analytical TLC on silica gel plates with solvent systems (A) *n*-BuOH-AcOH-H_2O (4:1:5), (B) *n*-BuOH-AcOH-H_2O-EtOAc (1:1:1:1), (C) *n*-BuOH-AcOH-H_2O-pyridine (15:3:12:10), visualizing spots with Pauly reagent;[33] (c) analytical reversed-phase HPLC on C_{18}-silica gel column using the appropriate CH_3CN-0.1 N NH_4OAc (pH 4) mixture, following elution by UV (250-nm detection).

Analytical data for all peptide are listed in Table V.

Registry No. 1, 51833-71-7; 2, 67037-14-3; 3, 3438-23-1; 4, 34305-50-5; 5, 57667-99-9; 6, 49707-73-5; 7, 111821-38-6; 8, 111821-39-7; 9, 37827-06-8; 10, 51887-63-9; 11, 111771-38-1; 12, 111771-39-2; 13, 101713-05-7; 14, 111821-40-0; 15, 111821-41-1; 16, 111821-42-2; 17, 111821-43-3; 18, 49707-74-6; 19, 111771-40-5; 20, 111771-41-6; 21, 111771-42-7; 22, 111771-43-8; 23, 111821-44-4; 24, 111821-45-5; 25, 49707-72-4; 26, 111771-44-9; 27, 111771-45-0; 28, 111771-46-1; 29, 111821-46-6; 30, 111771-47-2; 31, 111771-48-3; 32, 95841-12-6; 33, 111771-49-4; 34, 111771-50-7; 35, 111771-51-8; 36, 38027-95-1; 37, 25061-67-0; 38, 90937-06-7; 39, 111771-52-9; 40, 25061-71-6; 41, 53935-04-9; 42, 111821-47-7; 43, 35492-37-6; 44, 6663-62-3; 45, 47917-11-3; 46, 111821-48-8; 47, 111771-53-0; 48, 111771-54-1; AII, 11128-99-7; H-DL-Bph-OEt, 111771-55-2; H-D-Bph-OEt, 111771-56-3; H-D-Bph-OH, 111821-49-9; BOC-D-Bph-OH, 111771-57-4; H-D-(αMe)Phe-OH, 17350-84-4; BOC-D-(αMe)Phe-OH, 111771-58-5; BOC-D-(αMe)Phe-OH·DCHA, 111771-59-6.

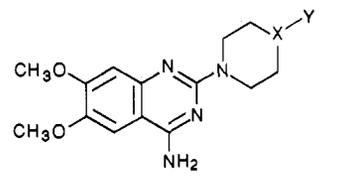
2,4-Diamino-6,7-dimethoxyquinazolines. 4. 2-[4-(Substituted oxyethoxy)piperidino] Derivatives as α_1-Adrenoceptor Antagonists and Antihypertensive Agents

Simon F. Campbell,* John C. Danilewicz, Colin W. Greengrass, and Rhona M. Plews

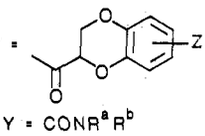
Department of Discovery Chemistry, Pfizer Central Research, Sandwich, Kent, United Kingdom. *Received August 4, 1987*

A series of 4-amino-6,7-dimethoxy-2-[4-(substituted oxyethoxy)piperidino]quinazoline derivatives (**2**) was synthesized and evaluated for α-adrenoceptor affinity and antihypertensive activity. Most compounds showed binding affinities within the nanomolar range for α_1-receptors, although **25** and **26** showed enhanced potency (K_i, ca. 1.5×10^{-10} M), equivalent to that of prazosin. Series **2** also displaced [^{3}H]clonidine from α_2-adrenoceptors, but at relatively high doses of 10^{-6} M, and selectivity for α_1 sites still predominated. In a rabbit pulmonary artery preparation, **12**, **16**, and **25** were potent antagonists of the α_1-mediated, postjunctional vasoconstrictor activity of norepinephrine with no effect at the prejunctional α_2 sites which modulate transmitter release. Physicochemical measurements gave a pK_a of 7.63 ± 0.10 for **12**, and N-1 protonation will be favored (60%) at physiological pH to provide the α_1-adrenoceptor pharmacophore, **28**. Antihypertensive activity of series **2** was evaluated following oral administration to spontaneously hypertensive rats, and blood pressure was measured after 1 and 6 h. Compounds **12**, **13**, **16**, **23**, and **37** displayed moderate efficacy and duration of action in lowering blood pressure, but the plasma half-life (ca. 2 h) of **16** in dogs was not compatible with potential once-daily administration in humans.

