2,4-diamino-6-quinazolinesulfonyl chloride sulfate, 5.1 g (0.04 mol) of 4-chlorobenzenamine, and 50 mL of EtOH was heated under reflux for 1 h, allowed to cool slightly, and poured into H_2O. The precipitate was collected and recrystallized from a mixture of EtOH, H_2O, and NH_4OH to afford 1.3 g (37%) of **19**, mp 327–328 °C.

Acknowledgment. We thank the late Dr. Leo Rane of the University of Miami for the antimalarial testing and Dr. C. L. Heifetz for the antibacterial testing. We also acknowledge C. E. Childs and associates for the microanalyses, Dr. J. M. Vandenbelt and co-workers for determination of spectral data, and J. Dickinson and A. Johnson for synthetic assistance.

Registry No. 1, 21811-06-3; 2, 21811-10-9; 3, 92144-19-9; 4, 92144-20-2; 5, 21882-31-5; 6, 92144-21-3; 7, 21882-32-6; 8, 86670-18-0; 9, 92144-22-4; 10, 92144-23-5; 11, 56044-06-5; 12, 56044-07-6; 13, 92144-24-6; 14, 56044-08-7; 15, 56044-16-7; 16, 56044-10-1; 17, 92144-25-7; 18, 92144-26-8; 19, 92144-27-9; 20, 92144-28-0; 21, 92184-45-7; 22, 92144-29-1; 23, 92144-30-4; 24, 92144-31-5; 25, 56044-17-8; 26, 92144-32-6; IV (Z = H), 81080-73-1; IV (base, Z = H), 1899-48-5; V (Z = H), 92144-33-7; V (Z = Cl), 92144-34-8; V (Z = CH_3), 92144-35-9; VI (Z = CH_3), 17511-22-7; VI (Z = Cl), 17511-20-5; NH_3, 7664-41-7; $HN(CH_3)_2$, 124-40-3; $HN(C_2H_5)_2$, 109-89-7; $HN(CH_2CH_2CH_3)_2$, 142-84-7; $HN(CH_2CH_2OH)_2$, 111-42-2; $NH(CH_3)CH(CH_3)_2$, 4747-21-1; $HN(CH_3)CH_2CH_2N(C_2H_5)_2$, 104-79-0; 4-$ClC_6H_4NH_2$, 106-47-8; 3,4-$Cl_2C_6H_3NH_2$, 95-76-1; 3-$BrC_6H_4NH_2$, 591-19-5; 3-$ClC_6H_4NHCH_3$, 7006-52-2; $C_6H_5NHCH_3$, 100-61-8; 3,4-$Cl_2C_6H_3CH_2NHCH_3$, 5635-67-6; 2-$C_{10}H_7NH_2$, 91-59-8; piperidine, 110-89-4; pyrrolidine, 123-75-1; 1,4′-bipiperidine, 4897-50-1; morpholine, 110-91-8; thromorpholine, 123-90-0; 1-methylpiperazine, 109-01-3; ethyl 1-piperazinecarboxylate, 120-43-4; 2-benzylpiperidine, 32838-55-4; 1,2,3,4-tetrahydroisoquinoline, 91-21-4.

Tetrahydropyrrolo[1,2-*a*]quinoxalines and Tetrahydropyrrolo[1,2-*a*]pyrido[3,2-*a*]pyrazines: Vascular Smooth Muscle Relaxants and Antihypertensive Agents

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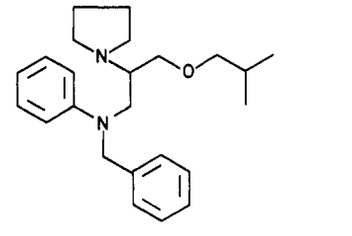
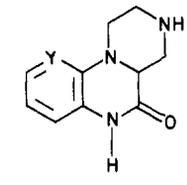
Received May 7, 1984

