dried, the solvent removed, and the residual solid recrystallized from *i*-PrOH to give 7.4 g (65.8%) of **12**: mp 102–104 °C; NMR ($CDCl_3$) δ 1.4–2.0 (6 H, m, 3 CH_2), 2.26 (3 H, s, CH_3), 2.76 (2 H, t, J = 7 Hz, CH_2), 3.9–4.6 (6 H, m, 2 OCH_2, NCH_2), 5.83 (3 H, s, CH), 6.89 (1 H, d, J = 9 Hz, aromatic), 7.79 (1 H, dd, J = 9 Hz, aromatic), 7.95 (1 H, d, J = 2 Hz, aromatic). Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

5-(4,5-Dihydro-2-oxazolyl)-2-[[5-(3-methyl-5-isoxazolyl)pentyl]oxy]benzenemethanol (30). To a solution of 2.3 g (3.5 mmol) of **29** in 10 mL of CH_3OH was added portionwise with stirring at room temperature 200 mg (5.3 mmol) of $NaBH_4$. After the addition was complete, the solution was stirred at room temperature for 1 h and then treated with acetic acid dropwise until the solution was slightly acidic. After the solution was diluted with 50 mL of H_2O, the precipitated solid was collected and recrystallized from EtOAc to give 1.2 g (99%) of **30**: mp 140–141 °C; NMR ($CDCl_3$) δ 4.7 (2 H, s, CH_2OH). Anal. ($C_{19}H_{24}N_2O_4$) C, H, N.

5-[5-[2-(Difluoromethyl)-4-(4,5-dihydro-2-oxazolyl)phenoxy]pentyl]-3-methylisoxazole (31). To a solution of 3.2 g (0.01 mol) of (diethylamino)sulfur trifluoride (DAST) in 10 mL of CH_2Cl_2 was added dropwise 3.0 g (0.01 mol) of **29** in 5 mL of CH_2Cl_2 at room temperature. The solution was stirred for 24 h, diluted with an additional 50 mL of CH_2Cl_2, extracted with H_2O, and dried. Removal of the solvent gave a residue, which was purified by MPLC[21] (EtOAc). The solid obtained was recrystallized from *i*-PrOAc to give 1 g of **31** (27%): mp 88–89 °C; NMR ($CDCl_3$) δ 6.6 (1 H, s, CHF_2). Anal. ($C_{19}H_{22}F_2N_2O_3$) C, H, N.

5-[5-[2-Ethenyl-4-(4,5-dihydro-2-oxazolyl)phenoxy]pentyl]-3-methylisoxazole (36). To a suspension of 5.2 g (0.015 mol) of triphenylmethylphosphonium bromide in 75 mL of THF was added at 0 °C under nitrogen 10 mL of 1.55 M *n*-butyllithium.[22] After the addition was complete, the mixture was stirred at room temperature for 2 h, and then 5.0 g (0.0146 mol) of **29** in 25 mL of THF was added dropwise. The resulting suspension was left at room temperature for 18 h. The suspended solid was removed by filtration and the filtrate concentrated to dryness. The residual solid was purified by MPLC ($CHCl_3$) in order to remove triphenylphosphine oxide. Recrystallization of the resulting solid from EtOAc gave 1.8 g of **36** (33%): mp 116–117 °C; NMR ($CDCl_3$) δ 5.25–5.35, 5.80–5.90 (2 H, d, C=CH_2), 6.95–7.15 (1 H, d, CH=C cis and trans). Anal. ($C_{20}H_{24}N_2O_3$) C, H, N.

5-(4,5-Dihydro-2-oxazolyl)-2-[[5-(3-methyl-2-isoxazolyl)pentyl]oxy]benzoic Acid (32). To a solution of 4.0 g (12 mmol) of **29** in 60 mL of ethanol was added at room temperature 6 mL of a 4.6 M solution of aqueous silver nitrate, and the mixture was stirred for 15 min.[23] Sixty milliliters of a 1.0 M solution of aqueous KOH was added slowly, and the mixture was stirred for 2 h. The mixture was filtered and acidified with concentrated HCl to pH 2. The precipitate was filtered and the filter cake washed with 1 M HCl. The resulting paste was dried in vacuo briefly and recrystallized from CH_3OH to yield 1.6 g (36%) of **32**: mp 170–171 °C; NMR (Me_2SO-d_6) δ 12.8 (1 H, s, COOH). Anal. ($C_{19}H_{22}N_2O_5$) C, H, N.

Acknowledgment. We thank Dr. S. Clemans for determining NMR and mass spectra and M. Fancher, P. Felock, P. Warner, and W. Shave for their technical assistance.

Registry No. 1, 87495-31-6; 4 (X = Cl, Y = H), 98033-80-8; 5 (X = Y = H), 81428-58-2; 5 (X = CF_3, Y = H), 105639-29-0; 5 (X = $CH_2CH=CH_2$, Y = H), 105639-30-3; **5a**, 98033-81-9; **5b**, 98033-92-2; **5c**, 105639-19-8; **5d**, 105639-20-1; **5e**, 98034-05-0; **5f**, 105639-21-2; **5g**, 105639-22-3; **5h**, 105639-23-4; **5i**, 105639-24-5; **5j**, 98033-64-8; **5k**, 105639-25-6; **5l**, 105639-26-7; **5m**, 105639-27-8; **5n**, 98033-59-1; **5o**, 105639-28-9; **10**, 98034-30-1; 11, 98033-98-8; **12**, 98033-68-2; **13**, 98033-87-5; **14**, 98033-82-0; **15**, 105639-02-9; **16**, 98033-68-2; **17**, 105639-03-0; **18**, 98033-69-3; **19**, 105639-04-1; **20**, 105639-05-2; **21**, 105639-06-3; **22**, 105639-07-4; **23**, 105639-08-5; **24**, 105639-09-6; **25**, 105639-10-9; **26**, 98033-66-0; **27**, 105639-11-0; **28**, 105639-12-1; **29**, 105639-13-2; **30**, 105639-14-3; **31**, 105639-15-4; **32**, 105639-16-5; **34**, 105639-17-6; **35**, 105639-18-7; **36**, 105663-64-7; $H_2N(CH_2)_2OH$, 141-43-5; 5-(4-bromobutyl)-3-methylisoxazole, 98033-94-4; 5-(5-bromopentyl)-3-methylisoxazole, 98033-85-3; 5-(6-bromohexyl)-3-methylisoxazole, 98033-83-1; 5-(7-bromoheptyl)-3-methylisoxazole, 91945-38-9; ethyl 3-chloro-4-hydroxybenzoate, 16357-41-8.

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Octahydropyrazino[2′,3′:3,4]pyrido[1,2-*a*]indoles. A New Class of Potent Antihypertensive Agents

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Simplifications and modifications of the vincamine molecule led to the discovery of antihypertensive 1,2,3,4,4a,5,6,12b-octahydro-12-methylpyrazino[2′,3′:3,4]pyrido[1,2-*a*]indoles. Stereoselective syntheses of both 4a,12b-cis and 4a,12b-trans isomers represent new annulation strategies for the construction of fused piperazines. Compounds of the trans series were at least 10 times more potent than the corresponding cis isomers. Antihypertensive activity and α_1-adrenoceptor blocking properties peaked with a simultaneous introduction of 4-methylethyl and 1-alkyl substituents. Compound **15j** (AY-28,228; atiprosin), (4a,12b-*trans*)-1-ethyl-1,2,3,4,4a,5,6,12b-octahydro-12-methyl-4-(1-methylethyl)pyrazino[2′,3′:3,4]pyrido[1,2-*a*]indole, was chosen for a detailed preclinical evaluation.

