Karen Bergstrom, and Bryan Roberts with the bioassays. We are indebted to Jasmine Fazzari and Sandra Williams for amino acid analyses. The authors thank Diane Nagami and Tai-Yin Yang for performing the pK_a determinations and Ram Tahilramani for prep-HPLC purification of one of the analogues. The encouragement and advice of Dr. John Moffatt is gratefully acknowledged.

Registry No. **1a**, 88549-09-1; **1b**, 88549-10-4; **1c**, 88549-11-5; **1d**, 88549-12-6; **1f**, 88562-94-1; **2a**, 81440-37-1; **2b**, 88549-13-7; **2c**, 88549-14-8; **2d**, 88549-15-9; **2e**, 81440-40-6; **2f**, 88549-16-0; **3a**, 81440-45-1; **3b**·HOAc, 88549-18-2; **3c**·HOAc, 88549-20-6; **3d**, 88549-21-7; **3e**, 81440-41-7; **3f**·$^1/_2$HOAc, 88549-23-9; **4a**, 81440-44-0; **4b**, 88549-24-0; **4c**, 88562-95-2; **4d**, 88562-96-3; **4e**, 81440-42-8; **4f**, 88562-97-4; **5**, 81440-38-2; **6**·HOAc, 88549-25-1; **7**, 81440-47-3; **8**, 88562-98-5; **9**, 88562-99-6; **10**, 88563-00-2; **11**, 88563-01-3; **12**, 88563-02-4; **13**, 88563-03-5; **14**, 88563-04-6; **15**, 88563-05-7; **16**, 88563-06-8; *o*-phenylenediamine, 95-54-5; 2,3-naphthalenediamine, 771-97-1; 4,5-dimethyl-1,2-benzenediamine, 3171-45-7; 4,5-dichloro-1,2-benzenediamine, 5348-42-5; *o*-hydroxyaniline, 95-55-6; acid chloride of α-benzyl *N*-(benzyloxycarbonyl)-D-aspartate, 75626-73-2; α-benzyl *N*-(benzyloxycarbonyl-D-asparate, 81440-35-9; *o*-aminophenyl disulfide, 1141-88-4.

Tri- and Tetrapeptide Analogues of Kinins as Potential Renal Vasodilators

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Tri- and tetrapeptide analogues were synthesized and evaluated as renal vasodilators. These peptides were prepared by standard coupling reactions, which also provided good yields with hindered α-methyl amino acid derivatives. Preliminary evidence of renal vasodilator activity was determined in anesthetized dogs by measuring the effects on renal blood flow and calculating the accompanying changes in renal vascular resistance. The most potent compounds contained, in their basic structure, the L-prolyl-DL-α-methylphenylalanyl-L-arginine and L-prolyl-DL-α-methylphenylalanylglycyl-L-proline arrays. Substitution on the N-terminal proline with 4-phenylbutyryl and 4-(4-hydroxyphenyl)butyryl side chains produced enhanced renal vasodilator activity and, in certain cases, selectivity for the renal vasculature.

The renal vasodilator activity of the selective peripheral dopamine agonist 6-chloro-7,8-dihydroxy-1-(4-hydroxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SK&F 82526) was described in an earlier report.[1] This compound is being evaluated clinically and should prove to be an important agent in furthering our understanding of the importance of renal blood flow (RBF) in essential hypertension.[2] Another goal of our research effort was the discovery of other selective renal vasodilators not having a dopaminergic mechanism or component of vasodilatation. Compounds as diverse as acetylcholine, histamine, prostaglandins, captopril, isoproterenol, and theophylline are reported to be vasodilatory.[3] Peptides exemplified by bradykinin, eledoisin, substance P and secretin produce vasodilatation.[3i,4] The vasodilator peptides seemed to offer viable opportunities for development of novel and specific vasodilators. Bradykinin, eledoisin, and substance P have as a common feature a phenylalanine as the fifth amino acid from the carboxy terminus, which might suggest possible structural importance to overall activity, perhaps by way of binding and/or recognition. When bradykinin, i.e., Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg, was tested in our anesthetized dog protocol used to screen for intrinsic renal vasodilator activity, it exhibited, at an intravenous (iv) infusion dose of 0.1 to 30 μg/(kg min), an average maximum decrease in renal vascular resistance (RVR) of 67%. Although bradykinin showed a dose-related decrease in RVR resulting in enhanced RBF, bradykinin produced nonselective vasodilatation and a substantial decrease in systemic arterial blood pressure—a typical kinin response. A carboxy-terminal pentapeptide fragment of bradykinin, Phe-Ser-Pro-Phe-Arg (**36**), was marginally effective in the dog protocol as a renal vasodilator but showed a cardiovascular profile different from that of bradykinin (see Structure–Activity Relationships). Encouraged by the biological difference of the pentapeptide fragment and the renal vasodilator activity displayed by a terminal tripeptide fragment analogue of Pro-Phe-Arg, i.e., C_6H_5CO-Pro-Phe-Arg-NHC_6H_4-NO_2-*p*, a compound used to assay for kallikrein activity, it was decided to focus on the structure–activity relationships (SAR) of bradykinin fragments

† Medicinal Chemistry.
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(1) Weinstock, J.; Wilson, J. W.; Ladd, D. L.; Brush, C. K.; Pfeiffer, F. R.; Kuo, G. Y.; Holden, K. G.; Yim, N. C. F.; Hahn, R. A.; Wardell, Jr., J. R.; Tobia, A. J.; Setler, P. E.; Sarau, H. M.; Ridley, P. A. *J. Med. Chem.* **1980**, *23*, 973.
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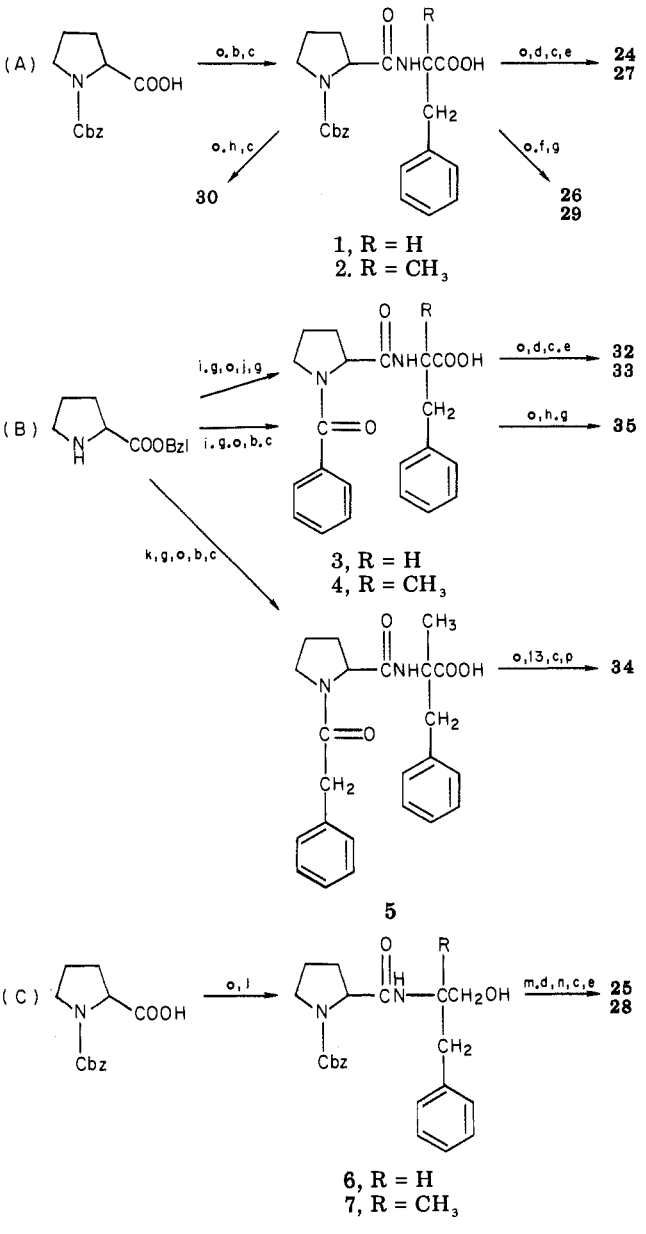
and analogues. Some background SAR for intact bradykinin derivatives and analogues[5] and fragments were reported. The biological actions of the bradykinin fragments showed several orders of magnitude of diminished potency relative to the nonapeptide parent.[5c,6] The reported peptides or fragments were not tested for renal vasodilator activity. In this report the synthesis and renal vasodilator activity of certain tri- and tetrapeptide analogues are reported.

Chemistry. Compounds related to the tripeptide Pro-Phe-Arg (**24**), the blocked derivative **31**, and the pentapeptide Phe-Ser-Pro-Phe-Arg (**36**) are listed in Tables I–III. The amide bonds were routinely prepared by using DCC with either HOSu or HOBt.[7] The intermediates **1** and **2** were prepared from *N*-carbobenzoxy-L-proline (Scheme I, A) as precursors to the tripeptide analogues **24**, **26**, **27**, **29**, and **30**. Compounds **32–35** were designed as derivatives of **31** and were prepared from the N-acylated acids **3–5** (Scheme I, B). The alcohols **6** and **7** were oxidized to the intermediate aldehydes with oxalyl chloride in dimethyl sulfoxide,[8] and reductive amination with sodium cyanoborohydride[9] and a protected L-arginine, followed by deblocking, afforded the dihydro derivatives **25** and **28** (Scheme I, C).

The 4-phenylacyl derivatives listed in Table II are related to **36** and were derived from the acids **8–10** (Scheme II, A). The L-phenylalanyl (**37**), the D-phenylalanyl (**38**), and the DL-α-methylphenylalanyl (**41**) analogues were prepared from **9**. 3-Aminopropylamides **39** and **43** were synthesized from **11** and **12**, respectively. Analogue **47** was prepared from **12** and L-proline benzyl ester. Compounds **40** and **42** were obtained from an alternative coupling sequence involving the protected dipeptide **13** and using the acids **8** and **10** (Scheme II, B). The 3,4-dimethoxyphenylalanyl derivative **45** was synthesized from the intermediate acid **14** (Scheme II, C). Compound **14** was obtained from the coupling of DL-α-methyl-3,4-dimethoxyphenylalanine methyl ester and **9**. Dihydro analogue **46** was prepared by the two-step reaction sequence described for **25** and **28** (Scheme II, D). The intermediate alcohol **15** was synthesized from **9** and DL-2-amino-2-methyl-3-phenylpropanol, which was prepared from diborane reduction of DL-α-methylphenylalanine. *N*-(1-Adamantylacetyl)-L-proline (**16**) was converted to **44** by a route using the arginine analogue **13**, followed by basic hydrolysis of the arginyl methyl ester and catalytic hydrogenolysis of the nitro group blocking the guanidino moiety (Scheme II, E).

Scheme I. Synthesis of Tripeptide Analogues[a]



[a] Reagents: (a) DCC-HOBt-NEM; (b) L- and D-$H_2NC(R)(CH_2C_6H_5)COOCH_3$·HCl; (c) aqueous 2.5 N NaOH-MeOH; (d) N^{ω}-nitro-L-arginine methyl ester hydrochloride; (e) 10% Pd/C-H_2-EtOH-HOAc; (f) $H_2N(CH_2)_3NHCbz$·HCl; (g) 10% Pd/C-H_2-EtOH; (h) L-proline benzyl ester hydrochloride; (i) C_6H_5COCl-pyridine; (j) L-phenylalanine benzyl ester hydrochloride; (k) $C_6H_5CH_2COCl$-pyridine; (l) L- and DL-$H_2NC(R)(CH_2C_6H_5)CH_2OH$; (m) ClCOCOCl-$Me_2SO$-$Et_3N$-$CH_2Cl_2$; (n) $NaCNBH_3$-MeOH; (o) DCC-HOSu-THF; (p) 5% Pd/$BaSO_4$-EtOH-HOAc.

4-(4-Hydroxyphenyl)butyryl derivatives listed in Table III are related to tri- and tetrapeptide analogues of **36**. Acid **17** was used as a general intermediate and was prepared by DCC–HOBt condensation of 4-(4-hydroxyphenyl)butyric acid with L-proline benzyl ester, followed by hydrogenolysis (Scheme III, A). Compounds **48** and **49** were prepared from **18**, the DL-α-methyl-3,4-dimethoxyphenylalanyl analogues **50** and **51** were obtained from **19**, and the DL-α-methyltyrosyl derivatives **52** and **53** were prepared from **20**. Compound **58** was synthesized from methyl 6-aminocaproate and **18**. The glycylproline analogues **54–57** were prepared by amination of the acids **18** and **20–22** with glycyl-L-proline benzyl ester and un-

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(7) Abbreviations used are: DCC, dicyclohexylcarbodiimide; HOBt, 1-hydroxybenzotriazole; HOSu, *N*-hydroxysuccinimide; NEM, *N*-ethylmorpholine; THF, tetrahydrofuran; DMF, dimethylformamide; Cbz, carbobenzoxy; Boc, *tert*-butoxycarbonyl.

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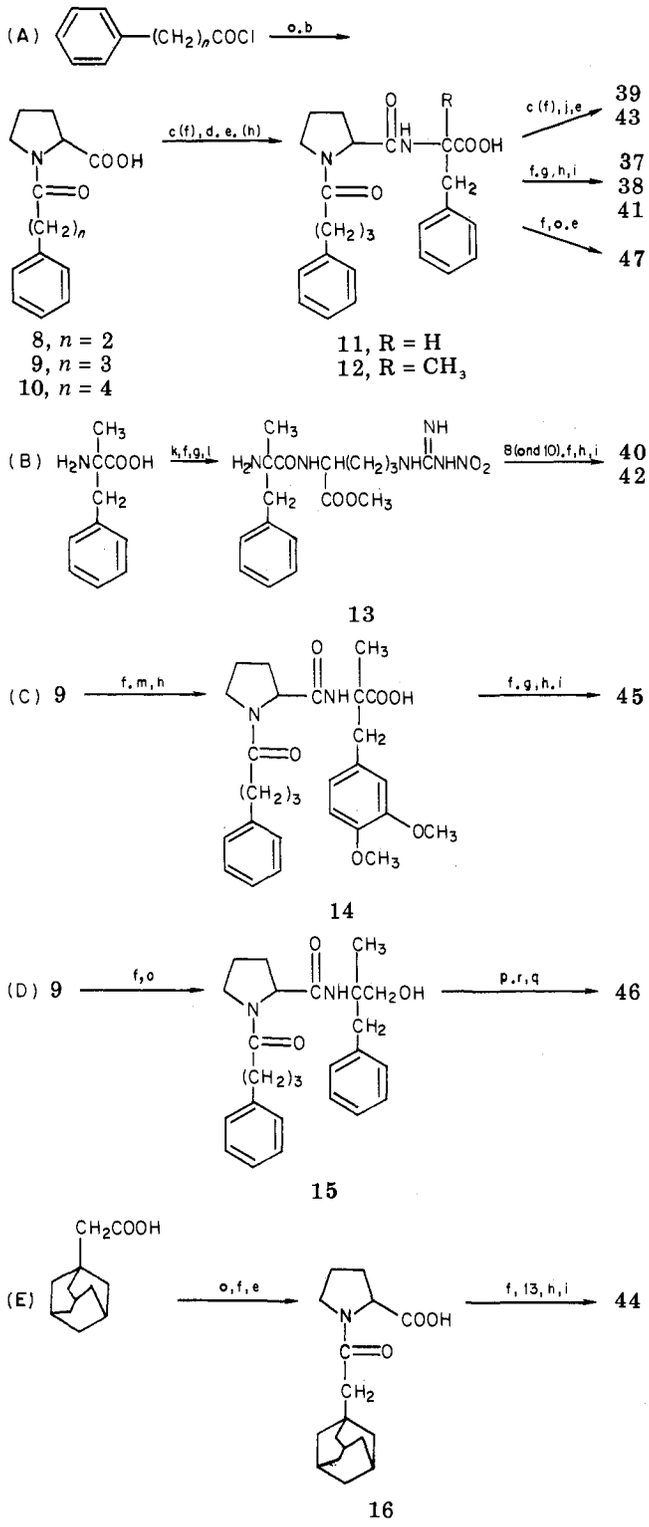
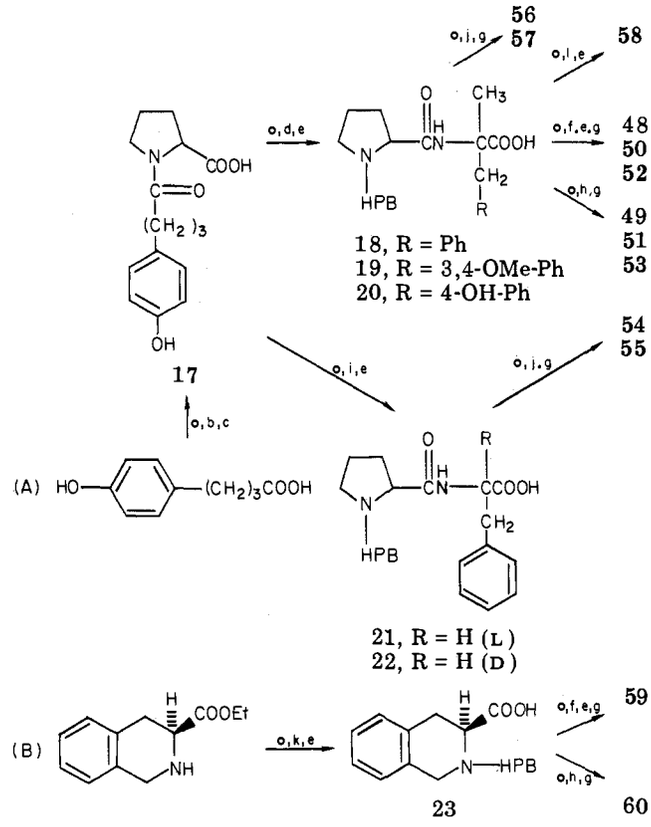
Scheme II. Synthesis of Tetrapeptide Analogues[a]