A series of tetrahydropyrrolo[1,2-*a*]quinoxalines and tetrahydropyrrolo[1,2-*a*]pyrido[3,2-*a*]pyrazines were synthesized and tested for their ability to relax K^+-depolarized aortic smooth muscle and antihypertensive activity. It was shown that compounds producing the most relaxation of aortic smooth muscle (5-[(2,6-dimethoxyphenyl)methyl]-1,2,3,3a-tetrahydropyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one and 5-[(2,6-dimethoxyphenyl)methyl]-5,6,6a,7,8,9-hexahydropyrrolo[1,2-*a*]pyrazine, **10** and **19**, respectively) demonstrated the least hypotensive activity. Those compounds that were the most effective hypotensive agents (6a,7,8,9-tetrahydro-5-(phenylmethyl)pyrido[3,2-*a*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one and 6a,7,8,9-tetrahydro-5-(4-pyridinylmethyl)pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one, **12** and **13**, respectively) displayed little vascular smooth muscle relaxant activity.

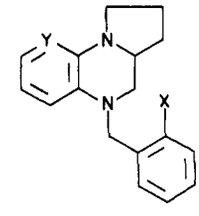
In an effort to develop compounds that inhibit Ca^{2+}-dependent force development in vascular smooth muscle with antihypertensive properties, molecular hybrids between the calcium antagonist bepridil[1] (**1**) and the antihypertensive pyrazinoquinoxaline[2] **2a** and tetrahydropyrazino[1,2-*a*]pyrido[3,2-*e*]pyrazines[3,4] **2b** were investigated. The hybrid molecules **3** contain the entire carbon skeleton of **2a** or **2b** but are devoid of the additional piperazino amine functionality. Hybrid compounds **3** also contain most of the carbon skeleton of bepridil but in cyclized form. We hypothesized that the alkyl ether functionality of **1** could be compensated for by the introduction of an ether substituent (X) on the aromatic ring. The hybrid compounds **3a,b** also facilitated an examination of the effects of structural variations on the antihypertensive activities of compounds **2a** and **2b**.



1



2a, Y = CH
b, Y = N



3a, Y = CH
b, Y = N

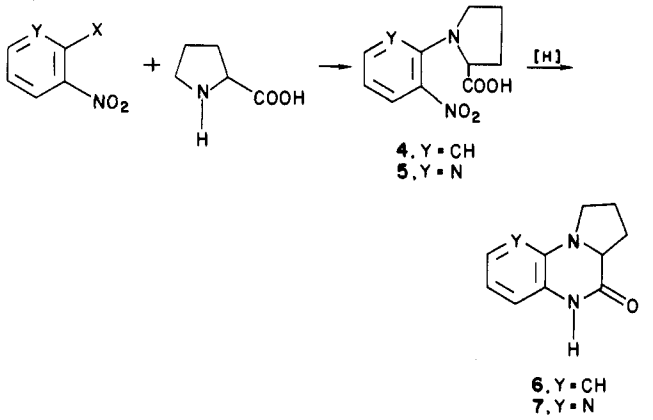
Chemistry. The key starting intermediates **6** and **7** were prepared by reacting 1-fluoro-2-nitrobenzene or 2-chloro-3-nitropyridine with L-(−)-proline in Me_2SO in the presence of triethylamine at 60 °C to afford the corresponding nitro acids **4** and **5** in 82% and 87% yields, respectively. The nitro acids were reductively cyclized via alkaline sodium dithionite[5] or iron in glacial acetic acid[6] to afford **6** and **7** (Scheme I).

The sodium dithionite reduction was found to be a pH-sensitive reaction; optimum yields (61% for compound **6** and 39% for compound **7**) were obtained at pH 8. Alkylations of **6** and **7** with the appropriately substituted

