another 3 days. An oil separated, which could not be crystallized: ir (film) a band at 1690 cm^{-1} indicated the presence of a $-N{=}C(CH_3)_2-$ structure. The oil was dissolved in water (25 ml) and the solution left at room temperature overnight. Evaporation yielded 0.5 g of an oil which could not be crystallized: ir (film) 3200–3300 cm^{-1} (NH_2), no band at 1690 cm^{-1}. A small amount was purified for analysis by preparative tlc developed in ethanol. *Anal.* ($C_{20}H_{29}BrN_2$) C, H, N.

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[1-β-Mercapto-β,β-pentamethylenepropionic acid]oxytocin, a Potent Inhibitor of Oxytocin†

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[1-β-Mercapto-β,β-pentamethylenepropionic acid]oxytocin was prepared from β-Mpa(β-$(CH_2)_5$)(Bzl)-Tyr(Bzl)-Ile-Gln-Asn-Cys(Bzl)-Pro-Leu-Gly-NH_2 by removal of the Bzl-protecting groups with Na–NH_3 followed by cyclization of the resulting disulfhydryl compound with $K_3Fe(CN)_6$. The analog was purified by desalting on Sephadex G-15 in 50% HOAc and gel filtration on Sephadex G-25 and LH-20. The protected intermediate above was synthesized from Z-Cys(Bzl)-Pro-Leu-Gly-NH_2 by the stepwise *p*-nitrophenyl ester method using N^{α}-Boc protection at the penta-, hexa-, and octapeptide stages. The analog was found to be a potent inhibitor of the oxytocic and avian vasodepressor effects of oxytocin (pA_2 values of 7.43 and 8.30, respectively) but was only a weak inhibitor of the rat pressor effect of 8-lysine-vasopressin. The rat antipressor potency of [1-deaminopenicillamine]oxytocin was also determined in this study: pA_2 = 6.27. Of the alkyl-substituted 1-position analogs of oxytocin studied so far, [1-β-mercapto-β,β-pentamethylenepropionic acid]oxytocin is the most potent antioxytocic agent.

When [1-L-penicillamine]oxytocin, [1-D-penicillamine]-oxytocin, and [1-deaminopenicillamine]oxytocin ([1-β-mercapto-β,β-dimethylpropionic acid]oxytocin) were found to be potent inhibitors[2] of the oxytocic and avian vasodepressor (AVD) activities of oxytocin (Figure 1), studies were undertaken of related modifications[3] in the 1 position of the highly potent deaminooxytocin.[4] [1-β-Mercapto-β,β-diethylpropionic acid]oxytocin[3] ([1-β-Mpa(β-Et_2)]oxytocin) was found to be the most potent inhibitor of the compounds that had been prepared, having pA_2 values of 7.24 in the antioxytocic and 8.11 in the anti-AVD assays in comparison with corresponding pA_2 values for [1-deaminopenicillamine]oxytocin of 6.94 and 7.88, respectively.

As a further variation, the incorporation of a β-mercapto-β,β-pentamethylenepropionic acid residue [β-Mpa(β-$(CH_2)_5$)] into the 1 position of oxytocin is reported here. This residue is structurally similar to β-Mpa(β-Et_2) and can be looked upon as having the β-geminal ethyl groups connected by a methylene bridge. The possible conformations of the β-alkyl substituents are thus limited and the overall lipophilicity of the residue is increased.

[1-β-Mpa(β-$(CH_2)_5$)]oxytocin was prepared from the protected polypeptide β-Mpa(β-$(CH_2)_5$)(Bzl)-Tyr(Bzl)-Ile-Gln-Asn-Cys(Bzl)-Pro-Leu-Gly-NH_2 by removal of the benzyl-protecting groups with Na–NH_3[5] followed by cyclization with potassium ferricyanide[6] solution. The hormone analog was purified by desalting in 50% HOAc on Sephadex G-15 by the method of Manning[7] followed by gel filtration in 0.2 *N* HOAc on Sephadex G-15 and in DMF on Sephadex LH-20.

