(Imidazolylphenyl)pyrrol-2-one Inhibitors of Cardiac cAMP Phosphodiesterase[1]

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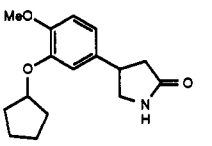
Seven 3-alkyl-4-aryl-1,5-dihydro-2*H*-pyrrol-2-ones were prepared as potential inhibitors of cardiac cAMP phosphodiesterase (PDE). The design of these compounds made use of rolipram, a known inhibitor of the brain cAMP PDE isozyme, as a lead structure and was guided by a model which describes the features required for potent inhibition of the cardiac isozyme. Syntheses for the new compounds are described, together with the results of theoretical and crystallographic studies aimed toward ascertaining their three-dimensional structures. The activities of these compounds as inhibitors of the cardiac and brain cAMP PDE isozymes and their positive inotropic activity in ferret papillary muscle are also reported. Selected compounds were further examined in an in vivo hemodynamic model. One compound, 1,5-dihydro-4-[4-(1*H*-imidazol-1-yl)phenyl]-3-methyl-2*H*-pyrrol-2-one, was identified as a potent and selective positive inotropic agent and inhibitor of cardiac cAMP PDE.

Congestive heart failure (CHF) is a debilitating condition which affects some 3 million Americans.[2] The prognosis for those suffering from this syndrome remains poor, despite considerable efforts being made by the scientific community toward developing new forms of treatment.[3-5] Although a variety of approaches toward the management of CHF have been adopted, including the use of nitrates, diuretics, and ACE inhibitors, much of the current work devoted toward developing improved therapies has been centered on the search for improved positive inotropic agents, or "digitalis replacements",[6] compounds which share the inotropic profile of the cardiac glycosides while lacking their arrhythmogenic liability.

Among the various mechanistic approaches to the development of inotropic agents, the most commonly studied to date is the inhibition of cardiac cyclic AMP phosphodiesterase (cAMP PDE).[7] In connection with these studies, we and others have developed models which attempt to describe the topographical features of the cAMP PDE active site.[8-13] It is hoped that such models might provide the insight necessary to enable the design of a selective inotropic agent with the proper profile for the treatment of CHF.

The current topographical models have several features in common. These include binding regions for a heterocycle containing an electron-rich, polarizable group, such as an amide carbonyl, an adjacent aromatic system, and an electron-rich aromatic substituent, such as an amide or an imidazole. A central difference among some of the models lies in their predictions as to the torsional angle between the aromatic and heterocyclic systems which affords optimal binding. Our model[8,9] predicts a preferred angle of approximately 20°, whereas others predict a generally flat topography;[10,11] still others seek to reconcile these apparently different views.[13]

We reasoned that a good test of our model would be to apply its predictions in the optimization of a poor inhibitor of cardiac cAMP PDE. In so doing we hoped both to verify features of our model as well as to provide new leads for additional study. We chose rolipram,[14] 1, as our candidate for optimization. Although 1 already contains many of the features predicted to be necessary for PDE inhibition, it is essentially inactive as an inhibitor of the milrinone-sensitive cardiac enzyme; at the same time, it is an extremely potent inhibitor of the cAMP PDE isozyme found in brain tissue, and as such is of interest as an agent for use in the treatment of central nervous system disorders.[15-18] We therefore undertook a limited study to see if the cardiac cAMP PDE inhibitory activity of 1 could be improved to useful levels using our model as a guide for the optimization process. The compounds which we chose to prepare for study are shown in Figure 1. Compounds 2-4 were selected in order to examine the effects of changes in planarity of the heterocyclic ring and of changes in the torsional angle between the heterocyclic and phenyl rings on PDE inhibition. Compounds 5-8 additionally examine the effect of replacing the alkoxy substituents found in rolipram with a preferred aryl substituent such as imidazole.



1, Rolipram

Chemistry

Two general routes were used for the preparation of the compounds in this study. The first of these routes is shown in Scheme I. Horner-Emmons olefination[19] of 3,4-dimethoxyacetophenone provided the cinnamate ester 9 as a single isomer. The geometry of the double bond in 9 was assigned as *E* based on comparison of the NMR spectrum of 9 with the spectra of analogous compounds reported in ref 19, together with the well-known stereochemical preference of the Horner-Emmons reaction.[19] Allylic bromination of 9 with NBS[20] gave bromo ester 10, which on treatment with ammonia gave pyrrolone 3 in good yield. The corresponding dihydro compound 2 was obtained from 3 by catalytic hydrogenation. Treatment of 3 with 2 equiv of LDA and then with methyl iodide followed by workup and conjugation of the double bond

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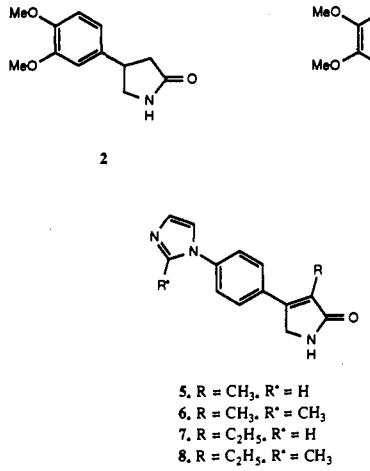
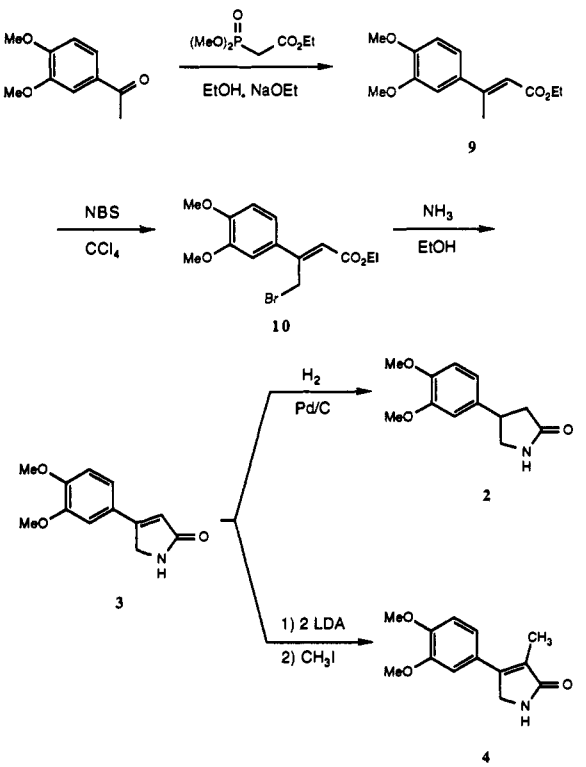


Figure 1.