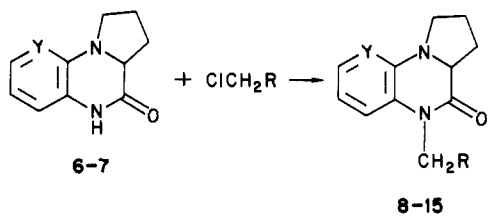
(1) Cosnier, D.; Duchene-Morullax, P.; Rispot, G.; Streichenberger, G. *Arch. Int. Pharmacodyn.* **1977**, *225*, 133. The correct structure of bepridil was reported in Zelesko, M. J.; McComsey, D. F.; Hageman, W. E.; Nortey, S. O.; Baker, C. A.; Maryanoff, B. E. *J. Med. Chem.* **1983**, *26*, 230.
(2) Freed, M. E.; Potoski, J. R. U.S. Patent 4 089 958, 1978.
(3) Freed, M. E.; Potoski, J. R. U.S. Patent 4 138 564, 1979.
(4) Freed, M. E.; Potoski, J. R. U.S. Patent 4 225 713, 1980.
(5) Fieser, L. F.; Fieser, M. *J. Am. Chem. Soc.* **1934**, *56*, 1565.
(6) Van Dusen, R.; Schultz, H. P. *J. Org. Chem.* **1956**, *21*, 1326.

0022-2623/84/1827-1743$01.50/0

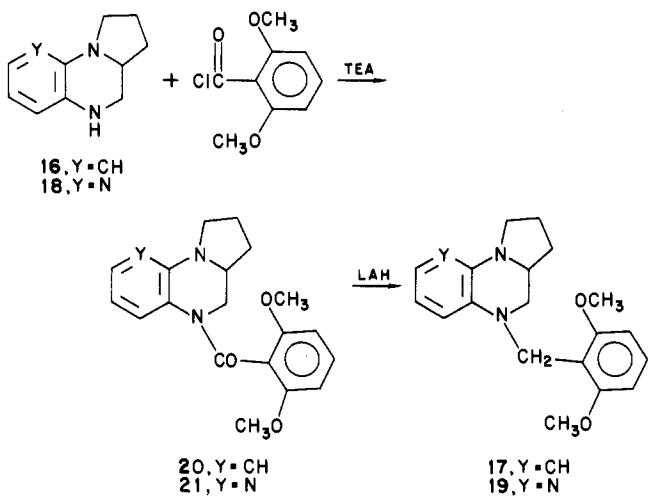
Scheme I



Scheme II



Scheme III



alkyl or aralkyl halides were carried out in DMF in the presence of sodium hydride to afford the corresponding tetrahydropyrrolopyridopyrazinones (Scheme II; Table II). The desired hybrid molecules **17** and **19** were prepared via the reduction of compounds **10** and **14** with lithium aluminum hydride in a mixture of anhydrous ether–tetrahydrofuran.[7]

Compounds **17** and **19** were preferably prepared in higher yields by an alternate syntheses in which 2,6-dimethoxybenzoyl chloride[8] was reacted with reduced quinoxaline **16** or pyridopyrazine **18** in acetone in the presence of triethylamine to afford the corresponding *N*-aroyl derivatives **20** and **21** in 81% and 87% yields, respectively. Lithium aluminum hydride reduction of **20** and **21** in THF afforded compounds **17** and **19** in 87% and 65% yields, respectively (Scheme III).

In an attempt to elicit antihypertensive activity, the pharmacophoric (aryloxy)propanolyl moiety was joined to

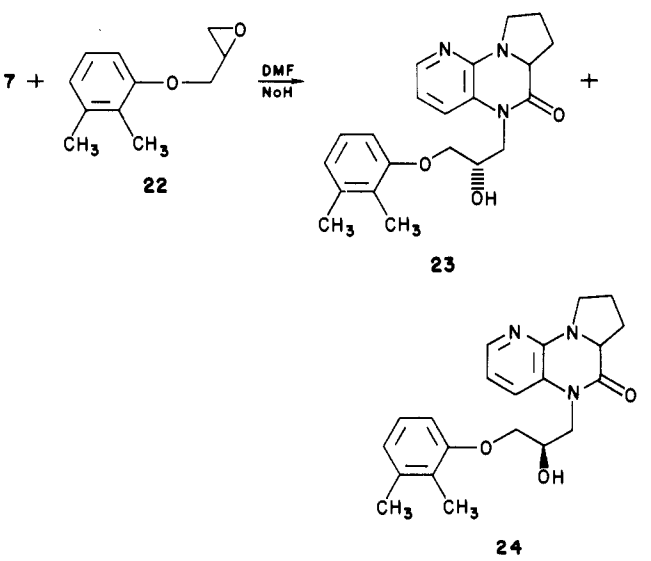
(7) Atrico, M.; DeMartino, G.; Nacci, V. *Ann. Chim. (Rome)* **1967**, *57*, 1431.
(8) Doyle, F. P.; Hardy, K.; Nayler, J. H.; Goulal, M. J.; Stove, E. R.; Waddington, H. R. J. *J. Chem. Soc.* **1962**, 1454.