Over the years, the family of indole alkaloids has been a source of naturally occurring antihypertensive principles, and structural prototypes possessing the indole nucleus have given rise to a number of useful drugs. Among the more recently studied indole alkaloids are those of the *Vinca* species. Vincamine (1) has interesting cardiovascular properties,[1-4] exhibits moderate antihypertensive effects[1,2] through its vasodilative mode of action,[2,3] and appears to be successful in the treatment of pathological

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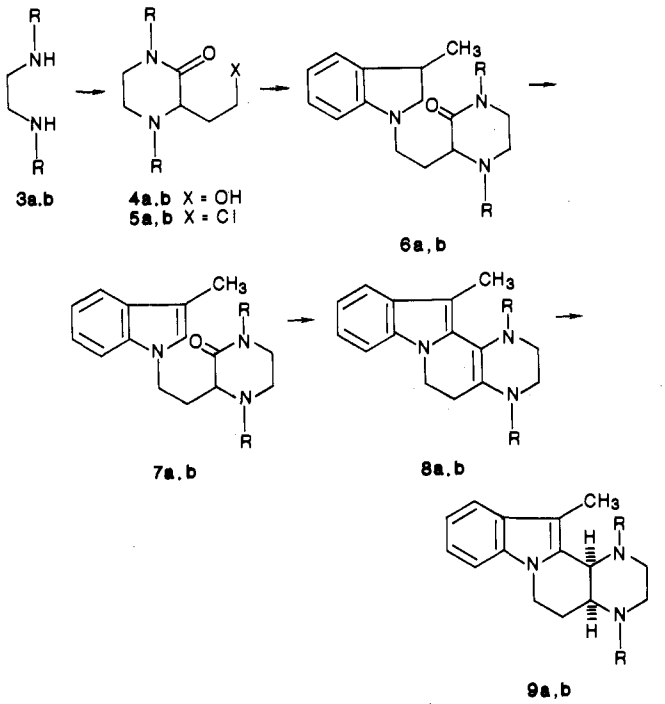
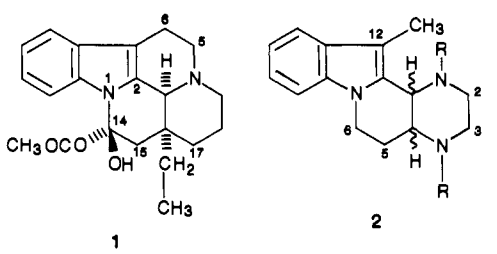
Scheme I[a]



[a] R = CH_3 in all structures designated **a**. R = CH_3CH_2 in all structures designated **b**.

conditions associated with cerebral vascular insufficiencies.[5]

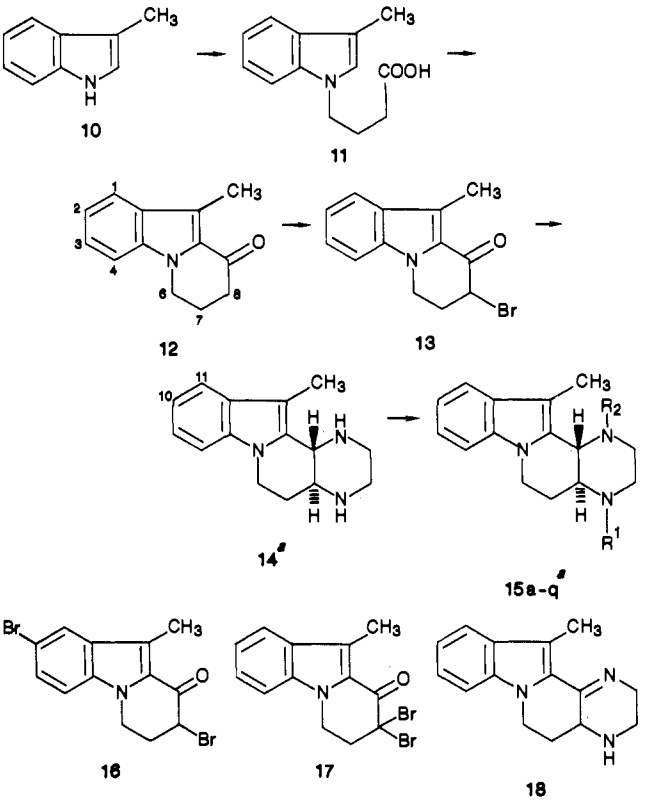


Some time ago, we scrutinized the vincamine pentacyclic molecule from the point of view of possible structural simplifications. In the course of our initial studies,[6] aimed at modified and truncated analogues of **1**, we became interested in the 17-aza-5,6-seco derivatives of the vincamine skeleton. Such molecules appeared to be especially attractive, since they combined the indole and the piperazino nuclei in a semirigid system that could be endowed with unusual biological activities. The purpose of this paper is to describe the synthesis and preliminary pharmacological evaluation of (4a,12b-*cis*)-1,2,3,4,4a,5,6,12b-octahydropyrazino[2′,3′:3,4]pyrido[1,2-*a*]indoles (17-aza-16-desethyl-14,15-dihydro-5,6-secoeburnamenines)[7] and their trans isomers (general formula **2**).

Chemistry

Construction of polycyclic systems may be viewed in terms of the sequence in which rings are added. Our synthetic approach to the tetracyclic system **2** was patterned after the Torgov synthesis of steroids and could be classified as an AB → ABD → ABCD sequence. Conforming to this strategy, we linked the indolic component AB to a precursor of the ring D, and the resultant ABD intermediate was then subjected to transformations that locked the ring C (Scheme I).

Scheme II[a]



[a] 10-Bromo and 10-methoxy analogues were prepared in a similar manner (cf. Experimental Section).

The synthons that we envisaged as the ultimate source of ring D were prepared in two steps. Condensation of *N,N′*-dialkylethylenediamines **3a,b** with α-butyrolactone yielded (hydroxyethyl)piperazinones **4a,b**, which were converted to rather unstable chlorides **5a,b** upon treatment with $SOCl_2$.

Several attempts were made to accomplish alkylation of 3-methylindole with **5**, but all were fruitless. In contrast, similar N-alkylations of 3-methylindoline proceeded smoothly to give **6a,b**. Before the Bischler-Napieralski cyclization in the formation of ring C was employed, these intermediates were aromatized to indoles **7a,b**. Oxidation of **6** was examined by using a variety of reagents, the best yields being obtained with a mixture of MnO_2 and Pd/C in refluxing xylene. Cyclodehydration of the resultant lactams **7a,b** with $POCl_3$ led to air sensitive 1,2-enediamines **8a,b**, which could not be fully characterized. We have been unsuccessful in preparation of the corresponding imonium[8] or ammonium dichlorophosphates, perchlorates, and tetrafluoroborates. Our failure to reduce **8a,b** by a number of routine methods (catalytic hydrogenation, $NaBH_4$, diborane, Zn/AcOH) strongly indicated that we were not dealing with Schiff bases. On the other hand, these results implied that our intermediates were double enamines whose π-orbital was stabilized[8] by the lone-

(5) Witzmann, H. K.; Blechacz, W. *Arzneim.-Forsch.* **1977**, *27*, 1238.
(6) A portion of this work will be published elsewhere.
(7) Note that the latter name is illustrative, but violates both the rules for numbering of fused systems and replacement nomenclature.
(8) Enediamine to amino ketimine tautomerization is a high-energy process. Reactivity of the C atoms in 1,2-enediamines is considerably lower than that of enamines and 1,1-enediamines. Cf. Hickmott, P. W. *Tetrahedron* **1984**, *40*, 2989 and references therein.

electron pairs of both nitrogen atoms, in addition to a stabilization through conjugation effects.

Dissolving metal reduction is often the only useful methodology that can be applied to conjugated systems. On treatment with sodium in anhydrous ethanol, **8a,b** were converted to diamines **9a,b** in a stereoselective manner. The midfield portions of NMR spectra of **9a,b** were not well resolved, and the peaks due to the ring junction protons were not discernible. In the spectra of the corresponding salts, the H-12b resonance emerged as a broad singlet at δ 5.25, which has resolved into a narrow doublet (J = 3.5 Hz) upon deuteriation. The small coupling constant presents tangible evidence for the cis-fusion of the rings.

