Synthesis and Antihypertensive Activity of *N*-(Alkyl/alkenyl/aryl)-*N*′-heterocyclic Ureas and Thioureas

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Abstract □ A variety of *N*-(alkyl/alkenyl/aryl-*N*′-heterocyclic ureas and thioureas were synthesized as potential antihypertensives. The selected heterocyclic nuclei were the 6-substituted quinoline and the pyridine. Eleven synthesized compounds and seven related compounds in the series were evaluated orally at a dose of 100 mg/kg in conscious deoxycorticosterone acetate/saline-treated hypertensive rats by the tail-cuff method. Seventeen out of the eighteen tested compounds possessed significant antihypertensive activity ($p < 0.05$). 1-*n*-Propyl-3-[2′-(6-methoxy)quinolyl]urea (**9**), showing 29.1% reduction in systolic blood pressure, was the most active compound in the series. Two other compounds producing a fall in systolic blood pressure of the same magnitude were 1-allyl-3-[2′-(6-methyl)quinolyl]thiourea (**4**) and 1-*n*-propyl-3-[(2′-pyridyl)methyl]urea (**17**). Compound **17** with rapid onset caused significant relaxation ($p < 0.01$) of isolated rabbit femoral artery and guinea pig atrium but had no effect on heart rate. However, none of these exhibited higher potency than prazosin (5 mg/kg). The potency, onset, and duration of action improved when the heterocyclic nucleus was pyridine.

Hypertension is a frequently occurring disease and is the major risk factor in coronary heart diseases and cardiovascular accident. The main thrust of antihypertensive therapy consists of chronic treatment with drugs. Recently, a significant number of compounds with the combined structural moieties of heterocyclic rings and urea or thiourea groups were synthesized and evaluated for biological activities. Among compounds of this type, substantial antihypertensive activity was found in 3-substituted-1-[4-(2-indol-3-ylethyl)piperazinyl]-ureas,[1] pyridinylidinearylureas,[2] (2-aminoethyl)thiourea derivatives,[3,4] 2,4-diamino-6,7−dimethoxyquinoline derivatives,[5] and 4-(substituted-carbonylamino)-2*H*-1-benzopyrans.[6]

A new series of ureas and thioureas incorporating heterocyclic rings was therefore synthesized (Table 1) and tested for antihypertensive action. Structural modification was made by varying the chemical features on both sides of the urea or thiourea function. The selected heterocyclic systems on one nitrogen of urea or thiourea was either a 6-substituted quinoline or 2-pyridylmethyl. These functions are related to the heterocycles of the active compounds, 2,4−diamino-6,7-dimethoxyquinoline,[5] centhaquin,[7] aprikalim,[8] and guanylhydrazones of 2−pyridine.[9] The function on the other nitrogen was varied from aliphatic groups such as propyl, heptyl, and octyl to alkene (allyl) or aromatic (4-methoxyphenyl) in order to provide a wide range of lipophilicity.

Antihypertensive evaluation of the newly synthesized some previously prepared[10] compounds and was carried out. The evaluation was performed by the indirect tail-cuff method in deoxycorticosterone acetate/saline-treated hypertensive rats (DHRs). The effects of the most promising compound with rapid onset, compound **17**, on isolated vascular smooth muscle and heart muscle were also studied.

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Experimental Section

Chemistry—Melting points were determined on a Kofler thermal microscope and are uncorrected. Infrared (IR) spectra were run as potassium bromide disks on a Perkin Elmer 1740 FTIR. The proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained with a JEOL FX 900 (90 MHz). Chemical shifts were reported in ppm related to the internal standard, tetramethylsilane. Mass spectra were measured on a JEOL FX 3000 double focusing spectrometer. TLC was carried out on 2.5 mm Merck silica gel GF 254 strips, and the purified compounds each showed a single spot. Analytical results from an elemental analyzer (Perkin Elmer 2400) obtained for all compounds were within ±0.4% of the theoretical value. Spectral (IR, MS, NMR) data were compatible with the assigned structures in all cases.