Table I. Vascular Smooth Muscle Relaxant and Antihypertensive Activity of Selected Tetrahydropyrrolo[1,2-*a*]quinoxalines and Pyridopyrazines

compd	vascular relaxtn,[a] %	antihypertensive act.,[b] (max SBP at 1.5 or 4 h, mmHg ± SE)
6	0	−26 ± 13
8	NT	−4 ± 15
9	NT	−2 ± 10
10	30	−19 ± 8
12	0	−39 ± 12*
13	0	−38 ± 5*
14	5	−18 ± 10
15	0	−22 ± 7
16	0	−17 ± 10 (8)
17	13	−5 ± 20
19	54	−6 ± 8 (8)
20	6	−13 ± 9
nifedipine	75 (10^{-7} M)	−68 ± 16* (5 mg/kg)

[a] Test drug was added to 10^{-5} M after 20 min of sustained contraction in high-K^+ (100 mM) solution and 2.5 mM $CaCl_2$. The ability of the compound to relax the muscle was assessed 20 min after dosing. Data are expressed as percent of relaxation of the developed force. NT = not tested. [b] Drug was administered orally by gavage. Four rats received single oral doses of the test compound. Data are expressed as $X \pm SE$ and refer to maximal change in systolic blood pressure (SBP) from pretreatment levels at either 1.5 or 4 h after dosing. Numbers in parentheses are the number of rats/group if different from four. Control groups received vehicle alone. (*) Statistically different from pretreatment control at $P < 0.05$, Student's t test.

7. Condensation of **7** with 1,2-epoxy-3-(2,3-dimethylphenoxy)propane (**22**) in DMF in the presence of sodium hydride at 60 °C afforded two products, **23** and **24**, in 57% and 17% yields. Both **23** and **24** contain the 3-(2,3-dimethylphenoxy)-2-hydroxypropyl functionality, which exists in many of the pharmacologically active β-blockers.[9,10]



Results and Discussion

The vascular smooth muscle relaxant activity (Table I) is expressed as percent relaxation of the developed isometric tension in potassium depolarized rabbit aortic smooth muscle, while the antihypertensive activity is reported in terms of millimeters of mercury (mmHg) blood pressure drop in spontaneous hypertensive rats at the stated time at a dose of 50 mg/kg.

(9) Large, M. S.; Smith, L. H. *J. Med. Chem.* **1982**, *25*, 1286.
(10) Smith, L. H. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 201.

Table II. Tetrahydropyrroloquinoxalines and Tetrahydropyrrolopyridopyrazinones

no.	Y	R	mp, °C	% yield	formula	anal.
8	CH	C_6H_5	156–157[a]	63	$C_{18}H_{18}N_2O$	C, H, N
9[b]	CH	4-C_6H_4N	185–187[a]	60	$C_{17}H_{17}N_3O$	C, H, N
10	CH	2,6-$(OCH_3)_2C_6H_3$	128–130[c]	75	$C_{20}H_{22}N_2O_3$	C, H, N
11	CH	$CH_2N(CH_3)_2$	162–163[d]	71	$C_{15}H_{21}N_3O{\cdot}2HCl$[f,e]	C, H, N, Cl
12	N	C_6H_5	139–141[f]	65	$C_{17}H_{17}N_3O$	C, H, N
13[g]	N	4-C_6H_4N	200–202[h]	55	$C_{16}H_{16}N_4O$	C, H, N
14	N	2,6-$(OCH_3)_2C_6H_3$	220–223[h]	79	$C_{19}H_{21}N_3O_3{\cdot}HCl$	C, H, N
15	N	$CH_2N(CH_3)_2$	248–251[i]	56	$C_{14}H_{20}N_4O{\cdot}2HCl$	C, H, N, Cl