In previous papers, the synthesis and biological activities of two series of 2-[4-(1,4-benzodioxan-2-ylcarbonyl)-piperazin-1-yl]- and 2-[4-[(substituted amino)carbonyl]-piperidino]quinazoline derivatives **1a** and **1b** were reported.[1,2] In these studies, the roles of the relatively rigid



1a, X = N, Y =

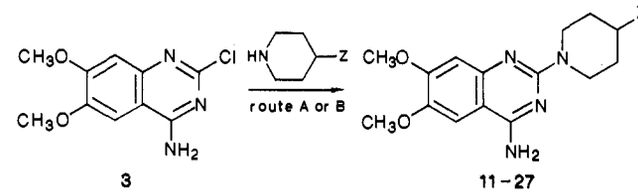


b, X = CH, Y = $CONR^aR^b$

c, X = N, Y = heteroaryl

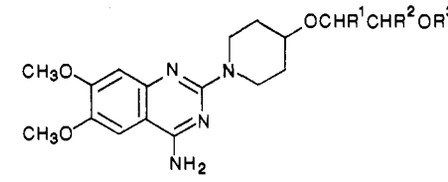
(**1a**) and flexible (**1b**) carboxamide moieties were compared with respect to effects on α_1-adrenoceptor affinity and antihypertensive activity. Subsequently, it was also demonstrated that the carbonyl function present in **1a** and **1b** could be replaced by an appropriately substituted heteroaromatic π system (**1c**) with no adverse effects on in vitro or in vivo activity.[3] These structure–activity relationship (SAR) studies suggested that, although the quinazoline 2-substituents play an important role in modulating α_1-adrenoceptor affinity and antihypertensive activity, more

Scheme I



3 **11–27**

marked structural variations than those already reported might also be tolerated. In this paper, the carbonyl or heteroaromatic π systems common to the previously disclosed series are replaced by an ethylenedioxy function (**2**),



2

and further substitution of the alkyl chain is explored for effects on in vitro receptor affinity and in vivo antihypertensive activity.

Chemistry. All of the compounds for pharmacological testing were prepared by condensation of 4-amino-2-chloro-6,7-dimethoxyquinazoline (**3**) with an appropriate 4-alkoxypiperidine derivative in butanol under reflux (Scheme I).[4] In route A, chromatographic purification of **13–15**, **22**, and **24–27** was required whereas in route B,

(1) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49.
(2) Alabaster, V. A.; Campbell, S. F.; Danilewicz, J. C.; Greengrass, C. W.; Plews, R. M. *J. Med. Chem.* **1987**, *30*, 999.
(3) Campbell, S. F.; Plews, R. M. *J. Med. Chem.* **1987**, *30*, 1794.
(4) Campbell, S. F.; Danilewicz, J. C.; Greengrass, C. W. Br. Patent Appl. 2,010,824A, 1979 and 2,041,373A, 1980.

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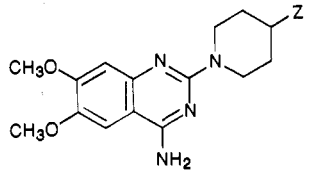
Table I. Synthetic Routes and Physical Data for Variation of the Piperidine Substituent (Z)



no.	Z	route	mp, °C	formula	anal.
11	$O(CH_2)_2OCH_3$	B	220–222	$C_{18}H_{26}N_4O_4 \cdot HCl$	C, H, N
12	$O(CH_2)_2OC_2H_5$	A	210–220	$C_{19}H_{28}N_4O_4 \cdot HCl$	C, H, N
13	$O(CH_2)_2OC_4H_9$	A	199–201	$C_{21}H_{32}N_4O_4 \cdot HCl$	C, H, N
14	$O(CH_2)_2OCH(CH_3)_2$	A	130–134	$C_{20}H_{30}N_4O_4$	C,[a] H, N[a]
15	$O(CH_2)_2O$-c-C_5H_9	A	210–211	$C_{22}H_{32}N_4O_4 \cdot HCl$	C, H, N
16	$O(CH_2)_2OC_6H_5$	B	232–233	$C_{23}H_{28}N_4O_4 \cdot HCl$	C, H, N
17	$O(CH_2)_2OH$	B	252–253	$C_{17}H_{24}N_4O_4 \cdot HCl$	C, H, N
18	$OCH_2CH(CH_3)OCH_3$	B	239–241	$C_{19}H_{28}N_4O_4 \cdot HCl$	C, H, N
19	$OCH_2C(CH_3)_2OCH_3$	B	239–242	$C_{20}H_{30}N_4O_4 \cdot HCl$	C, H, N
20	$OCH_2CH(CH_3)OC_2H_5$	B	217–218	$C_{20}H_{30}N_4O_4 \cdot HCl \cdot 0.5H_2O$	C,[b] H, N
21	$OCH_2CH(CH_3)OH$	B	245–246	$C_{18}H_{26}N_4O_4 \cdot HCl \cdot 0.5H_2O$	C, H, N
22	$OCH_2C(CH_3)_2OH$	A	204–205	$C_{19}H_{28}N_4O_4$	C, H, N
23	$OCH(C_6H_5)CH_2OC_2H_5$	B	229–230	$C_{25}H_{32}N_4O_4 \cdot HCl$	C, H, N
24	$OCH_2CH(C_6H_5)OC_2H_5$	A	234–235	$C_{25}H_{32}N_4O_4 \cdot HCl$	C, H, N[c]
25	$OCH_2C(CH_3)(C_6H_5)OC_2H_5$	A	231–233	$C_{26}H_{34}N_4O_4 \cdot HCl$	C, H, N
26	$OCH_2CH(C_6H_5)OH$	A	241–243	$C_{23}H_{28}N_4O_4 \cdot HCl$	C, H, N
27	$OCH_2C(CH_3)(C_6H_5)OH$	A	146–148	$C_{24}H_{30}N_4O_4 \cdot H_2O$	C, H, N

[a] C: calcd, 61.5; found, 60.9. N: calcd, 14.4; found, 13.8. [b] C: calcd, 55.1; found, 55.6. [c] N: calcd, 11.5; found, 11.0.

products **11**, **16–21**, and **23** were isolated directly from the reaction mixture. Final compounds were generally characterized as hydrochloride salts (Table I).

