Derivatives of 1,3-Disubstituted 2,4(1*H*,3*H*)-Quinazolinediones as Possible Peripheral Vasodilators or Antihypertensive Agents[1]

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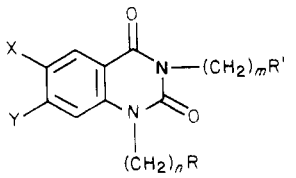
A series of 1,3-disubstituted 2,4(1*H*,3*H*)-quinazolinediones was prepared from the 3-substituted 2,4(1*H*,3*H*)-quinazolinediones by treatment with sodium hydride and the desired alkyl halide in xylene. These compounds showed varying degrees of vasodilation and antihypertensive activity without significant blockade of α-adrenergic receptors. 1-[3-(*N*,*N*-Dimethylamino)propyl]-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1*H*,3*H*)-quinazolinedione, which was selected for further studies, was more potent than papaverine in inducing vasodilation and induced a prolonged decrease in systolic blood pressure of hypertensive rats upon oral administration.

In an attempt to obtain a compound with vasodilator and antihypertensive actions due to direct relaxation of vascular smooth muscle, rather than to impairment of adrenergic transmission, we have synthesized a series of 1,3-disubstituted 2,4(1*H*,3*H*)-quinazolinediones. The compounds chosen for study are illustrated by the general formula I, where X, Y, R, and R′ are as indicated in Table I.



I

These compounds were prepared by treatment of the 3-substituted 2,4(1*H*,3*H*)-quinazolinediones with sodium hydride and an alkyl halide (Scheme I). The 6-acetamido derivative was prepared by a reduction of the 6-nitro compound in acetic anhydride.

Most of the 1,3-disubstituted 2,4(1*H*,3*H*)-quinazolinediones possess pharmacological activities similar to those of the 3-substituted 2,4(1*H*,3*H*)-quinazolinedione (**1**).[2] The prototype (**3**) induced vasodilation in the femoral bed of the dog and produced an antihypertensive effect in the rat but was devoid of α-adrenergic antagonism in the rabbit aortic strip.

Blood flow was measured in pentobarbital-anesthetized dogs with a calibrated electromagnetic flow-meter sensor placed around a femoral artery. Compounds were injected intraarterially at increasing doses through a branch of the main vessel, and peak increases in flow after each dose were noted. The data obtained were used to plot dose–response curves and the ED_{100}, mL/min (the effective dose for increasing flow by 100 mL/min over control values), was calculated for each compound by extrapolation from the curves. Papaverine, which directly acts on vascular smooth muscle, was tested for comparison.

Arterial hypertension was produced in female Wistar rats by applying a figure of eight ligatures to one kidney and removing the contralateral kidney.[3] Systolic blood pressure was determined indirectly in the tail with an inflatable occluding cuff and a pulse detector. Animals with systolic pressures exceeding 160 mmHg were considered hypertensive and were used for evaluation of compounds. Pressures were determined in groups of ten animals before and 2, 4, 6, and 8 h after oral administration of drugs at a dose of 31 mg/kg. Mean decreases in blood pressure observed over the 8-h period of observation were used as a measure of antihypertensive effect.

In order to rule out the possibility of these compounds producing vasodilation and hypotension through blockade of α-adrenergic receptors, their influence on responses to epinephrine was assessed in the rabbit aortic strip.[4] After sensitization by repeated contact with 0.01 mcg/mL of epinephrine, responses to this concentration of catecholamine were compared with those obtained after incubation for 200 s with increasing concentrations of the test compounds. Percent blockade of responses observed after each concentration was calculated and the corresponding ED_{50} (the effective concentration blocking responses by 50%) was determined by extrapolation from the dose–response curve. The α-adrenergic blocking agent phentolamine was tested for comparison.

These results suggest that substitution in the 1 position of the quinazolinedione moiety decreases the antiadrenergic effect of the unsubstituted parent compound **1** but retains the direct relaxant activity on vascular smooth muscle. Further structural changes of the prototype **3** lead to important changes in pharmacological properties. Thus, compounds with variations in the 2-carbon intermediate chain (**2** and **4–7**) generally retain the vasodilator and antihypertensive effects but acquire variable degrees of α-adrenergic antagonism. Changes in the dimethylaminopropyl (**8–11**) or piperazine (**13** and **14**) groups, as well as substitutions in the phenyl ring (**12**, **15**, and **16**) or in the quinazolinedione nucleus (**17–20**) lead to decreased vasodilator and/or antihypertensive activity.

It is interesting to note that antihypertensive activity correlated reasonably well with vasodilation, since all potent dilators, with the exception of **13**, **15**, and **19**, were antihypertensive, while compounds without vasodilator activity failed to reduce blood pressure. No correlation between antihypertensive and adrenergic blocking effects was apparent.