[a] Acetone. [b] $[\alpha]^{25}_D$ −27.31° (c 0.875, $CHCl_3$). [c] Aqueous ethanol. [d] Ethanol. [e] Monohydrate. [f] Ethanol; 222–225 °C for the HCl salt, $[\alpha]^{25}_D$ −5.06° (c 0.83, C_2H_5OH). [g] 262–265 °C for the 2HCl salt. [h] Ethanol. [i] Ethanol–acetone. [j] Monohydrate.

Compounds **10** and **19**, which have structures closely analogous with bepridil, are the only members of the series to significantly inhibit force development. Apparently this activity is tolerant of (1) displacing the ether functionality to the *N*-benzyl phenyl ring, (2) introducing a pyrido nitrogen on the *N*-phenyl ring, and (3) fusing the pyrrolidino ring into a cyclic structure. This activity was greatly diminished by the introduction of the amide carbonyl into the 6-position (**14** vs. **19**).

Among the compounds tested for antihypertensive activity, compounds **12** and **13** were the most potent in the series and elicited moderate reductions in blood pressure. However, direct effects on K^+-depolarized force development were minimal. The pyrido nitrogen significantly enhanced antihypertensive activity (**12** vs. **8** and **13** vs. **9**; **8** and **9** had no effect on blood pressure).

Experimental Section

All melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer Model 240 elemental analyzer by the Analytical Section of these laboratories. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4%. IR spectra were recorded as KBr pellets on a Perkin-Elmer 299 infrared spectrophotometer. NMR spectra were obtained on a JEOL Model C-60HL, a Varian XL-100, or a Varian FT-88 NMR spectrometer with Me_4Si as the internal standard. Mass spectra were recorded with an Kratos MS 25 high-resolution mass spectrometer. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter.

6a,7,8,9-Tetrahydropyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-6-(5*H*)-one (7). A solution of 49.94 g (0.315 mol) of 2-chloro-3-nitropyridine, 36.38 g (0.316 mol) of L-(−)-proline, and 60 mL of triethylamine in 450 mL of dimethyl sulfoxide was heated at 60 °C with stirring for 18 h.

The mixture was diluted with 1.5 L of cold water and extracted with diethyl ether, and the aqueous layer was acidified to pH 3 with concentrated hydrochloric acid and extracted repeatedly with methylene chloride. The combined methylene chloride extracts were dried (Na_2SO_4) and concentrated. The solid was filtered, and recrystallization from ethyl acetate/pentane yielded 65 g (87%) of *N*-(3-nitro-2-pyridinyl)pyrrolidine-2-carboxylic acid (**5**): mp 137–139 °C; IR (KBr) 3250 (OH), 1710 cm^{-1} (CO); NMR ($CDCl_3$) δ 2.8–3.5 (m, 4 H, pyrrolidine), 4–4.5 (m, 2 H, pyrrolidine), 4.7–4.9 (m, 1 H, pyrrolidine), 6.75 (dd, *J* = 8 and 5 Hz, 1 H, pyridine H), 8.05 (dd, *J* = 8 and 2 Hz, 1 H, pyridine H), 8.3 (dd, *J* = 5 and 2 Hz, 1 H, pyridine H), and 9.2 (br, 1 H, COOH); MS, *m/e* 237 (M^+). Anal. ($C_{10}H_{11}N_3O_4$) C, H, N.