Scheme I

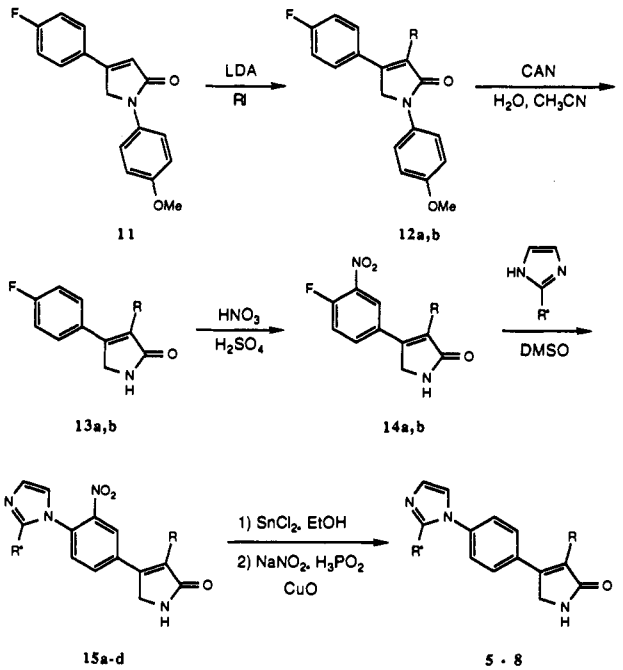


using catalytic *p*-toluenesulfonic acid provided the 3-alkyl compound **4**. Alkylations carried out in this fashion generally produced significant amounts of 5-alkyl and 3,5-dialkyl contaminants, the removal of which required difficult chromatography.

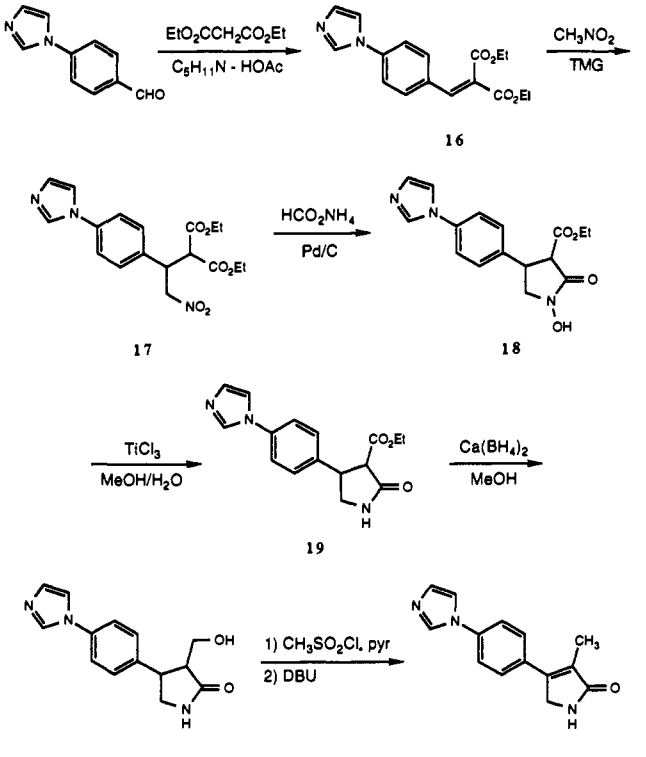
An improved method for introducing the 3-alkyl substituents was used in the preparation of imidazole-containing compounds **5–8**, as shown in Scheme II. In this scheme the definitions of R and R′ are the same as in Figure 1; the substituents for specific compounds are described in the Experimental Section. Pyrrolone **11** was prepared from 4-fluoroacetophenone and 4-methoxyaniline in a fashion analogous to that described for the synthesis of **3**. Treatment of **11** with 1 equiv of LDA and an alkyl iodide afforded the desired 3-alkyl compounds **12** with much greater selectivity and without the need for chromatography. Oxidative dearylation with ceric ammonium nitrate[21] then provided the deprotected compounds **13**.

It proved necessary to activate the fluorine in **13** to allow introduction of imidazole substituents. Nitration of **13**

Scheme II



Scheme III



with nitric acid in sulfuric acid gave the 4-fluoro-3-nitrophenyl compounds **14**, which were reacted with excess imidazole or 2-methylimidazole to yield the displaced products **15**. Removal of the activating nitro substituent by stannous chloride[22] reduction to the amine followed by diazotization in the presence of hypophosphorus acid[23] afforded the target compounds **5–8**. This in situ reduction of the diazonium ion led to purer products than could be obtained when isolation of the diazonium salt was attempted.

A second synthetic route to the imidazole-substituted compounds is shown in Scheme III, illustrated by the preparation of **5**. This shorter route is related to that used for the preparation of rolipram itself.[24] Condensation

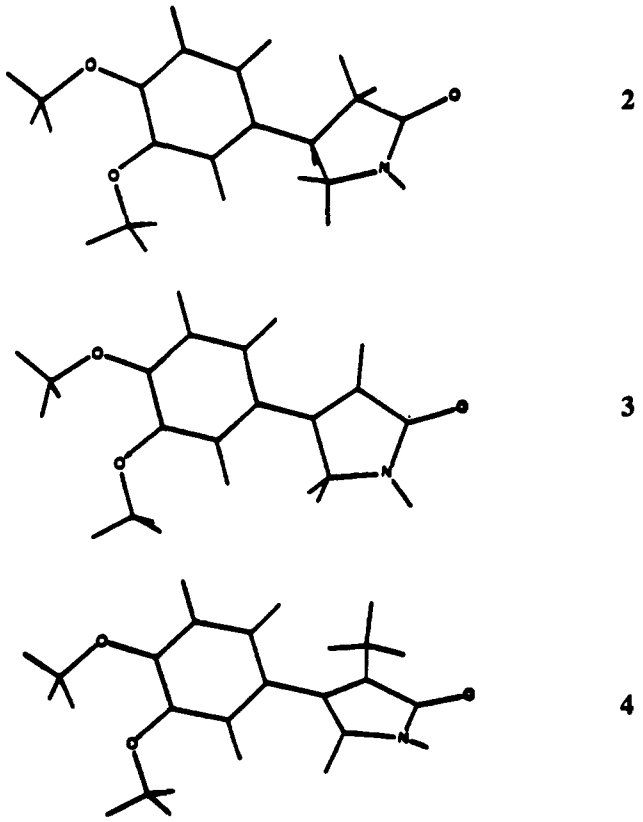


Figure 2. AM1-minimized structures of compounds 2–4.

