0.29 mole of PhLi was added dropwise to a stirred soln of 6.66 g (0.25 mole) of 1-fluoro-1-trifluoromethyl-2,2-diphenylethylene in 20 ml of Et_2O cooled in ice. The reaction mixt was worked up as for **12** and the solvent was evaporated. The product was recrystd from pentane to give 4.5 g as colorless crystals.

1-Trifluoro-1-(*p*-perfluoroisopropylphenyl)-2,2-diphenylethylene (13).—To a soln of 0.04 mole of BuLi in 25 ml of hexane and 25 ml of Et_2O at 0° was added 14.3 g (0.044 mole) of *p*-bromo(perfluoroisopropyl)benzene[11] in 25 ml of Et_2O. After 30 min, 9.0 g of **51** was added dropwise at 0–10°. The reaction mixt was stirred overnight and filtered and the filtrate was distd to give 11.1 g of **13** as a colorless, viscous liquid, bp 128–129° (0.4 mm), that solidified on cooling.

1,1,2-Triphenylperfluoro-1-butene (17).—A sample of 6.1 g (0.34 mole) of perfluorothiopropionyl fluoride[7] was slowly distd into a dry, stirred soln of diphenyldiazomethane[10] (from 0.34 mole of benzophenone hydrazone) in pentane at 5°. The reaction mixt was distd, bp 98° (0.55 mm), to give a mixt of 1 part of 1,1-diphenylperfluoro-1-butene to 4 parts of 2-fluoro-2-perfluoroethyl-3,3-diphenylthiirane (identified by ^{19}F nmr spectrum). To a soln of this mixt in Et_2O at 0° was added 0.045 mole of PhLi in 21 ml of Et_2O–PhH. The mixt was worked up in the usual manner, the solvent was evapd, and the residue was recrystd from pentane to give 2.0 g of **17** as colorless crystals.

Procedure I. 1-(Trifluoromethyl)-1,2,2-triphenylethane (52).—A mixt of 2.88 g (8.8 mmole) of 1-(trifluoromethyl)-1,2,2-triphenylethylene (**1**) and 30 ml of 57% HI was heated at reflux 18 hr and cooled. The solid that formed was filtered off, washed (H_2O), and recrystd from heptane (a little solid $NaHSO_3$ was used to remove the I_2 color) to give 2.21 g (77%) of **52** as colorless crystals: mp 102–103°; ^{19}F nmr (CCl_3F) δ 64.5 ppm (d, J = 8 Hz, 3F); ^1H nmr (CCl_3F) τ 2.5–3.2 (m, 15 H) 5.38 (d, J = 12 Hz, 1 H) 5.80 (d, J = 12 Hz to quartets, J = 8 Hz, 1 H). *Anal.* ($C_{21}H_{17}F_3$) C, H, F.

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Synthesis and Hormonal Activities of 8-L-Homolysine-vasopressin[1]

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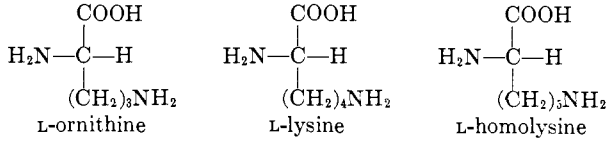
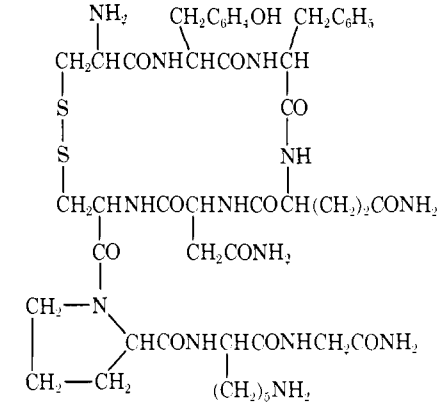
An analog of lysine-vasopressin in which the lysine residue was replaced by L-homolysine was synthesized stepwise by the nitrophenyl ester method. In the rat, the new hormone analog is a potent pressor and antidiuretic agent, both activities being comparable with those of the parent hormone.

The hormone analog 8-L-ornithine-vasopressin[3,4] is a potent pressor agent in the rat, but shows only a fraction of the antidiuretic activity of the parent hormone, lysine-vasopressin.[5] Thus the length of the side chain of the basic amino acid residue seems to play a significant role in the interaction between the hormone and the antidiuretic receptor site. The studies presented in this paper aimed at further exploration of the influence of this chain length. Since ornithine has a 3-C and lysine a 4-C side chain, it was decided to substitute the latter with L-homolysine (2,7-diaminoheptanoic acid) which has 5 C atoms in the corresponding part of the molecule.