Stereoselective formation of **9a,b** may be explained on thermodynamical grounds.[9,10] The steric course of the reduction can also be rationalized by assuming a successive electron-addition process that generates first an anion radical whose protonation occurs from the less hindered face. An analogous argument of steric approach control is even more convincing for the second protonation.

Synthetic Scheme I was not adaptable to the preparation of unsubstituted compounds **2** (R = H). Our initial endeavors to construct the parent system **2** were based on an alternate route (Scheme II). This linear sequence, AB → ABC → ABCD, had presented numerous difficulties, and it became practical only after systematic studies of the steps **12** → **13** → **14**.

Condensation of 3-methylindole (**10**) with α-butyrolactone provided carboxylic acid **11**, which was cyclized in hot PPA to give pyridoindolone **12**. Bromination of ketone **12** with a variety of reagents[11] produced ca. 6:2:1 mixtures of **13** and dibromides **16** and **17**, respectively. Attempts to suppress the formation of **16** by changing reaction conditions met with limited success. Moreover, compounds **13** and **16** could hardly be differentiated on column chromatography.

We propose that **13** and **17** are immediate products of the bromination of **12** and that a subsequent debromination–bromination process[12,13] that requires the presence of HBr is responsible for the nuclear bromination. This problem was finally avoided by treatment of **12** with trimethylphenylammonium tribromide (TPAT),[14] which led smoothly to pure bromo ketone **13**.

In the reductive condensation of **13** with ethylenediamine/$NaBH_4$, cyclic Schiff base **18** is a logical intermediate. Owing to its unstable nature, **18** could not be isolated, although we were able to obtain evidence of intermediacy of an analogous tetrahydropyrazine in a related series of compounds.[6] In contrast to enediamines **8a,b**, compound **18** already contains a chiral center at C-4a, and molecular models indicate that **18** has little conformational mobility. Assuming that H-4a is pseudoaxial, the preference for attack by borohydride at C-12b from the opposite side is not surprising, since the reagent approaches along the reaction coordinate that avoids potential interactions with three pseudoaxial hydrogens (H-3, H-4a, H-6) and eventually a torsional strain of ring junction C–H bonds. Geometrically, the transition state of the reduction resembles the reactant **18**, and thus, stereoselective formation of the trans isomer **14** proceeds with minimum conformational adjustment. The NMR spectrum of **14** dimethanesulfonate salt showed a characteristic one-proton doublet (J = 11 Hz) attributable to H-12b.

Due to stereoelectronic effects, the nitrogen atoms N-1 and N-4 in compound **14** exhibit different reactivities. Regioselective alkylation of N-4 is comparable to that observed with 2-phenylpiperazine, where the nitrogen atom proximate to a bulky aryl substituent is sterically hindered.[15] Treatment of **14** with alkyl halides and K_2CO_3 in DMF or benzene at 20–70 °C afforded corresponding 4-alkyl derivatives (e.g., **15a–c**) in high yields. Preparation of 1,4-dialkyl analogues necessitated more vigorous conditions and longer reaction time. Similar alkylations with methyl halides produced complex mixtures containing quaternary salts. Consequently, we resorted to a mild reductive methylation of **14** with formaldehyde/sodium cyanoborohydride to obtain **15d**. 10-Bromo derivatives **15f** and **15k** and 10-methoxy analogue **15l** were prepared according to Scheme II, with **16** and 5-methoxy-3-methylindole as starting materials, respectively.

1-Alkyl derivatives of **14** could not be prepared directly without using a protecting group that would prevent the preferential 4-alkylation (vide supra). Therefore, **14** was subjected to the Schotten–Baumann reaction with benzoyl chloride, the resultant 4-benzoyl diamine was 1-alkylated with ethyl iodide, and hydrolytic deprotection yielded 1-ethyl analogue **15o**.

Trans configuration of products **15a–o** has been evident from NMR spectra of the corresponding salts in Me_2SO-d_6. In monosalts, H-12b proton gives rise to a diagnostic doublet (δ 4.5–5.1) with a coupling constant J = 10–11 Hz; an analogous signal appears at δ 5.15–5.33 in the spectra of disalts. These data confirm selective monoprotonation of N-4.

As expected, the base strengths of N-1 and N-4 are remarkably different. Subjected to a base-weakening hyperconjugation effect, N-1 should exhibit a lower pK_a value, which would be further reduced by a strong –I effect[16] of the first protonated N-4. Indeed, compounds **14** and **15j** had pK_a values 7.8 and 3.5, and 8.3 and 2.5, respectively.

Biological Results and Discussion

Compounds of the present series were screened orally at 50–10 mg/kg in cannulated spontaneously hypertensive rats (SHR). Selected compounds were further evaluated at lower doses. Changes in the mean arterial blood pressure (MABP) were recorded at different time periods in order to determine the onset and duration of action as well as the maximum effect observed. Antagonism of the pressor response to epinephrine was used as a measure of the α_1-adrenoceptor blocking activity.

(9) Having no butane-gauche interactions, the trans isomer of system **2** (R = H) is thermodynamically more stable. However, with substitution of both nitrogen atoms (R = alkyl), the total number of nonboding interactions increases, the cis–trans difference in enthalpy (energy) becomes sufficiently small, and other factors may determine thermodynamic preference. Cf. Allinger, N. L. *J. Org. Chem.* **1956**, *21*, 915, and Allinger N. L.; Coke, J. L. *J. Org. Chem.* **1961**, *26*, 2096.

(10) An examination of Dreiding models reveals that the 12-methyl group may impinge upon a 1-substituent quite severely, especially in the trans series.

(11) Dioxane dibromide, pyridinium perbromide, Br_2 in Et_2O, AcOH, CH_2Cl_2, $CHCl_3$, and THF.

(12) Crowne, C. W. P.; Evans, R. M.; Green, G. F. H.; Long, A. G. *J. Chem. Soc.* **1956**, 4351.

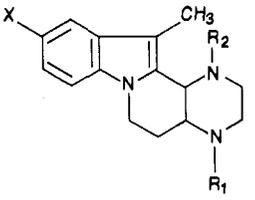
(13) Warnhoff, E.; Rampersad, M.; Sundara Raman, P.; Yerhoff, F. W. *Tetrahedron Lett.* **1978**, 1659.

(14) TPAT probably serves as a source of bromine in a low, steady-state concentration.

(15) Beck, K. M.; Hamlin, K. E.; Weston, A. W. *J. Am. Chem. Soc.* **1952**, *74*, 605.

(16) Albert, A. In *Physical Methods in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1963; Vol. 1, pp 17–18.

Table I. Antihypertensive Activity of 1,2,3,4,4a,5,6,12b-Octahydropyrazino[2′,3′:3,4]pyrido[1,2-*a*]indoles in SHR