N^{α}-*tert*-Butyloxycarbonyl (Boc) protection was used on the penta-, hexa-, and octapeptide intermediates. Boc removal was accomplished by treatment with trifluoroacetic acid (TFA) at room temperature. In the case of the Boc-Tyr(Bzl)-terminal octapeptide it is important that the deprotection period be no longer than 15 min. Longer periods lead to removal of the benzyl ether protection. *p*-Nitrophenyl esters[8] were used for coupling reactions throughout. β-(*S*-Benzylmercapto)-β,β-pentamethylenepropionic acid was prepared from ethyl cyclohexylidineacetate[9] by means

† This work was supported in part by Grant HL-11680 from the National Heart and Lung Institute, U. S. Public Health Service. All optically active amino acids are of the L configuration. The symbols for the amino acids follow the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature.[1] Where analyses are indicated only by symbols for the elements, analytical results obtained for the elements were within ±0.4% of the theoretical values.

Table I. Inhibitory Properties of Certain β-Dialkyl-Substituted 1-Position Analogs of Oxytocin

Analog	Antioxytocic		Antiavian vasodepressor		Antipressor	
	$\times 10^7 \bar{M}$[a]	pA_2[a]	$\times 10^8 \bar{M}$	pA_2	$\times 10^7 \bar{M}$	pA_2
[1-β-Mpa(β-Me_2)]oxytocin	1.16 (36),[b] $\sigma = 0.51$	6.94[b]	1.31 (27),[b] $\sigma = 0.61$	7.88[b]	5.42 (23), $\sigma = 1.91$	6.27
[1-β-Mpa(β-Et_2)]oxytocin	0.58 (9),[b] $\sigma = 0.12$	7.24[b]	0.78 (8),[b] $\sigma = 0.17$	8.11[b]	5.73 (20),[c] $\sigma = 2.72$	6.24[c]
[1-β-Mpa(β-$(CH_2)_5$)]oxytocin	0.37 (33), $\sigma = 0.12$	7.43	0.50 (22), $\sigma = 0.20$	8.30	Weak	

[a] pA_2 values (see Schild[16]) represent here the negative log to the base 10 of the average molar concentration ($\bar{M}$) of an antagonist which will reduce the response of the uterine horn, the chicken, or the rat to $2x$ units of pharmacologically active compound (agonist) to the response to x units of the agonist. The number of individual determinations is given in parentheses and σ is the standard deviation. Specific details of these assays are described by Vavrek, *et al.*,[3] and by Dyckes, *et al.*[17] Synthetic oxytocin was the agonist used in the antioxytocic and antiavian vasodepressor assays and synthetic LVP in the antipressor assays. Concentrations of the antagonists were calculated on the basis of a 10-ml tissue bath (oxytocic) or assumed blood volumes of 150 ml in the chickens and 6.7 ml/100 g in the rats. [b] Vavrek, *et al.*[3] [c] Dyckes, *et al.*[17]

of a boron trifluoride etherate catalyzed‡ Michael addition of benzyl mercaptan followed by saponification. The corresponding *p*-nitrophenyl ester was prepared from the acid by treatment with *N,N'*-dicyclohexylcarbodiimide and *p*-nitrophenol in EtOAc.

[1-β-Mpa(β-$(CH_2)_5$)]oxytocin was found to be devoid of oxytocic, AVD, and pressor activities when tested against the U.S.P. posterior pituitary reference standard§ but produced inhibition of the oxytocic and AVD responses to synthetic oxytocin and of the rat pressor response to synthetic 8-lysine-vasopressin (LVP). Inhibitory potencies were determined and expressed as pA_2 values as defined by Schild[16] (see footnote to Table I).

