of the carboline nuclei **5** and **5a**. Additionally we appreciate the support of Dr. Gwen Chmurny for determination of 100-MHz NMR spectra, Richard Ware for mass spectral determinations and the Analytical Department of Pfizer Central Research for elemental analyses.

Registry No. **2a**, 74311-69-6; **2a** (amide), 98717-38-5; **2a**·HCl, 98675-08-2; **2b**, 74311-68-5; **2c**, 74311-70-9; **2d** (amide), 98651-75-3; **2d**·HCl, 98675-07-1; (±)-**5**, 69623-07-0; (±)-**5** ($(CH_2)_2OH$ deriv), 98634-60-7; (±)-**5** (CH_2CN deriv), 98634-61-8; (±)-**5** ($(CH_2)_3CN$ deriv), 77378-64-4; (±)-**5** ($(CH_2)_5CN$ deriv), 98634-62-9; (±)-**5** ($(CH_2)_2COPh$ deriv), 98634-63-0; (±)-**5** ($(CH_2)_3COOEt$ deriv), 98634-64-1; (±)-**5** ($(CH_2)_4NHz$ deriv), 98651-79-7; (±)-**5** ($(CH_2)_6$ NHz deriv), 98651-80-0; (±)-**5** ($(CH_2)_2NHz$ deriv), 98651-81-1; **5a**·**6a**, 76700-26-0; **5a**·HCl, 83502-36-7; **5b**·**6b**, 76700-24-8; **5b**·HCl, 98818-01-0; **6a**, 54896-72-9; **6b**, 949-45-1; (±)-**7**, 76700-29-3; **7**, 75738-79-3; **8**, 98634-89-0; **9**, 58038-68-9; **9** ($(CH_2)_3CN$ deriv), 58039-14-8; **9** ($(CH_2)_5CN$ deriv), 83535-77-7; **9** ($(CH_2)_3COOEt$ deriv), 98634-65-2; **9** ($(CH_2)_6NH_2$ deriv), 83545-87-3; **10a**·HCl, 58039-02-4; (±)-**10b**·HCl, 98634-82-3; **11a**, 98634-66-3; (±)-**11b**, 98634-67-4; **12a**, 98634-68-5; (±)-**12b**·HCl, 77378-81-5; **13g**·HCl, 98634-83-4; (±)-**13b**·HCl, 98634-84-5; (±)-**14**, 98634-59-4; (±)-**15**, 98634-70-9; (±)-**16**, 98634-71-0; **17**, 98651-78-6; (±)-**18**, 98651-76-4; (±)-**19**, 98634-72-1; (±)-**20**·HCl, 98651-82-2; **21**, 98634-73-2; **23** (n = 5), 98634-74-3; (±)-**25**, 83514-71-0; (±)-**26**, 83514-73-2; **27**, 98634-85-6; **28**, 98634-86-7; (±)-**29a**, 83514-78-7; **29b**, 98675-09-3; **30**, 98634-87-8; **31**, 98634-88-9; **32**, 72358-71-5; **33**, 98634-75-4; **33**·$PhCH_2Br$, 98634-77-6; **34a**·HCl, 98634-76-5; **34b**, 98634-79-8; **34b**·HCl, 98634-80-1; **34c**, 98634-81-2; (±)-4-$FC_6H_4CH(OH)(CH_2)_2CO_2H$, 75738-74-8; ($R$)-4-$FC_6H_4CH(OH)(CH_2)_2CO_2H$-*d*-ephedrine, 75738-76-0; (R)-4-$FC_6H_4CH(OH)(CH_2)_2CO_2H$, 75738-75-9; C_6H_5Br, 108-86-1; $C_6H_5NH_2$, 62-53-3; (±)-$C_6H_5CH(CH_2OH)CO_2H$, 552-63-6; C_6H_5NCO, 103-71-9; $Br(CH_2)_5Br$, 111-24-0; 4-$FC_6H_4NH_2$, 371-40-4; 4-BrC_6H_4F, 460-00-4; $C_6H_5CH_2Br$, 100-39-0; 4-$C(CH_2)_3COC_6H_4F$, 3874-54-2; D-(+)-phenyalanine, 673-06-3; L-(−)-phenylalanine, 63-91-2; 2-(4-aminobutyl)tetrahydro-γ-carboline, 98634-69-6; 9-(β-chloroethyl)carbazole, 1140-35-8; 2-bromo-*N*-methylpyridinium iodide, 52693-56-8; *N*-phenylcyclohexylamine, 1821-36-9; cyclohexylamine, 108-91-8; hydantoin, 461-72-3; 4-chloropyridine hydrochloride, 7379-35-3; 1-benzyl-4-[*N*,*N*-bis[(4-fluorophenyl)amino]]-2*H*-pyridine, 98634-78-7.

Synthesis and Antihypertensive Activity of a Series of 4-Amino-6,7-dimethoxyquinazoline Derivatives

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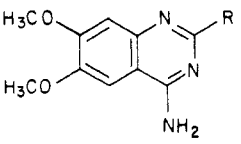
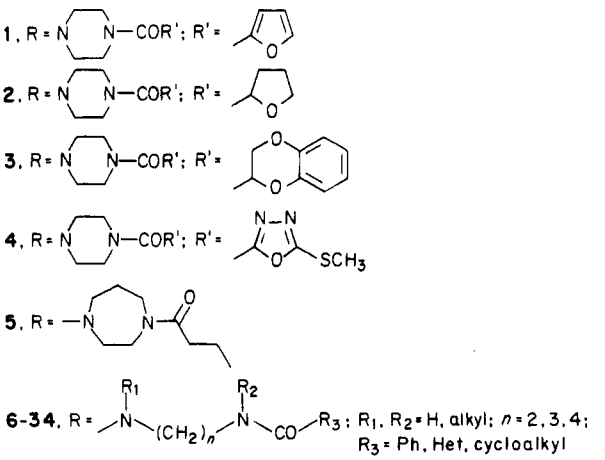
A series of N^2-[(acylamino)alkyl]-6,7-dimethoxy-2,4-qui[illegible]olinediamines was synthesized as potential α_1-adrenoceptor antagonists. When administered to spontaneously hy[illegible]ensive rats at 10 mg/kg po, a number of propanediamine derivatives showed good antihypertensive activity, wh[illegible]s the ethanediamine derivatives, albeit being structurally more closely related to prazosin, were devoid of this property. The most active derivative, *N*-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydro-2-furancarboxamide hydrochloride, alfuzosin (**12**), showed high selectivity for peripheral α_1-postjunctional adrenoceptors. At equiactive antihypertensive doses, its effect on the pressor response to postural changes in conscious dog was less marked than that shown by prazosin. In the light of these results, alfuzosin was selected for clinical evaluation.