compd[a]	R_1	R_2	salt[b]	po dose, mg/kg	max % decrease of MABP[c]	activity rating[d]	HR[e]	vasopressor responses to epinephrine
9a	CH_3	CH_3	D	50	12 (3)	1	↓	antagonized
9b	CH_3CH_2	CH_3CH_2	D	50	25 (4)	2	↓	antagonized
				25	20 (1)		↓	antagonized
14	H	H	C	25	27 (4)	4	↓	slightly
				10	19 (4)			potentiated
15a	CH_3CH_2	H	E	50	31 (4)	3	↓↓	antagonized
				25	26 (4)		↓	no change
				10	23 (1)			no change
15b	$(CH_3)_2CH$	H	D	10	12 (1)	2		antagonized
15c	$PhOCH_2CH_2$	H	C	10	7 (4)	0		no change
15d	CH_3	CH_3	C	10	23 (4)	4	↓	reversed
				5	13 (4)		↓	antagonized
15e	CH_3CH_2	CH_3CH_2	D	10	32 (4)	5	↓↓	reversed
				5	28 (4)		↓↓	reversed
				1	14 (4)			reversed
15f (X = Br)	CH_3CH_2	CH_3CH_2	A	10	15 (4)	2		reversed
15g	CH_3CH_2	$CH_3CH_2CH_2$	B	10	42 (4)	6	↓↓	reversed
				2.5	24 (4)		↓	reversed
				1	13 (4)		↓	reversed
15h	CH_3CH_2	$CH_3(CH_2)_3$	D	10	36 (4)	5	↓	reversed
				1	16 (4)			reversed
15i	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	B	10	18 (4)	4	↑	reversed
				5	12 (4)		↑	reversed
				2.5	16 (4)		↓	reversed
				1	13 (1)		↓	antagonized
15j	$(CH_3)_2CH$	CH_3CH_2	C	10	56 (4)	6	↓↓	reversed
				2.5	52 (4)		↓	reversed
				1	40 (4)		↓	reversed
				0.25	20 (4)		↓	antagonized
15k (X = Br)	$(CH_3)_2CH$	CH_3CH_2	D	50	18 (2)	2		reversed
15l (X = CH_3O)	$(CH_3)_2CH$	CH_3CH_2	D	50	43 (4)	5	↓↓	reversed
				5	33 (4)		↓	reversed
				0.5	8 (1)			antagonized
15m	$(CH_3)_2CH$	$CH_3CH_2CH_2$	B	10	40 (4)	6	↓↓	reversed
				2.5	25 (4)		↓	reversed
				1	19 (4)		↓	reversed
15n	$PhOCH_2CH_2$	CH_3CH_2	D	50	22 (2)	2		reversed
15o	H	CH_3CH_2	C	10	14 (1)	2	↓	no change
indoramin				25	40 (4)	5	↓↓	antagonized
				5	29 (4)		↓	antagonized
				2.5	12 (4)			antagonized
prazosin				10	49 (4)	6	↓	reversed
				1	46 (4)			reversed
				0.5	35 (4)			reversed

[a] X = H unless specified otherwise. [b] A = monohydrochloride, B = monohydrobromide, C = monomaleate, D = dihydrochloride, E = dihydrobromide. [c] MABP = mean arterial blood pressure (the numbers in parentheses are time in hours to peak effect). [d] 0 = no significant activity at 50 mg/kg; 1 = MABP decreased by 10–15% at 50 mg/kg (the changes in MABP under "activity rating 1" are not necessarily statistically significant); 2 = lowering MABP by 15–25% at 50 mg/kg and/or by 10–15% at 10 mg/kg; 3 = lowering MABP by 25–35% at 25 mg/kg and still significant effect at 10 mg/kg; 4 = MABP reduced by 15–25% and an appreciable antihypertensive effect observed at 2.5–5 mg/kg; 5 = lowering MABP by 20–30% at 5 mg/kg and by 10–20% at 1–2.5 mg/kg; 6 = a decrease of MABP by >40% at 10 mg/kg and by 10–20% at 0.25–1 mg/kg. [e] Heart rate after 4 h reduced by 10–25% = ↓, marked bradycardia = ↓↓.

From the MABP ratings shown in Table I it appears that the most important correlates of marked antihypertensive activity and good duration of action are (1) trans configuration of the ring junction and (2) presence of two alkyl groups (R_1 and R_2) attached at N-1 and N-4 atoms. The monosubstituted derivatives **15a–c** were considerably less potent than the parent compound **14**. Highest activity was observed with 1,4-dialkyl (C_2–C_3) compounds possessing an isopropyl group in position 4 (**15j**, **15m**). Introduction of a 10-bromo substituent (**15f**, **15k**) caused an ablation of antihypertensive effects. Compound **15l**, the 10-methoxy analogue of **15j**, did not match the potency of the parent compound at lower doses. A suspected metabolite of **15j**, the 1-ethyl compound **15o**, displayed an unimpressive blood pressure lowering activity.

The most promising candidate for further development, **15j**, is a potent, orally active antihypertensive agent with a duration of action well in excess of 4 h. Compound **15j** is 14 times more potent than indoramin and about one-sixth as potent as prazosin. A subchronic test of **15j** in SHR clearly indicated that tachyphylaxis did not develop to its antihypertensive activity (on day 1, blood pressure decreased 40% and 52%, while on day 29 decreases of 54% and 56% were recorded after doses of 1.0 and 2.5 mg/kg

per day, respectively). The α_1-adrenoceptor blocking property[17] is a dominant characteristic of **15j**.

In summary, (4a,12b-*trans*)-1,4-dialkyl-1,2,3,4,4a,5,6,12b-octahydro-5-methylpyrazino[2′,3′:3,4]-pyrido[1,2-*a*]indoles represent a novel class of antihypertensive agents, some with marked oral potency. The best compound of this series, **15j** (AY-28,228;atiprosin), was chosen for a detailed preclinical evaluation.

Experimental Section

Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Analytical results for indicated elements were within ±0.4% of theoretical values. Proton NMR spectra were recorded on a Varian CFT-20 instrument at 80 MHz; chemical shifts are reported in ppm (δ) relative to Me_4Si. Electron-impact (70 eV) mass spectra were obtained on an LKB-9000S instrument. IR and UV spectra were measured with Perkin-Elmer 225 and Zeiss DMR 21 spectrophotometers, respectively. Only significant spectral data are reported. Chromatographic (gravity column) purifications were performed on silica gel 60 (Merck, mesh 70–230). All solvent evaporations were carried out with a Büchi rotavapor under water aspirator reduced pressure.

3-(2-Hydroxyethyl)-1,4-dimethylpiperazin-2-one (4a). A solution of α-bromobutyrolactone (100 g, 0.6 mol), *N,N′*-dimethylethylenediamine (53 g, 0.6 mol), and Et_3N (60.6 g, 0.6 mol) in THF (1 L) was refluxed overnight. After cooling, the mixture was diluted with Et_2O (200 mL), the precipitated salts were removed by filtration, solvents were evaporated, and the oily residue was chromatographed. Elution with $CHCl_3$/MeOH (50:1) afforded 67.1 g (65%) of **4a**: NMR ($CDCl_3$) δ 2.11 (pseudo q, 2 H, CH_2), 2.44 (s, 3 H, CH_3N), 2.59 (doublet of m, J_{gem} = 10 Hz, 1 H, CHNCO), 2.95 (m with a singlet spike, 5 H, CH_2N and CH_3NCO), 3.24 (t, J = 4 Hz, 1 H, CHCO), 3.45 (dd, J_{gem} = 10 Hz, J = 4 Hz, 1 H, CHNCO), 3.70 (t, J = 5.5 Hz, 2 H, CH_2O), 4.45 (br, 1 H, OH, exchangeable). The picrate salt was crystallized from MeOH: mp 157–159 °C; IR(KBr) 3220, 1650 cm^{-1}; NMR (Me_2SO-d_6) δ 2.05 (m, 2 H, CH_2), 2.9 (s and broad signal, 6 H, CH_3 and CH_2), 3.55 (s and broad signal, 6 H, CH_3 and CH_2), 3.98 (obscured triplet, 1 H, CHCO), 6.05 (br, 2 H, OH exchangeable), 8.56 (s, 2 H, Ar H). Anal. ($C_{14}H_{19}N_5O_9$) C, H, N.

Preparation of **4b** was carried out in the same manner in 73% yield. The picrate salt was crystallized from MeOH–Et_2O: mp 127–129 °C; NMR (Me_2SO-d_6) δ 1.05 (t, J = 7.5 Hz, 3 H, CH_3), 1.25 (t, J = 7.5 Hz, 3 H, CH_3), 3.96 (t, J = 5.5 Hz, 1 H, CHCO), 8.55 (s, 2 H, Ar H). Anal. ($C_{16}H_{23}N_5O_9$) C, H, N.