The inhibitory potencies of [1-β-Mpa(β-$(CH_2)_5$)]oxytocin are compared with those of [1-β-Mpa(β-Et_2)]oxytocin and [1-β-Mpa(β-Me_2)]oxytocin in Table I. It can be seen that [1-β-Mpa(β-$(CH_2)_5$)]oxytocin is the most potent inhibitor of this series in both the antioxytocic and anti-AVD assays. For purposes of comparison in this work the rat antipressor activity of [1-β-Mpa(β-Me_2)]oxytocin[2] was determined and is reported here. Although both [1-β-Mpa(β-Et_2)]oxytocin and [1-β-Mpa(β-Me_2)]oxytocin are potent antipressor agents when assayed against synthetic LVP, [1-β-Mpa(β-$(CH_2)_5$)]oxytocin shows only weak inhibitory activity.

As the difference in inhibitory potency between [1-β-Mpa(β-$(CH_2)_5$)]oxytocin and [1-β-Mpa(β-Et_2)]oxytocin was not great, a further series of antioxytocic assays was performed wherein these analogs were directly compared by means of alternate injections in the same assay preparation. [1-β-Mpa(β-$(CH_2)_5$)]oxytocin was significantly more potent than [1-β-Mpa(β-Et_2)]oxytocin as determined by the t test for paired observations[18] ($N = 8$; 95% confidence level). Furthermore, it was noted that the inhibitory effect of [1-β-Mpa(β-$(CH_2)_5$)]oxytocin was persistent. Following an inhibitory dose of this compound, a standard washing schedule failed to restore the tissue to its normal state, as judged by its response to oxytocin given 6 min later. Normal responses were usually observed to the third such dose of oxytocin (18 min), whereas following a dose of [1-β-Mpa(β-Et_2)]oxytocin the normal response was usually restored within 6 min.

‡ This procedure was suggested by Professor G. Edwin Wilson, Jr., based on work[10] carried out in his laboratory.

§ Oxytocic assays were performed on isolated uteri from virgin rats in natural estrus according to the method of Holton,[11] as modified by Munsick,[12] with the use of Mg-free van Dyke-Hastings solution as the bathing fluid. Avian vasodepressor assays were performed on conscious chickens by the method of Coon,[13] as modified by Munsick, Sawyer, and van Dyke.[14] Pressor assays were carried out on anesthetized male rats as described in the U. S. Pharmacopeia.[15]

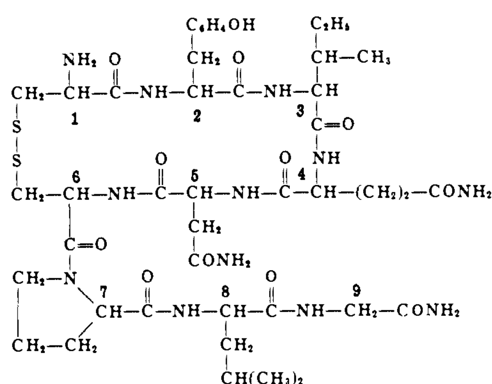

Figure 1. Structure of oxytocin with numbers indicating the position of the individual amino acid residues.

Thus [1-β-Mpa(β-$CH_2)_5$)]oxytocin is a more potent and more persistent inhibitor of oxytocin than [1-β-Mpa(β-Et_2)]oxytocin in the antioxytocic assay system. These results suggest that the incorporation of the extra methylene group in the 1-position residue of [1-β-Mpa(β-$(CH_2)_5$)]oxytocin may have caused a significant enhancement in receptor binding. Further investigations of the dependence of inhibitory potency on the relative contributions of lipophilicity and steric bulk in the 1-position residue should be of interest.

Experimental Section

Precoated plates of silica gel F-254 (0.25 mm, E. Merck) were used for thin-layer chromatography (tlc) of spots containing 5–20 μg of compound and were developed with the following solvent systems: (A) $CHCl_3$–MeOH (9:1), (B) $CHCl_3$–MeOH–HOAc (8:2:0.5), (C) BuOH–HOAc–H_2O (3:1:1), (D) BuOH–pyridine–H_2O (20:10:11). Spots were visualized by exposure to I_2 vapor or by treatment with Cl_2 followed by KI–starch spray.