Prazosin (**1**) may be considered as the first member of a new class of antihypertensive agents for which the main mechanism of action appears to be the competitive antagonism of α_1-adrenoceptors.[1] The clinical efficacy of this agent[2] encouraged us to search, through modifications of the structure of its side chain, a new derivative in which the blockade of α_1-adrenoceptors would be associated with other desirable properties for the treatment of hypertension, such as diuresis, direct vasodilation, or the lack of serious orthostatic hypotension upon the administration of the first dose as it was reported for prazosin.[3] Although many derivatives of prazosin—terazosin[4] (**2**), doxazosin[5] (**3**), tiodazosin[6] (**4**), bunazosin (**5**)—are under clinical investigation, none, to our knowledge, appears to have a structure in which the piperazine moiety has been replaced by an alkanediamine chain. In this report, we describe the synthesis and biological activity of some N^2-[(acylamino)alkyl]-6,7-dimethoxy-2,4-quinazolinediamines (**6**–**34**).





Chemistry. The compounds listed in Table I were synthesized by the routes shown in Schemes I and II. The preparation involved the condensation, in refluxing isoamyl

(1) Cavero, I. *Life Sci.* **1980**, *27*, 1525.
(2) Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1977**, *14*, 163.
(3) Thien, T.; Koene, R. A. P.; Wijdeveld, P. G. A. B. *Lancet* **1977**, *1*, 363.
(4) Kyncl, J. J.; Hollinger, R. E.; Oheim, K. W.; Winn, M. *Pharmacologist* **1980**, *22*, 272.
(5) Timmermans, P. B. M. W. M.; Kwa, H. Y.; Ali, F. K.; Van Zwieten, P. A. *Arch. Int. Pharmacodyn. Ther.* **1980**, *245*, 218.
(6) (a) Schurig, J. E.; Cavanagh, R. L.; Roebel, L. E.; Buyniski, J. P. *Pharmacologist* **1977**, *19*, 213, abstr 485. (b) Buyniski, J. P.; Glick, A.; Ryan, J. R.; McMahon, F. G. *Clin. Pharmacol. Ther.* **1980**, *27*, 247.

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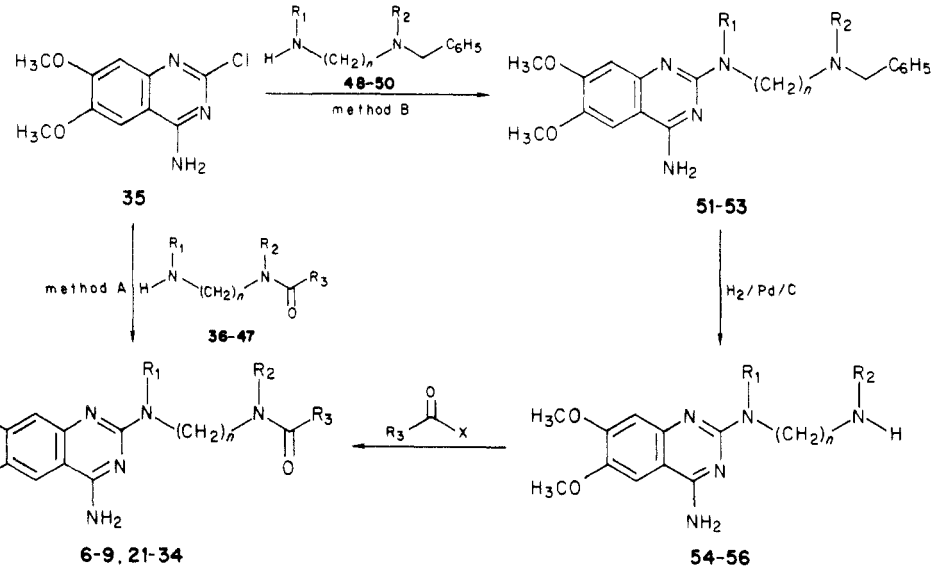
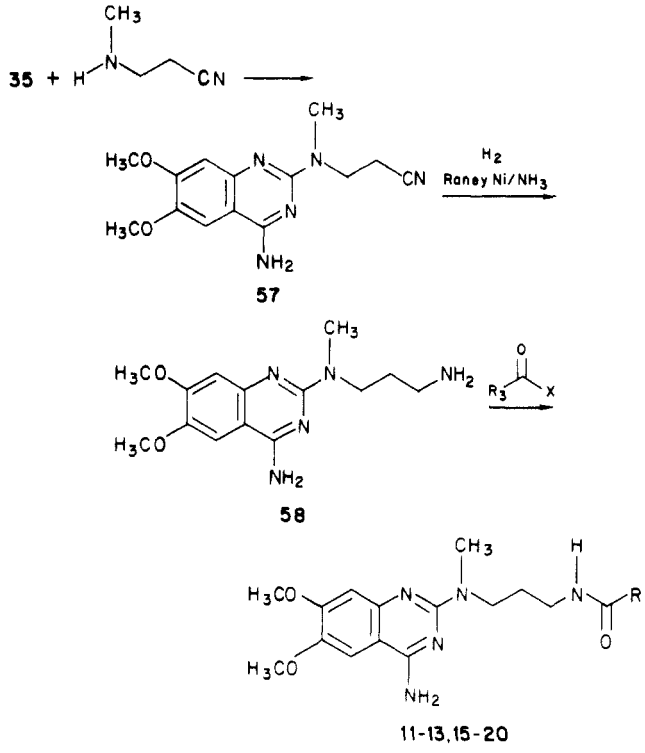
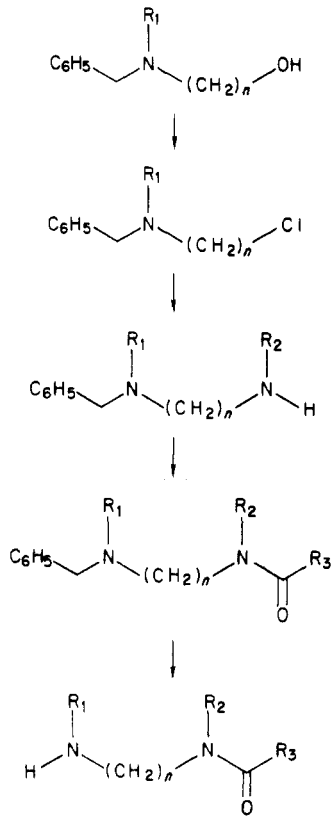
Scheme I



Scheme II. Method C



Scheme III. Method D



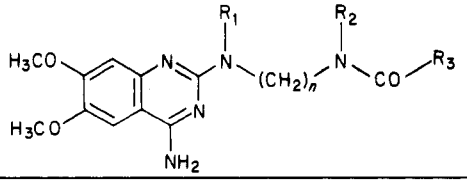
alcohol, of 2-chloro-4-amino-6,7-dimethoxyquinazoline[8] (**35**) with *N*-acylalkanediamine (**36–47**) (method A). Alternatively, the coupling of **35** with *N*-benzylalkanediamine (**48–50**), followed by catalytic hydrogenation afforded **54–56**, which were converted into **21–27** and **31–33** by acylation (method B, Scheme I). A number of 1,3-propanediamine derivatives (R_1 = CH_3, R_2 = H) were conveniently prepared by the condensation of **35** with 3-(methylamino)propanenitrile and catalytic reduction of the intermediate **57** to provide **58**, which was finally acylated to afford **13, 15, 16, 18–20** (method C, Scheme II).

