Satd aq NaCl (50 ml) was added, the soln was extd with C_6H_6 (4 × 100 ml), the solvent was evapd, and the tacky residue was chromatographed (Florisil, petr ether, bp 60–100°). The viscous product weighed 7.54 g (80% yield). It was dissolved in EtOH (100 ml) and HCl (7.7 ml) and hydrogenated at 3.71 kg/cm² in the presence of 5% Rh/C (3 g) at 45° for 45 hr. Filtration from the catalyst, evapn of EtOH, addition of LiOH, extn with $CHCl_3$, and evapn of the solvent yielded oily **1**, di(5-nitrobarbiturate): yellow crystals from H_2O (5.2 g, 62%); mp 251–252°. *Anal.* ($C_{26}H_{28}N_2O_{11}\cdot H_2O$) C, H, N. The di-*d*-tartrate was prepd. in Me_2CO and crystd from MeOH, mp 161–162°. *Anal.* ($C_{20}H_{34}N_2O_6$) C, H, N. Mass spectrum of liberated oily **1** ($C_{12}H_{22}N_2$) revealed *m/e* 194.

3-(2-Pyridyl)-3-quinuclidinol (3b).—A soln of 55 g (0.35 mole) of 2-bromopyridine in 50 ml of Et_2O was added rapidly to a stirred soln of *n*-BuLi (0.35 mole) in hexane at −50° under N_2. After stirring for 20 min, a soln of 3-quinuclidinone (12.5 g, 0.1 mole) in Et_2O (100 ml) was added dropwise. The mixt was stirred for 2.5 hr while the temp was allowed to rise gradually to 25°, poured on ice–AcOH, and extd with Et_2O. The H_2O layer was made ammoniacal and extd exhaustively with $CHCl_3$. The exts were dried (Na_2SO_4) and evapd, and the residue was crystd from Me_2CO; yield 8.5 g (42%); mp 163–164°. The product sublimed at 130° (0.1 mm). *Anal.* ($C_{12}H_{16}N_2O$) C, H, *m/e* 204.

3-(2-Pyridyl)-1-azabicyclo[2.2.2]-2-octene.—An intimate mixt of **3b** (4.7 g, 23 mmoles) and powdered potassium pyrosulfate (40 g) was fused at 240° for 1 min.[7] After cooling, the melt was treated with ice, and the soln was made ammoniacal and extd exhaustively ($CHCl_3$). Evapn of the solvent and chromatography using Florisil and hexane yielded 2.87 g (64%) of colorless crystals, mp 75–76°. *Anal.* ($C_{12}H_{14}N_2$) C, H; *m/e* 186.

3-(2-Piperidinyl)quinuclidine (2).—A soln of 4.5 g (24 mmoles) of the unsatd pyridine deriv in EtOH (100 ml) and HCl (4.5 ml) was hydrogenated at 25° and 3.51 kg/cm² with PtO_2 (0.58 g) for 1.5 hr. The soln was filtered and evapd, and the residue was made basic with LiOH and extd with $CHCl_3$. The oily residue from the ext was treated with 600 ml of an EtOH soln of 5-nitrobarbituric acid (8.65 g, 0.05 mole). A ppt which formed immediately was collected, dried, and recrystd from H_2O (200 ml). Yellow rosettes (3.54 g) had mp 252–254° dec. The base was regenerated (aq KOH), extd (Et_2O), and crystd (anhyd Et_2O) at −30°: yield 1.1 g; mp 61–62° (diastereomer **2A**); tlc [Al_2O_3, $CHCl_3$–Et_2NH (5%)] R_f 0.4. *Anal.* ($C_{12}H_{22}N_2$) C, H, N; *m/e* 194.

Diastereomer 2B.—The aq mother liquor of the dilturate was concd to 50 ml and cooled to 0°. It deposited 4.86 g of yellow needles, mp 261–262° dec. The diastereoisomeric base was regenerated and recrystd as above; yield 1.7 g; mp 69–70°; tlc as above, R_f 0.6. *Anal.* ($C_{12}H_{22}N_2$) C, H, N; *m/e* 194.

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Deamino-D-oxytocin[1]

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We have previously reported[2] that the optical antipode of the posterior pituitary hormone oxytocin did not possess detectable avian vasodepressor or oxytocic activity, whereas oxytocin possesses approximately 500 units/mg of each of these activities. No indication of an inhibitory effect of D-oxytocin on these activities of oxytocin could be detected. Since deaminooxytocin is much more potent than oxytocin, it was decided to synthesize deamino-D-oxytocin and test it for these biological activities.