The disappearance of the free peptide amine during coupling reactions was followed by the quantitative Kaiser test.[17,19] The presence of excess diisopropylethylamine (*i*-Pr_2EtN) in the reaction mixture was maintained by the addition of further aliquots of *i*-Pr_2EtN as needed. The atmosphere of the reaction vessel was periodically checked for *i*-Pr_2EtN by means of moist litmus paper.[20] Melting points were determined in open capillaries and are corrected.

β-(*S*-Benzylmercapto)-β,β-pentamethylenepropionic Acid (1). A mixture of ethyl cyclohexylidineacetate[9] (10.0 g, 0.06 mol), redistilled boron trifluoride etherate (11.4 g, 0.08 mol), benzyl mercaptan (7.44 g, 0.06 mol), and benzene (60 ml) was refluxed under N_2 for 8 hr.[10] The cooled reaction mixture was washed with 150 ml

of 5% $NaHCO_3$ solution (four portions), dried over Na_2SO_4, and distilled at reduced pressure to remove starting materials [to 102° (22 mm)].

The residue was hydrolyzed in a solution of K_2CO_3 (12 g) in 25% aqueous MeOH during a 24-hr reflux period. The MeOH was distilled out and the aqueous residue was diluted to 150 ml with water. The aqueous solution was washed with Et_2O and made strongly acidic with concentrated HCl. The yellow oil which separated was extracted into Et_2O. The organic layer was dried over $MgSO_4$, filtered, stripped of Et_2O, and diluted with 90–110° ligroine (40 ml). The product crystallized as small needles on cooling: 2.74 g (17% overall); mp 89–90°; homogeneous to tlc (A, 0.47). A sample was recrystallized from ligroine (90–110°) in 80% recovery to yield colorless needles: mp 90–91°; nmr (CCl_4) τ 2.75 (s, 5), 6.30 (s, 2), 7.35 (s, 2), 8.3 (m, 10). *Anal.* ($C_{15}H_{20}O_2S$) C, H, S.

p-Nitrophenyl β-(S-Benzylmercapto)-β,β-pentamethylenepropionate (2). A solution of the acid 1 (2.2 g, 8.33 mmol), *p*-nitrophenol (1.36 g, 9.8 mmol), and *N,N'*-dicyclohexylcarbodiimide (1.73 g, 8.4 mmol) in ethyl acetate (15 ml) was stirred at 0° for 1.5 hr and then at room temperature for 2 days. The solution was treated with 0.5 ml of HOAc and filtered, and the dicyclohexylurea precipitate was washed with 25 ml of EtOAc (in three portions). The filtrate was washed with 175 ml of 0.5 *N* NH_4OH solution saturated with EtOAc (in six portions), 1 *N* HCl (30 ml), and saturated NaCl solution (50 ml). The organic layer was dried over $MgSO_4$, filtered, and stripped of EtOAc. The residue was dissolved in a mixture of hot absolute EtOH (15 ml) and EtOAc (0.5 ml). The product crystallized as small, colorless needles on cooling: 2.28 g (68%); mp 65–66°; homogeneous to tlc (A, 0.61); nmr (CCl_4) τ 1.78, 2.62 (AB system, 4), 2.75 (s, 5), 6.23 (s, 2), 7.15 (s, 2), 8.2 (m, 10). *Anal.* ($C_{12}H_{23}NO_4S$) C, H, N, S.

Boc-Asn-Cys(Bzl)-Pro-Leu-Gly-NH$_2$ (3). Z-Cys(Bzl)-Pro-Leu-Gly-NH_2[21] (1.53 g, 2.5 mmol) in HOAc (5 ml) was deprotected by treatment with 7 *N* HBr–HOAc (10 ml, 1.25 hr). The deprotected salt was precipitated with Et_2O, collected on a frit, washed with Et_2O, and dried *in vacuo* to yield 1.71 g of white powder.