The general procedures for the synthesis of *N*-(alkyl/alkenyl/aryl)-*N*′-heterocyclic ureas and thioureas involved the reaction of the amino compound with the isocyanate or isothiocyanate carrying the selected side chains. When the amino compounds were commercially unavailable, such as 6-methyl-2-aminoquinoline, 6-methoxy-2-aminoquinoline, and 6-methoxy-4-aminoquinoline, they were prepared by the reported methods.[10]

The reaction conditions varied according to the starting materials. The reaction of allyl isocyanate with 2-amino-6-methyl- or 2-amino-6-methoxyquinoline was employed at 80 °C to give urea compounds **1** and **8** while allyl isocyanate reacted with 2-(aminomethyl)pyridine at room temperature to give compound **16**. For thiourea compounds **4** and **11**, the allyl isothiocyanate and 2-amino-6-substituted-quinolines were mixed together at 150 °C. For amino compounds reacting with propyl isocyanate, the aminoquinolines were refluxed in chloroform whereas 2-(aminomethyl)pyridine was mixed at 80 °C. The (4-methoxyphenyl)ureas of quinolines and pyridine (compounds **3**, **10**, and **18**) were synthesized by mixing the reagents neat or in chloroform at room temperature. The reaction time ranged from 0.5 to 4 h. The physical properties of the compounds synthesized are listed in Table 1. Representive methods used to prepare the target ureas and thioureas are described in the following examples.

1-Allyl-3-[2′-(6-methyl)quinolyl]urea (1)—A mixture of 2-amino-6-methylquinoline (0.55 g, 3.5 mmol) and allyl isocyanate (620 μL, 7.0 mmol) was heated at 80 °C for 2 h. The resulting solid was collected and recrystallized with ethanol to give 1-allyl-3-[2′-(6-methyl)quinolyl]urea as white needles (0.67 g, 79.76% yield) mp 176−178 °C. IR (KBr) (cm^{-1}): 3212 (N-H), 3016−3078 (aromatic C−H, olefinic C−H), 2920−2986 (aliphatic C−H), 1688 (C=O), 1467−1616 (aromatic C=C, cyclic C=N, olefinic C=C, N−H), 1313 (aromatic C−N), 1131−1165 (aliphatic C-N), 822 (parasubstituted aromatic C−H). ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H, CH_3-quinoline), 4.12 (t, J = 5.1 Hz, 2H, N*H*CH_2CH=), 5.21 (dd, J = 1.6 and 10.1 Hz, allyl-H_a), 5.37 (dd, J = 1.4 and 19.5 Hz, allyl-H_b), 6.08 (m, 1H, -C*H*$_2$CH=CH_2), 7.00 (d, J = 8.9 Hz, H3), 7.32 (d, J = 9.2 Hz, H4), 9.57 (bs, 1H, exchangeable with D_2O, quinoline-N*H*), 10.33 (bs, 1H, exchangeable with D_2O, CONHCH_2). Anal.—Calcd for $C_{14}H_{15}N_{30}$: C, 69.69; H, 6.26; N, 17.42. Found: C, 69.98; H, 6.24; N, 17.44.

1-(4-Methoxyphenyl)-3-[2′-(6-methyl)quinolyl]urea (3)—4-Methoxyphenyl isocyanate (400 μL, 2.1 mmol) was added dropwise to a stirred solution of 2-amino-6-methylquinoline (0.49 g, 2.1 mmol)

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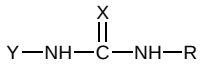
Table 1—*N*-(Alkyl/alkene/aryl)-*N'*-heterocyclic Ureas and Thioureas