of diethyl malonate with 4-imidazolylacetophenone followed by conjugate addition of nitromethane afforded the nitro diester 17.[24] Transfer hydrogenation[25] of 17 gave hydroxamate 18, which was reduced in high yield to the lactam 19 by titanium trichloride.[26] We were unsuccessful in our attempts to reduce 17 directly to 19. In analogy to the work of Klutchko and co-workers,[27] calcium borohydride reduction of 19 afforded the hydroxymethyl compound 20, which on treatment with methanesulfonyl chloride underwent mesylation followed by elimination and migration of the resulting double bond to give the pyrrolone 5.

Structural Studies

Compounds 2–4 were studied using computational methods in order to assess the extent to which their structural differences affected their conformations. Structures were optimized by molecular mechanics,[28] after which further refinement was carried out using AM1 semiempirical calculations[29] as implemented in AMPAC.[30] The AM1-minimized structures are shown in Figure 2, in which the view shown is along an axis perpendicular to the plane of the phenyl ring. As expected, the pyrrolidinone ring of 2 was found to be tilted up from the plane of the phenyl ring in such a fashion as to render the pyrrolidinone methylenes approximately equidistant from the phenyl ring. Introduction of a C-3, C-4 double bond flattens the structure, leading to the essentially planar compound 3; further introduction of a 3-methyl group to provide 4 twists the pyrrolone ring away from the plane of the phenyl ring. The torsional angles between the two rings in 3 and 4 were predicted to be 0.28° and 31.37°, respectively.

The structure of compound 5 was studied by X-ray crystallography. Crystallization of the compound from methylene chloride/2-propanol yielded fine needles in the centrosymmetric space group $C2/c$. Analysis revealed a disordered structure in which two diastereomeric rotamers were present; the rotamers differed only in the sense of rotation about the bond connecting the phenyl and pyrrolone rings. An ORTEP drawing for one of these rotamers is shown in Figure 3. The torsional angle between the phenyl and pyrrolone rings in both rotamers was found to be 28°. Taken together, the above studies support a generally planar conformation for pyrrolones such as 3, which lack C-3 substituents, and a non-planar conformation with a torsional angle of approximately 30° for 3-substituted pyrrolones such as 4–8.

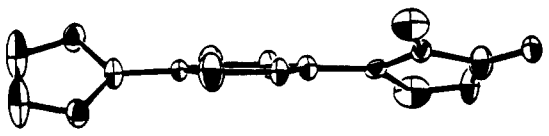


Figure 3. ORTEP drawing from the X-ray structure of compound 5.

Table I. In Vitro Pharmacology

compd	inhibition of cAMP PDE[a] IC_{50} (μM) brain	cardiac	papillary muscle[b] EC_{20} (μM)
1	0.8	(28%)	NR
2	(36%)	(3%)	NR
3	40	(46%)	6.5 (5, 8)[c]
4	100	26	3.8 (2–5)
5	(16%)	25	2.3 (2–3)
6	(10%)	30	10.2 (4–24)
7	(10%)	48	10.7 (4.5–20)[d]
8	(<5%)	39	4.8 (1–12)
milrinone	(34%)	5.5	0.5 (0.1–1.7)

[a] Concentration required to cause a 50% inhibition of cAMP phosphodiesterase from canine brain or cardiac tissue. IC_{50} values were determined from the mean of three separate dose–response determinations. In all cases, the range of inhibition at the test doses closest to the calculated IC_{50} was less than ±8%. In cases where an IC_{50} was not reached, the percent inhibition at 100 μM is given in parentheses. [b] Concentration required to cause a 20% increase in the force of contraction of isolated ferret papillary muscle strips. Data are expressed as the mean of at least four independent EC_{20} calculations, together with the range of values. NR indicates not reached at 100 μM. [c] Two EC_{20} determinations were performed. [d] Low doses of this compound showed negative inotropic effects. The values given are those for six out of nine experiments in which positive inotropy was observed at higher doses.

Results and Discussion

Compounds 1–8 were tested for their ability to inhibit partially purified preparations of canine cardiac and brain cAMP PDE.[31,32] Table I shows the results of these studies expressed as IC_{50} values. The compounds were additionally examined in vitro in ferret papillary muscle to assess their inotropic activity.[33] The dose required to produce a 20% increase in contractile force (EC_{20}) is given in Table I.

These data reveal several interesting trends in SAR. Replacement of the cyclopentyloxy group in 1 with a methoxy group reduces potency for inhibiting both brain and cardiac enzymes, although much more dramatically for the brain isozyme. Within the dimethoxyphenyl-substituted compounds, potency is increased at both enzymes, most notably at the cardiac isozyme, by introduction of a C-3, C-4 double bond (2, 3). Significantly, compound 3 shows inotropic activity, whereas 1 and 2 are inactive in this screen. Methylation at C-3 to give compound 4 further increases potency at the cardiac enzyme, while decreasing potency at the brain enzyme. This increase in PDE inhibitory potency is accompanied by a corresponding increase in inotropic activity. The above results are consistent with the observed variations in cardiac cAMP PDE inhibitory potency and selectivity

Table II. In Vivo Pharmacology[a]

compd	dose (mg/kg)	% increase dP/dt	% increase HR	% decrease MAP
5	1	40 ± 3	7 ± 5	3 ± 2
	3	75 ± 25	19 ± 5	14 ± 7
6	1	14 ± 6	7 ± 12	6 ± 9
	3	33 ± 10	14 ± 10	10 ± 8
7	1	21 ± 11	9 ± 6	13 ± 6
	3	44 ± 16	21 ± 8	22 ± 6
8	1	52 ± 26	8 ± 7	18 ± 17
	3	80 ± 31	22 ± 19	30 ± 13
milrinone	0.1	57 ± 55	19 ± 20	13 ± 12
	0.3	81 ± 56	32 ± 10	30 ± 18