[a] Reagents: (a) L-proline benzyl ester hydrochloride-pyridine or NEM; (b) 10% Pd/C-H_2-EtOH; (c) DCC-HOSu-THF; (d) D- and L-phenylalanine benzyl ester and DL-α-methylphenylalanine methyl ester; (e) 10% Pd/C-H_2-EtOH; (f) DCC-HOBt-NEM; (g) N^{ω}-nitro-L-arginine methyl ester hydrochloride; (h) aqueous 2.5 N NaOH-MeOH; (i) 10% Pd/C or 5% Pd/$BaSO_4$-H_2-EtOH-HOAc; (j) $NH_2(CH_2)_3NHCbz \cdot HCl$; (k) di-*tert*-butyl dicarbonate-Et_3N-DMF; (l) TFA-1,3-dimethoxybenzene; (m) DL-α-methyl-3,4-dimethoxyphenylalanine methyl ester hydrochloride; (n) 1-adamantaneacetic acid; (o) $NH_2C(CH_3)(CH_2C_6H_5)CH_2OH$; (p) ClCOCOCl-$Me_2SO$-$Et_3N$-$CH_2Cl_2$; (q) $NaCNBH_3$-MeOH; (r) L-arginine.

Scheme III. Routes to 4-Hydroxyphenylbutyryl (HPB) Tetrapeptide Derivatives[a]



[a] Reagents: (a) DCC-HOBt-NEM; (b) L-proline benzyl ester hydrochloride; (c) 10% Pd/C-H_2-EtOH; (d) DL-α-methylphenylalanine, DL-α-methyl-3,4-dimethoxyphenylalanine and DL-α-methyltyrosine as the methyl ester hydrochlorides; (e) aqueous 2.5 N NaOH-MeOH; (f) N^{ω}-nitro-L-arginine methyl ester hydrochloride; (g) 5% Pd/$BaSO_4$-H_2-EtOH-HOAc; (h) $H_2N(CH_2)_3NHCbz \cdot HCl$; (i) L- and D-phenylalanine benzyl ester hydrochloride; (j) glycyl-L-proline benzyl ester; (k) 4-hydroxyphenylbutyric acid; (l) $H_2N(CH_2)_5COOCH_3 \cdot HCl$.

masking of the free acid via hydrogenolysis. The tetrahydroisoquinoline analogues **59** and **60** were prepared from the *N*-[4-(4-hydroxyphenyl)butyryl] derivative **23**, which was synthesized from L-3-carbethoxy-1,2,3,4-tetrahydroisoquinoline.[10]

Structure–Activity Relationships. The biological activities of the peptide analogues are summarized in Tables I–IV. Renal vasodilator activity was determined in anesthetized dogs (7–17 kg) by techniques previously described.[1,11–13] The primary screen provided data (Tables I–III) on RBF, RVR, heart rate (HR), and mean arterial blood pressure (MABP). The RVR was calculated as the ratio of the MABP to mean RBF. Some of the most active compounds uncovered in this series in the primary renal vasodilator screen were subsequently studied in a secondary protocol as described earlier,[11] and the results are shown in Table IV. These cumulative dose–response data

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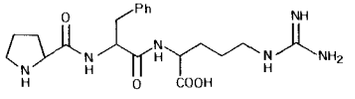
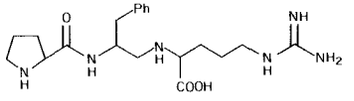
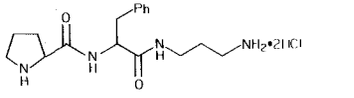
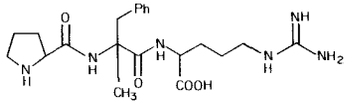
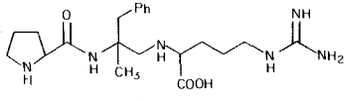
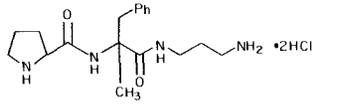
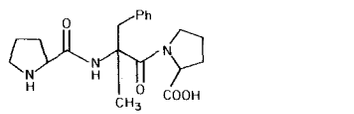
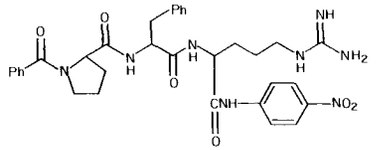
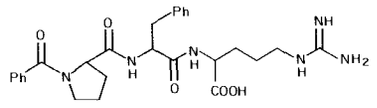
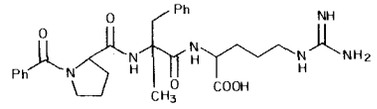
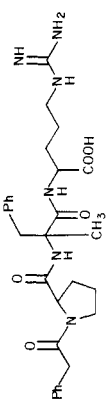
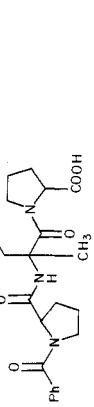
(13) Hahn, R. A.; Wardel, Jr., J. R. *J. Cardiovasc. Pharmacol.* **1980**, *2*, 583.

Table I. Tripeptide Analogues

no.	structure[b]	n[c]	dog renal vasodilator act.[a] dose, μg/(kg min)	% change MABP	RBF	RVR	HR	formula[d]	mp, °C	$[\alpha]^{25}_D$ (c 0.5, MeOH), deg
24[e]		1	3	−1	4	−5	−6	$C_{20}H_{30}N_6O_4$[f]	160–165	−23.9
			30	1	3	−2	3			
			300	−4	−3	0	6			
25		1	3	0	0	0	−3	$C_{20}H_{32}N_6O_4$[g]	156–158	−8.1
			30	0	3	−3	0			
			300	−2	0	−2	0			
26		2	3	−0.5	3.5	−3	−1.5	$C_{17}H_{26}N_4O_2 \cdot 2HCl$[h]	126–129	−19.9
			30	0	5	−5	−1			
			300	−3.5	6.5*	−9	−1			
27[i]		3	3	1	1.3	0.3	−0.7	$C_{21}H_{32}N_6O_4$[j]	118–120	−23.5[k]
			30	−0.3	9.3*	−7.3	0			
			300	−0.7	7.3*	−5.3	0			
28[i]		1	3	1	0	1	0	$C_{21}H_{34}N_6O_3$[l]	150–155	−25
			30	1	8	−6	4			
			300	−5	7	−11	−7			
29[i]		1	3	1	5	−4	−1	$C_{18}H_{28}N_4O_2 \cdot 2HCl$[m]	90–93	−17.2
			30	−1	1	−1	−1			
			300	−1	2	−3	0			
30[i]		1	3	1	0	1	0	$C_{20}H_{27}N_3O_4$[n]	230–232	−177[o]
			30	−0	0	0	0			
			300	−3	8	−10	0			
31		2	3	1.2	1.9	0	0	$C_{33}H_{38}N_8O_6$[p]		
			30	1.5	4.8	−3	−3			
			300	−26.6*	27*	−38.7*	−10*			
32		1	3	4	3	2	0	$C_{27}H_{34}N_6O_5$[g]	160–165	
			30	1	0	0	0			
			300	0	−10	11	0			
33[i]		1	3	−1	4	−5	−6	$C_{28}H_{36}N_6O_5$[r]	174–176	−120
			30	1	3	−2	3			
			300	−4	−3	0	6			

34[i]		1	3	0	4	−4	0	$C_{29}H_{38}N_6O_5$[s]	amorphous	−72.8	
			30	0	0	0	−2				
			300	5	−2	7	0				
35[i]		1	3	0	4	−4	3	$C_{27}H_{31}N_3O_5$[t]	180–185	−100.9[u]	
			30	−5	0	−5	−6				
			300	−4	0	−4	0				

[a] Renal blood flow (RBF) was measured in dogs by the protocol described in ref 11. Test drug was separately infused at increments of 3, 30, and 300 μg/(kg min) at approximately 15-min intervals, each infusion being of 5-min duration. The renal vascular resistance (RVR) was calculated as the ratio of the mean arterial blood pressure (MABP)/mean RBF. HR is the cardiac rate. Minimum changes (percent) that are considered significant: one dog, RBF ±8.4, RVR ±13.2, MABP ±7.3, and HR ±8.1; two dogs, RBF ±5.9, RVR ±9.3, MABP ±5.2 and HR ±5.7; three dogs, RBF ±4.8, RVR ±7.6, MABP ±4.2, and HR ±4.7. Significant activity is noted by an asterisk. [b] Amino acids have the L configuration except where noted. [c] Number of dogs. [d] All compounds were analyzed for C, H, and N; results obtained were within ±0.4% of the theoretical values and exceptions are noted. [e] Pro-Phe-Arg. (ref 6a and 18). [f] Calculated for 1 mol of HOAc and 0.25 mol of H_2O. [g] Calculated for 3 mol of HOAc and 1 mol H_2O. [h] N; calcd, 14.32; found, 13.47. [i] DL-α-methylphenylalanyl derivative. [j] Calculated for 1 mol of H_2CO_3 and 1 mol of H_2O. [k] (c 1, MeOH). [l] Calculated for 0.46 mol of HOAc and 0.5 mol of H_2O. [m] Calculated for 1.72 mol of HCl and 1.25 mol of H_2O. Cl: calcd, 14.68; found, 14.91. [n] Calculated for 0.375 mol of H_2O. [o] (c 1, 50% aqueous MeOH). [p] Vega Biochemicals, Tucson, AZ. [q] Calculated for 1 mol of HOAc and 1 mol of H_2O. [r] Calculated for 2 mol of H_2O. [s] Calculated for 0.75 mol of H_2O. [t] Calculated for 1.5 mol of H_2O. [u] (c 1, $CHCl_3$).

were obtained by infusing the drug at progressively increasing infusion rates, and each dose level was infused for 5 min. The potency for each compound is expressed as the cumulative dose that decreased RVR by 15%. The maximum renal vasodilator effect is expressed as the maximum percent decrease in RVR obtainable with the compound. The selectivity ratios are the separations between the RVR ED_{15} and doses producing a 30% change in iliac vascular resistance (IVR), a 20% change in MABP, and a 20% change in HR. Other renal function parameters were not examined. The active compounds were usually evaluated in several dogs in both screens. Some inactive compounds in a close series of derivatives were examined in one dog, and the results provided only overall trends in the series but did not give rigorous evaluations of the inactive compounds.

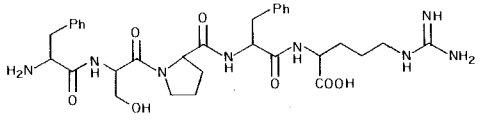
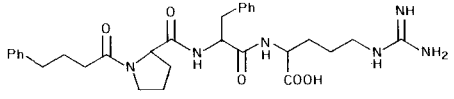
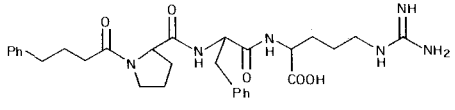
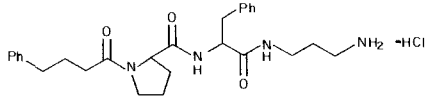
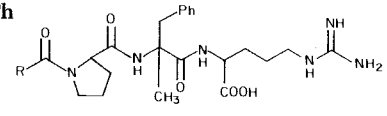
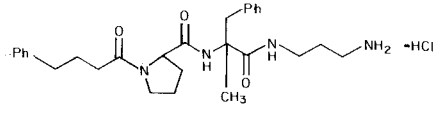
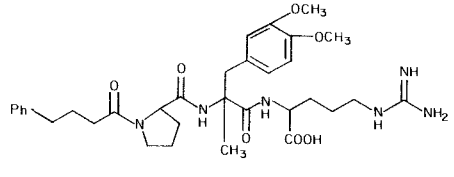
In Table I are found the renal vasodilator activity profiles of the tripeptide analogues related to Pro-Phe-Arg (**24**). Compound **31** was the most active derivative in this series and caused significant changes in all of the parameters measured; the prototype **24** was inactive. The α-methylphenylalanyl derivative **27**, i.e., Pro-α-MePhe-Arg, showed significant increases in RBF in three dogs. The 3-aminopropylamide analogue **26** exhibited increased RBF in two dogs, but the RVR change was fractionally below statistical significance.

The dihydro analogue **25** was not active, and the α-methylphenylalanyl dihydro analogue **28**, a reduced derivative of the active compound **27**, did not show statistically significant activity. Compound **29**, an analogue of **26**, was not active, nor was the diprolinyl compound **30**. The *N*-benzoyl derivatives **32**, **33**, and **35**, as well as the amide **34**, were not active, in contrast to the prototype **31**. The results in Table I show that small peptides per se are not necessarily renal vasodilators and that certain amino acid sequences are required to elicit a response. Rapid metabolism of the tripeptide **24** might be a factor in explaining the lack of activity. Peptides containing α-methyl-substituted amino acids are somewhat more resistant to enzymatic degredation.[14] The α-MePhe analogue **27** showed larger RBF increases when compared to the Phe derivative **24**. Tables II and III show additional examples of active α-methylphenylalanyl derivatives. Another property of peptide analogues having the α-methyl-substituted amino acid is the rigidity of structure with the concomitant reduction in the degrees of freedom about the Ψ and φ angles.[14]

Compound **36**, Phe-Ser-Pro-Phe-Arg, showed good renal vasodilator activity in two dogs at the 300 μg/(kg min) dose level (Table II). In contrast, the tripeptide **24**, Pro-Phe-Arg, was not active in this test. Apparently, two important hydrophobic binding or recognition sites for the pentapeptide **36** are the benzyl groups associated with the Phe-1 and -4 residues. Compound **31**, which contains a hydrophobic *N*-benzoyl group, also displayed renal vasodilator activity. Examination of models suggested that a 4-phenylbutyryl side chain might mimic the hydrophobic bulk on the amino terminus of certain peptide derivatives and provide a template similar to the constricted dimensions of the Phe-Ser portion of **36**. Most of the compounds listed in Table II are 4-phenylbutyryl analogues, except for **40**, **42**, and the adamantyl derivative **44**, and a higher proportion of active compounds are found in this group

(14) (a) Marhsall, G. R.; Bosshard, H. E.; Eilers, N. C.; Needleman, P. In "Chemistry and Biology of Peptides"; Meienhofer, J., Ed.; Ann Arbor Science Publishers: Ann Arbor, MI, 1972, pp 571–578. (b) Nagaraj, R.; Balaram, P. *Acc. Chem. Res.* **1981**, *14*, 356.