The new hormone analog, 8-L-homolysine-vasopressin, was synthesized by the stepwise approach[6] with nitrophenyl esters[7] as acylating agents. The synthesis closely followed that of lysine-vasopressin,[8] except that the dipeptide and the tetrapeptide intermediates were not isolated in pure form and diisopropylethylamine[9] rather than Et_3N was used as the acid-binding agent in steps involving reactive derivatives of *S*-benzyl-L-cysteine. For the preparation of DL-homolysine, methods described in the literature[10–12] were applied, and resolution was performed on the diacetyl derivative with the aid of acylase.[13] The monoacetyl-L-homolysine obtained was deacetylated, then converted to the ζ-tosyl derivative *via* the copper complex, carbobenzoxylated on the α-amino group, and finally esterified with *p*-nitrophenol.[14] The active ester thus obtained was allowed to react with glycine ethyl ester,



8-L-homolysine-vasopressin

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the benzyloxycarbonyl group was removed from the resulting protected dipeptide derivative, and the amino-deprotected dipeptide ester was acylated with benzyloxycarbonyl-L-proline *p*-nitrophenyl ester.[15] The chain was lengthened in this manner until the protected tetrapeptide stage, when treatment with NH_3 in MeOH afforded the corresponding amide. The protected pentapeptide derivative, benzyloxycarbonyl-L-asparaginyl-*S*-benzyl-L-cysteinyl-L-prolyl-N^{ϵ}-tosyl-L-homolysylglycinamide, was readily obtained in pure form simply by washing the crude product with EtOAc and EtOH. The same purification was applied to the hexa-, hepta-, octa-, and nonapeptide derivatives. Additional simplification of the procedure was possible by the application of 95% EtOH for the precipitation of the protected nonapeptide from the reaction mixture. For the removal of the protecting groups, Na in boiling NH_3 was used. The free nonapeptide was cyclized to the corresponding disulfide by oxidation with air. The cyclic peptide was adsorbed on a column of Amberlite IRC-50 and eluted with a solution of pyridine acetate. Further purification was achieved by ion-exchange chromatography on a column of CM-cellulose with a gradient of NH_4OAc. For the removal of trace amounts of inorganic impurities, gel filtration on Sephadex G-25 was used. The final product was secured as a white, fluffy solid by lyophilization. The highly purified hormone analog was found to be homogeneous on paper chromatograms in 2 different solvent systems and on high-voltage paper electrophoresis. After hydrolysis of a sample, quantitative amino acid analysis gave the expected ratios of the amino acid components.

On exposure to the proteolytic action of trypsin,[16] 8-L-homolysine-vasopressin yielded 2 fragments, glycinamide and a peptide that contained, in molar ratios, all the other constituent amino acids of the hormone analog.

In the rat pressor test[17] (5 animals), 8-L-homolysine-vasopressin is about as effective as its parent hormone: a potency of about 250 units/mg[18] was determined.[19] The antidiuretic activity of the new hormone analog is dose dependent in the rat. At a dose of 4.17×10^{-7} mg, a potency[20] of about 300 units/mg was found.[19] These results provide additional support to the observation made with 8-L-ornithine-vasopressin[3,4] that the antidiuretic receptor is sensitive to the side-chain length of the basic amino acid in position 8. The pressor receptor site is less discriminative: in respect to pressor effect, there is no significant difference between lysine-vasopressin and its 8-L-ornithine or 8-L-homolysine analogs.

Experimental Section[21]

DL-Homolysine·HCl was prepd according to a method published for the synthesis of ornithine[11] and also by a procedure described[10,12] for homolysine itself. The product was purified by ion-exchange chromatography on Dowex 50-W-X12 in NH_4^+ cycle with a gradient of NH_4OH as eluent. The free amino acid was eluted with 0.1–0.5 *M* NH_4OH. The chromatographically homogeneous (tlc, system A) product was dissolved in H_2O, neutralized with 2 *N* HCl (30 ml), boiled with charcoal, filtered, and concd until the hydrochloride started to sep. Crystn was completed by the addn of EtOH, mp 267–268°. *Anal.* ($C_7H_{17}ClN_2O_2$) C, H, N, Cl.