The 4-alkoxypiperidine intermediates (Table II) were prepared as outlined in Scheme II. Thus in route C, reaction of the sodium salt of 1-acetyl-4-hydroxypiperidine (**4**) with a 2-(alkoxy or aryloxy)bromoethane followed by protecting-group cleavage gave **29–32**. Yields for the first alkylation step were generally low, presumably due to competing elimination. Alternatively, **4** was reacted with an appropriately substituted propenyl bromide and intermediates **45–47** were subjected to oxymercuration/reduction in the presence of an alcohol (route D) or water (route E) to provide **5**. Regioselective reaction of **4** with styrene oxide (route F) gave the alcohol **6**, which could be converted (route G) into the corresponding alkoxy derivatives **7**. Finally, alkylation of **4** with α-bromophenylacetic acid followed by esterification and $LiBH_4$ reduction gave **9** (route H), which could also be further *O*-alkylated via route G. Deprotection of the intermediates **5–7**, **9**, and **10** could be achieved under acidic (HCl) or basic (NaOH) conditions.

Scheme II

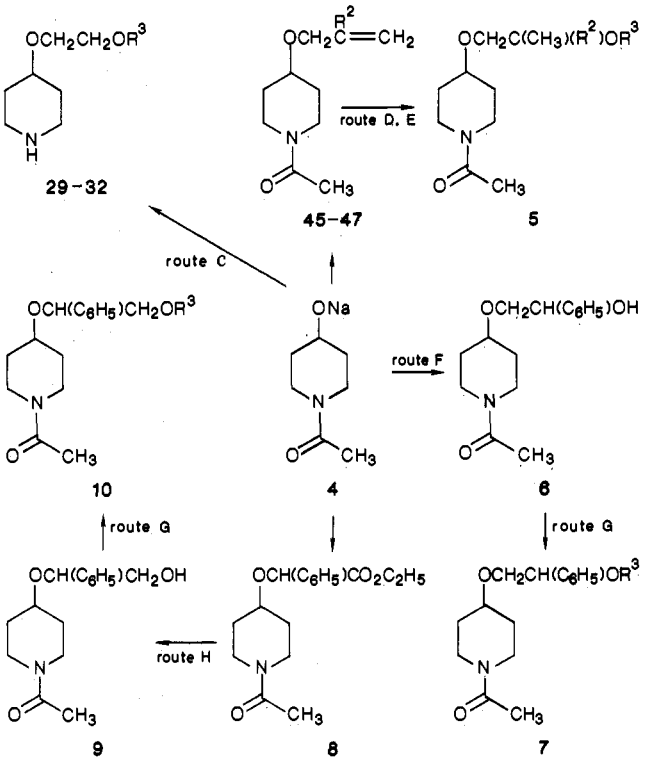
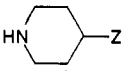


Table II. Synthetic Routes and Physical Data for 4-(Substituted oxyethoxy)piperidine Derivatives



no.	Z	route	mp, °C	formula	anal.
29	$O(CH_2)_2OCH_3$	C	86–88	$C_8H_{17}NO_2 \cdot C_2H_2O_4$	C, H, N
30	$O(CH_2)_2OC_2H_5$	C	93–95	$C_9H_{19}NO_2 \cdot C_2H_2O_4$	C, H, N
31	$O(CH_2)_2O$-*n*-C_4H_9	C	86–88	$C_{11}H_{23}NO_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$	C, H, N
32	$O(CH_2)_2OCH(CH_3)_2$	C		$C_{10}H_{21}NO_2$	*a*
33	$O(CH_2)_2O$-c-C_5H_9	G		$C_{12}H_{23}NO_2$	*a*
34	$O(CH_2)_2OC_6H_5$	C	144–145	$C_{13}H_{19}NO_2 \cdot C_2H_2O_4$	C,[b] H, N
35	$OCH_2CH(CH_3)OCH_3$	D	89–91	$C_9H_{19}NO_2 \cdot C_2H_2O_4$	C,[c] H, N
36	$OCH_2C(CH_3)_2OCH_3$	D	208–210	$C_{10}H_{21}NO_2 \cdot 0.5C_2H_2O_4$	C, H, N
37	$OCH_2CH(CH_3)OC_2H_5$	D	68–70	$C_{10}H_{21}NO_2 \cdot C_3H_3O_6$	C, H, N
38	$OCH_2CH(CH_3)OH$	E	104–105	$C_8H_{17}NO_2 \cdot C_2H_2O_4$	C, H, N
39	$OCH_2C(CH_3)_2OH$	D	80–82	$C_9H_{19}NO_2$	C, H, N
40	$OCH(C_6H_5)CH_2OC_2H_5$	G	137–139	$C_{15}H_{23}NO_2 \cdot C_2H_2O_4$	C, H, N
41	$OCH_2CH(C_6H_5)OC_2H_5$	G	136–137	$C_{15}H_{23}NO_2 \cdot C_2H_2O_4$	C, H, N
42	$OCH_2C(CH_3)(C_6H_5)OC_2H_5$	D	126–127	$C_{16}H_{25}NO_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$	C, H, N
43	$OCH_2CH(C_6H_5)OH$	F	174–175	$C_{13}H_{19}NO_2 \cdot HCl$	C,[d] H, N
44	$OCH_2C(CH_3)(C_6H_5)OH$	D	132–134	$C_{14}H_{21}NO_2 \cdot C_2H_2O_4$	C, H, N

[a] Characterized spectroscopically. [b] C: calcd, 57.9; found, 58.5. [c] C: calcd, 50.2; found, 49.6. [d] C: calcd, 60.6; found, 60.1.