The starting *N*-acylalkanediamines were prepared by two different pathways. One route (Scheme III) used the conversion of *N*-benzylamino alcohols into *N*-benzylalkanediamines, which were acylated and then debenzylated by catalytic hydrogenation to yield **36–38** and **45–47** (method D). The *N*-acylpropanediamines (R_1 or R_2 = H) were synthesized by a different route (Scheme IV, method E), namely, by using the 3-(methylamino)propanenitrile as the starting material, which was first acylated and then reduced to provide a mixture of primary and secondary amines. The proportion of each compound depended on the catalyst, on the reduction conditions, and also on the substituent R_3. Hydrogenation of 3-[(*N*-acyl)methylamino]propanenitrile in methanol saturated with ammonia, effected in the presence of Raney Ni, afforded only **44** when R_3 was a cyclopentyl group and a mixture 60/40

(7) (a) Igarashi, T.; Nakajima, Y.; Ohtake, S. *Jpn. Circ. J.* **1977**, *41*, 903. (b) Kawasaki, T.; Uezono, K.; Abe, I.; Nakamuta, G.; Ueno, M.; Kawazoe, N.; Omae, T. *Eur. J. Clin. Pharmacol.* **1981**, *20*, 399.

(8) Althuis, T. H.; Hess, H. J. *J. Med. Chem.* **1977**, *20*, 146.

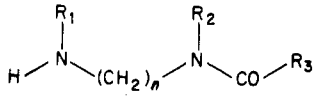
Table I. N^2-[(Acylamino)alkyl]-6,7-dimethoxy-2,4-quinazolinediamines



no.	n	R_1	R_2	R_3	formula[a]	meth	yield,[b] %	mp, °C	% fall in BP[d] (10 mg/kg po) 2 h	4 h
6	2	CH_3	CH_3	C_6H_5	$C_{23}H_{27}N_5O_7$	A	35	220	0	0
7	2	CH_3	CH_3	2-furyl	$C_{19}H_{24}ClN_5O_4$	A	47	262	0	0
8	3	H	H	C_6H_5	$C_{20}H_{24}ClN_5O_3$	A	51	269	−9	−7
9	3	H	CH_3	tetrahydro-2-furyl	$C_{19}H_{28}ClN_5O_4$	B	75	222–223	−8	−6
10	3	CH_3	H	C_6H_5	$C_{21}H_{26}N_5O_3Cl$	A	67	171	−31	−23
11	3	CH_3	H	2-furyl	$C_{19}H_{24}ClN_5O_4$	C	44	194–198	−20	−17
12	3	CH_3	H	tetrahydro-2-furyl	$C_{19}H_{28}ClN_5O_4$	A	53	225	−34	−24
13	3	CH_3	H	tetrahydro-3-furyl	$C_{19}H_{28}ClN_5O_4$	C	83	248	−24	−10
14	3	CH_3	H	cyclopropyl	$C_{18}H_{26}ClN_5O_3$	A	55	270	−19	−12
15	3	CH_3	H	cyclopentyl	$C_{20}H_{30}ClN_5O_3$	C	28	228–232	−30	−20
16	3	CH_3	H	2,3,5,6-tetrahydro-2-pyranyl	$C_{20}H_{30}ClN_5O_4$	C	76	125–128	−27	−7
17	3	CH_3	H	1,4-benzodioxan-2-yl	$C_{23}H_{28}ClN_5O_5$	A	30	185	+2	−6
18	3	CH_3	H	2,3-dihydro-2-benzofuranyl	$C_{23}H_{28}ClN_5O_4$	C	53	145	−22	−19
19	3	CH_3	H	2-benzofuranyl	$C_{23}H_{26}ClN_5O_4$	C	78	181	0	0
20	3	CH_3	H	cinnamyl	$C_{23}H_{28}ClN_5O_3 \cdot H_2O$	C	78	208	0	+3
21	3	CH_3	CH_3	C_6H_5	$C_{22}H_{28}ClN_5O_3$	B	75	218–220	−23	−15
22	3	CH_3	CH_3	3-Me-C_6H_4	$C_{23}H_{30}ClN_5O_3$	B	94	163	−10	0
23	3	CH_3	CH_3	3-OMe-C_6H_4	$C_{23}H_{30}ClN_5O_4$	B	90	191	−12	0
24	3	CH_3	CH_3	3,5-OMe-C_6H_3	$C_{24}H_{32}N_5O_5Cl$	B	77	166	−6	−2
25	3	CH_3	CH_3	3,4,5-OMe-C_6H_2	$C_{25}H_{34}ClN_5O_6$	B	58	196	−11	−6
26	3	CH_3	CH_3	3-pyridyl	$C_{21}H_{27}ClN_6O_3$	B	67	190	−5	−9
27	3	CH_3	CH_3	2-furyl	$C_{20}H_{26}ClN_5O_4$	B	78	163	−24	−20
28	3	CH_3	CH_3	tetrahydro-2-furyl	$C_{20}H_{32}ClN_5O_4$	A	85	182	−14	−7
29	3	CH_3	CH_3	2-CH_3S-1,3,4-oxadiazol-5-yl	$C_{19}H_{26}ClN_7O_4S$	B	84	166	−20	−6
30	3	CH_3	i-C_4H_9	C_6H_5	$C_{25}H_{34}ClN_5O_3$	A	66	206	0	+6
31	3	C_2H_5	CH_3	C_6H_5	$C_{23}H_{30}ClN_5O_3$	B	91	170	−16	−12
32	3	C_2H_5	C_2H_5	C_6H_5	$C_{24}H_{32}ClN_5O_3$	B	60	225	−1	−5
33	3	C_2H_5	C_2H_5	2-furyl	$C_{22}H_{30}ClN_5O_4$	B	50	166	−16	−11
34	4	CH_3	CH_3	C_6H_5	$C_{23}H_{30}ClN_5O_3$	A	89	258	−21	−12
prazosin										
10 mg/kg po									−37	−35[e]
3 mg/kg po									−30	−25[e]

[a] All compounds were identified as hydrochlorides (except **16**, which was an oxalate) and were analyzed for C, H, N. [b] Yields are not optimized. [c] Melting points are uncorrected. [d] Antihypertensive activity in spontaneously hypertensive rats (SHR) in which the drug was given orally at 10 mg/kg. [e] Mean values from five independent groups studied over the screening period of the new compounds.