N^{ϵ}-Acetyl-L-homolysine was prepd from DL-homolysine·HCl by treatment of the diacetyl derivative with acylase, as described for L-lysine by Greenstein and Winitz.[13] A chromatographically homogeneous (tlc, system A) product, mp 248–249°, darkening at 245°, was obtd in 38% yield; $[\alpha]^{30}D$ +17.7° (*c* 2, 5 *N* HCl). *Anal.* ($C_9H_{18}N_2O_3$) H, N; C: calcd, 53.5; found, 54.1.

L-Homolysine·HCl.—The monoacetyl derivative (2.6 g) was hydrolyzed with 4 *N* HCl (15 ml) by refluxing the soln for 2 hr. After evapn *in vacuo*, the residue was dissolved in hot 95% EtOH (15 ml), and the soln was neutralized by the addn of pyridine (1.7 ml). The crystals were collected after overnight storage in the refrigerator; they were washed with cold EtOH and Et_2O and dried *in vacuo*. The product (1.5 g, 59%, mp 263–264°) gave a single spot on tlc, $[\alpha]^{30}D$ +19.2° (*c* 2, 5 *N* HCl). The molar rotation calcd for the free base is 37.6°; the molar rotations of α,β-diaminobutyric acid, ornithine, and lysine are 37.7°, 37.5°, and 37.9°, respectively (*cf.* ref 13, p 2490).

Z-L-Pro-L-homolysyl(Tos)-Gly-OEt.—N^{ϵ}-Tosyl-L-homolysine was prepd from the amino acid·HCl according to the procedure described for N^{ϵ}-tosyl-L-lysine.[22] The product, mp 231–233°, was homogeneous by tlc (system A), $[\alpha]^{30}D$ +9.4° (*c* 2.4, 2 *N* HCl). N^{ϵ}-Tosyl-L-homolysine was treated with a small excess of benzyloxycarbonyl chloride and with enough NaOH to keep the reaction mixt alk. The N^{α}-Z derivative was obtained as an oil that was converted[14] into the cryst *p*-nitrophenyl ester: mp 126–128°; $[\alpha]^{39}D$ −14.3° (*c* 1.9, DMF). The active ester was used for the acylation of Gly-OEt as described in the synthesis of lysine-vasopressin.[8] The protected dipeptide ester (mp 64–66°) was used in the next step without purification. Hydrogenation in a 9:1 mixt of 95% EtOH and AcOH in the presence of a 10% Pd/C catalyst afforded the N^{α}-deprotected dipeptide derivative that was acylated with Z-L-Pro-ONP.[15] The protected tripeptide ester was purified on a column of Sephadex LH-20 with MeOH as eluent. The purified product, mp 110–113°, $[\alpha]^{30}D$ −51.3° (*c* 1, AcOH), was obtd in an overall yield of 25% calcd on N^{ϵ}-tosyl-L-homolysine. Because of the limited availability of L-homolysine, no attempt was made to improve yields. *Anal.* ($C_{31}H_{47}N_4O_9S$) C, H, N, S.

Z-L-Asn-L-Cys(Bzl)-L-Pro-L-homolysyl(Tos)-Gly-NH_2.—The protected tripeptide ester was hydrogenated as described above and the free amine was acylated with Z-(BZL)-L-Cys-ONP[15,23] in the presence of diisopropylethylamine.[9] The resulting protected tetrapeptide ester was treated with methanolic NH_3 as in the prepn of lysine-vasopressin.[8] The protected tetrapeptide amide, $[\alpha]^{30}D$ −31.7° (*c* 1, $CHCl_3$), failed to cryst and was treated, therefore, with HBr in AcOH. The hydrobromide was pptd with Et_2O and dissolved in dil $KHCO_3$ soln, and the free base was extd with $CHCl_3$. After removal of the solvent *in vacuo*, the residue was dissolved in DMF and allowed to react with Z-L-Asn-ONP.[15,24] Dilu of the reaction mixt with EtOAc yielded the protected pentapeptide amide: mp 171–173°; $[\alpha]^{30}D$ −39.3° (*c* 1, DMF). The product was homogeneous by tlc (system A, R_f 0.69; system B, 0.67). Calcd on the protected tripeptide ester, the yield was 72%.

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(17) "U. S. Pharmacopeia," 17th Revision, Mack Publishing Co., Easton, Pa., 1965, p 750.

(18) The potencies are expressed as units per mg of lyophilized material. No corrections were made for acetate or moisture.

(19) The antidiuretic and pressor assays were carried out by Professor Roderich Walter and Mrs. Arline Silverman at the Department of Physiology of Mount Sinai School of Medicine of the City University of New York.

