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[4-Phenylalanine]oxytocin, an Inhibitor of the Antidiuretic Effect of 8-Arginine-vasopressin[1]

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[4-Phenylalanine]oxytocin was prepared from Z-Cys(Bzl)-Tyr(Bzl)-Ile-Phe-Asn-Cys(Bzl)-Pro-Leu-Gly-NH_2 (4) by deprotection with Na in NH_3 followed by cyclization of the resulting disulfhydryl compound with ICH_2CH_2I. The protected peptide 4 was prepared from Boc-Asn-Cys(Bzl)-Pro-Leu-Gly-NH_2 by the stepwise solution method. Coupling was effected by a modification of the dicyclohexylcarbodiimide–1-hydroxybenzotriazole preactivation method wherein the precipitate of dicyclohexylurea is removed by filtration prior to mixing of the amino and carboxyl components. The analog was found to be an effective inhibitor of the antidiuretic (ADH) response to exogenous arginine-vasopressin. It produced marked diuresis in the anti-ADH assay at approximately the same dose level as does [Leu^4]oxytocin but, in contrast to [Leu^4]oxytocin, showed natriuretic activity only at relatively high dose levels. In addition, [Phe^4]oxytocin exhibited 0.15% of the oxytocic potency of oxytocin, weak antiavian vasodepressor activity ($pA_2 = 6.93$), and no measurable rat pressor activity.

In the course of studies aimed at elucidating the importance of the glutamine residue in position 4 of oxytocin (Figure 1) to the biological activities of this hormone, a series of analogs[2] was synthesized in which lipophilic, aliphatic amino acid residues were substituted in position 4 of oxytocin and deamino-oxytocin. The substantial potencies exhibited by these analogs in the oxytocic, avian vasodepressor (AVD), and milk-ejecting assays demonstrated that considerable variation is possible and that the carboxamide function is not essential for manifestation of these activities. A number of the analogs retained low but definite antidiuretic (ADH) potency as well, but most were inactive in the rat pressor assay.

Unexpectedly, one member of the series was found to possess antihormonal properties. Although [Leu^4]oxytocin possesses 2, 9, and 16%, respectively, of the oxytocic, AVD, and milk-ejecting potencies of oxytocin, it exhibits a weak depressor effect in the rat pressor assay and a strong diuretic effect in the antidiuretic assay.[3] The diuretic response to [Leu^4]oxytocin is due to a strong natriuretic effect as well as to an inhibition of the effect of the antidiuretic hormone 8-arginine-vasopressin.[3] Since [Leu^4]oxytocin can effectively reverse vasopressin-induced free-water reabsorption to free-water excretion but does not counteract the pressor response to vasopressin, it may be called an anti-ADH substance. No other member of this series displayed anti-ADH activity, although the length of the aliphatic side chain was varied from zero to four carbon atoms, and both branched- and straight-chain residues were used. The present synthesis of [Phe^4]oxytocin was undertaken in order to examine the effect of a further increase in lipophilicity and steric bulk in position 4.

The protected nonapeptide precursor to [Phe^4]oxytocin was prepared from Boc-Asn-Cys(Bzl)-Pro-Leu-Gly-NH_2[5] by the stepwise solution method, utilizing N^{α}-*tert*-butyloxycarbonyl (Boc) protection of the intermediate peptides and trifluoroacetic acid (TFA) deprotection at each step. Coupling was effected by means of a modification of the dicyclohexylcarbodiimide–1-hydroxybenzotriazole (DCC–HBt) preactivation method of König and Geiger[6] wherein the precipitate of dicyclohexylurea (DCU) is removed by filtration prior to mixing of the amino and carboxyl components. This procedure removes ~95% of the troublesome DCU by-product, and the peptide usually can be freed of

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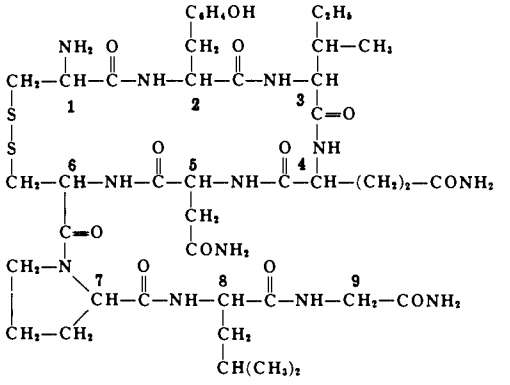