Table II. *N*-(Acylamino)alkylenediamines

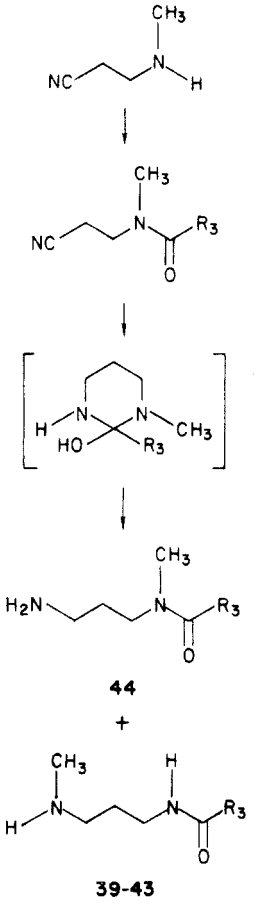


no.	n	R_1	R_2	R_3	formula[a]	meth	yield, %	mp or bp, °C (mmHg)
36	2	CH_3	CH_3	C_6H_5	$C_{11}H_{16}N_2O$	D	69	135–140 (0.01)
37	2	CH_3	CH_3	2-furyl	$C_9H_{14}N_2O_2$	D	75	128–132 (0.01)
38	3	H	H	C_6H_5	$C_{10}H_{14}N_2O$	D	50	143[b]
39	3	CH_3	H	C_6H_5	$C_{11}H_{16}N_2O$	E	38	155–158 (0.1)
40	3	CH_3	H	cyclopropyl	$C_8H_{16}N_2O$	E	72	97–100 (0.07)
41	3	CH_3	H	cyclopentyl	$C_{10}H_{20}N_2O$	E	79	115–120 (0.07)
42	3	CH_3	H	tetrahydro-2-furyl	$C_9H_{18}N_2O_2$	E	53	114–116 (0.07)
43	3	CH_3	H	1,4-benzodioxan-2-yl	$C_{13}H_{18}N_2O_3$	E	32	121[c]
44	3	H	CH_3	cyclopentyl	$C_{10}H_{20}N_2O$	E	20	190[c]
45	3	CH_3	CH_3	tetrahydro-2-furyl	$C_{10}H_{20}N_2O_2$	D	79	122 (0.05)
46	3	CH_3	i-C_4H_9	C_6H_5	$C_{15}H_{24}N_2O$	D	80	133–135 (0.01)
47	4	CH_3	CH_3	C_6H_5	$C_{13}H_{20}N_2O$	D	80	145 (0.05)

[a] Compounds for which formulas are given were analyzed for C, H, N. [b] Characterized as the hydrochloride. [c] Characterized as the oxalate.

of primary and secondary amines when R_3 was a tetrahydrofuryl moiety. The same reaction in the presence of Rh/C provided only the secondary amines (**39–43**) in most cases. When the products were obtained as a mixture of isomers, they could be separated by column chromatography or fractional crystallization of their salts. Isomer assignment was made on the basis of spectral and physical data. The structure was also confirmed by coupling **41** and **42** (R_3 = cyclopentyl or tetrahydro-2-furyl) with **35** to afford **12** and **15**, which were identical with the products obtained by direct acylation of the structurally well-defined primary amine **58**. By distillation or treatment in alkaline

Scheme IV. Method E



medium, **44** was partially converted into **41**, which seemed to be thermodynamically more stable. This conversion probably proceeded through an unstable hexahydro-1,3-pyrimidin-2-ol (Scheme IV), explaining the apparent migration of the methyl group from one nitrogen to the other.

Biological Results and Structure–Activity Relationships

A number of compounds showed good antihypertensive activity when given orally at 10 mg/kg to spontaneously hypertensive rats. The results of this primary screening test are given in Table I.

Derivatives of ethanediamine **6** and **7**, in contrast to those of 1,3-propanediamine, were completely devoid of blood pressure lowering effects. The most active compounds were those in which R_3 was either an unsubstituted phenyl (**10**, **21**), a furyl (**27**), a tetrahydrofuryl (**12**), or a cyclopentyl (**15**) ring. Derivative **34** with a butyl chain (n = 4) was somewhat less active than the propyl analogue (**21**). The introduction of a methyl (**22**) or methoxy groups (**23–25**) in the aromatic ring led to inactive derivatives. A similar relationship was noted for compounds in which R_3 was a pyridine ring (**26**), a benzodioxan (**17**), or a benzofuran (**19**) moiety. Replacement of the phenyl or furyl groups of **10** and **27** by 1,3,4-oxadiazolyl (**29**), tetrahydro-3-furyl (**13**), and 2-tetrahydropyranyl (**16**) moieties afforded compounds which were still active, but their duration of action was shorter than that of **12**, **15**, **18**, **21**, and **27**. Secondary amides, such as **10** and **12**, were somewhat more potent than the corresponding tertiary amides **21** and **28**. In contrast, the secondary amide **11**, in which R_3 was a furyl moiety, was less potent than the corresponding tertiary amide **27**. These results indicate that the furyl moiety can influence favorably the antihypertensive activity and also that the role played by R_2 is important. The derivatives in which R_1 and R_2 are methyl groups were much more potent than **30–33**, which bear bulkier substituents, while the secondary amines **8** and **9** (R_1 = H) lacked antihypertensive activity.

Discussion

At the beginning of our program on α_1 adrenoceptor antagonists we speculated that compound **7**, directly derived from prazosin by breaking the 2,3-carbon bond of the piperazine moiety of prazosin, would show antihypertensive properties, while its homologue **27**, was not expected to be as active. Such a prediction was arrived at by comparing the distances between the two nitrogen atoms in the side chain of compounds **7**, **27**, and prazosin. Thus, measurements of these distances on Dreiding models shows **7**, in its extended conformation (3.8 Å), to be closer to prazosin (3.2 Å) than is **27** (5.1 Å), equally in its extended conformation. Despite this apparent resemblance of **7** to prazosin, it turned out to be devoid of any activity in the SHR while **27**, surprisingly, exerted strong antihypertensive effects.

Data listed in Table I also show that R_1, R_2, and R_3 have a considerable influence on the potency of the derivatives since very slight changes of these substituents can completely abolish the blood pressure lowering effects. The fact that compounds **8** and **9**, in which R_1 is a hydrogen atom, are inactive suggests that the presence of a tertiary amino group in position 2 of the quinazoline ring is necessary. Replacement of the methyl group in **21** and **27** by bulkier substituents (**39–41**) increases the values of lipophilic and steric parameters and results in compounds with poor antihypertensive activity. Comparison of the lipophilicity of some compounds in the series did not permit to unveil a correlation between this physicochemical parameter and antihypertensive activity. For instance, the most potent derivative **12** has a lipophilicity very different from that of **10** or **15**, which, however, produce a decrease in blood pressure. In contrast, the very active compound **10** has a lipophilicity close to that of **17** and **19**, both of which do not exert antihypertensive effects.