Compound No.	Y	X	R	Recrystn Solvent	Mp (°C)	Yield (%)
1[a]	6-Methyl-2-quinolyl	O	$CH_2{=}CHCH_2$	EtOH	176–178	80
2[a]	6-Methyl-2-quinolyl	O	$CH_3(CH_2)_2$	EtOH–H_2O	197–198	72
3[a]	6-Methyl-2-quinolyl	O	CH_3OPh	DMF	236–238	88
4[a]	6-Methyl-2-quinolyl	S	$CH_2{=}CHCH_2$	$CHCl_3$–MeOH	181–183	56
5	6-Methyl-2-quinolyl	S	$CH_3(CH_2)_2$	EtOH	178–180	63
6	6-Methyl-2-quinolyl	S	$CH_3(CH_2)_6$	EtOH	100–102	71
7	6-Methyl-2-quinolyl	S	$CH_3(CH_2)_7$	EtOH	105–105.5	77
8[a]	6-Methyl-2-quinolyl	O	$CH_2{=}CHCH_2$	EtOH–H_2O	145–147	88
9[a]	6-Methyl-2-quinolyl	O	$CH_3(CH_2)_2$	EtOH–H_2O	208–210	62
10[a]	6-Methyl-2-quinolyl	O	CH_3OPh	DMF	218–220	55
11[a]	6-Methyl-2-quinolyl	S	$CH_2{=}CHCH_2$	$CHCl_3$–MeOH	178–181	57
12	6-Methyl-2-quinolyl	S	$CH_3(CH_2)_2$	EtOH	167.5–170	71
13	6-Methyl-2-quinolyl	S	$CH_3(CH_2)_6$	EtOH	144–145	68
14	6-Methyl-2-quinolyl	S	$CH_3(CH_2)_7$	EtOH	138.4–140	53
15	6-Methoxy-4-quinolyl	S	$CH_3(CH_2)_2$	$CHCl_3$–C_6H_{14}	168–170	40
16[a]	2-Pyridylmethyl	O	$CH_2{=}CHCH_2$	$CHCl_3$	76–78	58
17[a]	2-Pyridylmethyl	O	$CH_3(CH_2)_2$	$CHCl_3$	84–85	75
18[a]	2-Pyridylmethyl	O	CH_3OPh	$CHCl_3$	153–155	57

[a] Newly synthesized compounds.

in chloroform (30 mL). The reaction mixture was allowed to stir at room temperature for 1.5 h. The resulting solid precipitated, and the reaction mixture was filtered and recrystallized with dimethylformamide to give 1-(4-methoxyphenyl)-3-[2′-(6−methyl)quinolyl] urea as white crystals (0.57 g, 88.32% yield) mp 236−238 °C. IR (KBr) (cm^{-1}): 3200 (N-H), 3050−3150 (aromatic C−H), 2920−2980 (aliphatic C−H), 1960 (C=O), 1460−1610 (aromatic C−C, cyclic C=N, N−H), 1360 (C-O), 1310 (aromatic C−N), 1110−1130 (aliphatic C−N), 822 (parasubstituted aromatic C−H). ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3-quinoline), 3.75 (s, 3H, PhOCH_3), 6.70−8.20 (m, 9H, 5H-quinoline, 4H-Ph), 9.80 (bs, 1H, exchangeable with D_2O, quinoline-NH), 11.70 (bs, 1H, exchangeable with D_2O, CON*H*Ph). Anal.—Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67 Found: C, 70.32; H, 5.57: N, 13.75.