3-(2-Chloroethyl)-1,4-dimethylpiperazin-2-one (5a). To a solution of **4a** (1.9 g, 11 mmol) in CH_2Cl_2 (8 mL) was added $SOCl_2$ (0.9 mL, 12.3 mmol) by dropwise addition at 0 °C. The mixture was stirred for 1 h and poured onto an ice-cold 10% solution of $NaHCO_3$, and the product was extracted with CH_2Cl_2. Evaporation of the solvent afforded 2 g (95%) of **5a** as brownish oil, which was used without further purification: NMR ($CDCl_3$) δ 2.37 (s, 3 H, CH_3N), 2.94 (s, 3 H, CH_3NCO), 3.55 (m, 2 H, CH_2Cl); MS, m/e 192 (M + 2) and 190 (M^+).

The diethyl analogue **5b** was prepared in a similar manner: yield 98%; NMR ($CDCl_3$) δ 1.1 (overlapping triplets, 6 H, CH_3); MS, m/e 220 (M + 2) and 218 (M^+). Compounds **5a,b** rapidly decompose and cannot be stored overnight.

3-[2-(2,3-Dihydro-3-methyl-1*H*-indol-1-yl)ethyl]-1,4-dimethylpiperazin-2-one (6a). A solution of 2,3-dihydro-3-methylindole[18] (3.99 g, 30 mmol) and **5a** (5.76 g, 30 mmol) in anhydrous toluene (100 mL) was stirred at reflux under N_2 for 16 h. After cooling, the reaction mixture was treated with an ice-cold 10% solution of $NaHCO_3$, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. Evaporation of organic extracts gave 9 g of an oily product, which was chromatographed. Elution with $CHCl_3$/MeOH (30:1) afforded 6 g (70%) of **6a**: NMR ($CDCl_3$) δ 1.28 (d, J = 8 Hz, 3 H, CH_3), 2.37 (s, 3 H, CH_3N), 2.82 (s, 3 H, CH_3NCO), 6.55 (m, 2 H, Ar H), 6.94 (m, 2 H, Ar H); MS, m/e 287 (M^+).

Similarly prepared was **6b**: yield 72%; NMR ($CDCl_3$) δ 1.07 (overlapping triplets, J = 7.5 Hz, 6 H, CH_3 of ethyl), 1.27 (d, J = 8 Hz, 3 H, CH_3); MS, m/e 315 (M^+).

3-[2-(3-Methyl-1*H*-indol-1-yl)ethyl]-1,4-dimethylpiperazin-2-one (7a). A mixture of **6a** (2.87 g, 10 mmol), MnO_2 (2.8 g), 10% Pd/C (0.28 g), and xylene (200 mL) was heated to reflux overnight. The hot suspension was filtered, the filtrate was evaporated, and the residual oil was purified by chromatography ($CHCl_3$) to give 2.45 g (86%) of **7a** as a light tan oil: NMR ($CDCl_3$) δ 2.30 and 2.34 (singlets, 6 H, CH_3 and CH_3NCO), 4.09 (m, 2 H, indole (N)-CH_2), 6.86 (br s, 1 H, indolic H-2), 6.96–7.6 (m, 4 H, Ar H). The corresponding (*Z*)-2-butenedioate salt crystallized from MeOH–Et_2O: mp 130–134 °C; NMR (Me_2SO-d_6) δ 2.22 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3N), 2.82 (s, 3 H, CH_3NCO), 6.15 (s, 2 H, CH=CH), 6.9–7.5 (m, 5 H, Ar H). Anal. ($C_{21}H_{27}N_3O_5$) C, H, N.

In a similar manner compound **7b** was prepared in 63% yield. IR, UV, and NMR spectra were consistent with the structure.

(4a,12b-*cis*)-1,4,12-Trimethyl-1,2,3,4,4a,5,6,12b-octahydropyrazino[2′,3′:3,4]pyrido[1,2-*a*]indole (9a). A solution of **7a** (2.85 g, 10 mmol) in $POCl_3$ (10 mL) was refluxed for 3 h, then cooled, diluted with benzene (50 mL), and evaporated. After being placed under N_2, the residue was redissolved in abolute EtOH (15 mL), and sodium (1.7 g) was added gradually. Small amounts of absolute EtOH were periodically added to keep the reaction mixture boiling until the sodium dissolved. The cold mixture was diluted with H_2O and extracted with EtOAc. The combined extracts were washed with a solution of NH_4Cl, dried ($MgSO_4$), filtered, and evaporated. Crude product was chromatographed, eluting with $CHCl_3$/MeOH 20:1, to give 0.9 g (33%) of **9a**. The corresponding dihydrochloride was crystallized from MeCN: mp 223–224 °C; IR (Nujol) 2430 cm^{-1}; UV (MeOH) λ_{max} 284 nm (ϵ 6710), 276 (7210); NMR (Me_2SO-d_6) δ 2.35 (s, 3 H, CH_3), 2.65 (s, 3 H, CH_3N-1), 3.01 (s, 3 H, CH_3N-4), 5.21 (br, upon deuteriation d, J = 3.5 Hz, 1 H, H-12b). Anal. ($C_{17}H_{25}Cl_2N_3$) C, H, N. The dihydrochloride of **9b** was prepared from **7b** similarly to the above method: yield 30%; mp 238–240 °C; IR (Nujol) 2350 cm^{-1}; UV (MeOH) λ_{max} 284 nm (ϵ 7900), 276 (ϵ 8320); NMR (Me_2SO-d_6) δ 1.24 and 1.34 (overlapping triplets, J = 7.5 Hz, 6 H, CH_3 of ethyl), 2.34 (s, 3 H, CH_3), 5.22 (br s, 1 H, H-12b). Anal. ($C_{19}H_{29}Cl_2N_3$) C, H, N.

4-(3-Methyl-1*H*-indol-1-yl)butanoic Acid (11). Method A. An intimate mixture[19] of **10** (13.1 g, 0.1 mol) and NaH (4.8 g, 50% mineral oil dispersion, 0.1 mol) was heated under N_2 at 100 °C until evolution of H_2 ceased. The resultant material was dissolved in dry DMF (250 mL), and anhydrous butyrolactone (17.2 g, 0.2 mol) was added. The reaction mixture was refluxed for 12 h, cooled, poured on ice, and washed with Et_2O. The aqueous layer was acidified with hydrochloric acid and extracted with toluene. The extracts were evaporated, and the residue was purified by chromatography (toluene/EtOAc, 9:1) to give 13 g (60%) of **11**: mp 82–84 °C (benzene–hexane); IR ($CHCl_3$) 2900 (br), 1735 (inflex), 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.9–2.4 (m with a singlet spike at δ 2.22, 7 H, CH_2 and CH_3), 3.94 (t, J = 6 Hz, 2 H, CH_2N), 6.61 (s, 1 H, indole H-2), 7.15 (m, 3 H, Ar H), 7.35 (m, 1 H, indole H-4 or H-7). Anal. ($C_{13}H_{15}NO_2$) C, H, N.

Method B. A stirred mixture of **10** (13.1 g, 0.1 mol), dimethylacetamide (180 mL), anhydrous K_2CO_3 (42 g, 0.3 mol), and butyrolactone (51.6 g, 0.6 mol) was heated to reflux under N_2 for 48 h. The reaction mixture was diluted with H_2O, and the resulting solution was washed with toluene. The aqueous layer was acidified with hydrochloric acid and worked up as described in method A. Compound **11** was obtained in 70% yield. Prolonged reaction time and periodical additions of butyrolactone (up to 70 g total) afforded higher yields. The crude product can also be used for the next step without purification.

The 5-methoxy analogue of 11 was prepared from 5-methoxy-3-methylindole[20] in a similar fashion: yield 82% (method B); mp 69–71 °C (benzene–hexane) NMR (Me_2SO-d_6) δ 1.6–2.4 (m with a singlet spike at δ 2.24, 7 H, CH_2 and CH_3), 3.78 (s, 3 H,

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(19) Alternatively, a small amount of toluene can be used as a solvent.
(20) Heacock, R. A.; Hutzinger, O. *Can. J. Chem.* **1964**, *42*, 514.