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(21) Capillary melting points were taken and are reported without correction. Where analyses are indicated only by symbols of the elements, analytical results obtained for the elements were within ±0.4% of the theoretical values. For tlc, the following solvent systems were used: A, *n*-BuOH–AcOH–H_2O, 3:1:1; B, *n*-PrOH–H_2O, 7:3. For quantitative amino acid analysis, samples were hydrolyzed with constant boiling HCl in evacuated, sealed ampoules at 110° for 16 hr and analyzed according to the method of D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

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Anal. ($C_{43}H_{56}N_6O_{10}S_2$) C, H, N, S. Asp, 0.98; Pro, 1.00; Gly, 0.98; Bzl-Cys, 1.00.[25]

Z-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-homolysyl(Tos)-Gly-NH_2.—The Z group was removed from the protected pentapeptide with HBr in AcOH, and the chain was lengthened by the addn of Z-L-Gln-ONP,[15,24] as described in ref 8. The protected hexapeptide amide was secured in 88% yield. It was homogeneous by tlc, R_f (A) 0.66, (B) 0.64; mp 198–201°; $[\alpha]^{30}D$ −42° (*c* 1, DMF). *Anal.* ($C_{48}H_{64}N_{10}O_{12}S_2$) C, H, N, S. Asp, 0.97; Glu, 1.01; Pro, 1.06; Gly, 0.93; Bzl-Cys, 0.98.[25]

Z-L-Phe-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-homolysyl(Tos)-Gly-NH_2.—The lengthening of the chain from the hexapeptide derivative to the protected heptapeptide followed the procedure in ref 8. The product, mp 201–204°, was obtd in 90% yield, homogeneous in the tlc systems A and B with R_f values 0.69 and 0.67, respectively, $[\alpha]^{30}D$ −37.9° (*c* 1, DMF). *Anal.* ($C_{57}H_{73}N_{11}O_{13}S_2$) C, H, N, S. Asp, 1.00; Glu, 1.00; Pro, 1.00; Gly, 0.95; Phe, 1.03; Bzl-Cys, 0.98.[25]

Z-L-Tyr(Bzl)-L-Phe-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-homolysyl(Tos)-Gly-NH_2.—This protected octapeptide was prepared according to the procedure used for the synthesis of lysine-vasopressin.[8] The product, mp 215–219°, was secured in 87% yield, in homogeneous form: tlc, R_f A, 0.72, B, 0.70; $[\alpha]^{30}D$ −39.8° (*c* 1, DMF). *Anal.* ($C_{73}H_{88}N_{12}O_{15}S_2$) C, H, N, S. Asp, 0.98; Glu, 1.00; Pro, 1.00; Gly, 0.97; Tyr, 0.96; Phe, 1.04; Bzl-Cys, 1.01.[25]

Z-L-Cys(Bzl)-L-Tyr-L-Phe-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-homolysyl(Tos)-Gly-NH_2.—The procedure in ref 8 was followed with the notable exception that diisopropylethylamine[9] rather than Et_3N was used for the neutralization of HBr. Also, the fully protected nonapeptide was isolated by diln of the reaction mixt with 95% EtOH instead of EtOAc: yield, 82%; mp 218–221°; $[\alpha]^{30}D$ −42.8° (*c* 1, DMF). Homogeneous on tlc, R_f (A) 0.66. *Anal.* ($C_{76}H_{93}N_{13}O_{16}S_3$) C, H, N, S. Asp, 1.00; Glu, 0.97; Pro, 0.98; Gly, 0.92; Tyr, 0.98; Phe, 1.06; Bzl-Cys, 2.05.[25]