[a] Reported are the mean percent changes ± SEM from control in left ventricular dP/dt, heart rate (HR), and mean arterial pressure (MAP) in pentobarbital anesthetized dogs at 1 and 3 mg/kg, $n = 4$. The milrinone data are for doses of 0.1 and 0.3 mg/kg, $n = 6$.

arising from changes in the conformational preferences of the inhibitors, analogous to the results observed with milrinone-like inhibitors.[12] We postulate that pyrrolidinones 1 and 2 are poor inhibitors of the cardiac isozyme because in these compounds the phenyl ring is positioned above the plane of the heterocyclic ring, away from the aromatic binding region. In contrast, in pyrrolones 3 and 4 the bond connecting the phenyl and heterocyclic rings lies in the plane of the heterocyclic ring, positioning the phenyl group to interact with the aromatic binding region and thus increasing the potency of these compounds. Compound 4 is forced into a more favorable nonplanar conformation by the C-3 methyl substituent, improving the potency of this compound relative to that of 3. Although it is possible that the methyl substituent additionally contributes to the binding of 4 by interacting with an alkyl binding pocket, the computational and crystallographic studies discussed above strongly suggest the 4 exists in a twisted conformation, and the potency of this compound shows that this conformation is easily accommodated by the binding site.

Replacement of the aromatic ring alkoxy substituents with the imidazoles found in compounds 5–8 reduces the inhibitory potency of these compounds against the brain isozyme to negligible levels. Potency for inhibition of the cardiac isozyme is only marginally affected. Interestingly, cardiac PDE inhibitory potency is somewhat lower for the ethyl-substituted pyrrolones than for the corresponding methylated compounds. A possible explanation for this effect could be that the torsional angles in the ethyl-substituted compounds are increased beyond their optimal values due to the steric effect of the larger alkyl substituent; alternatively, the ethyl substituent could be encountering a steric protrusion at the active site. All of the imidazole-substituted compounds display inotropic activity; however, two of the compounds (6, 7) are somewhat less potent as inotropes than one would expect from their PDE inhibitory potency. This could suggest that multiple mechanisms of action are contributing to the activity of these compounds, although it is equally plausible that differences in the ability of the compounds to reach their intracellular site of action is affecting their inotropic potency.

Compounds 5–8 were further evaluated in an in vivo model in pentobarbital anesthetized dogs[31] in order to assess their effects on hemodynamic function. Compounds were administered intravenously at doses of 1 and 3 mg/kg, and their effects on left ventricular dP/dt, heart rate, and mean arterial pressure were monitored. The results of these studies are reported in Table II. The inotropic properties of these compounds in vivo generally paralleled those observed in vitro, with compounds 5 and 8 showing greater potency than 6 and 7. All of the compounds displayed moderate effects on heart rate and mean arterial pressure. Compound 5 was particularly noteworthy in the selectivity of its hemodynamic effects; at a dose of 1 mg/kg it produced therapeutically relevant increases in dP/dt without significantly affecting the other hemodynamic properties which were measured.

The results obtained with the above compounds indicate how judicious structural modification guided by an appropriate active site model can lead from weakly active lead structures to more potent, selective inhibitors of cardiac cAMP PDE. The SAR patterns observed within this compound series are wholly consistent with our model, and are comparable to those observed with compounds related to amrinone and milrinone.[12] They stand in contrast to the SAR patterns reported for the pyridazinone inhibitors, in which overall planar structures appear to be preferred.[10,11] This apparent discrepancy in the conformational preferences of the enzyme has been nicely rationalized in the recent work of Toma and co-workers,[13] who point out that puckering of the pyridazinone ring leads to structures which maintain overall planarity between the pyridazinone and phenyl rings, but in which at the same time the NCO plane of the heterocyclic amide is tilted away from the phenyl plane. The compounds in our current study have NCO planes which are essentially the same as those of the heterocyclic rings, and as such the results reported herein are consistent with and support the views of these workers.

Experimental Section

Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Sargent-Welch 3-300 or a Beckman Acculab 2 infrared spectrometer. NMR spectra were recorded at 300 MHz on a Varian XL-300 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal standard of tetramethylsilane. Elemental analyses were performed by Galbraith Laboratories, Microlit Laboratories, or the Berlex Analytical Section; results are within ±0.4% of the calculated values unless otherwise stated. Tetrahydrofuran was distilled from sodium/benzophenone prior to use. Other solvents and reagents were used as supplied unless otherwise noted. Organic extracts were dried over magnesium sulfate prior to evaporation. Solid products were routinely dried at 60 °C under reduced pressure for a minimum of 12 h. Reactions were monitored by thin-layer chromatography on silica gel (Merck) and alumina (Merck); plates were visualized by UV and iodine.

Ethyl (*E*)-3-(3,4-Dimethoxyphenyl)-2-butenoate (9). Trimethyl phosphonoacetate (69.5 mL, 350 mmol) was added to sodium ethoxide (from sodium, 8.85 g, 385 mmol, in ethanol, 350 mL) and the mixture was stirred for 10 min. 3,4-Dimethoxyacetophenone (63.09 g, 350 mmol) was added, and the mixture was stirred for 18 h at room temperature and then for 8 h at reflux. The reaction mixture was cooled, diluted with 700 mL of water, and extracted three times with ether. The organic extracts were washed twice with water and once with brine, dried, and evaporated to give 85.35 g (97%) of the title compound. This material was used without further purification; an analytical sample was obtained by vacuum distillation: bp 140–145 °C (0.1 Torr); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H), 2.57 (s, 3 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 4.22 (q, 2 H), 6.14 (s, 1 H), 6.86 (d, 1 H), 7.04 (d, 1 H), 7.12 (dd, 1 H). Anal. ($C_{14}H_{18}O_4$) C, H.

Ethyl (*E*)-3-(4-Fluorophenyl)-2-butenoate. Reaction of trimethyl phosphonoacetate and 4-fluoroacetophenone on a 3.1-mol scale following the procedure used for the preparation of 9 afforded after distillation 548 g (83%) of the title compound: bp 135–140 °C (0.1 Torr); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H), 2.55 (d, 3 H), 4.23 (q, 2 H), 6.12 (q, 1 H), 7.10 (t, 2 H), 7.50 (dd, 2 H). Anal. ($C_{12}H_{13}FO_2$) C, H.