CH_3O), 4.1 (t, J = 6 Hz, 2 H, CH_2N), 6.79 (dd, J_o = 9 Hz, J_m = 2 Hz, 1 H, H-6), 6.98 and 7.01 (2 br s, 1 H + 1 H, H-2 and H-4), 7.38 (d, J_o = 9 Hz, 1 H, H-7). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

6,7,8,9-Tetrahydro-10-methylpyrido[1,2-*a*]indol-9-one (12). A mixture of 11 (21.7 g, 0.1 mol) and polyphosphoric acid (100 g) was heated at 90 °C for 1 h and then poured (still warm) on ice. The resultant slurry was stirred for 4 h, diluted with H_2O, and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated. The residue crystallized from MeOH or Et_2O to give 19.1 g (96%) of **12**: mp 87–89 °C; IR ($CHCl_3$) 1648 cm^{-1}; UV (MeOH) λ_{max} 327 nm (ϵ 18 395), 245 (16 780); NMR ($CDCl_3$) δ 2.05–2.45 (m, 2 H, CH_2), 2.6 (m with a singlet spike, 5 H, CH_2CO and CH_3), 4.08 (t, J = 5.5 Hz, 2 H, CH_2N), 6.85–7.3 (m, 3 H, Ar H), 7.59 (m, 1 H, H-1). Anal. ($C_{13}H_{13}NO$) C, H, N.

The 2-methoxy analogue of 12 was prepared from the above described carboxylic acid in a similar way: yield 98%; mp 145–146 °C (Et_2O). Anal. ($C_{14}H_{15}NO_2$) C, H, N.

8-Bromo-6,7,8,9-tetrahydro-10-methylpyrido[1,2-*a*]indol-9-one (13). Bromination was carried out in the dark, under a N_2 atmosphere. To a solution of **12** (49.75 g, 0.25 mol) in CH_2Cl_2 (250 mL) was added a solution of trimethylphenylammonium tribromide (94 g, 0.25 mol) in CH_2Cl_2 (1200 mL) as fast as possible, while the inside temperature was maintained at 10 °C. The reaction mixture was stirred at room temperature for 24 h and evaporated, and the residue was partitioned between H_2O and benzene–Et_2O (1:1). The organic layer was dried ($MgSO_4$), filtered, and evaporated. Crude product was dissolved in $CHCl_3$ (55 mL), and Et_2O (600 mL) was added at once to precipitate small amounts of a dark-green material (the dibromo compound **16**). This minor contaminant was quickly removed by filtration, and the filtrate was chilled to 0 °C and allowed to crystallize. The resulting yellow-green crystals were collected by filtration and recrystallized from MeOH to give 63.9 g (92%) of **13**: mp 131–133 °C; purity 99.7% (GC). An analytical specimen was crystallized from Et_2O: mp 136–137 °C; IR ($CHCl_3$) 1655, 1530 cm^{-1}; NMR ($CDCl_3$) δ 2.65 (m with a singlet spike at δ 2.67, 5 H, CH_2 and CH_3), 4.29 (dd, J = 8 Hz, J_2 = 4 Hz, 2 H, CH_2N), 4.67 (t, J = 4 Hz, 1 H, CHBr), 7.30 (m, 3 H, Ar H), 7.67 (d, J_0 = 8 Hz, H-1). Anal. ($C_{13}H_{12}BrNO$) C, H, N.

In a similar manner, **the 2-methoxy analogue of 13** was prepared in 99% yield: mp 134–136 °C ($CHCl_3$–Et_2O); NMR ($CDCl_3$) δ 3.88 (s, 3 H, CH_3O), 4.72 (t, J = 4.5 Hz, 1 H, CHBr). The product was used in the next step without further purification.

2,8-Dibromo-6,7,8,9-tetrahydro-10-methylpyrido[1,2-*a*]indol-9-one (16) was prepared by a two-step bromination of **12**. To a solution of **12** (4.97 g, 25 mmol) in CH_2Cl_2 (100 mL) was added portionwise aged NBS (4.89 g, 27.5 mmol). The reaction mixture was stirred for 30 min at room temperature and washed successively with H_2O, 5% solution of $NaHCO_3$, and H_2O again. After drying ($MgSO_4$), the organic phase was evaporated, and the residue was crystallized from Et_2O to give 6.2 g (90%) of **2-bromo-6,7,8,9-tetrahydro-10-methylpyrido[1,2-*a*]indol-9-one**: mp 142–144 °C; NMR ($CDCl_3$) δ 2.34 (m, 2 H, CH_2), 2.57 (s, 3 H, CH_3), 2.68 (m, 2 H, CH_2CO), 4.11 (t, J = 5.5 Hz, 2 H, CH_2N), 7.10 (d, J_0 = 8.5 Hz, 1 H, H-4), 7.37 (dd, J_o = 8.5 Hz, J_m = 2 Hz, 1 H, H-3), 7.75 (d, J_m = 2 Hz, 1 H, H-1). This material was redissolved in CH_2Cl_2 (150 mL), and a solution of Br_2 (2 mL) in the same solvent (200 mL) was slowly added. The reaction mixture was washed successively with H_2O, 5% solution of $NaHCO_3$, and H_2O again. The organic layer was dried ($MgSO_4$), filtered, and evaporated to afford crude **16**. Crystallization from $CHCl_3$ gave 6.6 g (74% overall yield) of **16**: mp 156 °C; NMR ($CDCl_3$) δ 4.66 (t, J = 4 Hz, 1 H, CHBr). Anal. ($C_{13}H_{11}Br_2NO$) C, H, N.

(4b,12b-*trans*)-1,2,3,4,4a,5,6,12b-Octahydro-12-methylpyrazino[2′,3′:3,4]pyrido[1,2-*a*]indole (14). A solution of ethylenediamine (9.9 g, 165 mmol) in dioxane (11 mL) was added at once to a solution of **13** (8.34 g, 30 mmol) in dioxane (75 mL) at 15 °C, under a N_2 atmosphere. The mixture was stirred at ambient temperature for 18 h, cooled to 5 °C, and diluted with MeOH (75 mL) and H_2O (1 mL). $NaBH_4$ (3.1 g, 82 mmol) was added in portions, while the temperature was maintained at 5 °C. Stirring was continued at room temperature for 12 h, the reaction mixture was poured into cold 10% hydrochloride acid (90 mL), pH was adjusted to 2, and the diluted aqueous solution was washed with Et_2O, basified to pH 10.5 with 50% NaOH, and extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give 5.5 g (76%) of **14**: mp 196–197 °C (MeCN); IR ($CHCl_3$) 3340, 3290 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (s, 2 H, NH, exchangeable), 2.44 (s, 3 H, CH_3), 2.98 (narrow m, 4 H, NCH_2CH_2N), 7.10 (m, 3 H, Ar H), 7.42 (m, 1 H, H-11); MS, m/e (relative intensity, fragment) 241 (100, M^+), 240 (32, $M^+ - H$), 226 (30, $M^+ - CH_3$), 211 (32), loss of $CH_2{=}NH_2$), 183 (80, 6,7-dihydro-10-methylpyrido[1,2-*a*]indole). Anal. ($C_{15}H_{19}N_3$) C, H, N.

The corresponding (*Z*)-2-butenedioate salt was crystallized from MeOH–Et_2O: mp 229–231 °C. Anal. ($C_{19}H_{23}N_3O_4$) C, H, N.

Dimethanesulfonate salt of **14**: mp 247–249 °C (AcOH); NMR (Me_2SO-d_6) 2.40 (s, 6 H, CH_3SO), 2.45 (s, 3 H, CH_3), 4.90 (d, J = 11 Hz, 1 H, H-12b). Anal. ($C_{17}H_{27}H_3O_6S_2$) C, H, N.

The 10-methoxy analogue of 14 was prepared in the same manner: yield 89%; mp 153–155 °C (MeCN); NMR ($CDCl_3$) δ 1.80 (br, 2 H, NH, exchangeable), 2.43 (s, 3 H, CH_3), 3.00 (br s, 4 H, NCH_2CH_2N), 3.88 (s, 3 H, CH_3O). Anal. ($C_{16}H_{21}N_3O$) C, H, N.