1-Allyl-3-[(2-pyridyl)methyl]urea (16)—A mixture of 2-(aminomethyl)pyridine (580 μL, 5.6 mmol) and allyl isocyanate (500 μL, 5.6 mmol) was kept at room temperature for 0.5 h. The resulting solid was washed with diethyl ether and recrystallized with chloroform to give 1-allyl-3-(2′-methylpyridyl)urea as white crystals (0.62 g, 57.89% yield) mp 76−78 °C. IR (KBr) (cm^{-1}): 3328 (N−H), 3014−3149 (aromatic C−H, olefinic C−H), 2903−2980 (aliphatic C−H), 1626 (C=O), 1438−1595 (aromatic C=C, cyclic C=N, olefinic C=C, N−H), 1290 (aromatic C−N), 1150−1248 (aromatic C−N), 754 (monosubstituted aromatic C−H). ^{1}H NMR ($CDCl_3$): δ 2.77 (t, J = 5.5 Hz, 2H, NHCH_2CH=), 4.42 (d, J = 5.5 Hz, 2 H, pyridine-CH_2), 5.01 (dd, J = 1.7 and 9.9 Hz, allyl-H_a), 5.21 (dd, J = 1.7 and 13.1 Hz, allyl-H_b), 5.77 (m, 1H CH$_2$CH=CH_2), 6.42 (bs, 2H, exchangeable with D_2O NHCONH), 7.09 (d, J = 7.5 Hz, H5), 7.23 (d, J = 7.8 Hz, H3), 7.59 (dt, J = 1.7 and 7.5 Hz, H4), 8.40 (d, J = 4.1 Hz, H6). Anal.—Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97 Found: C, 62.67; H 6.73; N, 21.60.

Antihypertensive Testing—Compounds were screened for antihypertensive activity in the DHRs by the indirect tail cuff method. The male Wistar rats, 180−200 g at starting, were placed in individual cages after the implantation of deoxycorticosterone acetate and were provided with a 1% sodium chloride solution for drinking water throughout the experimental period to induce hypertension. The systolic blood pressure (SBP) was measured indirectly from the tail of unanesthetized rats to monitor the hypertension using an electronic blood pressure recorder with a piezoelectric transducer (Ugo Basile, Model 8006). Two to four weeks were allowed for the development of hypertension. The animals with SBP exceeding 180 mmHg were considered to be hypertensive. Before being employed in the antihypertensive evaluation, the DHRs were trained to get used to the tail-cuff.

The DHRs were distributed into 20 groups of five DHRs, eighteen of which were drug treated, each group receiving a suspension of test substance orally at dose of 100 mg/kg. The other two groups were negative and positive control groups. The negative control group was treated orally with 6% acacia alone, and the positive control group received prazosin, orally, at a dose of 5 mg/kg. The SBP was measured at 0, 0.5, 1, 2, 3, 4, 6, and 24 h after dosing. The measurement was continued until the return of the SBP to the predosed value (±10% of SBP at 0 hour).

The antihypertensive effects were evaluated by grading the reduction in SBP into four levels. The grading system was less than 10% (−), 10−15% (+), 15−20% (++), and >20% (+++) reduction of SBP. The statistical significance between the control and the treated groups was accessed by analysis of variance and followed by a t test (Duncan multiple range test). All differences having a p-value of less than 0.05 were considered to be statistically significant.

Effects on Isolated Vascular Smooth Muscle and Heart Muscle—*Relaxation of Vascular Smooth Muscle*—Rabbits (New Zealand white, 1.5−2.0 kg body weight) were sacrificed and the femoral arteries were removed, cleaned, and cut into segments (1 cm in length). The arteries were placed in 25 mL water-jacketed organ baths containing Krebs−Henseleit solution maintained at 37 °C and aerated with a 95% oxygen and 5% carbon dioxide gas mixture. Arteries were attached to a force-displacement transducer and recorder under a resting tension of 0.5 g. After 45 min of equilibration time, the arteries were induced to contract by a submaximal dose of phenylephrine. After a sustained contraction was reached, compound **17** was added. The ability of test compound to relax the tissue was examined by recording the amplitudes of contractions in gram tension. Relaxation of vascular smooth muscle was expressed as the percentage reduction of the vasomotor tension from the control.