Results and Discussion

SARs for in Vitro α-Adrenoceptor Affinity. In Table III, the influence of a wide range of ethylenedioxy substituents in series **2** on α_1- and α_2-adrenoceptor binding affinity is summarized. Incorporation of a 2-methoxyethoxy moiety (**11**) provided α_1-adrenoceptor binding af-

Table III. Binding and Antihypertensive Activities for 4-Amino-2-[4-(substituted oxyethoxy)piperidino]-6,7-dimethoxyquinazoline Derivatives

compd	α-receptor binding affinity[a]		% reduction in SHR (n = 6) blood pressure[h] (dose, 5 mg/kg, po)	
	α_1[b]	α_2[c]	1 h	6 h
11	2.12 ± 0.17	53.0 ± 3.1	57	28
12	1.81 ± 1.45	65.3 ± 4.5	22	20
13	1.03 ± 0.07	76.0 ± 3.0	27	20
14	0.67 ± 0.33	73.4 ± 4.1	26	15
15	NT[d]	NT	20	11
16	0.48 ± 0.3	79.3 ± 3.5	26	18
17	2.20 ± 0.23	NA	8	10
18	1.41 ± 0.58	68.7 ± 5.9	34	16
19	1.14 ± 1.7	75.7 ± 3.2	20	9
20	0.99 ± 0.26	74.3 ± 4.0	43	20
21	3.52 ± 1.96	55.0 ± 7.9	30	19
22	1.28 ± 0.49	61.7 ± 4.7	40	22
23	10.0[e]	NA	24	19
24	0.52 ± 0.39	84.5[f]	16	12
25	0.15 ± 0.08	97.5[f]	20	13
26	0.15 ± 0.10	91.0[f]	26	16
27	0.62 ± 0.32	97.0 ± 1.2	23	20
prazosin	0.15 ± 0.01	4830 ± 1280[g]	33	29

[a] Rat brain homogenate preparation; all results are the mean ± SEM of at least three separate experiments performed in triplicate. [b] K_i, nM, for displacement of [^{3}H]prazosin. [c] Percentage displacement of [^{3}H]clonidine at 10^{-6} M; NA indicates less than 50%. [d] NT, not tested. [e] K_i estimated, nonsigmoidal displacement of [^{3}H]prazosin. [f] Means of two values only. [g] K_i, nM. [h] Falls in blood pressure below 10% are not physiologically significant.[1]

Table IV. Functional α-Antagonist Activity for **12**, **16**, **25**, and Prazosin in the Rabbit Pulmonary Artery

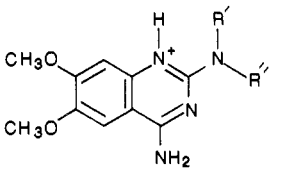
compd	EC_{40}-post[a]	EC_{40}-pre[a]
12	38[b]	NA[d]
16	44[b]	NA[d]
25	15[b]	NA[d]
prazosin	4.5[c] ± 1.2	1300

[a] EC_{40}-pre is defined as a concentration (nM) of the compound producing a 40% increase in [^{3}H] overflow and EC_{40}-post as the concentration (nM) producing a 40% reduction in contractile response. [b] $n = 2$. [c] $n = 6$. [d] NA indicates no activity at 10^{-5} M.

finity in the nanomolar region, which was maintained as the terminal alkyl substituent was extended (**12**, **13**) and which was enhanced some 3–4-fold with the isopropyl (**14**) and phenyl (**16**) derivatives. Introduction of additional alkyl substituents into the ethylenedioxy chain led to an approximate doubling of α_1 affinity (**18–20**, **22**) whereas potency in the prazosin range was displayed by the corresponding phenyl analogues **24–27**. Comparison of **26** with **17** demonstrates a 15-fold increase in α_1-adrenoceptor affinity, which corresponds to an additional binding energy of approximately 1.7 kcal/mol. Interestingly, incorporation of a similarly located aryl moiety into series **1b** led to an identical increase in binding affinity.[2] However, it is not clear whether these results reflect a specific interaction between the phenyl ring and the receptor protein, or the entropic gain as additional water molecules are squeezed out of the active site.

By contrast with the previous quinazoline series **1a–c**, most of the compounds in Table III displayed consistent affinity for the α_2-adrenoceptor sites labeled by [^{3}H]clonidine, albeit at relatively high concentrations of 10^{-6} M. Thus, series **2** still displays a marked preference for α_1- rather than α_2-receptors, and this was confirmed by determination of functional α_1-antagonist activity against norepinephrine in the rabbit pulmonary artery (Table IV).[2,5] In this preparation, **12**, **16**, and **25** proved to be potent antagonists of the postjunctional, α_1-mediated, vasoconstrictor effects of norepinephrine with no activity at the prejunctional α_2 sites which modulate transmitter release.[6] In particular, **25** was only 3–4 times less potent than prazosin as an α_1-adrenoceptor antagonist, and the relatively high α_2-binding affinity was not expressed in functional terms (Table IV).