Method A. *N*-(3-Nitro-2-pyridinyl)pyrrolidine-2-carboxylic acid (26 g, 0.1 mol) was dissolved in 800 mL of water, and the pH was adjusted to 9–10 with 50% sodium hydroxide solution. To this stirred solution was added in small portions 70 g of sodium dithionite. The pH was monitored during the addition and was readjusted to pH 9. The reaction mixture was stirred for 1 h, then cooled, and acidified with concentrated hydrochloric acid to a pH of 2. The separated solid was filtered, washed with water, dried, and recrystallized from an ethanol–diethyl ether (1:1) mixture to give 8 g (39%) of the title compound, mp 182–184 °C. The hydrochloride salt was prepared by dissolving the free base in ethanol and then treating the solution with diethyl ether saturated with hydrogen chloride gas. The separated solid upon recrystallization from ethanol afforded **7** as white crystals: mp 268–270 °C; IR (KBr) 3200 (NH), 1690 cm^{-1} (CO); NMR (Me_2SO-d_6) 1.8–2.4 (m, 4 H, pyrrolidine), 3.5–4.0 (m, 2 H, pyrrolidine), 4.3–4.6 (m, 1 H, pyrrolidine), 6.9 (dd, *J* = 6 and 1.5 Hz, 1 H, pyridine H), 7.35 (dd, *J* = 6 and 1.5 Hz, 1 H, pyridine H), 7.6 (dd, *J* = 6 and 1.5 Hz, 1 H, pyridine H), 11.25 (s, 1 H, NH), 3.0–5.0 (br, HCl + H_2O); MS, *m/e* 189 (M^+). Anal. ($C_{10}H_{11}N_2O{\cdot}HCl{\cdot}^1/_2H_2O$) C, H, N, Cl.

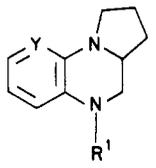
Method B. To a stirred solution of *N*-(3-nitro-2-pyridinyl)-pyrrolidine-2-carboxylic acid (26 g, 0.1 mol) in 250 mL of glacial acetic acid was added 12 g of iron powder over a period of 1 h. The temperature of the reaction was raised to 80 °C, and the reaction was allowed to stir at 60–65 °C for 3 h. The reaction mixture was cooled and filtered, and the acetic acid was evaporated under reduced pressure. The remaining slurry was extracted with three 300-mL portions of methylene chloride. The methylene chloride extracts were pooled, dried (Na_2SO_4), and evaporated under reduced pressure. The separated solid was recrystallized from ethanol–diethyl ether (1:1) mixture to afford 11 g (56%) of **7**, mp 182–184 °C.

5-[(2,6-Dimethoxyphenyl)methyl]-6a,7,8,9-tetrahydropyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one (14). To a stirred solution of 6a,7,8,9-tetrahydropyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one (2.7 g, 0.01 mol) in 30 mL of dry dimethylformamide was added sodium hydride (0.5 g, 0.02 mol of a 50% dispersion in mineral oil). When the evolution of hydrogen subsided, 2.7 g (0.01 mol) of 2,6-dimethoxybenzyl chloride was added. The reaction mixture was stirred at room temperature for 18 h, and the dimethylformamide was removed under reduced pressure. The residue was triturated with cold water and the separated solid was filtered. Recrystallization from ethanol yielded white crystals of the title compound: 2.7 g (89%); mp 200–202 °C; hydrochloride salt, mp 220–223 °C; NMR ($CDCl_3$) δ 1.7–2.5 (m, 4 H, pyrrolidine), 3.3–3.8 (m, 2 H, pyrrolidine), 3.7 (s, 6 H, $(OCH_3)_2$, 3.8–4.0 (m, 1 H, pyrrolidine), 4.9–5.4 (q, *J* = 16 Hz, 2 H, CH_2 Ar), 6.25–6.5 (m, 3 H, Ar H), 6.9–7.3 (m, 2 H, pyridine H), 6.7 (dd, *J* = 5 and 2 Hz, 1 H, pyridine H); MS, *m/e* 339 (M^+). Anal. ($C_{19}H_{21}N_3O_3{\cdot}HCl$) C, H, N.