Table II. 4-Phenylbutyryl Tripeptide Analogues

compd	structure[b]	n[c]	dog renal vasodilator act.[a] dose, μg/(kg min)	% change MABP	RBF	RVR	HR	formula[d]	mp, °C	$[\alpha]^{25}_D$ (c 0.5, MeOH), deg
36[e]		2	3	−1.2	3	−3.8	0.8	$C_{32}H_{44}N_8O_7$[f]		
			30	0.5	6.5*	−5.1	0			
			300	−5.7*	26.2*	−24.8*	4.8*			
37		3	3	1	5.3*	−5.7	2	$C_{30}H_{40}N_6O_5$[g]	136–140	−40
			30	0.3	4	−3.7	1.7			
			300	−0.7	−1.7	1	−1.7			
38[h]		1	3	0	3	−3	−3	$C_{30}H_{40}N_6O_5$[i]	120–124	−3.2
			30	1	2	−1	0			
			300	0	4	−4	−2			
39		1	3	0	0	0	0	$C_{27}H_{36}N_4O_3 \cdot HCl$[g]	92–94	−48.9
			30	0	5	−3.8	0			
			300	−2.7	6.5	−8.9	−5.3			
40[j]	R = $(CH_2)_2Ph$ 	1	3	−2	5	−7	8	$C_{30}H_{40}N_6O_5$[g]	amorphous	−62.6
			30	−3	2	−5	1			
			300	1	1	0	−1			
41[j]	R = $(CH_2)_3Ph$, structure as above	1	3	3	0	3	−3.6	$C_{31}H_{42}N_6O_5$[k]	129–135	−53
			30	2.8	4.6	−1.8	0			
			300	1	1	0	−1			
42[j]	R = $(CH_2)_4Ph$, structure as above	1	3	1	4	−2	−1	$C_{32}H_{44}N_6O_5$[l]	amorphous	−44.7
			30	3	1	1	−1			
			300	1	3	−2	−6			
44[j]	R = CH_2–  , structure as above	2	3	−0.5	13*	−11.5*	3.5	$C_{33}H_{48}N_6O_5$[g]	amorphous	−44.9
			30	1	0.5	−0.5	0.5			
			300	3	−14*	21.5*	−2			
43[j]		2	3	0	4	−3.5	−1.5	$C_{28}H_{38}N_4O_3 \cdot HCl$[g]	98–102	−52.2
			30	−0.5	5.5	−6	0.3			
			300	−3.5	10*	−11.5*	0.5			
45[m]		2	3	−2	7.5*	−8.5	4.5	$C_{33}H_{46}N_6O_7$[o]	145–148	−48.5[p]
			30	−1	8.5*	−8.5	1			
			300	−2	5.0	−7	2.5			
			accumulative effect:[n] RBF +39*, RVR −26*							

46[j]		1	3	−2	11*	−12	0	$C_{31}H_{44}N_6O_4$[g]	amorphous	−43.9
			30	0	10*	−9	−7			
			300	8	4	−4	−23			
			accumulative effect:[n] HR −27*							
47[j]		1	3	0.5	3	−8	0	$C_{30}H_{37}N_3O_5$	amorphous	−120.5[p]
			30	0	2	−2	0			
			300	1	4	−3	−2			

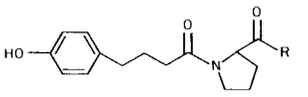
[a] See footnote a in Table I for test elaboration. [b] Amino acids have the L configuration, except where noted. [c] Number of dogs. [d] All compounds were analyzed for C, H, and N; results obtained within ±0.4% of the theoretical values, and exceptions are noted. [e] Pro-Ser-Pro-Phe-Arg. (ref 6a and 18). [f] Peninsula Laboratories, Inc. San Carlos, CA. [g] Calculated for 1 mol of H_2O. [h] D-phenylalanyl analogue. [i] Calculated for 1 mol of HOAc and 2.5 mol of H_2O. [j] DL-α-methylphenylalanyl derivative. [k] Calculated for 2.5 mol of H_2O. [l] Calculated for 1 mol of CH_3OH and 0.5 mol of H_2O. [m] DL-α-methyl-3,4-dimethoxyphenylalanyl derivative. [n] Change (percent) from initial base-line control values after cumulative dosing. [o] Calculated for 1 mol of HOAc and 2 mol of H_2O. [p] (c 1, MeOH).

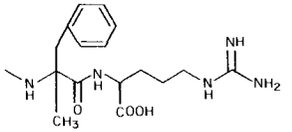
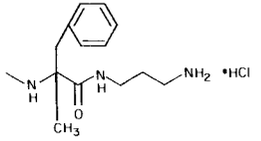
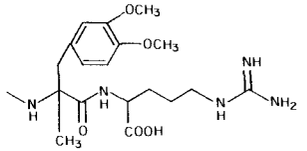
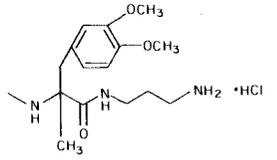
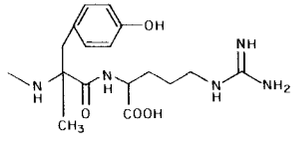
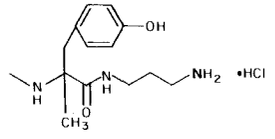
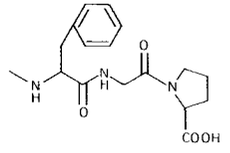
relative to those reported in Table I. Compound **37** showed statistically significant increases in RBF in three dogs, but the D-Phe isomer **38** and the α-MePhe derivative **41** were inactive in this test. Compound **39** did not show significant activity, but the amine **43** exhibited statistically significant activity in two dogs. The amide **40**, with a shortened side chain, and the longer tetramethylene isomer **42**, were inactive in this protocol. The 1-adamantylacetyl derivative **44** was active in two dogs, indicating that different hydrophobic groups might be tolerated on the amino terminus. The 3,4-dimethoxyphenyl derivative **45** exhibited good activity, as did the dihydro analogue **46**. The diprolyl compound **47** was inactive in this test. The data in Table II suggest that relatively potent renal vasodilators can be obtained from tripeptides substituted with the 4-phenylbutyryl side chain on the proline at the amino terminus.

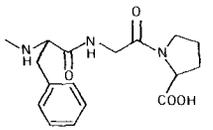
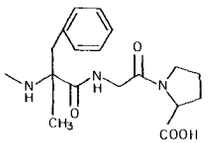
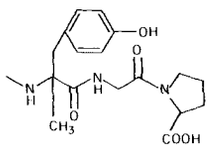
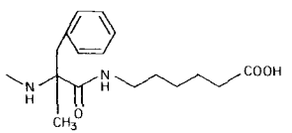
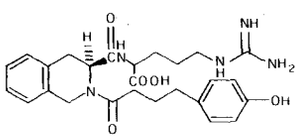
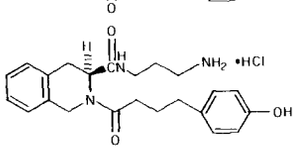
It can be seen in Table III that a large percentage of the tri- and tetrapeptide derivatives exhibited significant activity. All the compounds are *N*-[4-(4-hydroxyphenyl)-butyryl] (HPB) analogues. The 4-hydroxyphenyl group on compounds **48–60** imparted, generally, enhanced activity over the unsubstituted phenyl analogues shown in Table II. The tripeptide derivative **48**, i.e., HPB-Pro-α-MePhe-Arg, the 3,4-dimethoxyphenyl analogue **50** and the α-methyltyrosyl analogue **52** were good renal vasodilators in the dog protocol, with **50** showing the best activity of these three analogues. Compounds **50** and **51** have somewhat similar structures; both have the 3,4-dimethoxy-substituted phenyl groups but differ in the amide group linked to the α-methyl-3,4-dimethoxyphenylalanyl segment, and **50** and **51** each exhibit good activity. Compounds **49**, **51**, and **53** contain the (3-aminopropyl)amino group and each was active in at least two dogs. This group was also on the carboxy terminus of **26** and **43**, which displayed significant activity. The tetrapeptides **54–57** have the terminal Gly-Pro group. The D-Phe analogue **55**, the α-methyl derivative **56**, and the α-methyltyrosyl analogue **57** exhibited statistically significant activity. The 6-aminocaproate derivative **58** was marginally active on accumulative dosing. The 1,2,3,4-tetrahydroisoquinolines **59** and **60** were not active in this protocol and are examples of "cyclic" phenylalanyl derivatives.

In Table IV are listed the renal vasodilator activity and selectivity ratios for some of the more active analogues tabulated in Tables I–III. The nonapeptide bradykinin was tested in four dogs and exhibited an RVR ED_{15} of 2.8 μg/kg and an average maximum decrease in RVR of 67%. The ratios of IVR, MABP, and HR vs. RVR ED_{15} indicate little or no selectivity for the renal vasculature. The blocked tripeptide **31**, having the Pro-Phe-Arg array, was not as active as bradykinin and also showed unfavorable selectivity ratios. In contrast, the pentapeptide **36** exhibited an RVR ED_{15} of 5.2 μg/kg, more than half the potency relative to bradykinin, and large selectivity ratios, suggesting selective renal vasodilator activity. The adamantyl derivative **44** showed a modest RVR ED_{15} of 72 μg/kg but was not selective either for the renal or iliac vascular beds. Compound **50** exhibited a good average maximum decrease in RVR of 31% but was one of the least potent compounds tested in this assay. Although the tyrosyl derivative **52** showed selectivity of renal vasodilation vs. MABP and HR, the average maximum decrease in RVR was only 16%. Compound **56** exhibited selectivity for the renal vasculature equivalent to **36**, and the RVR ED_{15} and average maximum decrease in RVR were in the same range as **36**. Compound **57** showed a maximum decrease in RVR of 13% in three dogs, but this change was not statistically significant.

Table III. *N*-[4-(4-Hydroxyphenyl)butyryl]-L-prolyl Tri- and Tetrapeptide Analogues



compd[b]	R	n[c]	dog renal vasodilator act.[a] dose, μg/(kg min)	% change MABP	% change RBF	% change RVR	% change HR	formula[d]	mp, °C	$[\alpha]^{25}_D$ (*c* 0.5, MeOH), deg
48[e]		1	3	−4	8	−12	0	$C_{31}H_{42}N_6O_6$[f]	104-106	−44.7[g]
			30	2	12*	−9	0			
			300	0	11*	−11	0			
49[e]		3	3	−0.7	3.3	4	0.7	$C_{28}H_{38}N_4O_4 \cdot HCl$[h]	125-127	
			30	3	4.3	−4.7	1.3			
			300	−1.4	11.7*	−11.3*	8*			
50[i]		3	3	−2.7	4.3	−6.7	1.7	$C_{33}H_{46}N_6O_8$[j]	122-125	−44
			30	−7.7*	18.0*	−21.3*	6.3*			
			300	−32.0*	29.5*	−44.5*	16.0*			
51[i]		2	3	1.5	13.5*	−11*	0.5	$C_{30}H_{42}N_4O_6 \cdot HCl$[k]	133-136	−50.8
			30	−2	16.5*	−15.5*	−1			
			300	−1.5	10.5*	−10*	1.5			
52[l]		2	3	−2.5	20*	−19*	3.5	$C_{31}H_{42}N_6O_7$[n]	146-149	−40.9
			30	−3	28*	−20*	−7.5			
			300	1	28*	−17*	2.4			
			accumulative effect:[m]		RBF +28*, RVR −16*					
53[l]		2	3	−2	8.5*	−9.5*	1.5	$C_{28}H_{38}N_4O_5 \cdot HCl$[o]	154-156	−44.9[p]
			30	1	3.5	−3	4			
			300	0	10*	8.5	3.5			
54		2	3	−2	2.5	−4.5	−2.5	$C_{31}H_{38}N_4O_7$[h]	112-115	−98.8
			30	−1	−43*	74.5*	−1.5			
			300	−1.5	7	−8.5	1.5			

55[q]		1	3	0	2	−2	1	$C_{31}H_{38}N_4O_7$[h]	120–128	−38
			30	−1	0	−1	−2			
			300	−1	−1	−1	−1			
			accumulative effect:[m]		RBF +55*, RVR −32*					
56[e]		1	3	−5	17*	−18*	6	$C_{32}H_{40}N_4O_7$[r]	115–117	−78.9
			30	−9*	16*	−21*	10*			
			300	−6	14*	−17*	6			
57[l]		2	3	−2	4	−6	−7	$C_{32}H_{40}N_4O_8$[s]	117–122	−64.7
			30	1	0.5	−0.5	0			
			300	3	9*	−5.9	−1.5			
58[e]		1	3	0	1	−1	−4	$C_{31}H_{41}N_3O_6$[h]	75–77	−62
			30	2	−4	5	−2			
			300	1	5	−4	−6			
			accumulative effect:[m]		RBF +12*, RVR −7					
59		1	3	−1	7	−6	1	$C_{26}H_{33}N_5O_5 \cdot HCl$[l]	142–145	−12.7
			30	1	2	−1	0			
			300	−2	−12	11	0			
60		1	3	−2	3	−6	1	$C_{23}H_{29}N_3O_3 \cdot HCl$[h]	120–124	−8.5[p]
			30	−1	6	−6	−2			
			300	−2	5	−6	−1			

[a] See footnote *a* in Table I for test elaboration. [b] Amino acids have the L configuration, except where noted. [c] Number of dogs. [d] All compounds were analyzed for C, H, and N; results obtained were within ±0.4% of the theoretical values, and exceptions are noted. [e] DL-α-methylphenylalanyl derivative. [f] Calculated for 1.5 mol of HOAc and 1 mol of H_2O, N: calcd, 11.96; found, 11.28. [g] (*c* 1.5, aqueous MeOH). [h] Calculated for 0.5 of H_2O. [i] DL-α-methyl-3,4-dimethoxyphenylalanyl derivative. [j] Calculated for 1.5 mol of HOAc and 3 mol of H_2O; N: calcd, 10.52; found, 9.92. [k] Calculated for 0.75 mol of H_2O. [l] DL-α-methyltyrosyl derivative. [m] Change (percent) from initial baseline control values after cumulative dosing. [n] Calculated for 1 mol of HOAc and 1 mol of EtOH. [o] Calculated for 0.25 mol of H_2O. [p] (*c* 1, H_2O). [q] D-Phenylalanyl derivative. [r] Calculated for 1 mol of H_2O, N: calcd, 9.17; found, 8.74. [s] Calculated for 1 mol of EtOH, N: calcd, 8.56; found, 8.03. [t] Calculated for 1 mol of HOAc.