Physicochemical measurements demonstrated a pK_a of 7.63 ± 0.10 for **12**, and 60% of the N-1 protonated, α_1-adrenoceptor pharmacophore[7] (**28**) will be present at physiological pH. Both values for prazosin are somewhat



28

lower (pK_a 6.8, ca. 20% protonated), presumably reflecting the enhanced electron-withdrawing effects of the *N*–furoyl moiety compared to the exocyclic dioxa system in **12**. Formation of **28** would be expected to guarantee high affinity and selectivity for series **2** at α_1-adrenoceptors via interaction with an appropriately located carboxylate group in the receptor ground state conformation.[7,8] Interestingly, very recent studies have demonstrated considerable amino acid sequence homology between muscarinic and β-adrenoceptors,[9] and it has been suggested[10] that a common aspartate residue may serve as a counterion for the positively charged nitrogen centers in acetylcholine and norepinephrine respectively. These observations may be relevant for α_1-adrenoceptors and would support previously reported modelling studies.[1-3,7,8]

SARs for in Vivo Antihypertensive Activity. The compounds in Table III were evaluated for antihypertensive activity in spontaneously hypertensive rats (SHR) after oral administration (5 mg/kg). In order to compare both efficacy and duration of action, percentage reductions in blood pressure were determined after 1 and 6 h. Previous results demonstrated that 4-amino-6,7-dimethoxy-2-(4-methoxypiperidino)quinazoline was only poorly active in SHR (10% reduction in blood pressure at 1 h) in contrast to the exceptional efficacy displayed by the 2-methoxyethoxy derivative **11**. However, dose–response studies with **11** in SHR gave somewhat variable results, possibly because of differing rates of metabolic O-demethylation to the less active alcohol **17**. Extension of the terminal alkyl chain (**12–14**) or introduction of an aryl ring (**16**) reduced absolute efficacy, but differences between the blood pressure falls at 1 and 6 h were much less marked than for **11**, which is consistent with an overall improvement in in vivo performance. Introduction of monoalkyl (**18**, **20**) or dialkyl (**19**) substituents did not prolong du-

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(10) Applebury, M. L.; Hargrave, P. A. *Vision Res.* **1987**, *26*, 1881.

ration of action further although the alcohols **21** and **22** showed a marked improvement in antihypertensive efficacy over **17**. Incorporation of an aryl substituent appeared to be of limited benefit for **24–26**, although duration of action was moderately prolonged for **23** and **27**.

These results show that while many of the compounds in Table III are potent antihypertensive agents in SHR, activity tends to be maximal at 1 h rather than 6 h, in contrast to clinically useful agents such as prazosin and doxazosin.[11] However, **12**, **13**, **16**, **23**, and **27** do combine moderate efficacy with adequate duration of action, and pharmacokinetic studies were carried out with **16** in dogs. The plasma half-life proved to be shorter[12] (ca. 2 h) than for doxazosin, suggesting that **16** would not provide 24-h control of blood pressure in humans after once-daily administration.[13]

Experimental Section

Chemistry. Melting points were determined in a Büchi apparatus in glass capillary tubes and are uncorrected. Spectroscopic data for all compounds were recorded on Perkin Elmer-257 (IR), AEI MS12 or VG 7070F (MS), and Perkin-Elmer R12B, Varian XL 100, and Nicolet QE300 (NMR) instruments and were consistent with assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

Route A. 4-Amino-6,7-dimethoxy-2-[4-(2-ethoxyethoxy)-piperidino]quinazoline Hydrochloride (12). 4-Amino-2-chloro-6,7-dimethoxyquinazoline[14] (4.3 g, 18 mmol), 4-(2-ethoxyethoxy)piperidine (3.2 g, 18.5 mmol), and triethylamine (10 mL) in 1-butanol (400 mL) were heated at reflux overnight under an atmosphere of nitrogen. The mixture was cooled and evaporated, and the residue was basified (aqueous Na_2CO_3) and then extracted with chloroform. The combined chloroform extracts were evaporated, and the residue was purified by chromatography on neutral alumina (grade 1, 150 g, deactivated with 5 mL of water). Elution with chloroform gave a crude product (3.6 g), which was treated with HCl in ethanol and then recrystallized from ethanol/2-propanol to give 4-amino-6,7-dimethoxy-2-[4-(2-ethoxyethoxy)piperidino]quinazoline hydrochloride (3.4 g, 46%), mp 210–220 °C. Anal. ($C_{19}H_{28}N_4O_4$·HCl) C, H, N.

Route B. 4-Amino-6,7-dimethoxy-2-[4-(2-methoxypropoxy)piperidino]quinazoline Hydrochloride (18). 4-Amino-2-chloro-6,7-dimethoxyquinazoline (3.6 g, 15 mmol), 4-(2-methoxypropoxy)piperidine (3.9 g, 22.5 mmol), and triethylamine (1.5 g, 15 mmol) were heated under reflux in 1-butanol for 30 h. The solvent was evaporated, the residue was stirred with ether, and the solid was collected and recrystallized twice from 2-propanol to give 4-amino-6,7-dimethoxy-2-[4-(2-methoxypropoxy)-piperidino]quinazoline hydrochloride (2.8 g, 45%), mp 239–241 °C. Anal. ($C_{19}H_{28}N_4O_4$·HCl) C, H, N.