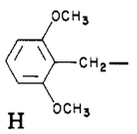
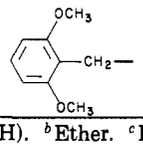
Compounds 8–15. These compounds were prepared according to the procedure described for compound **14** by using the appropriate alkyl or aryl halide (Table II).

5-[3-(2,3-Dimethylphenoxy)-2-hydroxypropyl]-6a,7,8,9-tetrahydropyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one (23 and 24). To a stirred solution of **7** (2.7 g, 0.015 mol) in 40 mL of dry DMF was added 0.6 g of sodium hydride (0.025 mol of 50% dispersion in mineral oil). After the evolution of gases subsided, 2.6 g (0.015 mol) of 1,2-epoxy-3-(2,3-dimethylphenoxy)propane was added. The reaction mixture was stirred overnight and the DMF was evaporated in vacuo. The residue was extracted with 200 mL of diethyl ether. The ether extract was dried and concentrated in vacuo to 30 mL. TLC indicated the presence of two products, one of which is a major component. The ether layer was cooled overnight, and the separated solid was filtered and recrystallized from diethyl ether to afford 1.8 g (51%) of **23**: mp 123–125 °C; NMR ($CDCl_3$) δ 1.8–2.5 (m, 4 H, pyrrolidine), 2.2 (s, 3 H, Ar CH_3), 2.3 (s, 3 H, Ar CH_3), 3.4–3.8 (m, 2 H, pyrrolidine), 3.8–4.5 (m, 9 H, remaining aliphatic H + OH), 6.5–6.9 (m, 3 H, 2 Ar H + 1 pyridine H), 7.0 (t, *J* = 8 Hz, 1 H, Ar H), 7.3 (dd, *J* = 5 and 1.5 Hz, 1 H, pyridine H), 7.85 (dd, *J* = 5 and 1.5 Hz, 1

Table III. Hexahydropyrroloquinoxalines and Pyridopyrazines



16-19

no.	Y	R^1	mp, °C	% yield	formula	anal.
16[a]	CH	H	82–84[b]	80	$C_{11}H_{14}N_2$	C, H, N
17	CH		124–125[c]	52	$C_{20}H_{24}N_2O_2$[d]	C, H, N
18	N	H	198–201[e]	65	$C_{10}H_{13}N_3 \cdot HCl$	C, H, N, Cl
19	N		211–213[e]	72	$C_{19}H_{23}N_3HO_2 \cdot HCl$[f]	C, H, N, Cl

[a] $[\alpha]^{25}_D$ −27.76° (*c* 0.145, C_2H_5OH). [b] Ether. [c] Ether–ethanol. [d] Hemihydrate. [e] Ethanol. [f] Hemihydrate.

H, pyridine H); MS, *m/e* 367 (M^+). Anal. ($C_{21}H_{25}N_3O_3$) C, H, N.

The mother liquor was treated with ethanol saturated with hydrogen chloride gas and the solvent was concentrated to 10 mL and cooled. The separated orange solid was filtered and dried. It afforded 0.9 g (17%) of **24** as the hydrochloride salt: mp 210–212 °C; MS, *m/e* 367 (M^+).

5-[(2,6-Dimethoxyphenyl)methyl]-5,6,6a,7,8,9-hexahydropyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazine (19). Lithium aluminum hydride (1 g) was dissolved in 100 mL of anhydrous diethyl ether. To the stirred solution was added over a period of 15 min a solution of 6a,7,8,9-tetrahydro-5-[(2,6-dimethoxyphenyl)-methyl]pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one (**14**); 1 g, 0.003 mol) in 50 mL of dry tetrahydrofuran. The reaction mixture was refluxed for 18 h and was worked up by adding wet ether, filtering, drying, and evaporating in vacuo. The residue (mp 110–112 °C) was dissolved in ethanol and treated with diethyl ether saturated with hydrogen chloride. The separated solid was recrystallized from methanol to afford 0.7 g (67%) of **19** as the hydrochloride salt, mp 211–213 °C. Anal. ($C_{19}H_{23}N_3O_2 \cdot HCl \cdot {}^1/_2H_2O$) C, H, N, Cl.