Ethyl (*E*)-4-Bromo-3-(3,4-dimethoxyphenyl)-2-butenoate (10). A solution of 85.35 g (341 mmol) of 9, 64.04 g (360 mmol)

of *N*-bromosuccinimide, and 0.51 g of benzoyl peroxide in 500 mL of carbon tetrachloride was heated at reflux for 4 h. The reaction mixture was filtered, the filter cake was washed with carbon tetrachloride, and the filtrate was evaporated to give 130 g of a reddish oil. Recrystallization from ethanol gave the title compound: mp 72–74 °C; ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 4.20 (q, 2 H), 5.16 (s, 2 H), 6.32 (s, 1 H), 7.04 (d, 1 H), 7.30 (m, 2 H). Anal. ($C_{14}H_{17}BrO_4$) C, H.

Ethyl (*E*)-4-Bromo-3-(4-fluorophenyl)-2-butenoate. Bromination of ethyl 3-(4-fluorophenyl)-2-butenoate on a 2.7-mol scale following the procedure used for the preparation of **10** using a reaction time of 4 days gave 950 g of the title compound as a crude oil, which was judged by GC to be 63% pure, the remainder being solvent and starting material. This material was carried on directly without further purification: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H), 4.25 (q, 2 H), 4.90 (s, 2 H), 6.10 (s, 1 H), 7.05 (t, 2 H), 7.50 (dd, 2 H).

4-(3,4-Dimethoxyphenyl)-1,5-dihydro-2*H*-pyrrol-2-one (3). Compound **10** (67.35 g, 205 mmol) was dissolved in 700 mL of ethanol which had been saturated with gaseous ammonia, and the mixture was stirred at room temperature for 18 h. The reaction mixture was cooled to −15 °C and the resulting precipitate was collected and washed with ethanol to give 39.06 g (87%) of the title compound as a pale yellow solid. An analytical sample was obtained by recrystallization from ethanol: mp 182–185 °C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 6 H), 4.41 (s, 2 H), 6.31 (s, 1 H), 6.81 (br s, 1 H), 6.89 (d, 1 H), 7.01 (d, 1 H), 7.07 (dd, 1 H). Anal. ($C_{12}H_{13}NO_3$) C, H, N.

4-(3,4-Dimethoxyphenyl)-1,5-dihydro-3-methyl-2*H*-pyrrol-2-one (4). Lithium diisopropylamide was generated from 14.6 mL (10.5 g, 104 mmol) of diisopropylamine and 68.8 mL (88.1 mmol) of a 1.28 M solution of *n*-butyllithium in hexane in 300 mL of tetrahydrofuran under a nitrogen atmosphere at −20 °C. The mixture was cooled to −78 °C and 8.77 g (40.0 mmol) of **3** was added. The mixture was allowed to stir at −20 °C for 4 h, after which it was cooled to −78 °C, and 3.7 mL (8.4 g, 59 mmol) of methyl iodide was added. The mixture was allowed to stir at 0 °C for 5 h, after which it was treated with 200 mL of saturated aqueous ammonium chloride. The mixture was diluted with water and extracted three times with methylene chloride, and the organic extracts were dried and evaporated. The residue was redissolved in 500 mL of methylene chloride and treated with 10 mg of *p*-toluenesulfonic acid for 18 h. The mixture was washed with saturated aqueous sodium bicarbonate, water, and brine, dried, and evaporated to give 10 g of the crude product. Recrystallization three times from ethanol gave 2.61 g (28%) of the pure title compound as a pale yellow solid: mp 183–185 °C; ^{1}H NMR ($CDCl_3$) δ 2.11 (t, 3 H), 3.92 (s, 3 H), 3.93 (s, 3 H), 4.23 (br s, 2 H), 6.60 (br s, 1 H), 6.93 (d, 1 H), 6.98 (d, 1 H), 7.02 (dd, 1 H). Anal. ($C_{13}H_{15}NO_3$) C, H, N.

4-(3,4-Dimethoxyphenyl)-2-pyrrolidinone (2). A suspension of 800 mg (3.65 mmol) of **3** in 200 mL of ethanol containing 0.53 g of 10% palladium on carbon was shaken on a Parr apparatus under 50 psi of hydrogen gas at room temperature for 6 h. The reaction mixture was filtered through Celite and evaporated to give 760 mg of the crude product, which was recrystallized from ethyl acetate/hexanes to give 523 mg (65%) of the title compound as a white solid: mp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 2.49 (dd, 1 H), 2.73 (dd, 1 H), 3.40 (dd, 1 H), 3.65 (quin, 1 H), 3.77 (t, 1 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 6.40 (br s, 1 H), 6.76 (d, 1 H), 6.83 (m, 2 H). Anal. ($C_{12}H_{15}NO_3$) C, H, N.

4-(4-Fluorophenyl)-1,5-dihydro-1-(4-methoxyphenyl)-2*H*-pyrrol-2-one (11). *p*-Anisidine (1000 g, 8.11 mol) and 950 g (2.08 mol, 63% pure) of ethyl 4-bromo-3-(4-fluorophenyl)-2-butenoate were combined in 4 L of ethanol, and the mixture was stirred for 24 h. The precipitate which formed was collected by filtration, washed with ethanol, and dried in vacuum to give 480 g (81%) of the title compound as a yellow solid: mp 195–197 °C; ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3 H), 4.74 (s, 2 H), 6.70 (s, 1 H), 6.96 (d, 2 H), 7.18 (t, 2 H), 7.58 (dd, 2 H), 7.68 (d, 2 H). Anal. ($C_{17}H_{14}FNO_2$) C, H, N.

4-(4-Fluorophenyl)-1,5-dihydro-1-(4-methoxyphenyl)-3-methyl-2*H*-pyrrol-2-one (12a). Lithium diisopropylamide was generated from 122 mL (88.1 g, 0.87 mol) of diisopropylamine and 348 mL (0.87 mol) of a 2.5 M solution of *n*-butyllithium in hexane in 1.5 L of tetrahydrofuran under a nitrogen atmosphere at −60 °C. Compound **11** (235 g, 0.83 mol) was added to this solution, and the mixture was stirred for 30 min at −50 °C and 1 h at 0 °C. The solution was recooled to −60 °C and transferred by cannula into a solution of 130 g (0.91 mol) of methyl iodide in 200 mL of tetrahydrofuran at −45 °C. The mixture was stirred for 5 h at −45 °C and 30 min at 10 °C, after which it was poured onto 1.5 L of 4 N HCl and stirred for 1 h. The mixture was extracted with methylene chloride, and the extracts were dried and evaporated. Recrystallization of the crude product from ethanol afforded 113 g (46%) of the title compound as a pale yellow solid: mp 146–147 °C; ^{1}H NMR ($CDCl_3$) δ 2.14 (t, 3 H), 3.82 (s, 3 H), 4.57 (q, 2 H), 6.94 (dd, 2 H), 7.18 (ddd, 2 H), 7.50 (ddd, 2 H), 7.69 (dd, 2 H). Anal. ($C_{18}H_{16}FNO_2$) C, H, N.