For the synthesis of deamino-D-oxytocin, the desired protected polypeptide amide precursor *S*-Bzl-β-mercaptopropionyl-D-Tyr-D-Ile-D-Gln-D-Asn-D-Cys(Bzl)-D-Pro-D-Leu-Gly-NH_2 (I) was prepared by the nitrophenyl ester method,[3] as employed for the synthesis of deamino-L-oxytocin,[4] starting with Z-D-Tyr(Bzl)-D-Ile-D-Gln-D-Asn-D-Cys(Bzl)-D-Pro-D-Leu-Gly-NH_2 (II).[2]

The protected polypeptide amide I was treated with Na in liquid NH_3,[5] and the resulting disulfhydryl compound was oxidized in dil aq soln with $K_3Fe(CN)_6$.[4] After removal of ferro- and ferricyanide ions with the ion-exchange resin AG3-X4 (in the Cl^- form), the soln gave a negative Ellman test.[6] The deamino-D-oxytocin thus obtd was purified by countercurrent distribution[7] or by partition chromatography[8] on Sephadex G-25 as described in the Experimental Section.

No avian vasodepressor[9] or oxytocic activity[10] was detected upon bioassay of deamino-D-oxytocin, whereas crystalline deamino-L-oxytocin possesses 975 units/mg of avian vasodepressor and 803 units/mg of oxytocic activity.[11] No indication of an inhibitory effect of deamino-D-oxytocin on the above activities of oxytocin could be detected.

Experimental Section[12]

***S*-Bzl-β-mercaptopropionyl-D-Tyr-D-Ile-D-Gln-D-Asn-D-Cys(Bzl)-D-Pro-D-Leu-Gly-NH_2 (I). Procedure A.**—A suspension of 0.6 g of II in 25 ml of F_3CCH_2OH[13] was saturated with HBr gas previously passed through towers of naphthalene and anhydrous $CaCl_2$. After 30 min the resulting soln was evapd to dryness, the residue was redissolved in F_3CCH_2OH, and the soln was evapd to dryness again. The solid residue obtained was dissolved in 40 ml of MeOH and neutralized with ion-exchange resin IRA-410 (OH). The suspension was filtered, and the filtrate, which gave a negative test for Br^- ($AgNO_3$), was evapd under vacuum and dried under vacuum over P_2O_5. A soln of 0.38 g of the free octapeptide thus obtained in 2 ml of DMF was treated with 0.17 g of *p*-nitrophenyl *S*-benzyl-β-mercaptopropionate. The waxy material formed overnight was treated with EtOH, filtered off, and washed 3 more times with EtOH; yield

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340 mg (59%); mp 238–240°; $[\alpha]^{19}D$ +41.5° (c 1, DMF); lit.[4] (L isomer) mp 239–240°; $[\alpha]^{20}D$ −42° (c 1, DMF).

Procedure B.—Octapeptide·HBr, obtained in a run identical with the one described in procedure A, was dissolved in 60 ml of MeOH and treated with 100 mg of imidazole. The resulting soln was evapd to a solid residue which was dried over P_2O_5 under vacuum. The dry residue was dissolved in 2 ml of DMF and condensed with *p*-nitrophenyl *S*-benzyl-β-mercaptopropionate as described in procedure A: yield 485 mg (84%); mp 241–243°; $[\alpha]^{19}D$ +41.6° (c 1, DMF). *Anal.* ($C_{57}H_{79}N_{11}O_{12}S_2$) C, H, N.