The same procedure was used to convert **16** into **the 10-bromo analogue of 14**: yield 60%; mp 185 °C (MeOH–MeCN); NMR ($CDCl_3$) δ 1.66 (br, 2 H, NH, exchangeable), 2.35 (s, 3 H, CH_3), 6.95 (d, J_o = 8 Hz, 1 H, H-8), 7.14 (dd, J_o = 8 Hz, J_m = 1.5 Hz, 1 H, H-9), 7.54 (br s, 1 H, H-11). Anal. ($C_{15}H_{18}BrN_3$) C, H, N. The corresponding dihydrochloride was crystallized from MeCN; mp 282 °C; NMR (Me_2SO-d_6) δ 4.34 (d, J = 11 Hz, 1 H, H-12b). Anal. ($C_{15}H_{20}BrCl_2N_3$) C, H, N.

General Procedure for 4-Alkylation of 14. Compound 15a. To a solution of **14** (4.82 g, 20 mmol) in DMF (150 mL) were added anhydrous K_2CO_3 (3.45 g, 25 mmol) and ethyl iodide (3.9 g, 25 mmol). The mixture was stirred at room temperature for 3 h and evaporated. The residue was partitioned between H_2O and $CHCl_3$, and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. Chromatographic purification, eluting with $CHCl_3$/MeOH (99:1), gave 3.6 g (67%) of **15a** as an oil: MS, m/e (relative intensity, fragment) 269 (100, M^+), 254 (15, $M^+ - Me$), 240 (49, $M^+ - Et$). The dihydrobromide salt was crystallized from MeOH–Et_2O: mp 237–238 °C; NMR (Me_2SO-d_6) δ 1.3 (t, J = 7 Hz, 3 H, CH_3 of ethyl), 2.46 (s, 3 H, CH_3), 5.12 (d, J = 10.5 Hz, 1 H, H-12b). Anal. ($C_{17}H_{25}Br_2N_3$) C, H, N.

With isopropyl iodide, **15b** was prepared in the same manner: yield 78% (reaction time 48 h): mp 125–126 °C (MeCN). Anal. ($C_{18}H_{25}N_3$) C, H, N. The dihydrochloride salt crystallized from MeOH: mp 239–241 °C; NMR (Me_2SO-d_6) δ 1.20 and 1.41 (doublets, J = 7 Hz, 6 H, CH_3 of isopropyl), 5.33 (d, J = 10 Hz, 1 H, H-12b). Anal. ($C_{18}H_{27}Cl_2N_3$) C, H, N.

An analogous procedure afforded **the 10-bromo derivative of 15b**: yield 66%; mp 138 °C (Et_2O); NMR ($CDCl_3$) δ 0.95 and 1.16 (doublets, J = 7 Hz, 6 H, CH_3 of isopropyl), 2.41 (s, 3 H, CH_3), 7.59 (d, J = 2 Hz, 1 H, H-11). Anal. ($C_{18}H_{24}BrN_3$) C, H, N.

Similarly, replacement of ethyl iodide by 1-bromo-2-phenoxyethane afforded **15c**: yield 52% (reaction temperature 70 °C); MS, m/e (relative intensity, fragment) 361 (100, M^+), 317 (60, loss of $CH_3CH{=}NH_2^+$). The (*Z*)-2-butenedioate salt crystallized from MeOH–Et_2O: mp 177–178 °C. Anal. ($C_{27}H_{31}N_3O_5$) C, H, N.

General Procedure for 1,4-Dialkyl Derivatives of 14. To a solution of **14** or **15a–c** (20 mmol) in DMF (~150 mL) were added anhydrous K_2CO_3 (60–80 mmol) and the appropriate alkyl iodide. The mixture was stirred at the temperature corresponding to the boiling point of the alkyl iodide for 24–48 h and evaporated. The residue was partitioned between H_2O and $CHCl_3$, and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. Column chromatography was performed where needed. Oily products were converted to crystalline salts.

Compound 15e: oil; yield 59%. The hydrobromide salt: mp 237–238 °C (MeOH–MeCN); UV (MeOH) λ_{max} 286 nm (ϵ 8020), 229 (ϵ 38 510); NMR (Me_2SO-d_6) δ 1.03 and 1.29 (triplets, J = 7.5 Hz, 6 H, CH_3 of ethyl), 2.32 (s, 3 H, CH_3), 4.74 (d, J = 11 Hz, 1 H, H-12b). Anal. ($C_{19}H_{28}BrN_3$) C, H, N. The hydrochloride salt: mp 200–202 °C (MeOH). Anal. ($C_{29}H_{28}ClN_3$) C, H, N. The hydriodide salt: mp 229–230 °C (MeOH). Anal. ($C_{19}H_{28}IN_3$) C, H, N.

Compound 15f: mp 130 °C; yield 77%. Anal. ($C_{19}H_{26}BrN_3$) C, H, N. The hydrochloride salt: mp 290–291 °C (MeCN); UV (MeOH) λ_{max} 294 nm (ϵ 6900), 288 (6650), 233 (35 500); NMR

(Me_2SO-d_6) δ 1.02 and 1.29 (triplets, J = 7.5 Hz, 6 H, CH_3 of ethyl), 2.31 (s, 3 H, CH_3), 4.96 (d, J = 10.5 Hz, 1 H, H-12b), 7.20 (m, 2 H, Ar H), 7.57 (br s, 1 H, H-11). Anal. ($C_{19}H_{27}BrClN_3$) C, H, N.

Compound 15g: oil; yield 47%. The hydrobromide salt: mp 252–254 °C (MeOH); NMR (Me_2SO-d_6) δ 0.8 (t, J = 7.5 Hz, 3 H, CH_3 of propyl), 1.29 (t, J = 7.5 Hz, 3 H, CH_3 of ethyl), 2.32 (s, 3 H, CH_3), 4.79 (d, J = 10 Hz, 1 H, H-12b). Anal. ($C_{20}H_{30}BrN_3$) C, H, N.

Compound 15h: oil; yield 70%. The dihydrochloride salt: mp 221–222 °C (MeCN–Et_2O); NMR (Me_2SO-d_6) δ 5.19 (d upon deuteriation, J = 10 Hz, 1 H, H-12b). Anal. ($C_{21}H_{33}Cl_2N_3$) C, H, N.

Compound 15i: oil; yield 41%. The hydrobromide salt: mp 246–248 °C (MeOH); NMR (Me_2SO-d_6) δ 0.80 and 0.97 (triplets, J = 7 Hz, 6 H, CH_3 of propyl), 4.76 (d, J = 10 Hz, 1 H, H-12b). Anal. ($C_{21}H_{32}BrN_3$) C, H, N.

Compound 15j: mp 79–80 °C (*i*-PrOH); yield 91%. Anal. ($C_{20}H_{29}N_3$) C, H, N. The dihydrobromide salt: mp 229–230 °C (MeOH). Anal. ($C_{20}H_{31}Br_2N_3$) C, H, N. The (*Z*)-2-butenedioate salt: mp 185–187 °C (AcOEt); UV (MeOH) λ_{max} 285 nm (ε 8300), 227 (44 200); NMR (Me_2SO-d_6) δ 1.05 (t, J = 7 Hz, 3 H, CH_3 of ethyl), 1.25 and 1.30 (doublets, J = 6.5 Hz, 6 H, CH_3 of isopropyl), 2.35 (s, 3 H, CH_3), 4.65 (d, J = 10 Hz, 1 H, H-12b). Anal. ($C_{24}H_{33}N_3O_4$) C, H, N.

Compound 15k: mp 125 °C (Et_2O); yield 78%. Anal. ($C_{20}H_{28}BrN_3$) C, H, N. The dihydrochloride salt: mp 228 °C (MeOH–*i*-PrOH). Anal. ($C_{20}H_{30}BrCl_2N_3$) C, H, N.