A solution of this powder in dimethylformamide (DMF, 3 ml) containing *i*-Pr_2EtN (1.5 ml, 8.7 mmol) was treated with Boc-Asn-ONp (1.06 g, 3.0 mmol) for 2 days. The reaction mixture was diluted with EtOAc (10 ml) and filtered, and the solid was washed with EtOAc. The crude product thus obtained (2.1 g, 122%) was washed with hot EtOAc and hot H_2O to remove *i*-Pr_2EtN and was dried *in vacuo:* 1.40 g (81%) of white powder; mp 219° dec; $[\alpha]^{24}D$ −69.0° (*c* 1, DMF); homogeneous to tlc (A, 0.05; B, 0.50). A sample was crystallized as needles from nitromethane in 80% recovery. *Anal.* ($C_{32}H_{49}N_7O_8S$) C, H, N.

Boc-Gln-Asn-Cys(Bzl)-Pro-Leu-Gly-NH$_2$ (4). The pentapeptide 3 (2.50 g, 3.61 mmol) was deprotected by treatment with redistilled trifluoroacetic acid (10 ml) for 0.5 hr at room temperature. The peptide amine salt was precipitated with Et_2O (100 ml), collected on a frit, washed with Et_2O, and dried *in vacuo:* 2.88 g.

The deprotected pentapeptide was dissolved in DMF (7 ml) containing *i*-Pr_2EtN (0.7 ml, 4 mmol) and the solution was treated with Boc-Gln-ONp (1.59 g, 4.33 mmol) for 2 days. The reaction mixture was diluted with EtOAc (20 ml). The product was collected, washed (EtOAc and 95% EtOH), and dried *in vacuo:* 2.79 g (94%); mp 214° dec. This material was crystallized from 50% EtOH in 90% recovery: white cubic crystals; mp 223.5° dec; $[\alpha]^{24}D$ −53.4° (*c* 1, DMF); homogeneous to tlc (B, 0.19; D, 0.58). *Anal.* ($C_{37}H_{57}N_9O_{10}S$) C, H, N.

Z-Ile-Gln-Asn-Cys(Bzl)-Pro-Leu-Gly-NH$_2$ (5). The hexapeptide 4 (1.18 g, 1.44 mmol) was treated with TFA for 1 hr at room temperature and the deprotected peptide amine salt was isolated as for 4: 1.24 g.

The deprotected hexapeptide was dissolved in DMF (3 ml) containing *i*-Pr_2EtN (0.26 ml, 1.5 mmol) and treated with Z-Ile-ONp (0.72 g, 1.87 mmol) for 2 days. The reaction mixture was diluted with EtOAc (10 ml) and filtered, and the solid was washed (EtOAc, 80% EtOH, EtOAc). The solid was dried *in vacuo:* 1.02 g (73%); mp 236° dec; $[\alpha]^{24}D$ −45.6° (*c* 0.5, DMF). This material was reprecipitated from 80% EtOH (80% recovery): white solid; homogenous to tlc (C, 0.64); mp 241° dec; $[\alpha]^{24}D$ −50.6° (*c* 0.5, DMF) [lit.[22] mp 241–243° dec; $[\alpha]^{20}D$ −50° (*c* 1, DMF)].

Boc-Tyr(Bzl)-Ile-Gln-Asn-Cys(Bzl)-Pro-Leu-Gly-NH$_2$ (6). Heptapeptide 5 (1.34 g, 1.39 mmol) in HOAc (20 ml) was treated with 7 *N* HBr–HOAc (10 ml) for 1 hr at room temperature. Isolation as for 3 yielded 1.41 g of peptide amine salt.