Route C. 4-(2-Methoxyethoxy)piperidine Oxalate (29). A solution of 1-acetyl-4-hydroxypiperidine (30.5 g, 210 mmol) in DMF (200 mL) was added dropwise to a stirred suspension of NaH (11.26 g, 50% dispersion in mineral oil) in DMF (300 mL) under an atmosphere of nitrogen. The reaction temperature was kept below 30 °C by external cooling, and after addition was complete, stirring was continued for a further 1.25 h. A solution of 1-bromo-2-methoxyethane (32.6 g, 230 mmol) in DMF (100 mL) was then added dropwise with external cooling, and the resulting clear solution was stirred at room temperature overnight. The reaction mixture was evaporated, the residue was partitioned between water and chloroform, and the organic layer was dried (Na_2SO_4) and evaporated. The aqueous phase was saturated with NaCl and reextracted with chloroform, and the organic phase was dried (Na_2SO_4) and evaporated. Both residues were combined and then heated overnight on a steam bath with hydrochloric acid (2 N, 243 mL). The mixture was extracted with chloroform, and the aqueous phase was concentrated, basified to pH 12 (NaOH), and then reextracted with chloroform. The organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to leave 4-(2-methoxyethoxy)piperidine (8.3 g, 24%). A sample of this product in ethyl acetate was converted to the oxalate salt by the addition of ethereal oxalic acid followed by recrystallization from ethanol, mp 86–88 °C. Anal. ($C_8H_{17}NO_2$·$C_2H_2O_4$) C, H, N.

Route D. 4-(2-Ethoxypropoxy)piperidine Sesquioxalate (37). A solution of 1-acetyl-4-(allyloxy)piperidine (6.4 g, 34 mmol) in absolute ethanol (10 mL) was added dropwise to a stirred suspension of mercuric acetate (11.5 g, 36 mmol) in ethanol (50 mL) at room temperature. After 0.3 h, the mercuric acetate had dissolved, the mixture was stirred for a further 0.6 h and cooled in ice water, and sodium hydroxide (5 N, 20 mL) was then added. A solution of $NaBH_4$ (1.3 g, 34 mmol) in sodium hydroxide (5 N, 20 mL) was added, the mixture was stirred for 0.15 h, and acetic acid was added (pH 6). The mixture was decanted from precipitated mercury and evaporated, and the aqueous residue was extracted with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated, and the residue (7.5 g) was taken up in ethanol (5.0 mL) and heated with sodium hydroxide (5 N, 20 mL) and water (20 mL) under reflux overnight. Most of the ethanol was then evaporated, the aqueous phase was extracted with ether, and the combined extracts were dried (Na_2SO_4) and evaporated to leave a residue (5.0 g). TLC (chloroform/methanol/aqueous ammonia, 80:20:1) indicated only partial cleavage of the acetyl function, so the residue was treated with hydrochloric acid (2 N, 20 mL) and heated on a steam bath for 10 h. The mixture was washed with ether, the aqueous phase was basified (Na_2CO_3) and extracted with ether, and the combined extracts were dried (Na_2SO_4) and then evaporated. Distillation of the residue (4.3 g) gave 4-(2-ethoxypropoxy)piperidine (3.0 g, 47%), bp 112–116 °C (10 mm). A sample of this product in ether was converted to the sesquioxalate salt by treatment with ethereal oxalic acid followed by recrystallization from ethyl acetate, mp 68–70 °C. Anal. ($C_{10}H_{21}NO_2$·$C_3H_3O_6$) C, H, N.

Route E. 4-(2-Hydroxypropoxy)piperidine Oxalate (38). 1-Acetyl-4-(allyloxy)piperidine (18 g, 98 mmol) in THF (30 mL) was added dropwise to a stirred suspension of mercuric acetate (34 g, 106 mmol) in a mixture of water (120 mL) and THF (120 mL). The suspension dissolved during the addition, the resulting clear solution was stirred at room temperature for 0.3 h, and then sodium hydroxide (5 N, 780 mL) was added accompanied by ice-water cooling. Sodium borohydride (2 g, 52 mmol) in sodium hydroxide solution (5 N, 40 mL) was then added, and after 0.15 h, any excess hydride was destroyed with glacial acetic acid. The liquid phase was decanted and saturated with NaCl, the organic phase was separated, and the remaining aqueous layer was extracted with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated to leave a colorless oil (23 g). The oil was stirred with sodium hydroxide (5 N) at room temperature for 16 h and then at 100 °C for 2 h. The solution was extracted with chloroform, and the combined extracts were dried (Na_2SO_4) and evaporated. The solid residue (16.1 g) was taken up in dichloromethane, filtered, and evaporated, and the residue was triturated with petroleum ether (bp 40–60 °C) to yield 4-(2-hydroxypropoxy)piperidine (11.0 g, 70%), mp 55–57 °C. A sample was converted to the oxalate salt as described previously followed by recrystallization from 2-propanol mp 104–105 °C. Anal. ($C_8H_{17}NO_2$·$C_2H_2O_4$) C, H, N.