5-(2,6-Dimethoxybenzoyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoxaline (20). To a stirred solution of the 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoxaline (**15**; 1.7 g, 0.009 mol) and 4 mL of dry triethylamine in 50 mL of dry acetone was added 2.5 g (0.01 mol) of 2,6-dimethoxybenzoyl chloride. The reaction mixture was stirred for 3 h and filtered, and the acetone was evaporated under vacuo. The residue was washed with water, dried, and recrystallized from aqueous ethanol to afford 2.4 g (79%) of compound **20**, mp 140–142 °C. Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

Compounds 16–18. These compounds were prepared following the procedure described for the preparation of compound **19** (Table III).

Antihypertensive Testing in the Conscious Rat. Male spontaneously hypertensive rats (SHR, Okamoto-Aoko strain), weighing approximately 300–400 g, were obtained from commercial breeding laboratories (Taconic Farms, Germantown, NY). Systolic blood pressure was recorded indirectly from the tail by plethysmography (Narco Bio-Systems). Animals were warmed in a heated chamber (38 °C) for 10 min prior to blood pressure measurement. Systolic pressure was recorded before and 1.5 and 4 h after drug administration. Rats were deprived of food for at least 16 h prior to testing. Drugs were administrated to groups of four SHR as a single oral dose of 50 mg/kg via a stomach tube. Control animals received equal volumes of vehicle.

Relaxation of Arterial Smooth Muscle.[11] New Zealand albino female rabbits (3–4 kg) were sacrified by intravenous injection of sodium pentobarbital. The thoracic aorta was removed and transferred to a Krebs physiological salt solution (KPSS) aerated with 95% O_2 and 5% CO_2. Transverse strips (10 × 2.5 mm) were suspended vertically in a 50-mL organ bath containing KPSS and maintained at 37 °C. The lower end of the muscle strip was attached to a fixed post and the upper end to a Statham UC-4 force displacement pressure transducer. An optimal passive isometric tension (4 g) was applied during a 90-min equilibration period. Following this interval, tension was readjusted to 4 g and the muscles were contracted for 10 min by the addition of a high K^+ (100 mM) substituted KPSS containing 2.5 mM $CaCl_2$. Strips were then rinsed with normal KPSS and allowed to relax to base-line values at which point they were recontracted by the high-K^+ solution. After 20 min of sustained contraction, test drug was added at a final concentration of 10^{-5} M. The extent of isometric tension 20 min after the addition of the compound was compared with the tension prior to the addition of the drug. Inhibition is expressed as percentage relaxation of maximal KCl-induced contraction.

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Registry No. **5**, 36976-98-4; **6**, 21550-86-7; **7**, 91622-91-2; **7**·HCl, 91622-92-3; **8**, 91623-03-9; (−)-**9**, 92622-52-1; **10**, 91623-04-0; **11**, 91623-12-0; **11**·2HCl, 91623-07-3; (−)-**12**, 91623-09-5; **13**, 91623-10-8; **14**, 91622-93-4; **14**·HCl, 91622-94-5; **15**, 91623-11-9; **15**·2HCl, 91623-01-7; (−)-**16**, 92622-53-2; **17**, 91623-05-1; **18**, 91622-97-8; **18**·HCl, 91622-98-9; **19**, 91622-96-7; **19**·HCl, 91622-95-6; **20**, 91623-02-8; **23** (isomer 1), 92622-54-3; **23** (isomer 2), 92622-55-4; 2,6-$(OCH_3)_2C_6H_3CH_2Cl$, 71819-90-4; $C_6H_5CH_2Cl$, 100-44-7; 4-$C_5H_4NCH_2Cl$, 10445-91-7; $(CH_3)_2NCH_2CH_2Cl$, 30438-74-5; 2-chloro-3-nitropyridine, 5470-18-8; L-proline, 147-85-3; 2,6-dimethylbenzoyl chloride, 21900-37-8; 1,2-epoxy-3-(2,3-dimethylphenoxy)propane, 41457-31-2.

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