These results suggest that lipophilicity does not play a decisive role in determining the antihypertensive potency of the various compounds in our chemical series. In contrast, steric effects of R_1 and R_2 seem to have a more important influence since an increase in their size (**30–33**) might modify the conformation of the propanediamine chain and afford molecules which cannot bind strongly to the receptor. Furthermore, aromatic ring substitution (**22**, **23**) or the replacement of phenyl in **10** and **21** by pyridine (**26**), benzofuran (**19**), and benzodioxan (**17**) moieties results in a reduced activity; thus, the structural requirements of R_3 are very strict.

This dependency of the antihypertensive activity upon substituent R_3 may appear surprising for a molecule which interacts with the α-adrenoceptors stimulated by the transmitter noradrenaline. Structurally, the 2-aminoquinazoline portion of the described compounds seems to recall the noradrenaline molecule more than any part of the side chain, for the fitting of α-adrenoceptors. The biological results would suggest that our derivatives, like prazosin, probably have another binding site close to but different from that of noradrenaline, and this site appears to have very strict structural requirements. Comparison of the antihypertensive activity of **12** with **13** and **16–19** or of **14** with **15** indicates that the position of substitution and the size and nature of the ring are of great importance. For instance, it is surprising the absence of blood pressure lowering properties of the benzofuranyl derivative **19** while the dihydrobenzofuranyl analogue **18** is active. A regres-

sion analysis was done in our series, but it did not permit to reveal any significant correlation.

Our results also show that other differences exist with the prazosin series since, for instance, **17**, an open analogue of the active doxazosin[5] **3**, does not exert any antihypertensive effects, suggesting moderate similarities between the two series, due to the fact that opening the piperazine ring and lengthening the alkylene chain together with certain R_3 substituents result in conformational changes which are not compatible with biological activity.

In conclusion, the antihypertensive properties of our molecules appear to strongly depend on the length of the alkanediamine chain, the size of R_1 and R_2, and the nature of R_3 substituents. Maximum activity is observed in compounds having a propyl chain between the two nitrogen atoms and in which R_1 is a methyl group, R_2 is a hydrogen atom or a methyl group, and R_3 is an unsubstituted aromatic or heterocyclic alicyclic ring such as furan, tetrahydrofuran, or cyclopentane.

The most potent derivatives (**10**, **12**, **15**) as antihypertensive agents were chosen for further pharmacological evaluation. When given orally in rats at 10 mg/kg during 7 days, **10** showed, like prazosin,[9] a progressive decrease in blood pressure lowering effects, indicating the development of tolerance. This drawback was not found with alfuzosin (**12**), which proved to be an antihypertensive agent one-third as potent as prazosin, in acute and chronic administration in rats and dogs.[10] The duration of the antihypertensive effects of **12** was the same as that of prazosin when equipotent doses are studied (Table I). Alfuzosin (**12**) also exhibited a relatively high selectivity for peripheral α_1-postjunctional adrenoceptor "in vitro" and "in vivo" pharmacological tests.[11] Moreover, **12**, unlike prazosin[12] but similarly to papaverine, was found to relax aortic strips contracted with either KCl or $CaCl_2$, a property which may be of clinical relevance. At equiactive antihypertensive doses, the inhibitory effects of **12** on the pressor response to postural changes were less marked than those shown by prazosin. In the light of these results, **12** (alfuzosin) is under clinical trials as a potential antihypertensive agent.

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 399 spectrophotometer. NMR spectra were obtained on a Bruker WP 80 or WP 200 SY spectrometer using tetramethylsilane as internal reference. Where analyses are reported by elemental symbols, results were within ±0.4% of the calculated values.

General Methods for the Preparation of N^2-[(Acylamino)alkyl]-6,7-dimethoxy-2,4-quinazolinediamines (Table I, 6–34). Condensation of 2-chloro-4-amino-6,7-dimethoxyquinazoline with amino amides, amino nitriles and diamines were achieved according the literature method.[8]

Method A. N-[3-[(4-Amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydro-2-furancarboxamide Hydrochloride (12). A mixture of 18.4 g (0.1 mol) of **42** and 21.5 g (0.09 mol) of 2-chloro-4-amino-6,7-dimethoxyquinazoline (**35**)[8] in 250 mL of isoamyl alcohol was stirred under argon and refluxed for 12 h. After being cooled, the precipitate was filtered off and washed with isoamyl alcohol and then with ethyl ether. The filtrate was concentrated in vacuo, and the residue was triturated in acetone and filtered off. The crude solid was recrystallized from a mixture of ethyl alcohol and ethyl ether to give 25.5 g (66%) of **12**, mp 223 °C. Anal. ($C_{19}H_{28}ClN_5O_4$) C, H, N, Cl.

Method B. N-Methyl-N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]-3-methoxybenzenecarboxamide Hydrochloride (23). (a) N^1,N^2-Dimethyl-N^2-(phenylmethyl)-N^1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-1,3-propanediamine (51). A mixture of 6 g (0.025 mol) of **35**, 9.7 g (0.05 mol) of N^1,N^2-dimethyl-N^1-(phenylmethyl)-1,3-propanediamine[13] and 2 mL of pyridine was heated at 130 °C for 30 min. The mixture was partitioned between aqueous $NaHCO_3$ and chloroform. The extract was dried and then concentrated in vacuo. The oily residue was purified by column chromatography on alumina with chloroform–methanol (9:1) as eluent to give after recrystallization from 2-propanol 7 g (70%) of **51**, mp 128 °C. Anal. ($C_{22}H_{29}N_5O_2$) C, H, N.

The derivatives **52** ($R_1 = C_2H_5$, $R_2 = CH_3$) and **53** ($R_1 = R_2 = C_2H_5$) were similarly prepared from the corresponding benzylated amines **49** and **50** with yields of 73% and 68%. They did not crystallize and were used without purification for the next step.

(b) N^1,N^2-Dimethyl-N^1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-1,3-propanediamine (54). A solution of 11.5 g (0.029 mol) of **51** in 250 mL of methanol and 17 mL of 3.4 N ethanolic HCl and 3 g of 5% Pd/C was hydrogenated at 80 °C at a 280 psi H_2 pressure until complete uptake of hydrogen. The catalyst was filtered off and washed with 70% methanol. The solvent was evaporated and the solid residue was washed twice with boiling methanol to provide 9.2 g (85%) of **54**, mp 240 °C. Anal. ($C_{15}H_{25}Cl_2N_5O_2$) C, H, N, Cl. Compounds **55** (mp 262 °C) ($R_1 = C_2H_5$, $R_2 = CH_3$) and **56** (mp 270 °C) ($R_1 = R_2 = C_2H_5$) were similarly obtained from **52** and **53** with yields of 86% and 78% and were identified as dihydrochlorides. Anal. **55** ($C_{16}H_{27}Cl_2N_5O_2$) C, H, N, Cl. Anal. **56** ($C_{17}H_{29}Cl_2N_5O_2$) C, H, N, Cl.

