-Ala-Gly)Gly-*1*-14C Et ester[1-3] (1). It has been found that antibody to this antigen is dependent on the conformation of the antigen.[4-7] The next phase of this work has been to study the specificity of these antibodies pertaining to the role of the tyrosyl residue. In this paper we wish to report the characterization of the specificity of antisera produced by rabbits against the antigen 1 as studied by cross-reactions and absorption studies. For this purpose the following polymers have been used: poly(OMe-Tyr-Glu-Ala-Gly)Gly-*1*-14C Et ester[8] (2), poly(Phe-Glu-Ala-Gly)Gly-*1*-14C Et ester[9] (3), poly(Ala-Glu-Ala-Gly)Gly-*1*-14C Et ester[5] (4), and poly(Trp-Glu-Ala-Gly)Gly Me ester (5).

Chemistry. The synthesis of polymers 1, 2, 3, and 4 have been reported.[4,5,8,9] The polymerizing unit Trp-*tert*-Bu-Glu-Ala-Gly pentachlorophenyl ester·HCl (6) and the necessary intermediates for its preparation were synthesized as detailed in the Experimental Section. The polymerization was performed at a reagent concentration of 100 mmoles/l. in the presence of a preformed monomer since this has been

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†All amino acids are of the L variety.