3-Ethyl-4-(4-fluorophenyl)-1,5-dihydro-1-(4-methoxyphenyl)-2*H*-pyrrol-2-one (12b). Alkylation of **11** with ethyl iodide on a 0.83-mol scale following the procedure used for the preparation of **12a**, with the difference that the ethyl iodide was added to the anion solution, afforded 104 g (40%) of the title compound as a pale yellow solid after recrystallization from ethanol: mp 138–140 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3 H), 2.56 (q, 2 H), 3.82 (s, 3 H), 4.56 (s, 2 H), 6.96 (d, 2 H), 7.20 (t, 2 H), 7.48 (m, 2 H), 7.70 (d, 2 H). Anal. ($C_{19}H_{18}FNO_2$) C, H, N.

4-(4-Fluorophenyl)-1,5-dihydro-3-methyl-2*H*-pyrrol-2-one (13a). A solution of 586 g (1.07 mol) of ceric ammonium nitrate in 1.8 L of water was added dropwise over 45 min to a suspension of 105 g (0.35 mol) of **12a** in 2 L of acetonitrile, during which time the temperature of the reaction mixture was maintained at 0–10 °C. After stirring for 30 min, 280 g of sodium sulfite was added. The mixture was stirred an additional 30 min and 400 g of sodium bicarbonate was added. After stirring for 30 min more the mixture was filtered, concentrated to 1 L, and extracted with methylene chloride and ethyl acetate. The extracts were dried and evaporated to give a residue which was chromatographed on silica gel eluting with 80:18:2 methylene chloride/ethyl acetate/methanol to yield 28.9 g (43%) of the title compound. Recrystallization from ethanol/ethyl acetate gave an analytical sample: mp 179–182 °C; ^{1}H NMR ($CDCl_3$) δ 2.08 (t, 3 H), 4.24 (q, 2 H), 7.06 (br s, 1 H), 7.17 (ddd, 2 H), 7.48 (ddd, 2 H). Anal. ($C_{11}H_{10}FNO$) C, H, N.

3-Ethyl-4-(4-fluorophenyl)-1,5-dihydro-2*H*-pyrrol-2-one (13b). Reaction of **12b** with ceric ammonium nitrate on a 0.329-mol scale following the procedure used for the preparation of **13a** afforded 38 g (57%) of the title compound as a pale yellow solid. Recrystallization from ethanol gave the analytical sample: mp 178–180 °C; ^{1}H NMR (DMSO-d_6) δ 1.06 (t, 3 H), 2.38 (q, 2 H), 4.20 (s, 2 H), 7.36 (m, 2 H), 7.60 (m, 2 H), 8.32 (s, 1 H). Anal. ($C_{12}H_{12}FNO$) C, H, N.

4-(4-Fluoro-3-nitrophenyl)-1,5-dihydro-3-methyl-2*H*-pyrrol-2-one (14a). Nitric acid (70%, 9.7 mL, 0.15 mol) was added dropwise to a solution of 23.2 g (0.12 mol) of **13a** in 82 mL of concentrated sulfuric acid while the temperature was maintained at 0–5 °C. The mixture was stirred for 1 h at 0 °C and then was poured onto 400 g of ice. The resulting precipitate was collected by filtration and washed with water until the washes were neutral. The solid was air-dried and then washed with acetone/ether to give 20.3 g (71%) of the title compound as a tan solid: mp 192–196 °C; ^{1}H NMR (DMSO-d_6) δ 1.96 (t, 3 H), 4.27 (q, 2 H), 7.75 (dd, 1 H), 7.98 (m, 1 H), 8.25 (dd, 1 H), 8.48 (s, 1 H). Anal. ($C_{11}H_9FN_2O_3 \cdot 0.25H_2O$) C, H, N.

3-Ethyl-4-(4-fluoro-3-nitrophenyl)-1,5-dihydro-2*H*-pyrrol-2-one (14b). Nitration of **13b** on a 0.183-mol scale following the procedure used for the preparation of **14a** afforded 27.9 g (61%) of the title compound as a pale yellow solid after recrystallization from acetonitrile: mp 176–178 °C; ^{1}H NMR (DMSO-d_6) δ 1.10 (t, 3 H), 2.42 (q, 2 H), 4.30 (s, 2 H), 7.76 (dd, 1 H), 7.98 (m, 1 H), 8.26 (dd, 1 H), 8.48 (s, 1 H). Anal. ($C_{12}H_{11}FN_2O_3$) C, H, N.

1,5-Dihydro-4-[4-(1*H*-imidazol-1-yl)-3-nitrophenyl]-3-methyl-2*H*-pyrrol-2-one (15a). A solution of 9.5 g (40 mmol) of **14a** and 8.2 g (120 mmol) of imidazole in 73 mL of dimethyl sulfoxide was heated to 50 °C under a nitrogen atmosphere for 7 h. The mixture was then cooled to room temperature, and water was added to give a precipitate. The mixture was kept cold for 1 h, after which the precipitate was collected by filtration, washed with water, and air-dried to provide 10.6 g (93%) of the title compound, which was used without further purification: ^{1}H NMR (DMSO-d_6) δ 2.02 (s, 3 H), 4.36 (s, 2 H), 7.17 (s, 1 H), 7.52 (s, 1 H), 7.86 (d, 1 H), 8.01 (s, 1 H), 8.05 (dd, 1 H), 8.36 (d, 1 H), 8.56 (s, 1 H).

1,5-Dihydro-3-methyl-4-[4-(2-methyl-1*H*-imidazol-1-yl)-3-nitrophenyl]-2*H*-pyrrol-2-one (15b). Reaction of **14a** with 2-methylimidazole on a 28-mmol scale following the procedure used for the preparation of **15a** afforded 7.9 g (95%) of the title compound, which was used without further purification: ^{1}H NMR (DMSO-d_6) δ 2.03 (s, 3 H), 2.16 (s, 3 H), 4.36 (s, 2 H), 6.98 (d, 1 H), 7.28 (d, 1 H), 7.87 (d, 1 H), 8.07 (dd, 1 H), 8.36 (d, 1 H), 8.57 (s, 1 H).