(c) Acylation of 54. A mixture of 7.5 g (0.02 mol) of **54** in 100 mL of chloroform was treated with 2.8 g (0.07 mol) of sodium hydroxide pellets and 60 mL of water. A solution of 3.75 g (0.022 mol) of 3-methoxybenzenecarboxylic acid chloride in 300 mL of chloroform was added dropwise and the mixture stirred for 1 h at room temperature. Workup afforded the free base, which was converted into its hydrochloride (**23**) (90%) and recrystallized from 2-propanol, mp 191 °C. Anal. ($C_{23}H_{30}ClN_5O_4$) C, H, N, Cl.

Method C. N-[3-[(4-Amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]cyclopentanecarboxamide Hydrochloride (15). (a) 3-[(4-Amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propanenitrile (57). A mixture of 14.4 g (0.06 mol) of **35** and 10 g (0.12 mol) of 1-(methylamino)-3-propanenitrile[14] in 100 mL of isoamyl alcohol was stirred and refluxed under argon for 5 h. After being cooled, the mixture was filtered off and washed several times with hot ethyl alcohol to afford 12.1 g (62%) of **57**, mp 270 °C. Anal. ($C_{14}H_{18}ClN_5O_2$) C, H, N.

(b) N^1-Methyl-N^1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-1,3-propanediamine (58). A 5.7-g (0.02 mol) quantity of **57** was dissolved in 120 mL of 15% alcoholic ammonia and hydrogenated over Raney Ni catalyst at 70 °C and 1000 psi H_2 pressure. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in dichloromethane and filtered. Evaporation of the filtrate gave an oil, which was converted into the hydrochloride in ethyl alcohol to afford 3 g (52%) of **58** recrystallized from 2-propanol, mp 270 °C. Anal. ($C_{14}H_{22}ClN_5O_2$) C, H, N, Cl.

(c) N-[3-[(4-Amino-6,7-dimethoxy-2-quinazolinyl)-methylamino]propyl]cyclopentanecarboxamide Hydrochloride (15). A solution of 16 g (0.14 mol) of cyclopentanecarboxylic acid in 300 mL of THF was treated with 22 g (0.14 mol) of carbonyldiimidazole and the mixture was heated with stirring at 40 °C for 1 h. After cooling at 10 °C, 29 g (0.1 mol) of **58** was added and the mixture was refluxed for 3 h. The solvent was evaporated and the residue was partitioned between 2 N NaOH

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and chloroform. Workup gave the free base, which was converted into hydrochloride salt and recrystallized from 2-propanol to give 32.1 g (75%) of **15**, mp 228–232 °C. Anal. ($C_{20}H_{30}ClN_5O_3$) C, H, N, Cl.

General Methods for the Preparation of *N*-(Acyl)alkylenediamines (Table II, 36–47). Method D. *N*-[3-(Methylamino)propyl]-*N*-(2-methyl-1-propyl)benzenecarboxamide (46). A solution of 60 g (0.24 mol) *N*-(phenylmethyl)-*N*-methyl-3-chloropropanamine[15] and 146 g (2 mol) of 2-methylpropanamine in 250 mL of methanol was refluxed for 3 h. The mixture was cooled and concentrated in vacuo; 5 N sodium hydroxide was added to the residue, which was extracted three times with ether and concentrated in vacuo and fractionated under reduced pressure to give 42.6 g (65%) of N^1-(phenylmethyl)-N^1-methyl-N^2-(2-methyl-1-propyl)propane-1,3-diamine (**59**), bp 128–131 °C (0.05 mm). Anal. ($C_{15}H_{26}N_2$) C, H, N.

The hydrochloride of **59** was prepared in 2-propanol, mp 106 °C.

A solution of 18.7 g (0.069 mol) of this salt in 100 mL of chloroform was treated with a solution of sodium hydroxide (4.2 g, 0.105 mol of NaOH pellets in 42 mL of water). A solution of 9.8 g (0.069 mol) of benzenecarboxylic acid chloride in 30 mL of chloroform was added dropwise and the mixture stirred for 1 h. Workup gave 23 g of the crude product, which was diluted with 250 mL of methanol and 25 mL of 2.9 N ethanolic HCl and hydrogenated over 10% Pd/C at 80 °C and a 1000 psi H_2 pressure until H_2 uptake was completed. The catalyst was filtered off and the filtrate concentrated.

The residue was diluted with 2 N sodium hydroxide and extracted with chloroform. After washing and drying, the organic phase was concentrated in vacuo and fractionated to afford 13.8 g (80%) of *N*-[3-(methylamino)propyl]-*N*-(2-methyl-1-propyl)-benzenecarboxamide (**46**), bp 133–135 °C (0.05 mm), which was converted into its hydrochloride from 2-propanol, mp 136 °C. Anal. ($C_{15}H_{25}ClN_2O$) C, H, N, Cl.

Method E. (a) Tetrahydro-*N*-[3-(methylamino)propyl]-2-furancarboxamide (42). (1) Tetrahydro-*N*-(3-cyanopropyl)-*N*-methylfurancarboxamide (60). A 32.4-g (0.3 mol) quantity of ethyl chloroformate was added dropwise at 0 °C to a solution of 34.8 g (0.3 mol) of tetrahydro-2-furancarboxylic acid and 30.3 g of Et_3N in 250 mL of THF. During the addition, the temperature of the mixture was kept below 5 °C. After completion of the addition, the mixture was stirred for 15 min at 5 °C and then a solution of 25.2 g (0.3 mol) of 3-(methylamino)propanenitrile in 100 mL of THF was slowly added. The mixture was stirred for 1 h and kept at room temperature overnight. The mixture was filtered off and the solvent evaporated. The residual liquid was distilled to give 41 g (75%) of **60**, bp 118–120 °C (0.05 mm). Anal. ($C_9H_{14}N_2O_2$) C, H, N.

(2) Tetrahydro-*N*-[3-(methylamino)propyl]-2-furancarboxamide (42). A solution of 26.5 g (0.145 mol) of **60** in 300 mL of 10% ethanolic ammonia was hydrogenated at 80 °C over Rh/C at 840 psi H_2 pressure. After H_2 uptake was completed, the mixture was cooled and the catalyst filtered off and the filtrate concentrated to afford 18.4 g (68%) of **42**: bp 120–122 °C (0.07 mm); NMR ($CDCl_3$) δ 2.66 (2 H, t), 2.45 (3 H, s), 2.4–1.5 (6 H, m), 1.5 (1 H, s); IR (film) 3500–3100, 1665, 1530 cm^{-1}. Anal. ($C_9H_{18}N_2O_2$) C, H, N.