In considering a member of the present group for further evaluation, marked dilator and antihypertensive effects in the absence of adrenergic blockade were established as criteria for selection, it being felt that a compound with cardiovascular actions attributable to direct relaxation of vascular smooth muscle could elicit less side effects than an agent acting through impairment of adrenergic transmission. On the basis of the above considerations, compound **3** was selected for further assessment as a vasodilator antihypertensive agent.

Experimental Section

All melting points are uncorrected and were determined with a Buchi capillary apparatus (W. Buchi, Glasapparatefabrik, Flawil, Switzerland). IR spectra were determined with a Perkin-Elmer Model 237 grating spectrophotometer and the NMR spectra were

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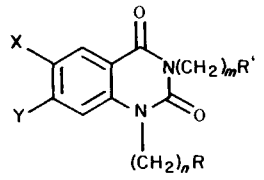
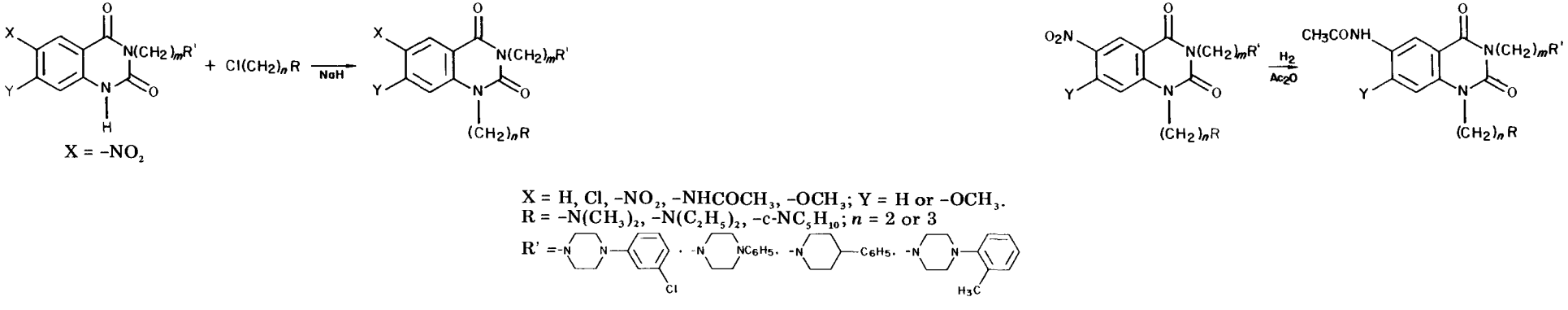
Table I



no.	X	Y	R	R'	n	m	% yield	recrystn solv	mp, °C	formula[a]
1	H	H	H	C_6H_5-c-$N(CH_2CH_2)_2N$	0	3		MeOH	208–209	$C_{21}H_{24}N_4O_2 \cdot HCl$
2	H	H	$(CH_3)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	2	17.5	MeOH	124–126	$C_{25}H_{33}N_5O_2 \cdot 2(CO_2H)_2$
3	H	H	$(CH_3)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	3	51.0	MeOH-Et_2O	257–258	$C_{26}H_{35}N_5O_2 \cdot 2HCl$
4	H	H	$(CH_3)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	4	25.9	MeOH	152–154	$C_{27}H_{37}N_5O_2 \cdot 2(CO_2H)_2$
5	H	H	$(CH_3)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	5	20.9	MeOH-Et_2O-H_2O	135–138	$C_{28}H_{39}N_5O_2 \cdot 2(CO_2H)_2$
6	H	H	$(CH_3)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	6	46.8	*i*-PrOH-H_2O	143–149	$C_{29}H_{41}N_5O_2 \cdot 2(CO_2H)_2$
7	H	H	$(CH_3)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	7	30.9	MeOH-Et_2O	154–155	$C_{30}H_{43}N_5O_2 \cdot 2(CO_2H)_2 \cdot CH_3OH$
8	H	H	c-$C_5H_{10}N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	3	51.6	MeOH-H_2O	185–187	$C_{29}H_{39}N_5O_2 \cdot 2(CO_2H)_2$
9	H	H	$(CH_3)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	2	3	20.7	MeOH-Et_2O	250–251	$C_{25}H_{33}N_5O_2 \cdot 2(CO_2H)_2$
10	H	H	$(C_2H_5)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	3	45.7	MeOH-Et_2O-H_2O	122–123	$C_{28}H_{39}N_5O_2 \cdot 2(CO_2H)_2 \cdot H_2O$
11	H	H	c-$C_5H_{10}N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	6	26.7	MeOH	132–134	$C_{32}H_{45}N_5O_2 \cdot 2(CO_2H)_2$[b]
12	H	H	$(CH_3)_2N$	3-ClC_6H_4-c-$N(CH_2CH_2)_2N$	3	3	37.5	*i*-PrOH-MeOH	249–250	$C_{26}H_{34}ClN_5O_2 \cdot 2HCl \cdot 0.75H_2O$
13	H	H	$(CH_3)_2N$	C_6H_5-c-$C_5H_{10}N$	3	3	47.9	MeOH-*i*-PrOH-Et_2O	272–275	$C_{27}H_{36}N_4O_2 \cdot 2HCl$
14	H	H	$(CH_3)_2N$	$(CH_3)_2N$	3	3	50.8	MeOH-Et_2O-H_2O	118–119	$C_{18}H_{28}N_4O_2 \cdot 2(CO_2H)_2$
15	H	H	$(CH_3)_2N$	2-$CH_3C_6H_4$-c-$N(CH_2CH_2)_2N$	3	3	21.4	MeOH	143–145	$C_{27}H_{36}N_5O_2 \cdot 2(CO_2H)_2 \cdot 0.5H_2O$
16	H	H	$(CH_3)_2N$	3-ClC_6H_4-c-$N(CH_2CH_2)_2N$	3	6	15.4	MeOH	132–133	$C_{29}H_{40}ClN_5O_2 \cdot 2(CO_2H)_2 \cdot H_2O$
17	Cl	H	$(CH_3)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	3	56.5	MeOH-H_2O	124–125	$C_{26}H_{34}ClN_5O_2 \cdot 2(CO_2H)_2$
18	NO_2	H	$(CH_3)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	3	21.3	MeOH	>280	$C_{26}H_{34}N_6O_4 \cdot 2HCl \cdot H_2O$
19	$NHCOCH_3$	H	$(CH_3)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	3	55.7	MeOH-H_2O	154–156	$C_{28}H_{38}N_6O_3 \cdot 2(CO_2H)_2 \cdot H_2O$
20	OCH_3	OCH_3	$(CH_3)_2N$	C_6H_5-c-$N(CH_2CH_2)_2N$	3	3	55.5	MeOH-Et_2O-H_2O	260–261	$C_{28}H_{39}N_5O_4 \cdot 2HCl \cdot 0.5H_2O$