Table IV. Renal Vasodilator Activity[a]

compd	RVR ED_{15},[b] μg/kg, iv	av max % decrease in RVR	IVR ED_{30}/ RVR ED_{15}	MABP ED_{20}/ RVR ED_{15}	HR ED_{20}/ RVR ED_{15}
31	297 (3)	20	>20	−4	>20
36	5.2 (2)	21	>1158	>1158	>1158
44	72 (3)	19	0	>84	>84
50	506 (3)	31	>12	>12	>12
52	45.5 (2)	16	<9	>1665	>1665
56	4.9 (3)[c]	20	>1226	>1226	>1226
57	(3)[d]	13			
bradykinin[e]	2.8 (4)	67	+25	−7	+8

[a] See ref 1 and 11 for details of methodology for determining RVR ED_{15}, average maximum percent decrease in RVR, and the selectivity ratios ED_{15} relative to iliac vascular resistant (IVR), mean arterial blood pressure (MABP), and heart rate (HR). The following changes were determined to be the minimum necessary for statistical significance ($p = 0.95$): RVR, 16%; MABP, ±6%; IVR, ±24%; HR, ±9%. [b] Number of dogs used in test in parentheses. [c] Compound showed a fair amount of variability on testing in the mongrel dogs. [d] Selectivity not calculated, since average maximum percent decrease in RVR was 13. [e] Tested as the acetate (2.5 mol) and pentahydrate.

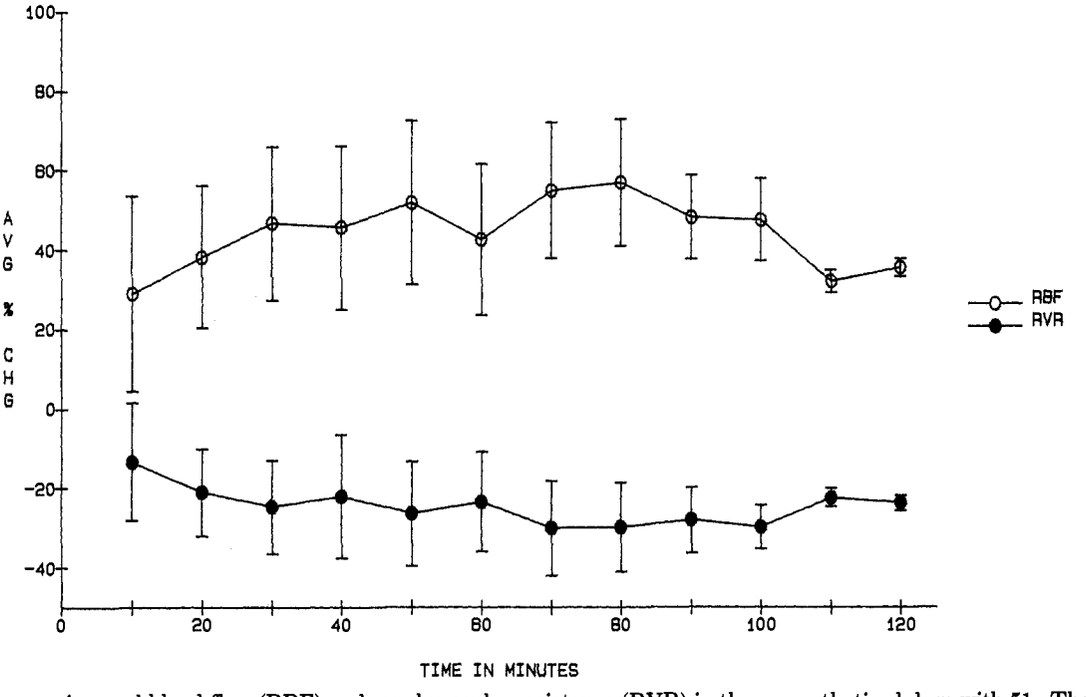


Figure 1. Changes in renal blood flow (RBF) and renal vascular resistance (RVR) in three anesthetized dogs with **51**. The dogs were infused according to the standard protocol, starting with a 5-min iv infusion at 0.1 μg/(kg min). Each dose was infused for 5 min to give a total cumulative dose of 2025 μg/kg. Time (in minutes) is after total dose (see Structure–Activity Relationship section).

In Figures 1 and 2 are shown the results of longer term cumulative effects on RBF and RVR for compounds **51** and **55**. The dogs were infused according to the standard protocol, starting with a 5-min infusion at 0.1 μg/(kg min) and increasing the dose in threefold increments to 270 μg/(kg min). Each dose was infused for 5 min to give a total cumulative dose of 2025 μg/kg during 45 min. The dogs were monitored for an additional 120 min after drug administration. In Figure 1, the data for **51**, the 3-aminopropyl amide, are shown. The RBF was increased a mean of 8% ($n = 3$) at the end of the infusion, reached a maximum increase of 57% 80 min after drug administration, and fell to 36% 120 min following drug administration; the RVR decreased a maximum of 30% 80 min following drug administration and 24% 120 min following drug administration. In Figure 2, the RBF for compound **55**, the D-Phe analogue, is shown to advance from an increase of 15% ($n = 3$) at the end of the infusion to a 76% increase at 120 min following drug administration; the RVR decreased from 8% at the end of the infusion to a 32% decrease at 120 min following drug administration. These data show that two different types of analogues in this series exhibited extended duration of significant renal vasodilatation. The data in Table IV provide evidence confirming that tri- and tetrapeptide fragments of bradykinin that are suitably modified provided compounds with equal or greater potency as renal vasodilators with greatly enhanced selectivity for the renal vasculature. A summary of the renal vasodilator data implies that (1) certain derivatized fragments of the carboxy terminus of bradykinin, i.e., Pro-Phe-Arg, are vasodilatory in the anesthetized dog, (2) tripeptide analogues having a 4-phenylbutyryl side chain on the N-terminal proline provide enhanced activity relative to the unsubstituted derivatives, (3) the 4-(4-hydroxyphenyl)butyryl group added to certain tri- and tetrapeptide derivatives gave compounds that were the best renal vasodilators of the series, and (4) arrays of Pro-Phe-Gly-Pro incorporating α-methylphenylalanine were active variants. Some of these compounds were characterized by their ability to provide selective renal vasodilatation, and the biological data reveal diverse profiles for these analogues, suggesting that more potent compounds might be obtained with a greater selectivity for the renal vasculature.

Experimental Section

All compounds were routinely checked by IR, NMR, TLC, and mass spectroscopy. Infrared spectra were run as Nujol mulls on

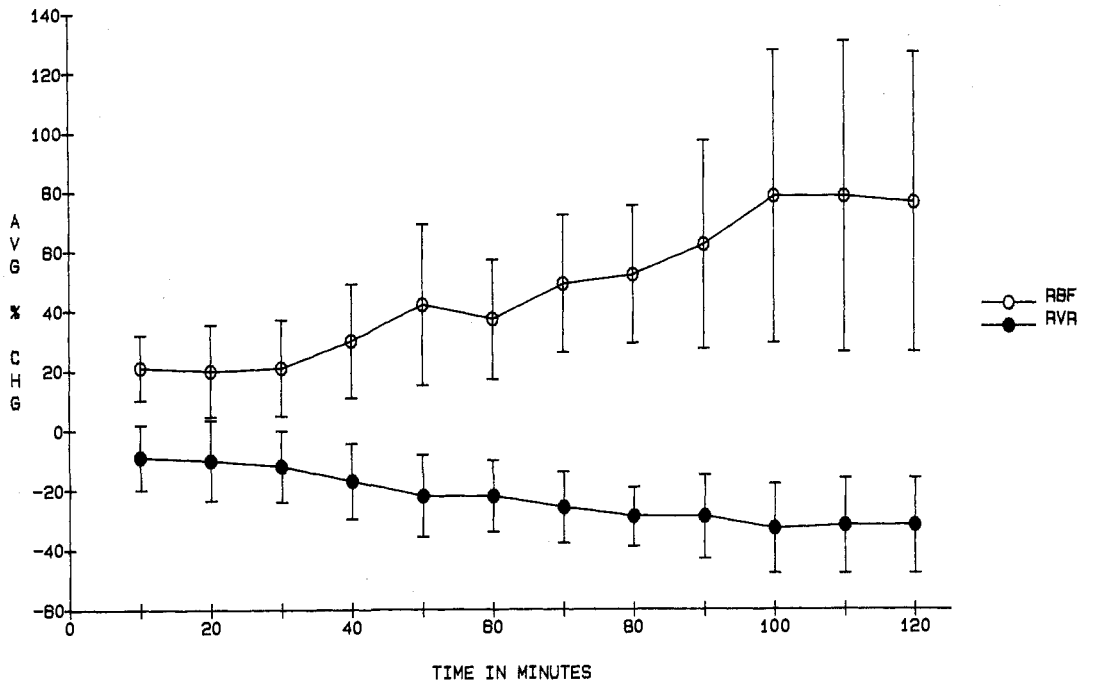


Figure 2. Changes in renal blood flow (RBF) and renal vascular resistance (RVR) in three anesthetized dogs with **55**. See Figure 1 for protocol. The total cumulative dose was 2025 μg/kg, and the time (in minutes) is after total dose.

a Perkin-Elmer Infracord Model 137. Proton magnetic spectra were determined on Perkin-Elmer R24 and Varian EM 360 instruments using Me_4Si as reference. TLC's were run on Uniplate silica gel plates, 250 μm (Analtech, Inc., Newark, DE); the following solvent systems were used for TLC: A, 5% MeOH in CH_2Cl_2; B, 7% MeOH in CH_2Cl_2; C, 10% MeOH in CH_2Cl_2; D, 20 mL of 3:1 CH_2Cl_2–MeOH with 10 drops of concentrated NH_4OH; E, 20 mL of 2:1 CH_2Cl_2–MeOH with 10 drops of concentrated NH_4OH; F, 63:31:6 CH_2Cl_2–MeOH–concentrated NH_4OH; G, 1:1 EtOAc–cyclohexane. Mass spectra were obtained on Hitachi Perkin-Elmer RMN-6E and Varian MAT CH-5 DF spectrometers using field-desorption (FD) and chemical-ionization (CI) techniques. Melting points were determined by using a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. Column chromatography was carried out on Merck silica gel 60 (MC/B, Cincinnati, OH). *N*-Carbobenzoxy-L-proline, N^{ω}-nitro-L-arginine methyl ester hydrochloride, and D-phenylalanine methyl ester hydrochloride were purchased from Vega Biochemicals, Tucson, AZ. L-Phenylalanine methyl ester hydrochloride, DL-α-methyltyrosine methyl ester hydrochloride, 1-adamantaneacetic acid, 4-(4-methoxyphenyl)-butyric acid, L-2-amino-3-phenyl-1-propanol, phenylacetic acid, 3-phenylpropionic acid, 4-phenylbutyric acid, and 5-phenylvaleric acid were purchased from Aldrich Chemical Co., Milwaukee, WI. Di-*tert*-butyl dicarbonate was obtained from Fluka Chemical Corp., Hauppauge, NY. DL-α-Methylphenylalanine methyl ester hydrochloride and DL-α-methyl-3,4-dimethoxyphenylalanine methyl ester hydrochloride (mp 152–154 °C, from CH_3CN) were synthesized by published procedures.[15] 4-(4-Hydroxyphenyl)-butyric acid was obtained from the hydrolysis of the precursor methoxy derivative with refluxing 48% HBr in HOAc. Glycyl-L-proline benzyl ester was prepared from the DCC coupling of L-proline benzyl ester with *N*-(*tert*-butoxycarbony)glycine, followed by unmasking of the amino group with CF_3COOH in CH_2Cl_2. The standard reaction conditions were as follows. (1) DCC coupling with HOBt:[16] equivalent amounts of the acid and amine and 2 equiv of HOBt were used, and the solution was neutralized to pH 7.0 to 7.5 with NEM (reaction time 2 h to 3 days), worked up by filtering the urea, concentrating the filtrate, partitioning between EtOAc and H_2O, and washing the organic extracts with a dilute HCl, H_2O, and 5% $NaHCO_3$ solution and brine. (2) DCC coupling with HOSu: as above except that 1 equiv of HOSu was used and activated ester could be isolated prior to the addition of the amine. (3) Basic hydrolysis: about 10 mmol of ester was dissolved in 75 mL of MeOH and 25 mL of 2.5 N NaOH and then stirred at 25 °C for 2 to 17 h, MeOH was evaporated, the aqueous residue was acidified with concentrated HCl, and the product was filtered or extracted with EtOAc. (4) Hydrogenolysis of the Cbz, benzyl, and N^{ω}-nitroarginine groups: 2 mmol of compound was dissolved in 25 mL of EtOH and 25 mL of HOAc (except only EtOH was used for benzyl esters) and shaken on the Parr apparatus with 0.5 g of 10% Pd/C or Pd/$BaSO_4$ (wet with a little H_2O) at 60 psi of H_2 until TLC showed the reaction was finished (2 to 18 h), the catalyst was filtered, the filtrate was concentrated, and the residue was azeotroped with EtOH and/or toluene. These peptide analogues tenaciously formed hydrates and solvates. Solvents were dried over $MgSO_4$. THF and DMF were dried over molecular sieves. Where analyses are indicated only by symbols of the elements, results were within ±0.4% of the theoretical values.

L-Prolyl-L-phenylalanyl-L-arginine (24). A mixture of 2.0 g (8 mmol) of *N*-carbobenzoxy-L-proline, 1.73 g (8 mmol) of L-phenylalanine methyl ester hydrochloride, 2.16 g (16 mmol) of HOBt, and 20 mL of THF was neutralized with NEM and was treated all at once with 1.81 g (8.8 mmol) of DCC at 0 °C. The suspension was then stirred at 25 °C for 18 h, and worked up in the standard fashion to give a quantitative yield (3.3 g) of the syrupy *N*-carbobenzoxy-L-prolyl-L-phenylalanine methyl ester: TLC (system C), R_f 0.68; FD mass spectrum, *m/e* 410 (intense peak). This product (3.3 g, 8 mmol) was dissolved in 40 mL of MeOH and 20 mL of 2.5 N NaOH solution and stirred for several hours or until TLC showed complete hydrolysis. The MeOH was evaporated, the aqueous residue was adjusted to pH 2 with 3 N HCl, and the oily precipitate was taken up in EtOAc and washed with H_2O. The dried, crude *N*-carbobenzoxy-L-prolyl-L-phenylalanine (1;[19] 3.1 g, 98%) was of sufficient purity to use for subsequent reactions: TLC (system C), R_f 0.17; FD mass spectrum, *m/e* 396 (intense). Compound 1 (1.5 g, 3.8 mmol) was coupled to N^{ω}-nitro-L-arginine methyl ester hydrochloride by the procedure described above and by using proportional quantities of other reagents to provide 2.1 g (95%) of *N*-carbobenzoxy-L-prolyl-L-

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(19) Fujii, S.; Toyonaka, Y.; Takashi, F.; Sugimoto, M. German Patent 29 43 582, 1980.

phenylalanyl-N^{ω}-nitro-L-arginine methyl ester: TLC (system C), R_f 0.69; FD mass spectrum, m/e 612. Basic hydrolysis of 1.0 g (1.6 mmol) of this ester afforded a white solid, which was dissolved in a small amount of MeOH and diluted with ethyl ether to give 600 mg (63%) of the free acid: mp 121–124 °C; $[\alpha]^{25}_D$ −47.1° (c, 0.5, MeOH); FD mass spectrum, m/e 597 (M), 598 (M + 1). Anal. ($C_{28}H_{35}N_7O_8$) C, H, N. This compound (1.0 g, 1.7 mmol) was hydrogenated by the standard conditions for 18 h. The residual product was dissolved in a minimum amount of MeOH, diluted with ethyl ether–EtOAc (1:1), and chilled to provide 554 mg (78%) of **24**:[6a,18] TLC (system F), R_f 0.34; FD mass spectrum, m/e 418 (M + 1). See Table I for additional data.