(b) *N*-[3-(Methylamino)propyl]cyclopentanecarboxamide (41) and *N*-Methyl-*N*-(aminopropyl)cyclopentanecarboxamide (44). (1) *N*-(3-Cyanopropyl)-*N*-methylcyclopentanecarboxamide (61). A solution of 53 g (0.4 mol) of cyclopentanecarboxylic acid chloride was added dropwise at 0 °C to a solution of 33.6 g (0.4 mol) of 3-(methylamino)propanenitrile and 55.8 mL of Et_3N in 100 mL of THF. The mixture was allowed to warm to room temperature and stirred for 1 h; precipitated Et_3N·HCl was removed by filtration and the filtrate was evaporated to dryness and the resultant oil was distillated to afford 65.3 g (91%) of **61**, bp 122–124 °C (0.07 mm). Anal. ($C_{10}H_{16}N_2O$) C, H, N.

(2) *N*-[3-(Methylamino)propyl]cyclopentanecarboxamide (41) and *N*-Methyl-*N*-(3-aminopropyl)cyclopentanecarboxamide (44). A solution of 27 g of **61** in 150 mL of 10% ethanol ammonia was hydrogenated at 80 °C over Rh/C at a 840 psi H_2 pressure. Workup yielded 21.7 g (79%) of a mixture of **41** and **44**.

A 72-g mixture of **41** and **44** was converted into the hydrochloride salt in $CHCl_3$ with 83.4 mL of 4.62 N ethanol HCl. The mixture was evaporated to dryness and the residue was crystallized from 2-propanol to yield after recrystallization from 2-propanol 53 g of **41** as hydrochloride salt: mp 162–164 °C; NMR ($CDCl_3$) δ 6.92 (1 H, s), 3.75 (2 H, 9), 2.7 (2 H, t), 2.52 (1 H, m), 2.45 (3 H, s), 1.72 (11 H, m); IR (film) 3280, 1640, 1540 cm^{-1}. Anal. ($C_{10}H_{21}ClN_2O$) C, H, N.

The 2-propanol filtrates were evaporated to dryness, and the residue was converted into free base. This base was treated with a half equimolar amount of oxalic acid in 2-propanol to give **44** recrystallized from 2-propanol as hemioxalate: mp 190 °C; NMR ($CDCl_3$) δ 3.52 (2 H, m), 3.07–2.97 (4 H, m), 2.73 (2 H, m), 1.75 (10 H, m), 1.37 (2 H, s); IR (film) 3200–3500, 1630–1640 cm^{-1}. Anal. ($C_{11}H_{21}N_2O_3$) C, H, N. When the hydrogenation of **61** was performed over Raney Ni instead of Rh/C, only **44** was obtained. Coupling **41** with **35** as described in method A afforded a compound which was the same as **15** obtained with method B.

Screening for Antihypertensive Activity. Experiments were carried out in spontaneously hypertensive male rats (Okamoto strain), which were at least 14 weeks old. They were placed for approximately 30 min in a temperature (28 °C) and humidity (60%) controlled cabinet before applying to the tail an inflatable cuff and a piezoelectric transducer to pick up arterial pulse waves (W and W BP Recorder, Model 8005) according to the technique described by Gerold and Tschirky.[16] Heart rate was measured by counting automatically the arterial pulses occurring over 10-s periods. The cuff pressure required to produce the disappearance of the arterial pulse is the value of the systolic blood pressure. Three blood pressure measurements were taken before giving any treatment, and the lowest one was chosen as a control value. Results are expressed as changes in blood pressure with respect to the control value. Groups of five animals were dosed orally with either placebo (2.0 mL/kg of a 0.2% v/v solution of Tween 80 in distilled water) or 10 mg of each newly synthetized compound dissolved in the same vehicle. In these experiments, prazosin was used as reference compound.

Table I reports the magnitude of the antihypertensive effect produced by each compound 2 and 4 h after the oral administration. No significant changes in heart rate were observed so these results are not given in Table I.

Registry No. **6**, 65189-44-8; **6**·HCl, 98902-19-3; **7**, 96649-38-6; **7**·HCl, 96649-39-7; **8**, 65189-52-8; **8**·HCl, 65189-53-9; **9**, 98902-34-2; **10**, 98902-35-3; **10**·HCl, 65189-49-3; **11**, 98902-36-4; **11**·HCl, 98902-29-5; **12**, 81403-80-7; **12**·HCl, 81403-68-1; **13**, 76362-32-8; **13**·HCl, 81403-72-7; **14**, 76362-35-1; **14**·HCl, 81403-75-0; **15**, 98902-37-5; **15**·HCl, 81403-71-6; **16**, 76362-34-0; **16**·HCl, 81403-74-9; **17**, 79959-12-9; **17**·HCl, 79959-09-4; **18**, 76362-36-2; **18**·HCl, 81403-77-2; **19**, 76377-81-6; **19**·HCl, 81403-76-1; **20**, 98902-38-6; **20**·HCl, 98902-30-8; **21**, 98902-39-7; **21**·HCl, 65189-29-9; **22**, 72766-65-5; **22**·HCl, 65189-55-1; **23**, 98902-40-0; **23**·HCl, 65189-56-2; **24**, 98902-41-1; **24**·HCl, 65189-57-3; **25**, 98902-42-2; **25**·HCl, 65189-58-4; **26**, 98902-43-3; **26**·HCl, 72766-63-3; **27**, 98902-44-4; **27**·HCl, 65189-43-7; **28**, 76362-33-9; **28**·HCl, 81403-73-8; **29**, 65189-36-8; **29**·HCl, 65189-35-7; **30**, 98902-45-5; **30**·HCl, 65189-47-1; **31**, 98902-46-6; **31**·HCl, 65189-50-6; **32**, 98902-47-7; **32**·HCl, 65189-48-2; **33**, 98902-48-8; **33**·HCl, 65189-51-7; **34**, 98902-49-9; **34**·HCl, 65189-54-0; **35**, 23680-84-4; **36**, 98902-12-6; **37**, 96649-52-4; **38**, 6108-74-3; **39**, 98902-17-1; **40**, 98902-18-2; **41**, 81403-70-5; **41**·HCl, 98902-32-0; **42**, 81403-67-0; **43**, 79959-07-2; **43**·oxalate, 98902-50-2; **44**, 72104-47-3; **44**·$^1/_2$oxalate, 98902-33-1; **45**, 98902-13-7; **46**, 98902-14-8; **46**·HCl, 98902-51-3; **47**, 98902-15-9; **48**, 60630-68-4; **49**, 98902-20-6; **50**, 98902-21-7; **51**, 65189-24-4; **51**·2HCl, 65189-23-3; **52**, 98902-22-8; **52**·2HCl, 98921-40-5; **53**, 98902-23-9; **53**·2HCl, 98902-24-0; **54**, 72779-30-7; **54**·2HCl, 65189-25-5; **55**, 98902-27-3; **55**·2HCl, 98902-25-1; **56**, 98902-28-4; **56**·2HCl, 98902-26-2; **57**, 76362-28-2; **58**, 76362-29-3; **58**·HCl, 81403-69-2; **59**·HCl, 98902-31-9; $PhCH_2N(Me)(CH_2)_2OH$, 101-98-4; $PhCH_2NH(CH_2)_3OH$, 4720-29-0; $PhCH_2N(Me)(CH_2)_3OH$, 5814-42-6; $PhCH_2N(Me)(CH_2)_4OH$, 98901-97-4; $PhCH_2N(Me)(CH_2)_2Cl$,