[a] All compounds were analyzed for C, H and N. [b] C: calcd, 60.74; found, 61.57.

Scheme I



X = H, Cl, $-NO_2$, $-NHCOCH_3$, $-OCH_3$; Y = H or $-OCH_3$.
R = $-N(CH_3)_2$, $-N(C_2H_5)_2$, -c-NC_5H_{10}; n = 2 or 3

R' =

Table II. Vasodilator, Antihypertensive, and α-Adrenergic Blocking Activity

compd	vasodiln ED_{100}, mcg[a]	antihypertensive effect mmHg[b]	α-adrenergic blockade ED_{50}, mcg/mL[c]
1	5	38 ± 11.67	0.03
2	388	38 ± 7.47	0.51
3	134	47 ± 8.83	>1.00
4	20	37 ± 7.55	0.25
5	1	42 ± 5.25	0.75
6	4	35 ± 4.51	1.00
7	205	12 ± 4.88	0.64
8	281	29 ± 3.98	>1.00
9	>2000	17 ± 3.59	0.30
10	399	0 ± 10.54	>1.00
11	1480	12 ± 8.87	0.02
12	97	26 ± 7.63	>1.00
13	96	3 ± 2.69	>1.00
14	>2000	1 ± 5.20	>1.00
15	36	12 ± 5.90	0.73
16	1172	12 ± 5.26	0.32
17	>2000	12 ± 5.46	1.00
18	54	25 ± 4.39	0.55
19	187	2 ± 5.29	0.31
20	>2000	7 ± 5.40	1.00
papaverine	1825		
phentolamine	117	45 ± 6.20	0.03

[a] Dose increasing dog femoral blood flow by 100 mL/min. [b] Mean decrease in systolic blood pressure over 8 h plus or minus standard error observed in renal hypertensive rats receiving 31 mg/kg po. [c] Dose blocking rabbit aortic strip responses to epinephrine by 50%.

determined with a Varian T60A NMR spectrometer. The NMR and IR spectra are consistent with assigned structures. Microanalyses are within ±0.4% of the calculated values unless otherwise stated.