Figure 1. Structure of oxyotcin with numbers indicating the position of the individual amino acid residues. In deaminooxytocin the NH_2 at position 1 is replaced with H.

the remainder by means of a simple EtOH wash without need of recrystallization. The protected nonapeptide, Z-Cys(Bzl)-Tyr(Bzl)-Ile-Phe-Asn-Cys(Bzl)-Pro-Leu-Gly-NH_2, was deprotected with Na–NH_3,[7] cyclized with ICH_2CH_2I,[8] and purified by partition chromatography[9] followed by gel filtration.[10]

[Phe^4]oxytocin exhibits only 0.15% of the oxytocic potency[11] of oxytocin and has no measurable rat pressor or AVD activity, although it shows weak activity as an inhibitor of the AVD effect of oxytocin ($pA_2 = 6.93$, $\bar{M} = 1.2 \times 10^{-7}$, $\sigma = 0.4 \times 10^{-7}$). The analog does not exhibit ADH activity when tested in the water-loaded rat and shows natriuretic activity only at relatively high dose levels. [Phe^4]oxytocin is an effective inhibitor of exogenous arginine-vasopressin and produces marked diuresis in the anti-ADH assay at approximately the same dose levels as does [Leu^4]oxytocin. It has very little kaliuretic activity. Thus [Phe^4]oxytocin has been shown to possess the unusual anti-ADH property of [Leu^4]oxytocin to approximately the same degree and to be overall a somewhat more specific compound which exhibits only very low levels of other activities, including the natriuretic.

Experimental Section

Precoated plates of silica gel F-254 (0.25 mm, E. Merck) were used for thin-layer chromatography (TLC) of spots containing 10–20 μg of compound and were developed with the solvent systems: (A) $CHCl_3$–MeOH–HOAc (9:1:1), (B) BuOH–HOAc–H_2O (3:1:1), (C) BuOH–pyridine–H_2O (20:10:11), and (D) $CHCl_3$–MeOH–HOAc (8:2:0.5). Spots were visualized by treatment with Cl_2 followed by KI–starch spray. Melting points were determined in open capillaries and are corrected.

Boc protection was removed from intermediate peptides by treatment with TFA at room temperature for 15 min in a 50-ml centrifuge tube. In each case the deprotected peptide amine salt was precipitated with Et_2O (~40 ml) and washed by centrifugation–decantation with Et_2O (2 × 40 ml). The precipitate was dried at the water pump and then in vacuo. The initial pump-down must be done slowly and carefully.

For the condensation reactions, a DMF solution of the deprotected polypeptide was brought to pH 7 (Gramercy Indicator) with i-Pr_2NEt before the addition of a solution of preactivated[6] amino acid. After a short reaction period the pH was brought back up to ~6.5 by the addition of a further aliquot of i-Pr_2NEt. The progress of the coupling reaction was followed by means of the Kaiser test.[22]

Boc-Phe-Asn-Cys(Bzl)-Pro-Leu-Gly-NH_2 (1). Boc-Asn-Cys(Bzl)-Pro-Leu-Gly-NH_2[5] (0.914 g, 1.32 mmol) was deprotected with TFA (7 ml) as above. Boc-Phe-OH (0.403 g, 1.52 mmol) was preactivated[6] by treatment with DCC (0.313 g, 1.52 mmol) and HBt (0.308 g, 2.28 mmol) in DMF (3 ml) for 1 hr at 0° and for 1 hr at room temperature. The DCU precipitate was removed by filtration through a glass wool plug in a Pasteur pipet and the DCU was washed with 0.5 ml of DMF in three portions. The filtrate was added to a solution of the deprotected pentapeptide and i-Pr_2NEt (0.25 ml, 1.45 mmol) in DMF (3 ml). An aliquot of i-Pr_2NEt (0.17 ml, 1 mmol) was added after 15 min and coupling was complete after 45 min.

The product was precipitated with 30 ml of H_2O, collected on a glass frit, washed (H_2O, 3 × 10 ml; 5% $NaHCO_3$, 2 × 10 ml; H_2O, 2 × 10 ml; EtOH, 10 ml; Et_2O, 10 ml), and dried in vacuo: 1.031 g (93%); mp 234° dec; homogeneous to TLC (A, 0.24). A sample was crystallized (needles) from 50% DMF–H_2O in 87% recovery: mp 246° dec; $[\alpha]^{21}D$ −50.2° (c 1, DMF). Anal. ($C_{41}H_{58}N_8O_9S$) C, H, N.