The deprotected heptapeptide was dissolved in DMF (8 ml) containing *i*-Pr_2EtN (0.44 ml, 2.6 mmol) and treated with Boc-Tyr(Bzl)-ONp (0.95 g, 1.93 mmol) for 2 days. The reaction mixture was diluted with 95% EtOH (20 ml) and filtered. The collected solid was washed (95% EtOH, hot EtOAc) and dried *in vacuo:* 1.53 g (93%) of white crystalline powder; mp 232° dec; $[\alpha]^{24}D$ −35.2° (*c* 0.5, DMF); homogeneous to tlc (D, 0.64). *Anal.* ($C_{59}H_{83}N_{11}O_{13}S$) C, H, N.

β-Mpa(β-(CH$_2$)$_5$)(Bzl)-Tyr(Bzl)-Ile-Gln-Asn-Cys(Bzl)-Pro-Leu-Gly-NH$_2$ (7). The octapeptide 6 (0.15 g, 0.15 mmol) was treated with TFA (1.5 ml) for less than 15 min at room temperature. The deprotected peptide TFA salt was precipitated with Et_2O (10 ml) and washed with Et_2O by centrifugation–decantation: 0.20 g.

A solution of the deprotected TFA salt and *i*-Pr_2EtN (0.04 ml, 0.23 mmol) in DMF (1.5 ml) was treated with the *p*-nitrophenyl ester 2 (0.07 g, 0.18 mmol). Because the reaction had slowed after 18 hr, an additional batch of 2 (0.03 g, 0.07 mmol) was added. When the reaction did not proceed rapidly to completion, 1-hydroxybenzotriazole (0.01 g, 0.07 mmol) was added as catalyst.[23] Coupling was complete within 4 hr. The reaction mixture was diluted with 95% EtOH (6 ml) and filtered. The precipitated product was washed with 95% EtOH (4 × 5 ml) and dried *in vacuo:* white powder (0.14 g, 71%); mp 245–246°; homogeneous to tlc (C, 0.70; D, 0.74). A sample was reprecipitated from DMF–EtOH (2:1) with 90% recovery: mp 245–246°; $[\alpha]^{22}D$ −44.3° (*c* 0.5, DMF). *Anal.* ($C_{69}H_{93}N_{11}O_{12}S_2 \cdot H_2O$) C, H, N.

[1-β-Mercapto-β,β-pentamethylenepropionic acid]oxytocin. A sample of 7 (0.115 g, 86.6 μmol) was dissolved in 100 ml of boiling liquid NH_3 (freshly distilled from Na). The solution was treated with a fresh stick of Na[5] (encased in a 4-mm glass tube) until the blue color of excess Na persisted for 20 sec. The excess was discharged with a few drops of glacial HOAc and the NH_3 was removed at the water aspirator.

The residue was dissolved in 0.1% TFA solution, the pH was adjusted to 6.8 with 2 *N* NH_4OH, and the disulfhydryl intermediate was cyclized with potassium ferricyanide[6] solution (0.01 *N*; 17.5 ml; 175 μmol). The oxidation was allowed to procede for 20 hr and the absence of SH was determined by the Ellman test.[24] The solution was filtered and treated with AG 3-X4 resin (10 ml, 1:1 slurry, TFA cycle) to remove Fe salts while the pH was maintained at 6.8. The resin was filtered and washed with deionized H_2O. The combined aqueous filtrate was reduced in volume to 175 ml and lyophilized.

The lyophilized powder, in 2 ml of 50% HOAc, was desalted[7] by gel filtration on Sephadex G-15 in 50% HOAc. The monomer peak (38% column vol) was lyophilized and subjected to gel filtration[25] in 0.2 *N* HOAc on Sephadex G-25. The product obtained by lyophilization from the single, symmetrical peak (80% column volume) appeared still to contain traces of dimer and was therefore subjected to gel filtration on Sephadex LH-20 (2.8 × 50 cm) in DMF. The product was isolated from the symmetrical peak at 43% column volume by lyophilization from glacial HOAc: 21.8 mg of white powder; homogeneous to tlc (C, 0.52; D, 0.65); $[\alpha]^{21}D$ −44.8° (*c* 0.5, DMF). Amino acid analysis[26] in a Beckman 116 analyzer after a 24-hr hydrolysis in 6 *N* HCl gave the following molar ratios: Asp, 1.09; Glu, 0.93; Pro, 1.08; Gly, 1.00; Ile, 1.02; Leu, 1.01; Tyr, 1.04; NH_3, 3.28. A sample hydrolyzed identically after a performic acid oxidation by the method of Moore[27] had a cysteic acid to Gly ratio of 1.1:1. *Anal.* ($C_{48}H_{77}N_{11}O_{14}S_2 \cdot 2H_2O$) C, H, N.