3-Ethyl-1,5-dihydro-4-[4-(1*H*-imidazol-1-yl)-3-nitrophenyl]-2*H*-pyrrol-2-one (15c). Reaction of **14b** with imidazole on a 48 mmol scale following the procedure used for the preparation of **15a** afforded 9.1 g (64%) of the title compound, which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 1.13 (t, 3 H), 2.45 (q, 2 H), 4.30 (s, 2 H), 7.10 (s, 1 H), 7.43 (d, 1 H), 7.80 (s, 1 H), 7.95 (m, 2 H), 8.20 (d, 1 H), 8.43 (br s, 1 H).

3-Ethyl-1,5-dihydro-4-[4-(2-methyl-1*H*-imidazol-1-yl)-3-nitrophenyl]-2*H*-pyrrol-2-one (15d). Reaction of **14b** with 2-methylimidazole on a 60-mmol scale following the procedure used for the preparation of **15a** afforded 16.1 g (86%) of the title compound, which was used without further purification.

1,5-Dihydro-4-[4-(1*H*-imidazol-1-yl)phenyl]-3-methyl-2*H*-pyrrol-2-one (5). A solution of 9.5 g (33 mmol) of **15a** and 38.7 g (172 mmol) of tin(II) chloride dihydrate in 450 mL of ethanol was heated to reflux under a nitrogen atmosphere for 30 min. The mixture was cooled, made basic with aqueous sodium bicarbonate, and filtered through Celite. The filter cake was washed with ethanol, and the filtrates were evaporated. Chromatography of the residue on alumina eluting with methanol provided 21.4 g of the crude aniline.

The aniline (11.0 g) was dissolved in 110 mL of concentrated HCl at 5 °C, and 45 mL (0.43 mol) of 50% aqueous hypophosphorus acid was added dropwise. Aqueous sodium nitrite (3.07 g, 44.5 mmol) was added, and the mixture was stirred for 10 min. A trace amount of copper(I) oxide was added, and the mixture was stirred an additional 1 h at 5 °C. The mixture was neutralized with sodium carbonate and extracted with *n*-butanol, and the extracts were evaporated. The residue was triturated with methanol and filtered, and the filtrates were evaporated. Chromatography of the residue on silica gel eluting with 75:20:4:1 acetonitrile/ethyl acetate/methanol/concentrated ammonia followed by recrystallization from ethanol afforded 1.28 g (16%) of the title compound as an off-white solid: mp 246–252 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.98 (s, 3 H), 4.26 (s, 2 H), 7.15 (s, 1 H), 7.69 (d, 2 H), 7.78 (d, 2 H), 7.85 (s, 1 H), 8.37 (s, 2 H). Anal. ($C_{14}H_{13}N_3O$) C, H, N.

1,5-Dihydro-3-methyl-4-[4-(2-methyl-1*H*-imidazol-1-yl)-phenyl]-2*H*-pyrrol-2-one (6). Reaction of **15b** on a 25-mmol scale following the procedure used for the preparation of **5** afforded 0.98 g (16%) of the title compound as a tan solid after recrystallization from ethanol/ethyl acetate: mp 219–222 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.98 (t, 3 H), 2.34 (s, 3 H), 4.26 (br s, 2 H), 6.98 (d, 1 H), 7.38 (d, 1 H), 7.60 (d, 2 H), 7.74 (d, 2 H), 8.42 (br s, 1 H). Anal. ($C_{15}H_{15}N_3O\cdot0.1H_2O$) C, H, N.

3-Ethyl-1,5-dihydro-4-[4-(1*H*-imidazol-1-yl)phenyl]-2*H*-pyrrol-2-one (7). Reaction of **15c** on a 21-mmol scale following the procedure used for the preparation of **5** afforded 1.25 g (23%) of the title compound as a white solid after recrystallization from ethanol: mp 236–238 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.09 (t, 3 H), 2.42 (q, 2 H), 4.26 (s, 2 H), 7.17 (s, 1 H), 7.67 (d, 2 H), 7.82 (d, 2 H), 7.86 (s, 1 H), 8.27 (s, 2 H). Anal. ($C_{15}H_{15}N_3O\cdot0.25H_2O$) C, H, N.

3-Ethyl-1,5-dihydro-4-[4-(2-methyl-1*H*-imidazol-1-yl)-phenyl]-2*H*-pyrrol-2-one (8). Reaction of **15d** on a 14.1-mmol scale following the procedure used for the preparation of **5** afforded 1.2 g (31%) of the title compound as a white solid after recrystallization from ethanol: mp 219–221 °C; ^{1}H NMR (DMSO-d_6) δ 1.10 (t, 3 H), 2.32 (s, 3 H), 2.42 (q, 2 H), 4.26 (s, 2 H), 6.96 (s, 1 H), 7.37 (s, 1 H), 7.58 (d, 2 H), 7.66 (d, 2 H), 8.40 (s, 1 H). Anal. ($C_{16}H_{17}N_3O$) C, H, N.

2-[[4-(1*H*-Imidazol-1-yl)phenyl]methylene]-1,3-propanedioic Acid Diethyl Ester (16). A solution of 4-(1*H*-imidazol-1-yl)benzaldehyde (15.9 g, 92 mmol) and 14.0 mL (14.8 g, 92 mmol) of diethyl malonate in 100 mL of benzene was treated with 0.5 mL of piperidine and 0.5 mL of acetic acid, and the mixture was heated at reflux, using a Dean–Stark trap for the removal of the water which was produced. After 28 h the mixture was cooled, diluted with methylene chloride, and washed with water. The organic phase was dried and evaporated, and the residue was triturated with ether and filtered to give 23.0 g (80%) of the title compound as a white solid: mp 98–99 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 1.35 (t, 3 H), 4.32 (q, 2 H), 4.36 (q, 2 H), 7.25 (s, 1 H), 7.32 (s, 1 H), 7.43 (d, 2 H), 7.60 (d, 2 H), 7.75 (s, 1 H), 7.90 (s, 1 H). Anal. ($C_{17}H_{18}N_2O_4$) C, H, N.