Boc-Ile-Phe-Asn-Cys(Bzl)-Pro-Leu-Gly-NH_2 (2). The hexapeptide 1 (0.939 g, 1.12 mmol) was deprotected with TFA (7 ml) as above. Boc-Ile-OH·0.5H_2O (0.309 g, 1.29 mmol) was preactivated (as under 1) by treatment with DCC (0.265 g, 1.29 mmol) and HBt (0.261 g, 1.93 mmol) in DMF (3 ml). The mixture was filtered (as under 1) into a solution of the deprotected hexapeptide and i-Pr_2NEt (0.23 ml, 1.3 mmol) in DMF (3 ml). An aliquot of i-Pr_2NEt (0.22 ml, 1.1 mmol) was added after 15 min and coupling was complete by 30 min. After 1.5 hr the product was precipitated with H_2O (30 ml), filtered, washed (H_2O, 3 × 20 ml; 5% $NaHCO_3$, 2 × 10 ml; H_2O, 2 × 10 ml; EtOH, 2 × 10 ml; Et_2O, 10 ml), and dried in vacuo: 0.992 g (93%); mp 232° dec; homogeneous to TLC (D, 0.51). A sample was crystallized (needles) from 50% DMF–H_2O in 92% recovery: mp 244° dec; $[\alpha]^{21}D$ −55.3° (c 0.5, DMF). Anal. ($C_{47}H_{69}N_9O_{10}S$) C, H, N.

Boc-Tyr(Bzl)-Ile-Phe-Asn-Cys(Bzl)-Pro-Leu-Gly-NH_2 (3). The heptapeptide 2 (0.864 g, 0.908 mmol) was deprotected with TFA (7 ml) as above. Boc-Tyr(Bzl)-OH (0.388 g, 1.04 mmol) was preactivated (as under 1) by treatment with DCC (0.215 g, 1.04 mmol) and HBt (0.212 g, 1.57 mmol) in DMF (3 ml). The mixture was filtered (as under 1) into a solution of the deprotected heptapeptide and i-Pr_2NEt (0.2 ml, 1.2 mmol) in DMF (4 ml). Additional i-Pr_2NEt (0.3 ml, 1.8 mmol) was added in three aliquots after 5 min, 1 hr, and 5 hr. Coupling was complete after an overnight reaction period.

The product was precipitated with H_2O (30 ml), filtered, and washed (H_2O, 5 × 10 ml; 5% $NaHCO_3$, 3 × 10 ml; H_2O, 10 ml; EtOH, 3 × 10 ml; Et_2O, 10 ml). The product was further washed in a centrifuge tube (EtOH, 2 × 15 ml; Et_2O, 10 ml) and dried in vacuo: 1.057 g (97%); mp 238° dec; $[\alpha]^{21}D$ −40.5° (c 0.4, DMF); homogeneous to TLC (A, 0.37). A sample was reprecipitated from 50% DMF–H_2O in 83% recovery: mp 239° dec. Anal. ($C_{63}H_{84}N_{10}O_{10}S·2H_2O$) C, H, N.

Z-Cys(Bzl)-Tyr(Bzl)-Ile-Phe-Asn-Cys(Bzl)-Pro-Leu-Gly-NH_2 (4). The octapeptide 3 (0.200 g, 0.166 mmol) was deprotected by treatment with TFA at room temperature for *no more than 15 min* and worked up as before. Z-Cys(Bzl)-OH (0.072 g, 0.208 mmol) was preactivated (as under 1) with HBt (0.042 g, 0.312 mmol) and DCC (0.043 g, 0.208 mmol) in 1 ml of DMF. The mixture was filtered (as under 1) into a solution of the deprotected octapeptide and i-Pr_2NEt (0.04 ml, 0.23 mmol) in DMF (2 ml). An aliquot of i-Pr_2NEt (0.05 ml, 0.29 mmol) was added after 0.5 hr and coupling was complete after an overnight reaction period.