L-Prolyl-DL-α-methylphenylalanyl-L-arginine (27). The overall procedure used to prepare **24** was followed. DL-α-Methylphenylalanine methyl ester hydrochloride (4.9 g, 0.02 mol) was coupled to *N*-carbobenzoxy-L-proline to provide a syrupy product, which was chromatographed over 200 g of silica gel with a 20 to 25% of EtOAc in cyclohexane gradient to afford 5.6 g (66%) of *N*-carbobenzoxy-L-prolyl-DL-α-methylphenylalanine methyl ester: TLC (system A) R_f 0.65; FD mass spectrum, m/e 424 (strong). This compound (5.6 g, 13.2 mmol) was hydrolyzed with NaOH in the usual way to give 5.2 g (96%) of an amorphous solid. This was passed through a short column of silica gel with a 1 to 2% of MeOH in CH_2Cl_2 gradient to provide an analytical sample of *N*-carbobenzoxy-L-prolyl-DL-α-methylphenylalanine (**2**): TLC (system C) R_f 0.51; FD mass spectrum, m/e 410 (intense). Anal. ($C_{23}H_{26}N_2O_5$) C, H, N. Compound **2** (3.5 g, 8.5 mmol) was coupled to N^{ω}-nitro-L-arginine methyl ester hydrochloride (2.3 g, 8.5 mmol) with DCC in the usual manner to give an amorphous solid, which was chromatographed over 200 g of silica gel with a 1 to 3% of MeOH in CH_2Cl_2 gradient to afford 3.7 g (70%) of *N*-carbobenzoxy-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester: TLC (system C) R_f 0.45; FD mass spectrum, m/e 626 (strong, M + 1). Basic hydrolysis of the methyl ester gave 3.0 g (83%) of the white powdery acid: TLC (system C with 4 drops of HOAc in 20 mL of solution) R_f 0.42; FD mass spectrum, m/e 612 (M + 1). Catalytic hydrogenation as described for **24**, followed by chromatography on 30 g of silica gel with a gradient of 1 to 2% of MeOH in CH_2Cl_2 containing a few drops of concentrated NH_4OH gave **27** (0.3 g, 14%) as the white carbonate salt: TLC (system F) R_f 0.31; FD mass spectrum, m/e 433 (intense, M + 1). See Table I for additional data.

L-Prolyl-L-phenylalanine 3-Aminopropylamide (26). A mixture of 1.5 g (3.2 mmol) of **1**, 0.92 (3.2 mmol) of 3-(carbobenzoxyamino)propylamine hydrochloride,[17] 0.864 g (6.4 mmol) of HOBt, and 30 mL of THF was neutralized with NEM, treated with 0.87 g (4.2 mmol) of DCC, and stirred at 25 °C for 18 h. The usual acid–base workup gave 1.9 g (100%) of syrupy *N*-carbobenzoxy-L-prolyl-L-phenylalanine 3-(carbobenzoxyamino)-propylamide: FD mass spectrum, m/e 586 (intense). This compound (1.2 g, 2.1 mmol) was dissolved in 75 mL of EtOH and reduced on the Parr apparatus. The oily product was dissolved in a small amount of MeOH and acidified with ethereal HCl to provide a white solid. A crystallization from MeOH/ethyl ether gave 497 mg (75%) of the dihydrochloride of **26**: TLC (system F) R_f 0.57; CI mass spectrum (CH_4), m/e 318 with correct fragments. See Table I for additional data.

Similarly prepared was L-prolyl-DL-α-methylphenylalanine 3-aminopropylamide dihydrochloride (**29**) starting with 2.0 g (4.7 mmol) of **2**, 1.27 g (4.7 mmol) of 3-(carbobenzoxyamino)propylamine hydrochloride, and proportionate amounts of other reagents to give 2.8 g (100%) of *N*-carbobenzoxy-L-prolyl-DL-α-methylphenylalanine 3-(carbobenzoxyamino)propylamide: FD mass spectrum, m/e 600 (strong). Hydrogenolysis of this product and crystallization of the derived hydrochloride salt from MeOH/ethyl ether gave 1.54 g (76%) of the white solid **29**: TLC (system F) R_f 0.57; FD mass spectrum, m/e 333 (intense M + 1). See Table I for additional data.

L-Prolyl-DL-α-methylphenylalanyl-L-proline (30). Compound **2** (3.0 g, 7.3 mmol) was coupled to L-proline benzyl ester hydrochloride (1.76 g, 7.3 mmol) by the procedure described for **24**. The crude product was chromatographed with a 20 to 50% of EtOAc in cyclohexane gradient to give 1.7 g (39%) of *N*-carbobenzoxy-L-prolyl-DL-α-methylphenylalanyl-L-proline benzyl ester as an amorphous solid: TLC (system B) R_f 0.64; FD mass spectrum, m/e 424 (strong). This product (1.7 g, 2.8 mmol) was hydrogenated to give a white solid. A crystallization from EtOH provided 360 mg (35%) of **30**: FD mass spectrum, m/e 373 (intense, M), 374 (intense, M + 1). See Table I for additional data.

***N*-Benzoyl-L-prolyl-DL-α-methylphenylalanyl-L-arginine (33).** A mixture of 12.0 g (0.05 mol) of L-proline benzyl ester hydrochloride in 100 mL of dry pyridine was cooled to 0 °C, and a solution of 10.5 g (8.7 mL, 0.075 mol) of benzoyl chloride in 50 mL of CH_2Cl_2 was added at a fairly rapid rate. Then the reaction was stirred at 25 °C for 3 h and poured into ice–H_2O, and the organic layer was washed with a 3 N HCl, H_2O, and 5% $NaHCO_3$ solution and brine. The dried product was hydrogenated in EtOH over Pd/C to give, after precipitation from CH_2Cl_2/ethyl ether, 7.0 g (65%) of *N*-benzoyl-L-proline. This compound (4.6 g, 0.021 mol) and HOSu (2.42 g, 0.021 mol) were mixed in 30 mL of THF, and 4.3 g (0.021 mol) of DCC was added. The suspension was stirred for 1.5 h, the urea was filtered, 0.021 mol of DL-α-methylphenylalanine methyl ester was added, and the mixture was stirred at 25 °C for 3 days. The usual workup gave 5.5 g (66%) of the syrupy *N*-benzoyl-L-prolyl-DL-α-methylphenylalanine methyl ester: $[\alpha]^{25}_D$ −97.0° (c 1, $CHCl_3$); TLC (system C), R_f 0.76; FD mass spectrum, m/e 394 (intense). Basic hydrolysis provided 5.2 g (98%) of the powdery *N*-benzoyl-L-prolyl-DL-α-methylphenylalanine (**4**): mp 95–98 °C; $[\alpha]^{25}_D$ −87.2° (c 1, $CHCl_3$); TLC (system C), R_f 0.31; FD mass spectrum, m/e 380 (strong). Anal. ($C_{22}H_{24}N_2O_4$) C, H, N. Compound **4** (3.3 g, 8.8 mmol) and N^{ω}-nitro-L-arginine methyl ester hydrochloride (2.4 g, 8.8 mmol) were coupled (72 h) with DCC and HOBt in the usual way to provide 1.5 g (29%) of *N*-benzoyl-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester: TLC (system C) R_f 0.63; FD mass spectrum, m/e 596 (significant, M + 1). Basic hydrolysis gave, after chromatography over 15 g of silica gel with a 1 to 10% of MeOH in CH_2Cl_2 gradient, 0.6 g (41%) of the free acid: TLC (system C) R_f 0.42; FD mass spectrum, m/e 582 (M + 1). Unmasking of the guanidino group by hydrogenolysis was performed as described for **24** and gave a solid, which was triturated with MeOH/ethyl ether to give 0.235 g (44%) of **33**: TLC (system F) R_f 0.51; FD mass spectrum, m/e 537 (strong, M + 1). See Table I for additional data.

***N*-Benzoyl-L-prolyl-L-phenylalanyl-L-arginine (32).** A mixture of 1.0 g (4.6 mmol) of *N*-benzoyl-L-proline, 1.3 g (4.6 mmol) of L-phenylalanine benzyl ester hydrochloride, 1.2 g (9.2 mmol) of HOBt, and 20 mL of THF was neutralized with NEM and then cooled to 0 °C, and 1.0 g (5.1 mmol) of DCC was added. The suspension was stirred at 0 °C for 1 h and at 25 °C for 2 h. The usual workup gave 1.8 g (86%) of syrupy *N*-benzoyl-L-prolyl-L-phenylalanine benzyl ester: $[\alpha]^{25}_D$ −76° (c 1, $CHCl_3$); TLC (system C) R_f 0.74; FD mass spectrum, m/e 456 (intense). The benzyl ester (3.5 g, 7.7 mmol) was subjected to hydrogenolysis in EtOH with Pd/C to provide 2.5 g (89%) of crude acid. An analytical sample was prepared by passing a small sample through silica gel with a 2 to 5% of MeOH in CH_2Cl_2 gradient to provide powdery, amorphous, and hydrated *N*-benzoyl-L-prolyl-L-phenylalanine (**3**): mp 90–93 °C (lit.[19] mp 200–202 °C); $[\alpha]^{25}_D$ −75.7° (c 1, $CHCl_3$); TLC (system C) R_f 0.38; FD mass spectrum, m/e 366 (strong). Anal. ($C_{21}H_{22}N_2O_4$) C, H, N. The procedure to prepare **32** from **3** was exactly as described for the synthesis of **33** from **4**. From 1.4 g (3.8 mmol) of **3** and 1.0 g (3.8 mmol) of N^{ω}-nitro-L-arginine methyl ester hydrochloride was obtained 1.7 g (77%) of powdery *N*-benzoyl-L-prolyl-L-phenylalanyl-N^{ω}-nitro-L-arginine methyl ester: mp 115 °C; $[\alpha]^{25}_D$ −63.9° (c 1, MeOH); TLC (system C), R_f 0.69; FD mass spectrum, m/e 581 (M), 582 (M + 1). Anal. ($C_{28}H_{35}N_7O_7$) C, H, N. From 1.0 g (1.7 mmol) of the methyl ester there was obtained 0.5 g (51%) of the free acid. This was crystallized from MeOH/ethyl ether: mp 148–152 °C; $[\alpha]^{25}_D$ −53.7° (c 0.5, MeOH); TLC (system C), R_f 0.27; FD mass spectrum, m/e 568 (weak, M + 1). Anal. ($C_{27}H_{33}N_7O_7$) C, H, N. Hydrogenolysis of the above compound provided 2.1 g (41%) of **32** as a white solid (from MeOH/EtOAc/ethyl ether): TLC (system F), R_f 0.52; FD mass spectrum, m/e 522 (significant). See Table I for additional data.

***N*-Benzoyl-L-prolyl-DL-α-methylphenylalanyl-L-proline (35).** Compound **4** (1.2 g, 3.2 mmol) was coupled to L-proline benzyl ester hydrochloride (0.76 g, 3.2 mmol) by the DCC procedure described for **24** and **30**. The crude product was chromatographed over 150 g of silica gel with a 1 to 2% of MeOH in

CH_2Cl_2 gradient to provide 1.3 g (72%) of *N*-benzoyl-L-prolyl-DL-α-methylphenylalanyl-L-proline benzyl ester: TLC (system C) R_f 0.66. This product was deblocked following the procedure used for **30** and reprecipitated from MeOH/ethyl ether to give 0.8 g (73%) of **35** as a flaky solid: TLC (system F) R_f 0.44; FD mass spectrum, *m/e* 477. See Table I for additional data.

***N*-(Phenylacetyl)-L-prolyl-DL-α-methylphenylalanyl-L-arginine (34).** L-Proline benzyl ester was converted to *N*-(phenylacetyl)-L-proline by the procedure used to prepare *N*-benzoyl-L-proline described in the synthesis of **33**. From 4.7 g (0.023 mol) of L-proline benzyl ester hydrochloride was obtained 4.2 g (57%) of *N*-(phenylacetyl)-L-proline benzyl ester: TLC (system A) R_f 0.85; CI mass spectrum (CH_4), *m/e* 323 and expected fragments. Hydrogenolysis of this product afforded 2.5 g (83%) of powdery *N*-(phenylacetyl)-L-proline (**5**): $[\alpha]^{25}_D$ −61.7° (*c* 0.5, MeOH); TLC (system C) R_f 0.48; FD mass spectrum, *m/e* 233. Anal. ($C_{13}H_{15}NO_3$) C, H, N. A mixture of 2.0 g (8.6 mmol) of *N*-(phenylacetyl)-L-proline, 3.7 g (8.6 mmol) of **13**, and 2.3 g (17.2 mmol) of HOBt was reacted by the standard technique at 25 °C for 3 days. The crude product after workup was chromatographed over 60 g of silica gel with a gradient of 0.5 to 2% of MeOH in CH_2Cl_2 to yield 1.7 g (32%) of syrupy *N*-(phenylacetyl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester: TLC (system C) R_f 0.57; FD mass spectrum, *m/e* 610 (M + 1). The methyl ester (1.6 g, 2.6 mmol) was converted to the free acid with NaOH to give 1.1 g (71%) of the amorphous, solid acid: TLC (system C) R_f 0.32; FD mass spectrum, *m/e* 596 (intense, M + 1). This product (1.1 g, 1.8 mmol) was hydrogenated by the procedure described for the synthesis of **24**. The crude product was chromatographed over 30 g of silica gel with 2 to 10% of MeOH in CH_2Cl containing 1% of concentrated NH_4OH to give 267 mg (27%) of the amorphous **34**: TLC (system F) R_f 0.55; FD mass spectrum, *m/e* 551 (M + 1). See Table I for additional data.

***N*$^{\alpha}$-[*N*-L-Prolyl-L-2-amino-1-phenylpropyl]-L-arginine (25).** A mixture of 2.0 g (8 mmol) of *N*-carbobenzoxy-L-proline, 1.2 g (8 mmol) of L-2-amino-3-phenyl-1-propanol, 2.16 g (16 mmol) of HOBt in 20 mL of THF was treated with 1.8 g (8.8 mmol) of DCC, stirred at 25 °C for 2.5 h and worked up under the standard acid–base conditions to give 3.1 g (100%) of crude white solid. A crystallization from aqueous EtOH afforded plates of *N*-carbobenzoxy-L-proline L-3-hydroxy-1-phenylpropylamide (**6**): mp 126–128 °C; $[\alpha]^{25}_D$ −96.4° (*c* 1, $CHCl_3$); TLC (system C) R_f 0.77; FD mass spectrum, *m/e* 382 (strong). Anal. ($C_{22}H_{26}N_2O_4$) C, H, N. This alcohol (2.0 g, 5.2 mmol) was dissolved in 10 mL of dry CH_2Cl_2 and added dropwise at −60 °C to a solution prepared by adding dropwise 1.1 mL (15.6 mmol) of dry Me_2SO to 0.68 mL (7.7 mmol) of oxalyl chloride in 10 mL of CH_2Cl_2 at −60 °C. The solution was stirred at −60 °C for 15 min, then 3.6 mL (26 mmol) of triethylamine was added slowly, and the temperature was allowed to rise to 25 °C. The mixture was diluted with H_2O, the layers were separated, and the organic layer was washed with H_2O. The concentrated, dried product was chromatographed over 100 g of silica gel with an EtOAc in hexane gradient to afford 1.4 g (70%) of the oily aldehyde: TLC (system G) R_f 0.48; FD mass spectrum, *m/e* 380; IR 1745 (CHO) cm^{-1}. This aldehyde (1.0 g, 2.6 mmol) and N^{ω}-nitro-L-arginine methyl ester hydrochloride (1.2 g, 4.5 mmol) were dissolved in 20 mL of absolute MeOH, and $NaCNBH_3$ (120 mg) was added. The mixture was stirred at 25 °C for 24 h, concentrated in vacuo, diluted with 5% $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extracts were washed with H_2O and dried, and the crude product was chromatographed over 40 g of silica gel with a gradient of 1 to 2% of MeOH in CH_2Cl_2 to give 0.71 g (45%) of N^{α}-[*N*-(*N*-carbobenzoxy-L-prolyl)-L-2-amino-1-phenylpropyl]-N^{ω}-nitro-L-arginine methyl ester: TLC (system C) R_f 0.46; $[\alpha]^{25}_D$ −40.2° (*c* 0.5, MeOH). Basic hydrolysis of this ester (0.9 g, 1.5 mmol) gave 0.6 g (68%) of the white powdery free acid: TLC (system F) R_f 0.64. This compound was reduced, and precipitation of the crude product from MeOH/ethyl ether gave the triacetate salt of **25**. See Table I for additional data.