Effects on Cardiac Muscle—Guinea pigs (300−400 g) were sacrificed and the hearts were removed. The atrias were separated and placed in 25 mL water-jacketed organ baths containing Krebs−Henseleit solution maintained at 37 °C aerated with a mixture of 95% oxygen and 5% carbon dioxide. The atrial tissue was mounted with one end attached to a force-displacement transducer and recorder under a resting tension of 0.5 g. After 60 min of equilibration time, a spontaneous atrial rate and the amplitude of contraction in gram tension were recorded. Compound **17** was added to the bath and the changes on the rate and amplitude were observed.

Results and Discussion

A series of heterocyclic ureas and thioureas were prepared for antihypertensive evaluation. Eleven new compounds were synthesized and seven previously reported related compounds in the same series were also prepared for the antihypertensive evaluation. The antihypertensive effects were determined

Table 2—Antihypertensive Effect of Test Compounds

Compound	Reduction in SBP[a] 0.5 h	1 h	2 h	3 h	4 h	6 h	24 h
Control	–	–	–	–	–	–	–
1	+	+	+ (NS)	+ (NS)	++	+	–
2	–	–	–	–	+ (NS)	+++	–
3	–	–	–	–	+ (NS)	+	–
4	–	+	++	++	++	+++	+
5	–	+	+ (NS)	+ (NS)	+ (NS)	–	–
6	–	–	–	–	–	++	–
7	–	–	–	–	+	++	–
8	–	–	+ (NS)	++	+ (NS)	+	+
9	–	–	–	++	+++	+++	+++
10	–	–	–	+ (NS)	+ (NS)	+	–
11	–	–	+	+	–	–	–
12	–	–	–	–	–	–	–
13	–	–	+ (NS)	–	–	–	–
14	–	++	++	+	++	++	+
15	–	+	–	–	–	+	–
16	–	+	++	+ (NS)	–	+	–
17	+	++	++	+++	++	++	+
18	–	–	–	–	–	–	–
Prazosin	+++	+++	+++	+++	+++	+++	+++

[a] – = <10%; + = 10–15; ++ = 15–20%; +++ = >20% reduction in SBP after dosing. NS indicates that the observed effect was not statistically significant at the $p < 0.05$ level as compared to the control.

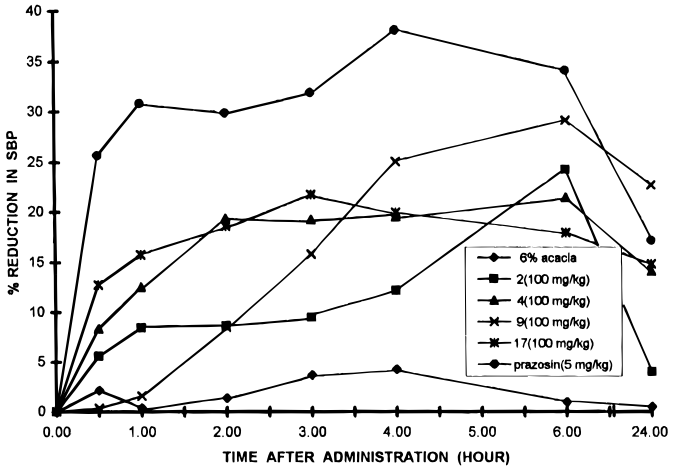


Figure 1—The time course of the antihypertensive effect of the propylureas (**2**, **9**, **17**) and allylthiourea (**4**) on SBP. Each point represented the mean of five DHRs. *$p < 0.05$ as compared with the control.

after a single oral administration at a dose of 100 mg/kg to conscious DHRs using the indirect tail-cuff method.

The results of antihypertensive activity are summarized in Table 2. All compounds except compound **18** were found to possess significant oral antihypertensive action ranging from 10.0% to 29.1% reduction in SBP. The urea **9** was the most active while urea **18** was the only inactive compound at the tested dose. Several members of the series were found to be marginally and moderately active; a decrease in SBP between 10 and 15% was observed in seven compounds. Although the 10−15% reduction was weak or marginal, the decrease was significant. Six compounds reducing SBP between 15 and 20% were considered moderate in activity. However, four compounds (**2**, **4**, **9**, and **17**) displayed potent action by lowering SBP more than 20%, as shown in Figure 1.