The product was precipitated with H_2O (30 ml), filtered, washed (H_2O, 3 × 30 ml; EtOH, 3 × 15 ml), and dried in vacuo: 0.221 g (93%) of grey powder containing a trace of Z-Cys(Bzl)-OH. This product was reprecipitated from 50% DMF–EtOAc in 70% recovery. A further reprecipitation from 75% DMF–H_2O in 96% recovery yielded 0.144 g: mp 255.5° dec; $[\alpha]^{22}D$ −49.0° (c 0.4, DMF). Anal. ($C_{76}H_{95}N_{11}O_{14}S_2·H_2O$) C, H, N.

[Phe^4]oxytocin. The protected nonapeptide 4 (300 mg, 0.21 mmol) was dissolved in ~200 ml of liquid NH_3 (freshly distilled from Na) and treated with a fresh stick of Na encased in a 4-mm glass tube until the blue color of excess Na remained for 20 sec.[7] The excess Na was consumed with a few drops of HOAc and the NH_3 was evaporated under a stream of N_2.[23] The residue was dissolved in N_2-saturated H_2O (0.5 l) and the disulfhydryl intermediate was cyclized at pH ~8 by treatment with a solution of ICH_2CH_2I[8] (0.06 g, 0.213 mmol) in 2 ml of MeOH. Cyclization was complete within several hours (Ellman test[24]). The solution was made acidic (pH ~5) with HOAc, concentrated to ~150 ml volume, and lyophilized. The residue was subjected to partition chromatography[9] on a column (2.8 × 69 cm) of Sephadex G-25 (100–200 mesh) in the solvent system BuOH–C_6H_6–3.5% aqueous HOAc containing 1.5% pyridine (3:2:5) at a flow rate of 22 ml/hr. The peptide content of the fractions was determined by the Folin–Lowry method.[25] Fractions comprising the major peak (R_f 0.30) were pooled and evaporated to dryness. The residue was dissolved in several milliliters of HOAc, diluted to ~150 ml with deionized H_2O, and lyophilized: 69 mg.

The purified [Phe^4]oxytocin was subjected to gel filtration[10] on a column (2.8 × 68 cm) of Sephadex G-25 (200–270 mesh) in 0.2 N

HOAc at a flow rate of 25 ml/hr. The peptide material was eluted as a single peak at 87% of the column volume and was recovered by lyophilization: 64 mg. This material was again subjected to partition chromatography as above in the solvent system BuOH–C_6H_6–HOAc–H_2O (8:3:2:8). [Phe^4]oxytocin was eluted as a broad peak at R_f 0.32 and was recovered by lyophilization from dilute HOAc as above: 64 mg (30% overall); $[\alpha]^{25}D$ +1.8° (*c* 0.7, 1 *N* HOAc); homogeneous to TLC (B, 0.55; C, 0.61). Amino acid analysis following 24-hr hydrolysis in 6 *N* HCl at 110° gave the following molar ratios: Asp, 1.00; Pro, 1.01; Gly, 1.00; Cys, 2.08; Ile, 0.91; Leu, 1.05; Tyr, 1.01; Phe, 1.03; NH_3, 1.89. Anal. $C_{47}H_{67}N_{11}O_{11}S_2 \cdot 3H_2O$) C, H, N.

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Cycloalkanones. 7.[1] Hypocholesterolemic Activity of Aliphatic Compounds Related to 2,8-Dibenzylcyclooctanone

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A series of 19 aliphatic analogs of 2,8-dibenzylcyclooctanone and 1,5-diphenyl-2,4-dimethyl-3-pentanone was examined. Separation of hypocholesterolemic activity from the previously observed uterotropic and antifertility activities was achieved by simplification of the parent compound to 2-octanone. There was no loss of hypocholesterolemic activity. Reduction of serum cholesterol levels in male rats to less than 50% of control values was obtained at a dose of 10 mg/kg/day.

2,8-Dibenzylcyclooctanone (**1**) has been shown to be an effective hypolipidemic agent in rats and mice.[2a] The acyclic analog 1,5-diphenyl-2,4-dimethyl-3-pentanone (**2**) has also demonstrated hypolipidemic activity.[2b] Both **1** and **2**, as well as the most active derivatives of **1**, have also shown a positive uterotropic effect.[2] Although the uterotropic effect is relatively small when compared to a standard such as diethylstilbestrol, elimination of this effect has been an objective of the SAR studies completed.[3] Compounds **1** and **2** also possess antifertility activity which has been separated from the hypolipidemic effects in subsequent analogs of the cyclic series.[3]

It has been shown that modifications of the cyclooctane ring and the aromatic moiety of **1** produce large changes in