1-[3-(*N*,*N*-Dimethylamino)propyl]-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1*H*,3*H*)-quinazolinedione Dihydrochloride (3). To 10.9 g (0.03 mol) of 3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1*H*,3*H*)-quinazolinedione in 150 mL of dry xylene was added 1.5 g (0.03 mol) of NaH with stirring under N_2. The reaction mixture was then heated under reflux for 5 h. The solution was cooled and another 1.5 g of NaH was added along with 4.75 g (0.03 mol) of 3-chloro-*N*,*N*-dimethylpropylamine hydrochloride. The mixture was then heated under reflux with stirring for 18 h. The solution was filtered while hot and the filtrate was concentrated in vacuo. The resulting oil solidified and the solid was recrystallized from *i*-PrOH to give 8.0 g of material melting at 88–90 °C. To 7.8 g (0.017 mol) of the free base in CH_3OH was added 5 mL of a 3.55 N HCl solution in CH_3OH. Upon addition of Et_2O, a solid precipitated, which was recrystallized from CH_3OH and Et_2O to give 8.0 g of material melting at 257–258 °C. Anal. ($C_{26}H_{39}Cl_2N_5O_2$) C, H, N. All the other 1,3-disubstituted compounds with hydrogen in the 6 and 7 positions were similarly prepared and are recorded in Table I.

6-Nitro-1-[3-(*N*,*N*-dimethylamino)propyl]-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1*H*,3*H*)-quinazolinedione Dihydrochloride Monohydrate (18). To 16.0 g (0.04 mol) of 6-nitro-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1*H*,3*H*)-quinazolinedione in 300 mL of xylene was added 2.0 g of NaH with stirring under N_2. The solution was heated under reflux for 4 h. The mixture was cooled and another 2.0 g of NaH was added along with 6.3 g (0.04 mol) of 3-chloro-*N*,*N*-dimethylpropylamine hydrochloride. The solution was heated under reflux for 2 h and then filtered. The filtrate was concentrated in vacuo and the residue solidified. The yellow solid was recrystallized from CH_3OH to give 9.0 g of material melting at 122–124 °C. The hydrochloride was prepared by adding 12.1 mL of a 1.65 N HCl solution in *i*-PrOH to 5.0 g of free base in CH_3OH. Upon addition of Et_2O, a solid precipitated to give 5.0 g of material melting at >280 °C. Anal. ($C_{26}H_{38}Cl_2N_6O_5$) C, H, N. The 6-chloro derivative was similarly prepared.

6-Acetamido-1-[3-(*N*,*N*-dimethylamino)propyl]-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1*H*,3*H*)-quinazolinedione Dioxalate Monohydrate (19). To 7.0 g (0.014 mol) of 6-nitro-1-[3-(*N*,*N*-dimethylamino)propyl]-3-[3-(4-phenyl-1-piperazinyl)-propyl]-2,4(1*H*,3*H*)-quinazolinedione was added 200 mL of AcOH, 100 mL of Ac_2O, and 3.0 g of 10% Pd/C. The mixture was hydrogenated under 50 psi. The calculated amount of H_2 was taken up in 1 h. The solution was filtered and the filtrate was concentrated in vacuo. The residue was treated with NH_4OH and the organic material extracted with $CHCl_3$. The $CHCl_3$ was washed with H_2O and then dried over $MgSO_4$. The $CHCl_3$ was concentrated in vacuo, leaving an oily free base. The oxalate was prepared by adding 2.5 g (0.028 mol) of oxalic acid to the free base in CH_3OH. Upon addition of Et_2O, a solid formed, which was recrystallized from H_2O and CH_3OH to give 5.5 g of material melting at 154–156 °C. Anal. ($C_{32}H_{43}N_5O_6$) C, H, N.

6,7-Dimethoxy-1-[3-(*N*,*N*-dimethylamino)propyl]-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1*H*,3*H*)-quinazolinedione Dihydrochloride (20). To 15 g (0.034 mol) of 3-[3-(4-phenyl-1-piperazinyl)propyl]-6,7-dimethoxy-2,4(1*H*,3*H*)-quinazolinedione in 250 mL of xylene was added 1.7 g of NaH with stirring under N_2. The solution was heated under reflux for 4 h. The solution was cooled and another 1.7 g of NaH was added along with 5.0 g (0.035 mol) of 3-chloro-*N*,*N*-dimethylpropylamine hydrochloride. The solution was heated under reflux for another 4 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo, giving 17.0 g of an oily free base. The hydrochloride was prepared by adding 40 mL of a 1.7 N HCl solution in *i*-PrOH to the free base. Upon addition of Et_2O, a solid formed which was recrystallized from H_2O, CH_3OH, and Et_2O to give 11.0 g of material melting at 260–261 °C. Anal. ($C_{28}H_{41}Cl_2N_5O_4$) C, H, N.

References and Notes

(1) Presented at the First Chemical Congress of the North American Continent in Mexico City, Dec. 4, 1975.
(2) S. Hayao, H. J. Havera, W. G. Strycker, T. J. Leipzig, R. A. Kulp, and H. E. Hartzler, *J. Med. Chem.*, **8**, 807 (1965).
(3) A. Grollman, *Proc. Soc. Exp. Biol. Med.*, **57**, 102 (1944).
(4) R. F. Furchgott and S. Bhadrakom, *J. Pharmacol. Exp. Ther.*, **108**, 129 (1953).