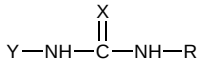
The onset of antihypertensive action following the oral administration ranged from 0.5 h to 6 h, and the duration of action ranged from 1 h to 24 h. Compounds **2**, **3**, **6**, and **12** were found to have a slow onset, exhibiting action at 6 h. Compounds **1**, **14**, and **17** were considered to be fast acting since these compounds showed significant antihypertensive action within 1 h after dosing.

Compounds **4**, **9**, **14**, and **17** had a long duration of antihypertensive action of about 24 h, which would suit the regimen of a once-daily dose. Moreover, the effect of compound **9** was not only potent at 24 h but also superior to the effect of prazosin at 24 h. The SBP of DHRs treated with compound **9** and prazosin returned to the predosed value at 30 and 26 h, respectively.

The summarized results in Table 3 showed the propyl ureas (**2**, **9**, and **17**) to be more potent than the propyl thioureas (**5**, **12**, and **15**). In addition to their potency, the propyl ureas **9** and **17** produced sustained reduction in SBP. It appeared that urea derivatives were more effective than thioureas. The allyl derivatives of 6-methylquinoline was exceptional since the 1-allyl-3-[2′-(6-methyl)quinoline] (**1**) was less active than the allyl thiourea (**4**) analogue.

An increase in the size or length of the chain resulted in a decrease in activity. The (4−methoxyphenyl)ureas **3**, **10**, and **13** were only marginally active or inactive. Exceptionally, when the alkyl of quinolylthiourea was lengthened from propyl (**5**) to heptyl (**6**) or octyl (**7**), the antihypertensive effect and duration increased, but the activity was still not as potent as that of the allyl derivative (**4**). Thus, the short side chain of about three carbon atoms in length in both ureas and thioureas contributed to good activity. Between the short side chains, allyl versus propyl, propylureas displayed better activity than allyl ureas, but the same conclusion could not be drawn for the thiourea derivatives. In contrast, the antihypertensive effect and duration were decreased dramatically when the allyl group in thiourea **4** was replaced by the propyl group in thiourea **5**.

Table 3—Structure–Activity Relationships of Test Compounds



Reduction in SBP[a] Y	X	R = CH_2=$CHCH_2$	R = $CH_3(CH_2)_2$	R = CH_3OPh	R = $CH_3(CH_2)_6$	R = $CH_3(CH_2)_7$
6-Methyl-2-quinolyl	O	++ (**1**)	+++ (**2**)	+ (**3**)	NA	NA
	S	+++ (**4**)	+ (**5**)	NA	++ (**6**)	++ (**7**)
6-Methoxy-2-quinolyl	O	++ (**8**)	+++ (**9**)	+ (**10**)	NA	NA
	S	+ (**11**)	+ (**12**)	NA	+ (**13**)	++ (**14**)
6-Methoxy-4-quinolyl	S	NA	+ (**15**)	NA	NA	NA
2-Pyridylmethyl	O	++ (**16**)	+++ (**17**)	– (**18**)	NA	NA

[a] – = <10%; + = 10–15%; ++ = 15–20%; +++ = >20% reduction in systolic blood pressure. The maximum effects within 6 h after dosing were significant at the $p < 0.05$ level as compared to the control. The number of the compound is indicated in parentheses. NA indicates that the specified compounds were not included in the synthesis and testing.

Concerning the substitution at the 6-position of quinoline, equipotency was found in six pairs (**1** versus **8**, **2** versus **9**, **3** versus **10**, **5** versus **12**, **6** versus **13**, and **7** versus **14**), whereas the potencies of the methyl analogues were greater than those of methoxy derivatives in one pair (4 versus 11). However, there seemed to be no distinct relationship between the activity and the 6-substituent in the quinoline ring. It was not possible to reveal the structure−activity relationship regarding the position of the substituent in the quinolyl thioureas because only one 4-substituted derivative was synthesized.