2-[1-[4-(1*H*-Imidazol-1-yl)phenyl]-2-nitroethyl]-1,3-propanedioic Acid Diethyl Ester (17). A solution of 22.1 g (70.1 mmol) of **16** in 95 mL of nitromethane was treated with 1.57 mL of tetramethylguanidine at −20 °C for 2 h. The mixture was diluted with methylene chloride and washed three times with water, and the organic phase was dried and evaporated to give 25.8 g (98%) of the title compound as a dark yellow oil. An analytical sample was obtained by chromatography on silica gel eluting with 98:2 methylene chloride/methanol: ^{1}H NMR ($CDCl_3$) δ 1.12 (t, 3 H), 1.28 (t, 3 H), 3.83 (d, 1 H), 4.05 (q, 2 H), 4.24 (m, 3 H), 4.92 (m, 2 H), 7.20 (s, 1 H), 7.25 (s, 1 H), 7.38 (s, 4 H), 7.84 (s, 1 H). Anal. ($C_{18}H_{21}N_3O_6$) C, H, N.

1-Hydroxy-4-[4-(1*H*-imidazol-1-yl)phenyl]-2-oxopyrrolidine-3-carboxylic Acid Ethyl Ester (18). A solution of 68.39 g (182 mmol) of **17** in 400 mL of methanol at 0 °C was treated first with 40.0 g of 10% palladium on carbon and then with 57.44 g (911 mmol) of ammonium formate. The mixture was allowed to warm to room temperature. After 30 min a vigorous reaction ensued, which was controlled by cooling the mixture with an ice bath. After 5 h the mixture was filtered through Celite and evaporated. The residue was stirred for 1 h in a two-phase mixture of water, ether, and methylene chloride. The resulting precipitate was collected by filtration and air-dried to give 36.5 g (64%) of the title compound as a white solid. An analytical sample was obtained by recrystallization from ethyl acetate: mp 190–193 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.17 (t, 3 H), 3.56 (m, 1 H), 3.73 (m, 1 H), 3.87 (m, 2 H), 4.13 (m, 2 H), 7.17 (s, 1 H), 7.55 (d, 2 H), 7.65 (d, 2 H), 7.80 (s, 1 H), 8.38 (s, 1 H), 10.09 (br s, 1 H). Anal. ($C_{16}H_{17}N_3O_4$) C, H, N.

4-[4-(1*H*-Imidazol-1-yl)phenyl]-2-oxopyrrolidine-3-carboxylic Acid Ethyl Ester (19). Titanium trichloride (197 mL of a 20% aqueous solution) was added dropwise over 1 h to a stirred suspension of 40.09 g (127 mmol) of **18** and 127 g of sodium acetate in 650 mL of methanol and 450 mL of water, and the mixture was stirred for an additional 2 h. Water (1 L) was added, and the mixture was evaporated by half. The solution was adjusted to pH 8 with sodium bicarbonate and extracted five times with methylene chloride. Evaporation of the dried organic extracts gave 37.3 g (98%) of the title compound as a yellow gum, which was used without further purification. An analytical sample was obtained by chromatography on silica gel eluting with 95:5 methylene chloride/methanol followed by recrystallization from ethyl acetate/hexanes, giving a yellow solid: mp 127–129 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H), 3.47 (dd, 1 H), 3.57 (d, 1 H), 3.87 (t, 1 H), 4.17 (q, 1 H), 4.26 (q, 2 H), 7.19 (br s, 1 H), 7.22 (s, 1 H), 7.28 (s, 1 H), 7.40 (s, 4 H), 7.86 (s, 1 H). Anal. ($C_{16}H_{17}N_3O_3$) C, H, N.

3-(Hydroxymethyl)-4-[4-(1*H*-imidazol-1-yl)phenyl]-2-pyrrolidinone (20). To a solution of 35.14 g (117 mmol) of **19** in 500 mL of methanol at 0 °C was added 15.64 g (141 mmol) of calcium chloride and 5.33 g (141 mmol) of sodium borohydride. After 1 h, an additional 1.33 g of sodium borohydride was added, and the solution was stirred for 3 h. Water (400 mL) and brine (400 mL) were added, and the mixture was extracted six times with 3:1 methylene chloride/2-propanol. The extracts were dried and evaporated to give a residue, which was triturated with hot ethyl acetate and filtered to give 38.2 g (>100%) of the title compound together with some contaminating salts as a white solid, which was used without further purification. An analytical sample was obtained by chromatography on silica gel eluting with 95:5 acetonitrile/concentrated ammonia followed by recrystallization from ethanol/ethyl acetate: mp 165–167 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (m, 1 H), 2.68 (t, 1 H), 2.86 (m, 1 H), 2.96 (t, 1 H), 3.04 (t, 1 H), 3.11 (dd, 1 H), 3.95 (br s, 1 H), 5.92 (s, 1 H), 6.25 (d, 2 H), 6.34 (d, 2 H), 6.44 (s, 1 H), 6.49 (s, 1 H), 6.87 (s, 1 H). Anal. ($C_{14}H_{15}N_3O_2$) C, H, N.

1,5-Dihydro-4-[4-(1*H*-imidazol-1-yl)phenyl]-3-methyl-2*H*-pyrrol-2-one (5). A suspension of 35.4 g (120 mmol) of crude **20** in 500 mL of pyridine at 0 °C under a nitrogen atmosphere was treated with 10.9 mL (16.1 g, 141 mmol) of methanesulfonyl chloride, and the mixture was stirred for 1 h. An additional 3.0

mL of methanesulfonyl chloride was added, and the mixture was allowed to warm to room temperature over 3 h. 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU; 81 mL, 82 g, 542 mmol) was added, and the mixture was stirred at room temperature for 1 h. The mixture was warmed to 100 °C over 6 h, during which time 9.4 mL of additional methanesulfonyl chloride and 21.5 mL of additional DBU were added in two portions. The mixture was cooled, diluted with methylene chloride and 2-propanol, and washed four times with half-saturated aqueous sodium carbonate. The organic phases were dried and evaporated to give a residue, which was triturated first with ether and then with ether/ethanol and then crystallized once from ethanol and twice from ethanol/methylene chloride to give 4.38 g (16%) of the title compound as an off-white solid, which was identical in all respects to the material prepared above. A sample was recrystallized from 2-propanol/methylene chloride to give the crystals used for X-ray crystallographic analysis.

Pharmacology. Experimental procedures for the cAMP phosphodiesterase,[31,32] ferret papillary muscle,[33] and hemodynamic studies[31] have been previously reported.

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Supplementary Material Available: Results from the X-ray crystallographic analysis of 5 (18 pages). Ordering information is given on any current masthead page.

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