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17542-47-1; $PhCH_2NH(CH_2)_3Cl$, 42245-33-0; $PhCH_2N(Me)(CH_2)_3Cl$, 3161-52-2; $PhCH_2N(Me)(CH_2)_4Cl$, 98901-98-5; $PhCH_2N(Me)(CH_2)_2NHMe$, 102-11-4; $PhCH_2NH(CH_2)_3NH_2$, 13910-48-0; $PhCH_2N(Me)(CH_2)_3NHBu$-*i*, 98901-99-6; $PhCH_2N(Me)(CH_2)_4NHMe$, 98902-00-2; $PhCH_2N(Me)(CH_2)_2N(Me)COPh$, 98902-01-3; $PhCH_2NH(CH_2)_3N(Me)COC_4H_3O$-2, 98902-02-4; $PhCH_2NH(CH_2)_3NHCOPh$, 98902-03-5; $PhCH_2N(Me)(CH_2)_3N(Me)COTHF$-2, 98902-04-6; $PhCH_2N(Me)(CH_2)_3N(Bu$-*i*$)COPh$, 98902-05-7; $PhCH_2N(Me)(CH_2)_4N(Me)COPh$, 98902-06-8; $PhCH_2N(Me)(CH_2)_2N(Me)COph\cdot HCl$, 98902-07-9; $PhCH_2NH(CH_2)_3N(Me)COC_4H_3O$-2·HCl, 98902-08-0; $PhCH_2NH(CH_2)_3NHCOPh\cdot HCl$, 98902-09-1; $PhCH_2N(Me)(CH_2)_3N(Me)COTHF$-2·HCl, 98902-10-4; $PhCH_2N(Me)(CH_2)_3N(Bu$-*i*$)COPh\cdot HCl$, 98902-11-5; $PhCH_2N(Me)(CH_2)_4N(Me)COPh\cdot HCl$, 98921-39-2; $NC(CH_2)_2NHMe$, 693-05-0; $NC(CH_2)_2N(Me)COPh$, 23873-66-7; *c*-$PrCON(Me)(CH_2)_2CN$, 98902-16-0; *c*-$C_5H_9CON(Me)(CH_2)_2CN$, 72104-46-2; $NC(CH_2)_2N(Me)COTHF$-2, 72104-44-0; $NC(CH_2)_2N(Me)COR$ (R = 1,4-benzodioxan-2-yl), 79959-06-1; tetrahydro-2-furancarboxylic acid, 16874-33-2; tetrahydro-3-furoic acid, 89364-31-8; 3-methylbenzoyl chloride, 1711-06-4; 3-methoxybenzoyl chloride, 1711-05-3; 3,5-dimethoxybenzoyl chloride, 17213-57-9; 3,4,5-trimethoxybenzoyl chloride, 4521-61-3; 3-pyridinecarbonyl chloride, 10400-19-8; 2-furancarbonyl chloride, 527-69-5; 2-(methylthio)-1,3,4-oxadiazole-5-carbonyl chloride, 62373-33-5; cyclopropanecarbonyl chloride, 4023-34-1; cyclopentanecarbonyl chloride, 4524-93-0; 1,4-benzodioxane-2-carbonyl chloride, 3663-81-8; tetrahydro-2-furancarbonyl chloride, 52449-98-6.

5-(Alkylsulfonyl)salicylanilides as Potential Dental Antiplaque Agents

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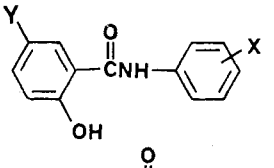
A series of 22 5-(alkylsulfonyl)salicylanilides was synthesized and evaluated for in vitro antibacterial and antiplaque activity against *Actinomyces viscosus* and *Streptococcus mutans*, adherent microorganisms implicated in periodontal disease and dental caries. The minimum inhibitory concentrations of 25 salicylanilides (including 5-acyl-, 5-alkyl-, and 5-(alkylsulfonyl)-4′-bromo- and -4′-(trifluoromethyl)salicylanilides) were found to correlate ($r = 0.94$) with estimated log *D* values. Several salicylanilides, such as 5-(decylsulfonyl)- and 5-(dodecylsulfonyl)-4′-(trifluoromethyl)salicylanilides (**15** and **19**) were found to exhibit high levels of in vitro antibacterial and antiplaque activity against *A. viscosus* and *S. mutans*.

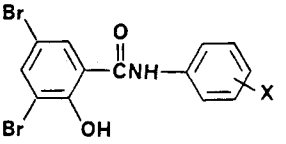
A number of 5-acyl- and 5-alkylsalicylanilides (**1a** and **1b**) have been reported to exhibit high levels of antibacterial activity against *Actinomycetes*,[1] adherent bacteria associated with marginal inflammatory gingivitis.[2] The development of **1a** and **1b** was based upon the antibacterial properties of 3,4′,5-tribromosalicylanilide (tribromsalan, TBS, **2a**), as well as the caries-inhibiting activity of fluorophene (**2b**) in the rat.[3-6] Salicylanilides, such as **1a**, were found to exhibit significant in vitro antiplaque activity in a quantitative antiplaque bioassay reflecting oral conditions.[7-9] TBS (**2a**) was a component of an oral preparation found to exhibit clinical effects against plaque formation and gingivitis in man.[10,11] Since usage of halogenated salicylanilides such as **2a** and **2b** has been restricted by the FDA,[12] due to photoallergic effects observed only with halogenated derivatives,[13] new nonhalogenated salicylanilides were sought with antimicrobial properties optimized against oral bacteria associated with gingivitis, periodontal disease, and caries.

Several 5-acyl derivatives, **1a**, appear to be more effective against *Actinomyces viscosus* in vitro than TBS.[1] One derivative of **1a**, Y = *n*-decanoyl, X = 4′-nitro (**1d**), has been reported to be more effective than TBS in inhibiting the development of gingivitis in Beagle dogs, when employed in an oral mouthrinse preparation.[14] The salicylanilides have not been reported to display the undesirable organoleptic and staining properties associated with cationic surfactant antimicrobials, and therefore, they represent a promising class of agents for the topical control of the development of caries and periodontal disease.

Since the electron-withdrawing 5-acyl group appeared more effective than the 5-alkyl group in enhancing both antimicrobial properties and solubility of these very lipophilic derivatives,[1] the 5-alkylsulfonyl group was chosen



1a, Y = -C(=O)R
b, Y = $-CH_2R$
c, Y = $-SO_2R$



2a, X = 4′Br
b, X = 3′CF_3

as an alternative substituent which would further increase phenol acidity and permit incremental adjustments in

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