***N*$^{\alpha}$-[*N*-L-Prolyl-DL-2-amino-2-methyl-3-phenylpropyl]-L-arginine (28).** A solution of 27.5 g (0.154 mol) of DL-α-methylphenylalanine[15] in 200 mL of THF was cooled to 0 °C (under N_2), and a solution of 250 mL of 1 M BH_3 in THF (0.25 mol) was added. The mixture was stirred for 4 h at 0 °C and then for 17 h at 25 °C and recooled, and excess MeOH was added cautiously. The solvents were evaporated, the residue was diluted with H_2O and extracted with EtOAc, and the washed, dried solution was concentrated to a syrup, which slowly crystallized. A crystallization from ethyl ether/petroleum ether gave 13.0 g (51%) of DL-2-amino-2-methyl-3-phenylpropanol: mp 89–91 °C (lit.[15] mp 99–100 °C, from heptane); TLC (system B), R_f 0.67; CI mass spectrum (CH_4), *m/e* 165. A DCC coupling reaction as described above using 5.28 g (0.032 mol) of DL-2-amino-2-methyl-3-phenylpropanol and 7.94 g (0.032 mol) of *N*-carbobenzoxy-L-proline gave a product, which was chromatographed over 250 g of silica gel with an elution gradient of 0.5 to 1% of MeOH in CH_2Cl_2 to give 8.1 g (63%) of the syrupy *N*-carbobenzoxy-L-proline DL-3-hydroxy-2-methyl-1-phenylpropylamide (**7**). Slow crystallization from ethyl ether gave the white solid **7**: mp 72–74 °C; $[\alpha]^{25}_D$ −20.6° (*c* 1, MeOH); TLC (system A) R_f 0.72; CI mass spectrum (CH_4), *m/e* 396. Anal. ($C_{23}H_{28}N_2O_4$) C, H, N.

The alcohol **7** was oxidized exactly as described for the procedure used for the oxidation of **6** using 7.7 g (19.4 mmol) of **7** and proportional amounts of other reagents. The crude product was chromatographed over 150 g of silica gel with a 16 to 25% of EtOAc in cyclohexane gradient to give 5.1 g (67%) of the syrupy aldehyde: $[\alpha]^{25}_D$ −59.1° (*c* 1, MeOH); TLC (system G), R_f 0.59; FD mass spectrum, strong *m/e* 394. Anal. ($C_{23}H_{26}N_2O_4$) C, H, N. This aldehyde (9.6 g, 0.0357 mol) was reductively aminated with the protected arginine as described in the synthesis of **25** and using proportional amounts of other reagents. The crude product was chromatographed over 150 g of silica gel with a 1 to 2% of MeOH in CH_2Cl_2 gradient to afford 3.5 g (64%) of N^{α}-[*N*-(*N*-carbobenzoxy-L-prolyl)-DL-2-amino-2-methyl-3-phenylpropyl]-N^{ω}-nitro-L-arginine methyl ester: TLC (system A), doublet centered at R_f 0.46 for the diastereoisomeric mixture; FD mass spectrum, *m/e* 611 (M), 612 (M + 1). Basic hydrolysis gave 2.8 g (82%) of the free acid as an amorphous powder: $[\alpha]^{25}_D$ −36.7° (*c* 1, MeOH); TLC (system C), R_f 0.24; FD mass spectrum, *m/e* 598 (strong, M + 1). Catalytic reduction of 2.5 g (4.2 mmol) of this nitro derivative afforded 1.25 g (71%) of **28** as a white solid: TLC (system F), R_f 0.34; FD mass spectrum, *m/e* 419 (strong, M + 1). See Table I for additional data.

***N*-(3-Phenylpropionyl)-L-proline (8), *N*-(4-Phenylbutyryl)-L-proline (9), and *N*-(5-Phenylpentanoyl)-L-proline (10).** These compounds were prepared by the procedure described for the synthesis of *N*-benzoyl-L-proline, an intermediate to **33**. The requisite acid chlorides were prepared with thionyl chloride with a few drops of DMF at 60 °C for 2 h. The crude acid chlorides were concentrated, azeotroped with toluene, and used directly for the acylation reactions with L-proline benzyl ester hydrochloride. The reaction of 8.0 g (0.049 mol) of 4-phenylbutyryl chloride and relative quantities of other reagents provided 16.0 g (93%) of the oily *N*-(4-phenylbutyryl)-L-proline benzyl ester. Hydrogenation of 8.5 g (0.024 mol) of this product gave 4.7 g (79%) of **9**. A dicyclohexylamine salt of **9** was prepared: mp 141–143 °C (from CH_3CN); $[\alpha]^{25}_D$ −33.9° (*c* 1, $CHCl_3$). Anal. ($C_{27}H_{42}N_2O_3$) C, H, N. Similarly prepared was **8**; from 0.023 mol of 3-phenylpropionyl chloride was obtained 4.9 g (63%) of syrupy *N*-(3-phenylpropionyl)-L-proline benzyl ester: $[\alpha]^{25}_D$ −68.1° (*c* 0.5, MeOH); TLC (system G), R_f 0.73; FD mass spectrum, *m/e* 337 (intense). Hydrogenation of the ester (4.9 g) in EtOH with 10% Pd/C gave 3.4 g (95%) of *N*-(3-phenylpropionyl)-L-proline (**8**): mp 103–104 °C (from EtOAc/ethyl ether); $[\alpha]^{25}_D$ −118.5° (*c* 0.5, MeOH); FD mass spectrum, intense *m/e* 247. Anal. ($C_{14}H_{17}NO_3$) C, H, N. In a similar fashion was prepared **10**: from 0.023 mol of 5-phenylpentanoyl chloride was obtained 3.4 g (40%) of syrupy *N*-(5-phenylpentanoyl)-L-proline benzyl ester after passage through a short column of silica gel with CH_2Cl_2: $[\alpha]^{25}_D$ −52.9° (*c* 0.5, MeOH); TLC (system G) R_f 0.69; FD mass spectrum, *m/e* 365 (intense). This benzyl ester was deblocked by catalytic hydrogenation to give 2.4 g (94%) of **10** as a syrup: $[\alpha]^{25}_D$ −54.3° (*c* 0.5, MeOH); FD mass spectrum, *m/e* 275. Anal. ($C_{16}H_{21}NO_3$) C, H, N.

***N*-(4-Phenylbutyryl)-L-prolyl-L-phenylalanyl-L-arginine (37).** A mixture of 4.0 g (0.016 mol) of **9**, 1.88 g (0.016 mol) of HOSu, and 60 mL of THF was reacted in the usual way with 3.36 g (0.016 mol) of DCC for 2 h and coupled to 4.0 g (0.016 mol) of L-phenylalanine benzyl ester. The solution was stirred at 25 °C for 24 h, the usual workup provided 7.2 g of crude product, and

column chromatography over 200 g of silica gel with a gradient of 0.5 to 1% of MeOH in CH_2Cl_2 gave 4.6 g (58%) of syrupy *N*-(4-phenylbutyryl)-L-prolyl-L-phenylalanine benzyl ester: TLC (system A) R_f 0.89; FD mass spectrum, intense *m/e* 498. Anal. ($C_{31}H_{34}N_2O_4$) C, H, N. The benzyl ester (2.2 g, 4.5 mmol) was subjected to catalytic hydrogenation, and the resulting crude product was chromatographed over 70 g of silica gel with a 1 to 10% of MeOH in CH_2Cl_2 gradient to afford the acid **11** which was converted to the potassium salt with potassium *tert*-butoxide in *tert*-butyl alcohol. The potassium salt was dissolved in dry EtOAc and precipitated with ethyl ether/petroleum ether to give 0.923 g (46%) of the potassium salt of **11**: mp 64–67 °C: $[\alpha]^{25}_D$ −29.7° (*c* 1, $CHCl_3$); FD mass spectrum, *m/e* 408 (intense, free acid). Anal. ($C_{24}H_{27}N_2O_4K$) C, H, N. The free acid of **11** (1.2 g, 3.0 mmol) was coupled with HOBt and the blocked L-arginine to provide 1.1 g (61%) of *N*-(4-phenylbutyryl)-L-prolyl-L-phenylalanyl-N^{ω}-nitro-L-arginine methyl ester: mp 93–95 °C (from MeOH/ethyl ether); $[\alpha]^{25}_D$ −41.7° (*c* 0.5, MeOH); TLC (system C), R_f 0.73; FD mass spectrum, *m/e* 624 (M + 1). Basic hydrolysis gave a white solid (0.51 g, 51%) of the arginine free acid: mp 124–127 °C (from MeOH/ethyl ether); $[\alpha]^{25}_D$ −39.7° (*c* 0.5, MeOH); TLC (system C), R_f 0.35; FD mass spectrum, *m/e* 610 (strong, M + 1). Anal. ($C_{30}H_{39}N_7O_7$) C, H, N. Hydrogenolysis of 0.416 g (0.7 mmol) of this acid afforded, after MeOH/ethyl ether precipitation, 0.276 g (70%) of the white powdery **37**; TLC (system F) R_f 0.67; FD mass spectrum, *m/e* 564 (M), 565 (M + 1). See Table II for additional data.

Similarly prepared was *N*-(4-phenylbutyryl)-L-prolyl-D-phenylalanyl-L-arginine (**38**). Coupling of compound **9** (5.0 g, 0.019 mol) and D-phenylalanine methyl ester hydrochloride with DCC/HOBt gave 4.2 g (52%) of the methyl ester after column chromatography with 1 to 2% of MeOH in CH_2Cl_2: TLC (system A) R_f 0.68. Basic hydrolysis of 4.1 g gave 3.6 g (91%) of *N*-(4-phenylbutyryl)-L-prolyl-D-phenylalanine; TLC (system B) R_f 0.27; electron-impact mass spectrum, *m/e* 408 (small) with acceptable fragmentation pattern. Coupling of 3.3 g (8.0 mmol) of this product with the protected arginine gave 4.2 g (86%) of *N*-(4-phenylbutyryl)-L-prolyl-D-phenylalanyl-N^{ω}-nitro-L-arginine methyl ester after column chromatography on silica gel as described above: TLC (system C) R_f 0.49; FD mass spectrum, intense *m/e* 624 (M + 1). Basic hydrolysis of 1.8 g gave 1.4 g (83%) of the arginine free acid: TLC (system C) R_f 0.21. After hydrogenolysis, this material afforded the white solid (1.45 g, 82%) **38**: TLC (system E) R_f 0.36; FD mass spectrum, *m/e* 565 (intense, M + 1). See Table II for additional data.

Also prepared was *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methylphenylalanyl-L-arginine (**41**). Coupling of **9** (4.6 g, 17.6 mmol) with DL-α-methylphenylalanine methyl ester hydrochloride by the HOBt method gave 6.5 g (85%) of *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methylphenylalanine methyl ester after chromatography on 250 g of silica gel with a 1 to 2% of MeOH in CH_2Cl_2 gradient: TLC (system A) R_f 0.74; CI mass spectrum (CH_4), *m/e* 436. Basic hydrolysis gave 5.6 g (89%) of the foamy free acid **12**: TLC (system A) R_f 0.48; CI mass spectrum (CH_4), *m/e* 422 (M + 1). This product (5.5 g, 0.013 mol) was coupled to the protected arginine to give, after chromatography with a gradient of 0.5 to 2% of MeOH in CH_2Cl_2, 5.2 g (63%) of *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester: TLC (system A) R_f 0.52; FD mass spectrum, *m/e* 637 (M), 638 (M + 1). Basic hydrolysis afforded 4.55 g (90%) of the arginine free acid as an amorphous solid, which was deblocked under the usual hydrogenolysis conditions to give 1.6 g (37%) of the amorphous, powdery **41**, FD mass spectrum, *m/e* 579 (strong, M + 1). See Table II for additional data.

***N*-(4-Phenylbutyryl)-L-prolyl-DL-α-methylphenylalanyl-L-proline (47).** The procedure for the preparation of **35** was followed. Compound **12** (6.8 g, 0.016 mol) was coupled to L-proline benzyl ester hydrochloride, and the usual workup and chromatography afforded 5.1 g (52%) of syrupy *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methylphenylalanyl-L-proline benzyl ester; $[\alpha]^{25}_D$ −106.8° (*c* 0.5, MeOH); TLC (system C) R_f 0.70; FD mass spectrum, *m/e* 609 (intense). Anal. ($C_{37}H_{43}N_3O_5$) C, H, N. The free acid was unmasked with $Pd/BaSO_4/H_2$ to provide the amorphous solid **47** (4.15 g, 95%): TLC (system C) R_f 0.72; FD mass spectrum, *m/e* 519 (intense, M), 520 (intense M + 1). See Table II for additional data.

DL-α-Methylphenylalanyl-N^{ω}-nitro-L-arginine Methyl Ester (13). A suspension of 6.4 g (0.036 mol) of DL-α-methylphenylalanine, 5.0 mL (3.6 g, 0.036 mol) of triethylamine, 100 mL of DMF, and 9.3 g (0.043 mol) of di-*tert*-butyl dicarbonate was stirred at 25 °C for 18 h. A small amount of insoluble material was removed by filtration, and the concentrated product was taken up in EtOAc and washed with H_2O, cold 1 N HCl, and H_2O. The dried, concentrated crude product solidified on standing and was crystallized from ether/hexane to provide 4.6 g (46%) of *N*-(*tert*-butoxycarbonyl)-DL-α-methylphenylalanine: mp 134–135 °C; CI mass spectrum (CH_4), *m/e* 279. Anal. ($C_{15}H_{21}NO_4$) C, H, N. This Boc derivative (4.4 g, 0.016 mol) was coupled to N^{ω}-nitro-L-arginine methyl ester hydrochloride by the DCC/HOBt method, and the product was chromatographed over 200 g of silica gel with 0.5 to 1% of MeOH in CH_2Cl_2 to provide 6.8 g (86%) of *N*-(*tert*-butoxycarbonyl)-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester. A crystallization from EtOH gave a white solid: mp 143–145 °C; $[\alpha]^{25}_D$ −33.9° (*c* 1, MeOH); FD mass spectrum, *m/e* 495 (strong, M + 1). Anal. ($C_{22}H_{34}N_6O_7$) C, H, N. A mixture of 3.4 g (6.9 mmol) of the Boc derivative, 5.0 mL of 1,3-dimethoxybenzene, and 15 mL of CH_2Cl_2 was cooled to 0 °C, and 5.0 mL of CF_3COOH was added. A clear solution was obtained and was stirred at 0 °C for 10 min and at 25 °C for 1 h. The solvents were evaporated in vacuo, dilute HCl was added, and the aqueous layer was washed well with EtOAc. The aqueous layer was concentrated to a white foam and azeotroped with EtOH to give 2.9 g (98%) of the hygroscopic hydrochloride salt of **13** as a foam: $[\alpha]^{25}_D$ −32.8° (*c* 1, H_2O); FD mass spectrum, *m/e* 395 (intense, M + 1). Anal. ($C_{17}H_{26}N_6O_5$) C, H, N.

***N*-(3-Phenylpropanoyl)-L-prolyl-DL-α-methylphenylalanyl-L-arginine (40).** Compound **8** (1.72 g, 7 mmol) was coupled to **13** (3.0 g, 7 mmol) by the DCC/HOBt method (3 days) and worked up in the usual way, and the crude product was chromatographed over 150 g of silica gel with a gradient of 0.5 to 2% of MeOH in CH_2Cl_2 to give a white amorphous solid (1.7 g, 39%): TLC (system A) R_f 0.65; FD mass spectrum, *m/e* 624 (strong, M + 1). Basic hydrolysis afforded 1.5 g (90%) of the amorphous solid *N*-(3-phenylpropanoyl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine: $[\alpha]^{25}_D$ −96.2° (*c* 0.5, MeOH); FD mass spectrum, *m/e* 610 (significant, M + 1). Hydrogenolysis gave an impure product, which was chromatographed over silica gel with a 3 to 10% of MeOH in CH_2Cl_2 gradient containing 1 to 3% of concentrated NH_4OH to provide 0.31 g (22%) of **40** as a foam: FD mass spectrum, *m/e* 565 (intense, M + 1); TLC (system F) R_f 0.61. See Table II for additional data.