Route F. 4-(2-Hydroxy-2-phenylethoxy)piperidine Hydrochloride (43). 1-Acetyl-4-hydroxypiperidine (5.0 g, 34 mmol) in THF (50 mL) was added to a stirred suspension of sodium hydride (1.84 g, 50% by weight dispersion in mineral oil) in THF (25 mL) under an atmosphere of nitrogen. When effervescence had ceased, styrene oxide (4.6 g, 38 mmol) in THF (25 mL) was added, and then the reaction mixture was diluted with DMF (25 mL) and stirred at 60 °C for 18 h. After addition of 2-propanol to the cooled solution, the solvent was removed, and the residue was treated with water, adjusted to pH 4 with 2 N hydrochloric acid, and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated to give 1-acetyl-4-(2-hydroxy-2-phenylethoxy)piperidine (**6**). This product in ethanol (50 mL) and sodium hydroxide solution (5 N, 100 mL) was heated under

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reflux for 3 h. The solvent was then removed, and the residue was taken up in water, extracted with chloroform, dried, and evaporated. The product in chloroform was converted to the hydrochloride salt by treatment with ethereal hydrogen chloride and evaporation of solvent. The residue was taken up in methanol and treated with ether, and the precipitated solid was separated and recrystallized from 2-propanol to give 4-(2-hydroxy-2-phenylethoxy)piperidine hydrochloride (0.6 g, 7%), mp 174–175 °C. Anal. ($C_{13}H_{19}NO_2$·HCl) H, N; C: calcd, 60.6; found, 60.1.

Route G. 4-(2-Ethoxy-2-phenylethoxy)piperidine Oxalate (41). 1-Acetyl-4-(2-hydroxy-2-phenylethoxy)piperidine (**6**) (8.0 g, 36 mmol) and 1,2-dimethoxyethane (0.3 g) in dry DMF (50 mL) were added dropwise to a stirred suspension of sodium hydride (2.96 g, 50% by weight dispersion in mineral oil) in dry DMF (50 mL). The suspension was stirred at room temperature for 3.5 h and cooled to 0–5 °C, and then a solution of ethyl iodide (9.6 g, 61 mmol) in DMF (25 mL) was added dropwise. The mixture was allowed to warm to room temperature and then stirred for 2 h. 2-Propanol (75 mL) was added, the solvent was removed, and the residue was partitioned between chloroform and water. The chloroform layer was dried, and the solvent was evaporated to give 1-acetyl-4-(2-ethoxy-2-phenylethoxy)piperidine (5.2 g, 49%).

This product in ethanol (50 mL) and sodium hydroxide solution (5 N, 50 mL) was heated under reflux for 3.5 h. The organic solvent was removed and the aqueous residue extracted with chloroform. The organic extract was dried (Na_2SO_4) and evaporated, and then the residue was partitioned between 2 N hydrochloric acid solution and ether. The aqueous phase was then basified (Na_2CO_3) and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and then evaporated, and the residue was taken up in ether and converted to the oxalate salt. Recrystallization from 2-propanol gave 4-(2-ethoxy-2-phenylethoxy)piperidine oxalate (1.6 g, 26%), mp 136–137 °C. Anal. ($C_{15}H_{23}NO_2$·$C_2H_2O_4$) C, H, N.

4-(2-Ethoxy-1-phenylethoxy)piperidine (**40**) was prepared similarly by starting from 1-acetyl-4-(2-hydroxy-1-phenylethoxy)piperidine and ethyl iodide, followed by basic hydrolysis of the 1-acetyl group. A sample was characterized as the oxalate salt, mp 137–139 °C. Anal. ($C_{15}H_{23}NO_2$·$C_2H_2O_4$) C, H, N.

4-[2-(Cyclopentyloxy)ethoxy]piperidine (**33**) was prepared similarly by using cyclopentyl mesylate instead of ethyl iodide. The hydrochloride salt formed as a gum and was characterized spectroscopically.

Route H. 1-Acetyl-4-(2-hydroxy-1-phenylethoxy)piperidine (9). (a) 1-Acetyl-4-hydroxypiperidine (27.5 g, 192 mmol) in dry DMF (100 mL) was added slowly to a stirred suspension of sodum hydride (25 g, 50% by weight dispersion in mineral oil) in DMF (150 mL) and 1,2-dimethoxyethane (10 mL). The suspension was stirred at room temperature for 3 h, and then α-bromophenylacetic acid (45 g, 209 mmol) in DMF (250 mL) was added slowly with ice-water cooling. The mixture was stirred at room temperature for 20 h, then 2-propanol was added, and the solvent was evaporated. The residue was taken up in water, acidified to pH 1 with 2 N hydrochloric acid, and extracted four times with chloroform (300 mL). The combined chloroform extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue in anhydrous ethanol (450 mL) with concentrated sulfuric acid (9 mL) was heated under reflux for 8 h. The cooled solution was cautiously neutralized with aqueous sodium carbonate solution, and the organic solvent was evaporated. The aqueous residue was adjusted to pH 10 with sodium carbonate solution and extracted twice with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated. Distillation of the residue gave α-[(1-acetyl-4-piperidinyl)oxy]-phenylacetic acid ethyl ester (37.2 g, 63%), bp 190–194 °C (0.18 mm). Anal. ($C_{17}H_{23}NO_4$) H, N; C: calcd, 66.9; found, 66.4.