To explore further the effect of a heterocyclic nucleus on activity, the pyridylmethyl urea compounds **16**−**18** were prepared. This change caused a dramatic improvement in potency, onset, and duration of the activity, comparing the propyl derivatives **2** and **17**.

It may be concluded that in the comparison between urea and thiourea analogues, the propylureas were found to be more potent than the propylthioureas. Concerning the alkyl/alkenyl/aryl groups, compounds containing propyl and allyl groups attained good antihypertensive activity, whereas the compounds with longer aliphatic chains or aromatic groups showed modest effects. In regard to the heterocyclic groups, there was no distinct differences in activity between the 6-methylquinoline and 6-methoxyquinoline derivatives. An improvement in both potency and onset was observed when the quinoline nucleus was replaced by 2-pyridylmethyl.

Compound **17**, with rapid onset, was selected for *in vitro* pharmacological testing. It significantly relaxed both vascular smooth muscle and cardiac muscle (Table 4) but had no effect on heart rate. The maximal reductions of the femoral artery vasoconstriction and the cardiac contraction were found to be 18% (0.4 mg/mL) and 32% (1.2 mg/mL), respectively. These effects suggest that the antihypertensive action could be accounted for by a relaxation of vascular smooth muscle and cardiac muscle. Pharmacological studies should be continued in order to delineate the mechanisms involved in the mediation of the cardiovascular actions.

Table 4—Effects of Compound 17 on Vascular Smooth Muscle and Cardiac Muscle

Tissue	Gram tension (SEM)		% Reduction
	control	compound 17	
artery	0.84 (0.01)	0.67 (0.03)[a]	17.78
atrium	0.42 (0.02)	0.28 (0.02)[a]	31.79

[a] $n = 6$, $p < 0.01$.

In summary, 17 of 18 compounds tested in the present study possessed significant antihypertensive action in DHRs. However, none of the test compounds had higher potency than prazosin. Since the effect of **1**, **4**, **9**, and **17** were both potent and long, they were considered as promising candidates for further pharmacological investigation.

References and Notes

1. Glamkoski, E. J.; Reitano, P. A.; Woodward, D. J. *J. Pharm. Sci.* **1987**, *67*, 1773−1774.
2. Ludden, C. T.; Scriabine, A.; Ulm, E. M.; Morgan, G.; Fisher, M. H.; Ruyl, W. V. *Experientia* **1979**, *35*, 799−801.
3. Tilley, J. W.; Levitan, P.; Kierstead, R. W. *J. Med. Chem.* **1980**, *23*, 1387−1392.
4. Tilley, J. W.; Ramuz, H.; Hefti, F.; Gerold, M. *J. Med. Chem.* **1980**, *23*, 1438−1439.
5. Campbell, S. F.; Hardstone, J. D.; Palmer, M. J. *J. Med. Chem.* **1988**, *31*, 1031−1035.
6. Ashwood, V. A.; Cassidy, F.; Coldwell, M. C.; Evans, J. M.; Hamilton, T. C. *J. Med. Chem.* **1990**, *33*, 2667−2672.
7. Gulati, A.; Hussain, G.; Srimal, R. C. *Drug Dev. Res.* **1991**, *23*, 307−323.
8. Chevalier, P.; Rouillard, C.; Montay, G. *J. Pharm. Sci.* **1994**, *83*, 372−374.
9. Foye, W. O.; Almasian, B.; Eisenberg, M. S.; Maher, T. J. *J. Pharm. Sci.* **1990**, *79*, 527−530.
10. Vajragupta, O.; Pananookooin, S.; Tuntiwachwuttikul, T.; Foye, W. O. *J. Sci. Soc. Thailand* **1988**, *14*, 51−59.

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