Similarly prepared was *N*-(5-phenylpentanoyl)-L-prolyl-DL-α-methylphenylalanyl-L-arginine (**42**). From 2.4 g (8.7 mmol) of **10** was obtained 2.0 g (35%) of amorphous *N*-(5-phenylpentanoyl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester: $[\alpha]^{25}_D$ −85.5° (*c* 0.5, MeOH); TLC (system C), R_f 0.62; FD mass spectrum, *m/e* 652 (strong, M + 1). Anal. ($C_{33}H_{45}N_7O_7$) C, H, N. Basic hydrolysis gave 1.8 g (94%) of the amorphous white arginine free acid derivative: TLC (system C), R_f 0.22; FD mass spectrum, *m/e* 638 (M + 1). Hydrogenolysis provided, after chromatography described for **40**, the amorphous solid **42** (0.87 g, 52%); TLC (system F) R_f 0.64; FD mass spectrum, *m/e* 593 (M + 1). See Table II for additional data.

***N*-(4-Phenylbutyryl)-L-prolyl-L-phenylalanine 3-Aminopropylamide (39).** The procedure for the synthesis of **26** was used. Compound **11** (1.4 g, 3.4 mmol) and 3-(carbobenzoxyamino)propylamine hydrochloride (0.6 g, 3.5 mmol) gave 0.71 g (35%) of *N*-(4-phenylbutyryl)-L-prolyl-L-phenylalanine 3-(carbobenzoxyamino)propylamide as a foam: TLC (system C) R_f 0.89; EI mass spectrum, *m/e* 598 and expected fragments. The amino group was unmasked as described previously, and the derived hydrochloride salt was precipitated from CH_2Cl_2/ethyl ether to provide 130 mg (24%) of the hydrochloride of **39**: TLC (system C) R_f 0.26. See Table II for additional data.

Similarly prepared was *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methylphenylalanine 3-aminopropylamide (**43**). From 1.0 g (2.4 mmol) of **12** was obtained, after chromatography over silica gel with 1% of MeOH in CH_2Cl_2, 0.41 g (27%) of *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methylphenylalanine 3-(carbobenzoxyamino)propylamide as a foam: TLC (system C) R_f 0.90; FD mass spectrum, *m/e* 612. The derived hydrochloride of **43** (0.22 g, 59%) was a white powder: TLC (system C) R_f 0.33; FD mass spectrum,

m/e 478 (M), 479 (M + 1). See Table II for additional data.

***N*-(4-Phenylbutyryl)-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanyl-L-arginine (45).** Compound **9** (1.17 g, 4.45 mmol) was coupled to DL-α-methyl-3,4-dimethoxyphenylalanine methyl ester hydrochloride by the DCC/HOBt method for 72 h at 25 °C. The usual workup afforded 2.2 g (98%) of the syrupy *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanine methyl ester; TLC (system B) R_f 0.64; CI mass spectrum (CH_4), *m/e* 496. Basic hydrolysis gave 2.0 g (93%) of the free acid **14**. This was coupled with the blocked arginine, and the crude product was chromatographed over 60 g of silica gel with a 1 to 2% of MeOH in CH_2Cl_2 gradient to give 1.6 g (55%) of the amorphous white solid *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanyl-N^{ω}-nitro-L-arginine methyl ester: TLC (system A) R_f 0.44; CI mass spectrum (CH_4), *m/e* 697. Basic hydrolysis and hydrogenolysis in the usual way provided the off-white solid **45** in an overall yield of 66%: TLC (system E) R_f 0.36; FD mass spectrum, *m/e* 639 (strong, M + 1). See Table II for additional data.

***N*-(1-Adamantylacetyl)-L-prolyl-DL-α-methylphenylalanyl-L-arginine (44).** 1-Adamantaneacetic acid (7.76 g, 0.04 mol) was coupled to L-proline benzyl ester hydrochloride (9.6 g, 0.04 mol) by the DCC/HOBt method to give a near quantitative yield of *N*-(1-adamantylacetyl)-L-proline benzyl ester: TLC (system A) R_f 0.73; FD mass spectrum, *m/e* 381 (strong). The usual hydrogenolysis conditions on 15.2 g of the benzyl ester gave a solid, which was crystallized from EtOAc to provide white plates of *N*-(1-adamantylacetyl)-L-proline (**16**): mp 174–176 °C; $[\alpha]^{25}_D$ −51.3° (*c* 1, MeOH). Anal. ($C_{17}H_{25}NO_3$) C, H, N. Compounds **16** (1.76 g, 6.0 mmol) and **13** (2.6 g, 6.0 mmol) were reacted with DCC/HOBt in the standard manner to give 3.5 g (88%) of the semisolid *N*-(1-adamantylacetyl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester: $[\alpha]^{25}_D$ −78.7° (*c* 0.5, MeOH); TLC (system C) R_f 0.63; FD mass spectrum, *m/e* 667 (M), 668 (M + 1). Basic hydrolysis of 0.9 g of this product was followed by hydrogenolysis and afforded 0.17 g (22%) of the amorphous solid **44**: TLC (system F) R_f 0.49; FD mass spectrum, *m/e* 609 (intense, M + 1). See Table II for additional data.

***N*$^{\alpha}$-[*N*-(4-Phenylbutyryl)-L-propyl-DL-2-amino-2-methyl-3-phenylpropyl]-L-arginine (46).** The procedure described for the preparation of **28** was followed. Compound **9** (4.6 g, 17.6 mmol) and DL-2-amino-2-methyl-3-phenylpropanol (2.9 g, 17.6 mmol) were coupled, and the crude product was chromatographed over silica gel to give 4.2 g (58%) of the syrupy *N*-(4-phenylbutyryl)-L-proline DL-3-hydroxy-2-methyl-1-phenylpropylamide (**15**): TLC (system A) R_f 0.51; CI mass spectrum (CH_4), *m/e* 408. The alcohol **15** (4.1 g, 10.0 mmol) was oxidized to the aldehyde by the procedure described for the synthesis of **25** and provided 2.4 g (59%) of syrupy aldehyde: TLC (system G) R_f 0.45; CI mass spectrum (CH_4), *m/e* 406. Reductive alkylation of the aldehyde with L-arginine (1.0 g, 5.9 mmol) and $NaCNBH_3$ (0.9 g) in 2-propanol (50 mL) gave, after chromatography, 240 mg (7%) of the amorphous solid **46**: FD mass spectrum, *m/e* 565 (M + 1). See Table II for additional data.

***N*-[4-(4-Hydroxyphenyl)butyryl]-L-proline (17).** A mixture of 15.1 g (0.063 mol) of L-proline benzyl ester hydrochloride, 11.3 g (0.063 mol) of 4-(4-hydroxyphenyl)butyric acid, and 17.0 g (0.126 mol) of HOBt in 80 mL of THF and 40 mL of DMF was neutralized with NEM and treated all at once with 13.0 g (0.063 mol) of DCC. The resulting suspension was stirred at 25 °C for 17 h, and the usual workup gave 18.9 g (83%) of the syrupy *N*-[4-(4-hydroxyphenyl)butyryl]-L-proline benzyl ester: TLC (system A) R_f 0.48; FD mass spectrum, *m/e* 367 (intense). This benzyl ester (18.9 g, 0.051 mol) was dissolved in 100 mL of EtOH and agitated for 3 h with 2.5 g of 10% of Pd/C (wet with H_2O) at 60 psi of hydrogen. The reaction was filtered, concentrated, and azeotroped with EtOH and toluene to give 14.3 g (~100%) of the foamy **17**: TLC (system B) R_f 0.16; EI mass spectrum, *m/e* 277.

***N*-[4-(4-Hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanyl-L-arginine (50).** A mixture of 2.8 g (10 mmol) of **17** and 2.9 g (10 mmol) of DL-α-methyl-3,4-dimethoxyphenylalanine methyl ester hydrochloride were coupled as described for **17** (25 °C for 72 h), and the usual workup afforded 5.1 g (100%) of a foam: TLC (system A) R_f 0.21; FD mass spectrum, *m/e* (relative intensity) 512 (39.8). This methyl ester (5.0 g, 9.8 mmol) was dissolved in 75 mL of MeOH and 25 mL of 2.5 N NaOH solution and worked up in the standard manner. The residual aqueous solution was filtered from a small amount of insoluble material, and the filtrate was acidified with concentrated HCl to give a voluminous solid. This was extracted into CH_2Cl_2 containing a small amount of MeOH, and the organic extracts were washed with H_2O and concentrated to give *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanine (**19**; 3.2 g, 66%): TLC (system C) R_f 0.11; FD mass spectrum, *m/e* 498 (strong). Compound **19** (3.1 g, 6.2 mmol) and N^{ω}-nitro-L-arginine methyl ester hydrochloride were coupled with DCC and proportional amounts of other reagents as described above. After 2 days, the usual workup gave 3.8 g (92%) of the white gel-like *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanyl-N^{ω}-nitro-L-arginine methyl ester: TLC (system B) R_f 0.31; FD mass spectrum, *m/e* 714 (significant, M + 1). This ester (3.5 g, 5 mmol) was hydrolyzed with NaOH solution to afford 1.9 g (55%) of the free acid; TLC (system D) R_f 0.46; FD mass spectrum, *m/e* (relative intensity) 700 (intense, M + 1, 45.4). This acid (1.75 g, 2.5 mmol) in 40 mL of EtOH and 40 mL of HOAc was shaken on the hydrogenation apparatus with 2.5 g of 10% Pd/$BaSO_4$ for 18 h at 60 psi and filtered, and the filtrate was evaporated and azeotroped with toluene and then EtOH to give the white powdery acetate of **50** (1.5 g, 81%): TLC (system E) R_f 0.33; FD mass spectrum, *m/e* 655 (relatively strong, M + 1). See Table III for additional data.

N-[4-(4-Hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanyl-L-arginine (**48**) was similarly prepared by the following steps: coupling of **17** and DL-α-methylphenylalanine methyl ester hydrochloride [96% yield; R_f 0.34 (system A); FD mass spectrum, *m/e* 452]; basic hydrolysis, to give *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanine [**18**; 81% yield: R_f 0.11 (system C); FD mass spectrum, *m/e* 438]; coupling with the protected arginine [95% yield: R_f 0.19 (system B), FD mass spectrum, *m/e* 654 (M + 1)]; basic hydrolysis (75% yield: R_f 0.08 (system B); FD mass spectrum, *m/e* 639 (M), 640 (M + 1)]; hydrogenolysis, to give **48** [88% yield, R_f 0.35 (system E), FD mass spectrum, *m/e* 595 (M + 1)]. See Table III for other data.

Also prepared was *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyltyrosyl-L-arginine (**52**) by the following route: condensation of **17** with DL-α-methyltyrosine methyl ester hydrochloride [92% yield: R_f 0.42 (system B); CI mass spectrum (CH_4), *m/e* 468]; basic hydrolysis to give *N*-[4-(4-hydroxyphenyl)-butyryl]-L-prolyl-DL-α-methyltyrosine [**20**; 93% yield; R_f 0.08 (system B); FD mass spectrum, *m/e* 454]; coupling with the protected arginine [62% yield; R_f 0.38 (system C)]; basic hydrolysis [65% yield; R_f 0.14 (system A): FD mass spectrum, *m/e* 611 (M + 1)]; hydrogenolysis, to give **52** [92% yield; R_f 0.21 (system E)]. See Table III for additional data.

***N*-[4-(4-Hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanine 3-Aminopropylamide (49).** A mixture of 4.38 g (10 mmol) of compound **18**, 2.45 g (10 mmol) of 3-(carbobenzoxyamino)propylamine hydrochloride, 2.7 g (20 mmol) of HOBt, 45 mL of THF, and 15 mL of DMF was cooled in ice and neutralized with NEM, and 2.06 g (10 mmol) of DCC was added. The suspension was stirred at 25 °C for 48 h and worked up in the usual way and provided about 6 g of crude product. This was chromatographed over 200 g of silica gel with a 1 to 2% of MeOH in CH_2Cl_2 gradient to give 5.1 g (81%) of *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanine 3-(carbobenzoxyamino)propylamide as a white amorphous powder: TLC (system A) R_f 0.29; FD mass spectrum, *m/e* 628. This compound (4.0 g, 6.4 mmol) was shaken with 2 g of 10% Pd/C in 75 mL of EtOH and 25 mL of HOAc at 60 psi for 3 h. The filtered, concentrated, and EtOH-azeotroped residue was dissolved in a small amount of EtOH and acidified with ethereal HCl to provide 2.4 g (71%) of the white hydrochloride of **49**: CI mass spectrum (CH_4), *m/e* 496 (M + 2). See Table III for additional data.

Similarly prepared was *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanine 3-aminopropylamide hydrochloride (**51**) using 2.25 g (4.5 mmol) of **19** and proportional amounts of reagents to give 1.95 g of the intermediate 3-(carbobenzoxyamino)propylamide derivative [63% yield; R_f 0.32 (system A); CI mass spectrum (CH_4), *m/e* 688]. Deblocking with Pd/H_2 gave 1.1 g of the hydrochloride **51** [80% yield: FD mass spectrum, *m/e* 554]. See Table III for additional data.

Also prepared by this method was *N*-[4-(4-hydroxyphenyl)-butyryl]-L-prolyl-DL-α-methyltyrosine 3-aminopropylamide hydrochloride (**53**), starting with 1.04 g (2.3 mmol) of **20** and proportional amounts of other reagents to give, after chromatography, 700 mg of the intermediate 3-(carbobenzoxyamino)propyl amide [47% yield; R_f 0.16 (system B), FD mass spectrum, *m/e* 645 (M + 1)]. Hydrogenolysis of this product as above gave 370 mg of the white solid **53** (FD mass spectrum, *m/e* 510). See Table III for additional data.

***N*-[4-(4-Hydroxyphenyl)butyryl]-L-prolyl-D-phenylalanylglycyl-L-proline (55).** Compound **17** (3.71 g, 0.013 mol) was coupled to D-phenylalanine methyl ester hydrochloride (2.89 g, 0.013 mole) by the DCC/HOBt method to give 5.9 g (100%) of the syrupy *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-D-phenylalanine methyl ester: TLC (system A) R_f 0.59; CI mass spectrum (CH_4), *m/e* 438. Basic hydrolysis gave 5.4 g (93%) of the free acid **22**: TLC (system A) R_f 0.18; FD mass spectrum, *m/e* 424 (strong). This acid (3.18 g, 7.5 mmol) and an equivalent amount of glycyl-L-proline benzyl ester trifluoroacetate were condensed, and the crude product was chromatographed over 180 g of silica gel with a gradient of 1 to 4% of MeOH in CH_2Cl_2 to give 2.7 g (54%) of the amorphous white solid *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-D-phenylalanylglycyl-L-proline benzyl ester: TLC (system B) R_f 0.58; FD mass spectrum, *m/e* 668 (M), 669 (M + 1). Hydrogenolysis of 2.6 g of the benzyl ester afforded 1.8 g (80%) of the white solid **55** (after trituration with ethyl ether); TLC (system E) R_f 0.67; FD mass spectrum, *m/e* 578. See Table III for additional data.

Similarly prepared was *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-L-phenylalanylglycyl-L-proline (**54**). Compound **21**, the L-Phe isomer, was synthesized following the route described for the D isomer **22**. *N*-[4-(4-Hydroxyphenyl)butyryl]-L-prolyl-L-phenylalanylglycyl-L-proline benzyl ester was obtained in 59% yield from **21**: TLC (system B) R_f 0.58. Compound **54** was obtained in 66% yield from the benzyl ester and had an R_f identical with **55**: FD mass spectrum, *m/e* 578. See Table III for additional data.