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Synthesis of Isosteres of *p*-Amidinophenylpyruvic Acid. Inhibitors of Trypsin, Thrombin, and Pancreatic Kallikrein†

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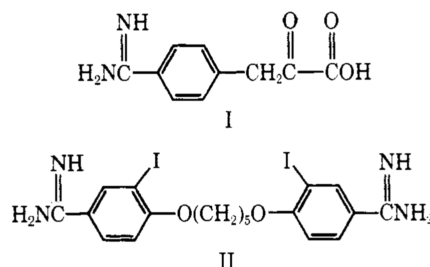
A series of amino acids, amidino acids, and amidino esters was synthesized and the compounds were evaluated for their inhibitory activity against bovine trypsin, bovine thrombin, and porcine pancreatic kallikrein and as anticoagulants. Among these compounds, ethyl 4-amidino-2-iodophenoxyacetate was found to be the most effective inhibitor of the enzymes in question, with a potency ($K_i = 3.16 \times 10^{-6}$ *M vs.* trypsin; $K_i = 4.8 \times 10^{-5}$ *M vs.* thrombin) similar to that of *p*-amidinophenylpyruvic acid ($K_i = 6.0 \times 10^{-6}$ *M vs.* trypsin; $K_i = 2.0 \times 10^{-5}$ *M vs.* thrombin). Ethyl 4-amidino-2-iodophenoxyacetate was also found to be the most effective in blocking the clotting activity of plasma, as indicated by significant prolongation of the partial thromboplastin time. This paper reports the synthetic methods, the enzyme inhibitory activity, and the structure–activity relationships observed.

In view of the fact that serine proteinases of physiopathological importance are being discovered whose inhibition may be of therapeutic value, chemical modification of known serine proteinase inhibitors is of considerable importance in a search for a more effective or selective inhibitor.

The development of reversible trypsin, thrombin, and kallikrein inhibitors was greatly stimulated by Mares-Guia and Shaw's discovery of the considerable potency of benzamidine and *p*-aminobenzamidine.[1] Since then many substituents have been introduced into the benzene ring of benzamidine,[2] leading to equal or greater inhibitory activity against proteinases. *p*-Amidinophenylpyruvic acid (I) has been found to be an excellent inhibitor of thrombin, plasmin, and trypsin.[2,3] More recently, aromatic diamidines such as pentamidine[4-6] and 4′,4″-diamidino-2′,2″diiodo-1,5-diphenoxypentane (II)[7] have been studied and shown to be even more effective serine proteinase inhibitors.

Due to the strong *in vitro* effectiveness of diamidino compounds, the aromatic diamidines have been investi-



gated for *in vivo* use in disease states where the kallikrein–kinin system is considered to play an important role. Such pathological conditions are inflammatory edema, shock, and arthritis. However, an obstacle found to the systemic application of those diamidines is the fact that they may also dramatically lower the blood pressure, promoting hypotensive shock.[8] On the other hand, *p*-amidinophenylpyruvic acid, which has shown to be less toxic,[9] is a potent and interesting inhibitor of serine proteinases and is a compound of possible clinical use. Therefore, systematic modification of this molecule seemed highly desirable to us. The compounds reported here represent part of such an effort, in particular a systematic study of some isosteric and isoelectronic analogs of *p*-amidinophenylpyruvic acid.

Chemistry. Synthesis of the new amino and amidino acids and esters listed in Table II–IV, prepared as isosteres

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