Compound 15l: mp 158–160 °C (*i*-PrOH); yield 47%. Anal. ($C_{21}H_{31}N_3O$) C, H, N. The dihydrochloride salt: mp 207–209 °C (EtOH); NMR (Me_2SO-d_6) δ 3.80 (s, 3 H, CH_3O), 5.62 (d, J = 10 Hz, 1 H, H-12b). Anal. ($C_{21}H_{33}Cl_2N_3O$) C, H, N.

Compound 15m: oil; yield 50%. The hydrobromide salt: mp 255–256 °C (MeOH). Anal. ($C_{21}H_{32}BrN_3$) C, H, N.

Compound 15n: oil; yield 56%. The dihydrochloride salt: mp 230–231 °C (MeOH–Et_2O); NMR (Me_2SO-d_6) δ 1.13 (t, J = 7 Hz, 3 H, CH_3 of ethyl), 2.41 (s, 3 H, CH_3), 5.30 (d, J = 10 Hz, 1 H, H-12b), 6.7–7.55 (m, 9 H, Ar H). Anal. ($C_{25}H_{33}Cl_2N_3O$) C, H, N.

(4a,12b-*trans*)-1,4,12-Trimethyl-1,2,3,4,4a,5,6,12b-octahydropyrazino[2′,3′:3,4]pyrido[1,2-*a*]indole (15d). A solution of **14** (4.82 g, 20 mmol) in EtOH (180 mL) was treated with 2.4 N ethanolic HCl (25 mL), and the mixture was evaporated to dryness. The residue was dissolved in 37% aqueous CH_2O (16.2 g, 200 mmol), and the mixture was stirred at room temperature for 2 h. A solution of $NaBH_3CN$ (9.5 g, 150 mmol) in MeOH (400 mL) was added dropwise, upon cooling. This was followed by addition of 4-Å molecular sieves (18 g), and the resulting reaction mixture was stirred at ambient temperature overnight. After coarse filtration, the filtrate was concentrated, and the residue was partitioned between 5% NH_4OH and $CHCl_3$. The organic layer was evaporated to give the crude product, which was purified by chromatography. Elution with AcOEt/hexane/Et_3N (60:35:5) afforded **15d** (3.66 g, 68%) as an oil; MS, m/e (relative intensity, fragment) 269 (100, M^+), 254 (4, $M^+ - CH_3$), 225 (9, loss of $CH_2{=}NH^+CH_3$), 211 (13, loss of $CH_3CH{=}NH^+CH_3$), 183 (43, vide supra). The (*Z*)-2-butenedioate salt: mp 178–180 °C (MeOH); NMR ($CDCl_3$) δ 2.35 (br s, 6 H, 1- and 12-CH_3), 2.89 (s, 3 H, 4-CH_3), 4.70 (d, J = 10 Hz, 1 H, H-12b), 6.22 (s, 2 H, CH=CHCO), 7.12 (m, 3 H, ArH), 7.49 (m, 1 H, H-11). Anal. ($C_{21}H_{27}N_3O_4$) C, H, N.

(4a,12b-*trans*)-4-Benzoyl-12-methyl-1,2,3,4,4a,5,6,12b-octahydropyrazino[2′,3′:3,4]pyrido[1,2-*a*]indole. A solution of **14** (4.82 g, 20 mmol) in CH_2Cl_2 (100 mL) was treated with 10% aqueous NaOH (30 mL) and the heterogeneous mixture was cooled to 0 °C upon stirring. While the temperature was kept at 0–5 °C, a solution of benzoyl chloride (2.71 g, 20 mmol) in CH_2Cl_2 was added dropwise over 5 min. The mixture was stirred for 15 min, and the organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered, and evaporated. The residue was crystallized from MeOH to yield 6.6 g (95%) of the title amide: mp 198–200 °C; MS, m/e (relative intensity, fragment) 345 (90, M^+), 330 (4, $M^+ - CH_3$), 240 (6, loss of benzoyl), 198 (100, loss of *N*-benzoylaziridine); NMR (Me_2SO-d_6) δ 2.38 (s, 3 H, CH_3) 4.26 (double m, J = 10 Hz, H-12b), 6.8–7.6 (m with a singlet spike at 7.42, 9 H, Ar H). Anal. ($C_{22}H_{23}N_3O$) C, H, N.

(4a,12b-*trans*)-1-Ethyl-12-methyl-1,2,3,4,4a,5,6,12b-octahydropyrazino[2′,3′:3,4]pyrido[1,2-*a*]indole (15o). A mixture of the above amide (6.9 g, 20 mmol), DMF (150 mL), ethyl iodide (6.24 g, 40 mmol), and anhydrous K_2CO_3 (5.52 g, 40 mmol), was stirred at 60 °C for 14 h and evaporated, and the residue was partitioned between H_2O and $CHCl_3$. The organic layer was concentrated and chromatographed; elution with $CHCl_3$/hexane (1:1) afforded 5 g (67%) of **4-benzoyl derivative of 15o**, which was converted to the (*Z*)-2-butenedioate salt: mp 136–138 °C (AcOEt–Et_2O); NMR (Me_2SO-d_6) δ 1.04 (t, J = 7 Hz, CH_3 of ethyl), 2.35 (s, 3 H, CH_3), 4.96 (d, J = 10 Hz, 1 H, H-12b), 6.16 (s, 2 H, CH=CHCO), 6.9–7.4 (m, 4 H, Ar H), 7.46 (m, 5 H, Ar H). Anal. ($C_{28}H_{31}N_3O_5$) C, H, N.

This material (5.86 g, 12 mmol) was suspended in ethanol (150 mL) and 10% NaOH (60 mL), and the mixture was refluxed for 18 h and evaporated. The residue was partitioned between H_2O and Et_2O, and the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to obtain 2.83 g (88%) of **15o**: mp 142–143 °C; NMR ($CDCl_3$) δ (t, J = 7 Hz, 3 H, CH_3 of ethyl), 1.88 (s, 1 H, NH, exchangeable), 6.95–7.16 (m, 3 H, Ar H), 7.47 (m, 1 H, H-11). The (*Z*)-2-butenedioate salt: mp 207–208 °C (EtOH); NMR (Me_2SO-d_6) δ 4.51 (d, J = 10 Hz, 1 H, H-12b). Anal. ($C_{21}H_{27}N_3O_4$) C, H, N.

Pharmacology. Assessment of Antihypertensive Activity in Spontaneously Hypertensive Rats (SHR). Male SHR (250–400 g, more than 12 weeks old) obtained from Charles River (Lakeview, MA) or Taconic Farms (Germantown, NY) were used in these studies. Prior to treatment, the mean arterial blood pressure (MABP) and heart rate (HR) were 169 ± 1 mmHg ± SEM and 433 ± 2 bpm ± SEM, respectively. The resting blood pressure of test animals was in the range from 145 to 222 mmHg. Each rat was anesthetized with halothane, and the left femoral artery and vein were cannulated with polyethylene tubing (o.d. 0.038 in.; i.d. 0.023 in.). The animals were wrapped in rubber mesh jackets, suspended from horizontal bars with towel clamps, and allowed to recover from the anesthesia. The arterial cannula was connected to a Gould Statham pressure transducer (Model P23), which in turn was attached to a polygraph to record MABP and HR. All test compounds were dissolved or dispersed in 0.5% solution of methylcellulose and prepared for oral dosing in a volume of 5 mL/kg of body weight. Doses tested ranged from 0.1 to 50 mg/kg; at each dose a minimum of four and a maximum of eight animals were tested. After a 1-h equilibration period, epinephrine was injected at 2 μg/kg iv, and 10 min later, upon recovery of the MABP, the test compound was administered by gastric gavage. MABP and HR were monitored for 4 h, while epinephrine was injected again at 1 h. Only maximal changes in MABP and HR are reported; the changes were evaluated for statistical significance by using two-way analysis of variance.

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