***N*-[4-(4-Hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanylglycyl-L-proline (56).** Compound **18** (1.43 g, 3.26 mmol) was coupled to glycyl-L-proline benzyl ester, and the crude benzyl ester was chromatographed on silica gel as described for the synthesis of **55** to afford the amorphous white solid (1.6 g, 72%) of *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanylglycyl-L-proline benzyl ester: TLC (system A) R_f 0.46; CI mass spectrum (CH_4), *m/e* 682. Hydrogenolysis provided 1.1 g (79%) of the white powdery **56**: TLC (system E) R_f 0.66; FD mass spectrum, *m/e* 592. See Table III for additional data.

Similarly prepared was *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyltyrosylglycyl-L-proline (**57**). Compound **20** (2.5 g, 5.5 mmol) was condensed with glycyl-L-proline benzyl ester by the procedure described for **55**, and the product was purified on a silica gel column with 2% of MeOH in CH_2Cl_2 to give 1.6 g (42%) of amorphous *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyltyrosylglycyl-L-proline benzyl ester: TLC (system A) R_f 0.42, doublet for diastereoisomers; FD mass spectrum, *m/e* 698 (M), 699 (M + 1). Hydrogenolysis afforded a solid, which was triturated with ethyl ether to give 1.18 g (88%) of white, powdery **57**; TLC (system E) R_f 0.18; FD mass spectrum, *m/e* 608. See Table III for additional data.

***N*-[4-(4-Hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanine 5-Carboxypentylamide (58).** Compound **18** (3.0 g, 6.82 mmol) was coupled to methyl 6-aminocaproate hydrochloride [from Fischer esterification of the acid, mp 87–89 °C (CH_3CN/MeOH); 1.81 g (10 mmol)] by the DCC/HOBt method and purified by chromatography over 120 g of silica gel with a 1 to 1.5% of MeOH in CH_2Cl_2 gradient to provide 1.61 g (41%) of amorphous *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanine 5-carbomethoxypentylamide: TLC (system A) R_f 0.48; FD mass spectrum, *m/e* 565. Basic hydrolysis gave 1.4 g (90%) of white solid **58**: TLC (system D) R_f 0.72; FD mass spectrum, *m/e* 552 (M + 1). See Table III for additional data.

***N*$^{\alpha}$-[2-[4-(4-Hydroxyphenyl)butyryl]-1,2,3,4-tetrahydro-3-carboxy-3-isoquinolinyl]-L-arginine (59).** 4-(4-Hydroxyphenyl)butyric acid (2.7 g, 0.02 mol) and 3-carbethoxy-1,2,3,4-tetrahydro-2*H*-isoquinoline[10] (2.42 g, 0.01 mol) were coupled by the usual DCC/HOBt conditions, and workup afforded 3.7 g (100%) of syrupy *N*-[4-(4-hydroxyphenyl)butyryl]-3-carbethoxy-1,2,3,4-tetrahydro-2*H*-isoquinoline: TLC (system A) R_f 0.54; CI mass spectrum (CH_4), *m/e* 367. Basic hydrolysis of 2.2 g of the ethyl ester produced 2.0 g (98%) of amorphous solid **23**. This acid (0.85 g, 2.5 mmol) was not purified but condensed with the protected L-arginine as described above to afford (1.3 g, 94%) of the amorphous solid arginyl adduct: TLC (system A) R_f 0.11. The methyl ester was hydrolyzed, and the nitro group was removed to give 0.385 g (33%) of buff, powdery **59**: TLC (system E) R_f 0.23; FD mass spectrum, *m/e* 496 (M + 1). See Table III for additional data.

Similarly prepared was 2-[4-(4-hydroxyphenyl)butyryl]-1,2,3,4-tetrahydro-3-[(3-aminopropyl)carbamyl]isoquinoline (**60**). Compound **23** (0.85 g, 2.5 mmol) and 3-(carbobenzoxyamino)-propylamine hydrochloride (0.614 g, 2.5 mmol) provided 1.3 g (98%) of the foamy solid adduct: TLC (system A) R_f 0.34; CI mass spectrum (CH_4), *m/e* 529. The hydrogenolysis product was dissolved in a little dilute HCl, filtered from a small amount of insoluble material, concentrated, and azeotroped with EtOH. A crystallization from EtOH/ethyl ether gave the white solid hydrochloride of **60**: TLC (system E), R_f 0.24; CI mass spectrum (CH_4), *m/e* 395. See Table III for additional data.

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Registry No. 1, 17350-17-3; **2**, 88084-12-2; **3**, 59191-06-9; **4**, 88084-13-3; **6**, 88084-14-4; **7**, 88084-15-5; **8**, 73030-06-5; **9**, 86778-86-1; **9** dicyclohexylamine, 88084-16-6; **10**, 88084-17-7; **11**, 88084-18-8; **11**·K, 88084-19-9; **12**, 88105-49-1; **13**, 88084-20-2; **13**·HCl, 86778-93-0; **14**, 86778-87-2; **15**, 88084-21-3; **15** (aldehyde derivative), 88084-22-4; **16**, 87113-92-6; **17**, 86778-72-5; **18**, 86778-84-9; **19**, 86778-74-7; **20**, 86778-34-0; **21**, 88105-50-4; **22**, 88105-51-5; **23**, 88084-23-5; **24**, 23846-09-5; **25**, 88105-52-6; **26**, 88084-24-6; **26**·2HCl, 88084-25-7; **27**, 88084-26-8; **28**, 88084-27-9; **29**, 88084-28-0; **29**·2HCl, 88084-29-1; **30**, 88084-30-4; **31**, 58840-30-5; **32**, 69677-92-5; **33**, 88084-31-5; **34**, 88084-32-6; **35**, 88084-33-7; **36**, 10318-24-8; **37**, 88084-34-8; **38**, 88105-53-7; **39**, 88084-35-9; **39**·HCl, 88105-25-3; **40**, 88084-36-0; **41**, 86778-98-5; **42**, 88084-37-1; **43**, 86778-95-2; **43**·HCl, 86778-96-3; **44**, 87113-95-9; **45**, 86778-88-3; **46**, 88084-38-2; **47**, 88084-39-3; **48**, 86787-35-1; **49**, 86779-01-3; **49**·HCl, 86778-85-0; **50**, 86778-77-0; **51**, 88084-40-6; **51**·HCl, 86778-79-2; **52**, 86778-81-6; **53**, 88084-41-7; **53**·HCl, 86778-83-8; **54**, 86850-55-7; **55**, 86850-57-9; **56**, 86850-54-6; **57**, 86850-56-8; **58**, 86779-00-2; **59**, 88105-54-8; **60**, 88105-55-9; **60**·HCl, 88105-56-0; *N*-carbobenzoxy-L-proline, 1148-11-4; L-phenylalanine methyl ester hydrochloride, 7524-50-7; *N*-carbobenzoxy-L-prolyl-L-phenylalanine methyl ester, 23631-72-3; N^{ω}-nitro-L-arginine methyl ester hydrochloride, 51298-62-5; *N*-carbobenzoxy-L-prolyl-L-phenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 6464-80-8; *N*-carbobenzoxy-L-prolyl-L-phenylalanyl-N^{ω}-nitro-L-arginine, 16152-74-2; DL-α-methylphenylalanine methyl ester hydrochloride, 64665-60-7; *N*-carbobenzoxy-L-prolyl-DL-α-methylphenylalanine methyl ester, 88105-57-1; *N*-carbobenzoxy-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 88130-44-3; *N*-carbobenzoxy-L-prolyl-DL-α-methyphenylalanyl-N^{ω}-nitro-L-arginine, 88130-45-4; 3-(carbobenzoxyamino)propylamine hydrochloride, 46460-73-5; *N*-carbobenzoxy-L-prolyl-L-phenylalanine 3-(carbobenzoxyamino)propylamide, 88105-58-2; *N*-carbobenzoxy-L-propyl-DL-α-methylphenylalanine 3-(carbobenzoxyamino)propylamide, 88130-46-5; L-proline benzyl ester hydrochloride, 16652-71-4; *N*-carbobenzoxy-L-prolyl-DL-α-methylphenylalanyl-L-proline benzyl ester, 88105-59-3; *N*-benzoyl-L-proline, 5874-58-8; DL-α-methylphenylalanine methyl ester, 88105-60-6; *N*-benzoyl-L-prolyl-DL-α-methylphenylalanine methyl ester, 88105-61-7; *N*-benzoyl-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 88130-47-6; *N*-benzoyl-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine, 88130-48-7; L-phenylalanine benzyl ester hydrochloride, 2462-32-0; *N*-benzoyl-L-prolyl-L-phenylalanine benzyl ester, 88105-62-8; *N*-benzoyl-L-prolyl-L-phenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 88105-63-9; *N*-benzoyl-L-prolyl-L-phenylalanyl-N^{ω}-nitro-L-arginine, 88105-64-0; *N*-benzoyl-L-proline benzyl ester, 88130-49-8; *N*-(phenylacetyl)-L-proline benzyl ester, 88105-65-1; *N*-(phenylacetyl)-L-

proline, 2752-38-7; *N*-(phenylacetyl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 88105-66-2; L-2-amino-3-phenyl-1-propanol, 3182-95-4; oxalyl chloride, 79-37-8; *N*-carbobenzoxy-L-prolyl-L-2-amino-1-phenylpropanal, 88105-67-3; N^{α}-[*N*-carbobenzoxy-L-prolyl-L-2-amino-1-phenylpropyl]-N^{ω}-nitro-L-arginine methyl ester, 88105-68-4; N^{α}-[*N*-carbobenzoxy-L-prolyl-L-2-amino-1-phenylpropyl]-N^{ω}-nitro-L-arginine, 88105-69-5; DL-α-methylphenylalanine, 1132-26-9; DL-2-methylphenylalanine, 21394-84-3; *N*-carbobenzoxy-L-prolyl-L-2-amino-2-methyl-1-phenylpropanal, 88105-70-8; N^{α}-[*N*-carbobenzoxy-L-prolyl-DL-2-amino-2-methyl-3-phenylpropyl]-N^{ω}-nitro-L-arginine methyl ester, 88105-71-9; N^{α}-[*N*-carbobenzoxy-L-prolyl-DL-2-amino-2-methyl-3-phenylprolyl]-N^{ω}-nitro-L-arginine, 88105-72-0; 4-phenylbutyryl chloride, 18496-54-3; *N*-(4-phenylbutyryl)-L-proline benzyl ester, 88105-73-1; 3-phenylpropionyl chloride, 645-45-4; *N*-(3-phenylpropionyl)-L-proline benzyl ester, 88105-74-2; 5-phenylpentanoyl chloride, 20371-41-9; *N*-(5-phenylpentanoyl)-L-proline benzyl ester, 88105-75-3; L-phenylalanine benzyl ester, 962-39-0; *N*-(4-phenylbutyryl)-L-prolyl-L-phenylalanine benzyl ester, 88105-76-4; *N*-(4-phenylbutyryl)-L-prolyl-L-phenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 88105-77-5; *N*-(4-phenylbutyryl)-L-prolyl-L-phenylalanyl-N^{ω}-nitro-L-arginine, 88105-78-6; D-phenylalanine methyl ester hydrochloride, 13033-84-6; *N*-(4-phenylbutyryl)-L-prolyl-D-phenylalanine methyl ester, 88105-79-7; *N*-(4-phenylbutyryl)-L-prolyl-D-phenylalanine, 88105-80-0; *N*-(4-phenylbutyryl)-L-prolyl-D-phenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 88105-81-1; *N*-(4-phenylbutyryl)-L-prolyl-D-phenylalanyl-N^{ω}-nitro-L-arginine, 88105-82-2; *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methylphenylalanine methyl ester, 88105-83-3; *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 88105-84-4; *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine, 86778-97-4; *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methylphenylalanyl-L-proline benzyl ester, 88105-85-5; *N*-(*tert*-butoxycarbonyl)-DL-α-methylphenylalanine, 86778-91-8; *N*-(*tert*-butoxycarbonyl)-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 86778-92-9; *N*-(3-phenylpropanoyl)-L-arginine methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 88105-86-6; *N*-(3-phenylpropanoyl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine, 88130-50-1; *N*-(5-phenylpentanoyl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 88105-87-7; *N*-(5-phenylpentanoyl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine, 88105-88-8; *N*-(4-phenylbutyryl)-L-prolyl-L-phenylalanine 3-(carbobenzoxyamino)-propylamide, 88105-89-9; *N*-(4-phenylbutyryl)-L-prolyl-LD-α-methylphenylalanine 3-carbobenzoxypropylamide, 86778-94-1; DL-α-methyl-3,4-dimethoxyphenylalanine methyl ester hydrochloride, 16024-44-5; *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanine methyl ester, 88105-90-2; *N*-(4-phenylbutyryl)-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanyl-N^{ω}-nitroarginine methyl ester, 88105-91-3; 1-adamantaneacetic acid, 4942-47-6; *N*-(1-adamantylacetyl)-L-proline benzyl ester, 87113-91-5; *N*-(1-adamantylacetyl)-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 87113-93-7; DL-2-amino-2-methyl-3-phenylpropanol, 21394-84-3; 4-(4-hydroxyphenyl)butyric acid, 7021-11-6; *N*-[4-(4-hydroxyphenyl)butyryl]-L-proline benzyl ester, 86778-71-4; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanine methyl ester, 86778-73-6; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 86778-75-8; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanyl-N^{ω}-nitro-L-arginine, 86778-76-9; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanine methyl ester, 88130-51-2; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine methyl ester, 88105-92-4; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanyl-N^{ω}-nitro-L-arginine, 88105-93-5; DL-α-methyltyrosine methyl ester hydrochloride *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyltyrosine methyl ester, 86778-80-5; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyltyrosyl-N^{ω}-nitro-L-arginine methyl ester, 88105-94-6; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyltyrosyl-N^{ω}-nitro-L-arginine, 88105-95-7; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanine 3-(carbobenzoxyamino)propylamide, 88105-96-8; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyl-3,4-dimethoxyphenylalanine 3-(carbobenzoxyamino)propylamide, 86787-33-9; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyltyrosine 3-(carbobenzoxyamino)propylamide, 88105-97-9; *N*-[4-(4-hydroxyphenyl]-L-prolyl-D-phenylalanine methyl ester, 86850-60-4; glycyl-L-proline benzyl ester trifluoroacetate *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-D-phenylalanylglycyl-L-proline benzyl ester, 86850-58-0; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-L-phenylalanylglycyl-L-proline benzyl ester, 88105-99-1; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanylglycyl-L-proline benzyl ester, 86850-61-5; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methyltyrosylglycyl-L-proline benzyl ester, 86857-05-8; methyl 6-aminocaproate hydrochloride, 1926-80-3; *N*-[4-(4-hydroxyphenyl)butyryl]-L-prolyl-DL-α-methylphenylalanine 5-carbomethoxypentylamide, 86778-99-6; 3-carbethoxy-1,2,3,4-tetrahydro-2*H*-isoquinoline, 15912-55-7; *N*-[4-(4-hydroxyphenyl)butyryl]-3-carbethoxy-1,2,3,4-tetrahydro-2*H*-isoquinoline, 88106-00-7; N^{α}-[2-[4-(4-hydroxyphenyl)butyryl]-1,2,3,4-tetrahydro-3-carboxy-3-isoquinolinyl]-N^{ω}-nitro-L-arginine methyl ester, 88130-52-3; 2-[4-(4-hydroxyphenyl)butyryl-1,2,3,4-tetrahydro-3-carboxyisoquinoline 3-(carbobenzoxyamino)-propylamide, 88106-01-8; *N*-(phenylacetyl)-L-prolyl-DL-2-methylphenylalanyl-N^{ω}-nitro-L-arginine, 88106-02-9.