8-L-Homolysine-vasopressin.—A sample (0.20 g) of the protected nonapeptide was dissolved in liq NH_3 (*ca.* 0.2 l.) and treated at the bp of the soln with small pieces of Na until the blue color persisted for about 3 min. A few drops of AcOH were added, the NH_3 was allowed to evap to a small vol, and the rest of the solvent was removed *in vacuo* by evapn from the solid state. The residue was dissolved in O_2-free H_2O (0.3 l.) and aerated at pH 6.5 for several hr until the reaction for SH group (sodium nitroferricyanide) neg. The pH was adjusted to 4 with AcOH, and the soln was passed through a column (2.4 × 13 cm) of Amberlite IRC-50 in H^+ cycle. The column was washed with 0.25% AcOH (0.4 l.) and H_2O (25 ml). The cyclic peptide was eluted with a mixt of pyridine, AcOH, and H_2O (30, 4, and 70 ml). The eluate was concd *in vacuo*, and the resulting syrup was dild with H_2O (15 ml). A small amt of solid sepd and was removed by filtration. The soln was applied on a column of CM-cellulose (Whatman CM-23, 18 g) that was pretreated with 0.5 *N* NaOH and 0.5 *N* HCl and was equilibrated with 0.05 *M* NH_4OAc. The column was packed under pressure to 2.5 × 20 cm. For elution, a linear gradient of NH_4OAc (0.05–0.5 *M*, 500–500 ml) was used. Fractions of 6 ml were collected at a flow rate of 50 ml/hr. The hormone analog was eluted in fractions 45–48, as detected by uv absorption at 280 nm. From the total absorption, a yield of 78% was calcd (based on the protected nonapeptide amide). The soln was concd *in vacuo* to about 30 ml and lyophilized. The residue was dissolved in 0.25% AcOH (6.5 ml), the soln was applied to a Sephadex G-25 column (2.5 × 30 cm) and eluted with the same solvent. Fractions were collected at 10-min intervals at a flow rate of 36 ml/hr. The purified product was detected in fractions 23–28°. The soln was lyophilized, redissolved in 0.25% AcOH, and relyophilized. The white fluffy solid was dried *in vacuo* over NaOH and P_2O_5 overnight: yield, 84 mg; $[\alpha]^{30}D$ −23° (*c* 1, 1 *N* AcOH). Homogeneous on paper chromatograms, in *n*-BuOH–AcOH–H_2O (4:1:5), R_f 0.35; in *n*-BuOH–pyridine–AcOH–H_2O (30:20:6:24), R_f 0.56. On paper electrophoresis at pH 4.2 (0.1 *M* pyridine acetate) at 24 V/cm, 8-L-homolysine-vasopressin traveled toward the cathode as a single spot, 12.5 cm in 2 hr. *Anal.* ($C_{47}H_{67}N_{13}O_{12}S_2 \cdot 2CH_3COOH \cdot 4H_2O$) C, H, N. (Best fit obtd for solvation with $4H_2O$). Asp, 1.01; Glu, 1.00; Pro, 1.01; Gly, 1.00; 0.5-Cys, 1.98; Tyr, 1.01; Phe, 1.03; homolysine, 1.04.[25]

(25) In the quant amino acid analysis of the protected intermediates, tosylhomolysine, incompletely hydrolyzed, interfered with the detn of NH_3. Therefore, no values are reported for these 2 constituents. In the hydrolysate of 8-L-homolysine-vasopressin, homolysine was detd on the short column of the Beckman-Spinco amino acid analyzer, but with the "B" buffer (pH 4.28) as eluent.

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Thyroxine Analogs. 21.[1] *o*- and *m*-L-Thyroxine and Related Compounds

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Thyroxine analogs with the phenolic OH group ortho or meta to the ether O were synthesized and tested for thyroid hormonal activity in the rat antigoiter assay. 3-[4-(3-Hydroxyphenoxy)-3,5-diiodophenyl]-L-alanine (*m*-3,5-diiodo-L-thyronine) was found to be active, while the corresponding ortho isomer was inactive. *m*-L-Thyroxine was inactive, and *o*-L-thyroxine was weakly active in both thyromimetic and thyroxine antagonist tests. Blocking of the 4′ position with a Me group in *o*- and *m*-3,5-diiodo-L-thyronine produced inactive compounds. The 2′,4′-dihydroxyphenyl ether of 3,5-diiodo-L-tyrosine was also inactive. These results are consistent with 4′-hydroxylation *in vivo* producing active metabolites of *m*-3,5-diiodo-L-thyronine and of *o*-L-thyroxine, and offer an alternate explanation to the concept that the potential for *o*-quinoid oxidation is associated with the biological activity of *o*-L-thyroxine.

Niemann[2] has proposed that the potential for the phenolic ring of thyroxine (**1**) to undergo reversible oxidation to a quinoid form (**2**) is related to its biological activity. In support of this hypothesis, *o*-DL-thyroxine[3] (**3**) showed low thyroxine-like activity, while *m*-DL-thyroxine[4] (**4a, b**) was inactive.[5] The activity of **1** and **3** was related to their potential for oxidation to *p*- and *o*-quinoid forms, resp, whereas the inactive meta analog (**4a, b**) could not be oxidized in this manner. Structure **4a** was originally assigned to *m*-DL-thyroxine, but the isomeric 4′,6′-I_2 substitution pattern of **4b** was later considered to be more likely for this compound[2] and for

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