Deamino-D-oxytocin.—The debenzylation of 200 mg of amide I was performed with Na in 400 ml of liq NH_3 freshly distd from Na.[5] The soln was concd, and the last 30 ml of liq NH_3 was lyophilized. The residual white powder was dissolved in 150 ml of 0.25% AcOH, the pH was adjusted to 6.8 with 1 *N* NH_4OH, and the resulting clear soln was titrated with 0.011 *M* $K_3Fe(CN)_6$ until a yellow color began to appear (27 ml). Then excess ferricyanide (8 ml) was added. After 30 min the soln gave a negative Ellman test, and it was passed through a column of AG3-X4 (Cl^-). The soln of the crude product thus obtained was divided into 2 equal portions, each of which was purified by a different method. One half of the soln was concd to 15 ml and subjected to countercurrent distribution in the solvent system *n*-BuOH–*n*-PrOH–0.5% AcOH contg 0.1% pyridine (6:1:8). After 200 transfers a main peak (K = 4.4) was obtained, as detd by measurement of the Folin–Lowry color values.[14] The contents of tubes 155–170 were combined, concd, and lyophilized to yield 25 mg of a white fluffy powder. A sample was hydrolyzed in 6 *N* HCl at 120° for 20 hr for amino acid analysis,[15] and the following molar ratios were found, with the value of Gly taken as 1.0: Gly, 1.0; Leu, 1.0; Pro, 1.0; Asp, 1.0; Glu, 1.1; Ile, 0.93; aIle, 0.07; Tyr, 1.0; Cys, 0.24; the mixed disulfide of cysteine and β-mercaptopropionic acid, 0.67; NH_3, 2.9.

The other half of the crude soln of deamino-D-oxytocin was concd to a low vol and purified by partition chromatography by the method of Yamashiro.[8] A Sephadex G-25 column (2.15 × 113 cm) was employed with the solvent system *n*-BuOH–C_5H_5N–3.5% AcOH contg 1.5% pyridine (1:1:2). Elution with the upper phase was performed at a rate of 30 ml/hr. The Folin–Lowry color values showed a main peak with R_f 0.19. The correspg value for deamino-L-oxytocin is 0.19.[11] Fractions correspg to the main peak were combined, concd, and lyophilized: yield 37 mg of white fluffy powder; $[\alpha]^{20}D$ +104° (c 0.5, 1 *N* AcOH); lit.[4] (amorphous L isomer) $[\alpha]^{21}D$ −107° (c 0.5, 1 *N* AcOH). A sample of deamino-D-oxytocin was hydrolyzed in 6 *N* HCl at 120° for 20 hr for amino acid analysis. The following molar ratios were obtd, with the value of Gly taken as 1.0: Gly, 1.0; Leu, 1.0; Pro, 1.0; Asp, 1.0; Glu, 1.0; Ile, 1.0; aIle, 0.02; Tyr, 1.0; Cys, 0.34; the mixed disulfide of cysteine and β-mercaptopropionic acid, 0.62; NH_3, 2.9. *Anal.* ($C_{43}H_{65}N_{11}O_{12}S_2$) C, H, N.

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New Compounds

α-Bromo- and α-Chloropyridylalanines[1]

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Phenylalanine analogs have exhibited biological activity in certain mammalian phenylalanine, tryptophan, and tyrosine hydroxylase systems.[2–5] *p*-Chlorophenylalanine depletes brain serotonin in the rat[6] thus causing an abnormal psychic behavior of the animal.[7] The synthesis of the α-fluoro- and α-hydroxypyridylalanines has been described in an earlier study and certain of these compounds are toxic to the growth of various microorganisms.[8] In this report the synthesis of the bromo and chloro analogs is described.

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Experimental Section

A Thomas-Hoover capillary melting point apparatus was employed for all mp determinations, and the melting points reported are uncorr. Uv spectra were determined with a Beckman DBG recording spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ± 0.4% of the theoretical values unless otherwise specified. The aminopicolines were obtained from Aldrich Chemical Co., Inc. and J. T. Baker Laboratory Chemicals.

The following reaction procedures are given for specific compds; compds indicated by reference to the particular table were prepared in like manner.

α-Bromopicolines.—The appropriate aminopicoline was diazotized as previously reported[9] utilizing HBr, Br_2, and $NaNO_2$. The boiling points and melting points agreed in all cases with those reported above.

α-Chloropicolines.—The appropriate aminopicoline was diazotized as reported[10] employing HCl and $NaNO_2$. The boiling points were in agreement with those reported in the literature.

2-Bromo-3-bromomethylpyridine·HBr (Table I, 1–8).—2-Bromo-3-methylpyridine (29.2 g, 0.17 mole), NBS (30.2 g, 0.17 mole), and 1.5 g of benzoyl peroxide in 500 ml of $MgSO_4$-dried CCl_4 were refluxed several hours. The succinimide was removed by filtration, and the filtrate was concd *in vacuo* to about 100 ml. The soln was washed with 100 ml of each of the following: 4% NaOH, H_2O, and 2% aq HBr. Et_2O was added to the org layer to make a total of 175 ml, and the dried soln was satd with anhyd

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