(b) 1-Acetyl-4-(2-hydroxy-1-phenylethoxy)piperidine. Lithium borohydride (3.24 g, 148 mmol) was added portionwise to a solution of α-[(1-acetyl-4-piperidinyl)oxy]phenylacetic acid ethyl ester (11.2 g, 36 mmol) in dry THF (200 mL). When the hydrogen evolution had subsided, the reaction mixture was heated under reflux for 4 h. Water was added to the cooled solution, the solvent was evaporated, and then the residue was taken up in chloroform (200 mL) and washed with dilute HCl, water, and brine. The chloroform extract was dried ($MgSO_4$), and the solvent was evaporated. TLC analysis (chloroform/methanol, 95:5) of the product indicated that reduction was incomplete; therefore the product in THF (100 mL) was treated with a further quantity of lithium borohydride (3.24 g, 148 mmol) and heated under reflux for 4 h. The reaction mixture was treated as above to give 1-acetyl-4-(2-hydroxy-1-phenylethoxy)piperidine (9.5 g, 98%) as an oil, which solidified on standing. A sample was crystallized from ether, mp 92–94 °C. Anal. ($C_{15}H_{21}NO_3$) C, H, N.

1-Acetyl-4-(allyloxy)piperidine (45). A solution of 1-acetyl-4-hydroxypiperidine (100 g, 700 mmol) in DMF (250 mL) was added dropwise to sodium hydride (38 g, 50% dispersion in mineral oil) under an atmosphere of nitrogen. The mixture was stirred for 2 h, and then allyl bromide (93 g, 768 mmol) was added dropwise while the reaction temperature was maintained at 25 °C by external cooling. The mixture was then stirred at room temperature overnight, diluted with 2-propanol (20 mL) and ether (50 mL), filtered, and evaporated. Distillation of the residue gave 1-acetyl-4-(allyloxy)piperidine (108.8 g, 85%), bp 128 °C (2 mm), which was characterized spectroscopically.

1-Acetyl-4-[(2-methylallyl)oxy]piperidine (**46**), bp 128 °C (1 mm), and 1-acetyl-4-[(2-phenylallyl)oxy]piperidine (**47**), bp 170–180 °C (0.3 mm), were prepared similarly.

Biology. Experimental details for the determination of α-adrenoceptor binding, functional potencies, and antihypertensive activities have been detailed previously.[1,2]

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Registry No. **3**, 23680-84-4; **6**, 76041-60-6; **7** (R = Et), 76041-61-7; **8**, 73415-71-1; **9**, 76041-64-0; **11**, 111380-88-2; **11**·HCl, 70978-83-5; **12**, 70978-66-4; **12**·HCl, 70979-24-7; **13**, 111380-89-3; **13**·HCl, 70978-67-5; **14**, 70978-70-0; **15**, 111380-90-6; **15**·HCl, 70978-72-2; **16**, 77219-50-2; **16**·HCl, 70978-84-6; **17**, 111380-91-7; **17**·HCl, 70978-74-4; **18**, 111380-92-8; **18**·HCl, 70978-73-3; **19**, 111380-93-9; **19**·HCl, 70978-87-9; **20**, 111380-94-0; **20**·HCl, 70978-86-8; **21**, 111380-95-1; **21**·HCl, 70978-85-7; **22**, 70978-68-6; **23**, 111380-96-2; **23**·HCl, 76041-48-0; **24**, 111380-97-3; **24**·HCl, 76041-52-6; **25**, 111380-98-4; **25**·HCl, 76041-54-8; **26**, 111380-99-5; **26**·HCl, 76041-51-5; **27**, 76041-53-7; **29**, 70978-88-0; **26**·oxalate, 70979-16-7; **30**, 70978-93-7; **30**·oxalate, 70978-94-8; **31**, 70978-91-5; **31**·oxalate, 70978-92-6; **32**, 70979-01-0; **33**, 70979-05-4; **33**·HCl, 77218-21-4; **34**, 70978-89-1; **34**·oxalate, 70978-90-4; **35**, 70979-02-1; **35**·oxalate, 70979-19-0; **36**, 70978-97-1; **36**·$^1/_2$ oxalate, 70978-98-2; **37**, 70724-68-4; **37**·$1^1/_2$ oxalate, 70979-17-8; **38**, 70724-69-5; **38**·oxalate, 70979-18-9; **39**, 70724-71-9; **40**, 76041-47-9; **40**·oxalate, 77218-23-6; **41**, 76041-62-8; **41**·oxalate, 76041-63-9; **42**, 76041-68-4; **42**·oxalate, 76041-69-5; **43**, 77218-18-9; **43**·HCl, 76041-59-3; **44**, 76041-66-2; **44**·oxalate, 76041-67-3; **45**, 70978-95-9; **46**, 70978-96-0; 47, 77218-24-7; $Br(CH_2)_2OMe$, 6482-24-2; $Br(CH_2)_2OEt$, 592-55-2; $Br(CH_2)_2OBu$, 6550-99-8; $Br(CH_2)_2OPr$-*i*, 54149-16-5; $Br(CH_2)_2OPh$, 589-10-6; $PhCHBrCO_2H$, 4870-65-9; 4-(2-hydroxyethoxy)piperidine, 40256-14-2; 1-acetyl-4-(2-hydroxyethoxy)piperidine, 70979-23-6; 1-acetyl-4-hydroxypiperidine, 4045-22-1; sytrene oxide, 96-09-3; cyclopentyl mesylate, 16156-57-3.