to pretreatment values for each group as described (footnote *d*, Table I).

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Registry No. 1, 76574-80-6; **2**, 77206-70-3; **3**, 77206-69-0; **4**, 77206-81-6; **5**, 84279-04-9; **6**, 84279-05-0; **7**, 84279-06-1; **8**, 77206-73-6; **9**, 84279-07-2; **10**, 77206-71-4; **11**, 77206-84-9; **12**, 84279-08-3; **13**, 84279-09-4; **14**, 84279-10-7; **15**, 84279-11-8; **16**, 84279-12-9; **17**, 84279-13-0; **18**, 77206-86-1; **19**, 84279-14-1; **20**, 84279-15-2; **21**, 84279-16-3; **22**, 84279-17-4; **23**, 84279-18-5; **24**, 84279-19-6; **25**, 77206-72-5; **26**, 84279-20-9; **27**, 77206-82-7; **28**, 77206-83-8; **29**, 84279-21-0; **30**, 84279-22-1; **31**, 77206-76-9; **32**, 77206-85-0; **33**, 84279-23-2; **34**, 84279-24-3; **35**, 84279-25-4; **36**, 84279-26-5; **37**, 84279-27-6; **38**, 84279-28-7; **39**, 84279-29-8; **40**, 84279-30-1; **41**, 77206-80-5; **42**, 84279-31-2; **43**, 84279-32-3; **44**, 84279-33-4; **45**, 84279-34-5; **46**, 84279-35-6; **47**, 84279-36-7; **48**, 84279-37-8; **49**, 77206-74-7; **50**, 77206-75-8; **51**, 84279-38-9; **52**, 84279-39-0; **53**, 84279-40-3; **54**, 84279-41-4; **55**, 77206-77-0; **56**, 84279-42-5; **57**, 84279-43-6; **58**, 77206-79-2; **59**, 84279-44-7; **60**, 77206-78-1; **61**, 84279-45-8; i, 84279-46-9; cyanamide, 420-04-2.

Pyrimidine Derivatives. 4.[1] Synthesis and Antihypertensive Activity of 4-Amino-2-(4-cinnamoylpiperazino)-6,7-dimethoxyquinazoline Derivatives[1]

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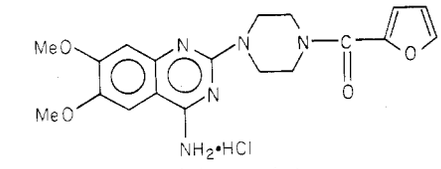
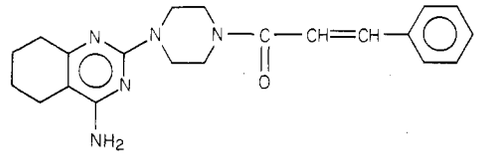
A series of 30 4-amino-2-(4-cinnamoylpiperazino)-6,7-dimethoxyquinazoline derivatives was prepared and tested for their ability to reduce blood pressure in conscious, spontaneously hypertensive rates (SHR). A number of these compounds, notably 4-amino-2-(4-cinnamoylpiperazino)-6,7-dimethoxyquinazolines **3a** (R^1 = H; R^2 = Ph), **3j** (R^1 = H; R^2 = 4-EtOPh), and **5a** (R^1 = H; R^2 = 2-furyl), showed activity at oral doses of 0.3–10 mg/kg. The effects of the 4-substituents of the piperazino group on activity are discussed. Compounds **3a**, **3j**, and **5a** were effective in renal hypertensive rats at oral doses of 3 and 10 mg/kg and showed α-adrenoceptor blocking effects in isolated aortas of rats. A 5-day consecutive oral administration of **3a** and **3j** in SHR did not lead to development of tolerance.

Prazosin (1), 4-amino-6,7-dimethoxy-2-[4-(2-furoyl)-



1 (prazosin)

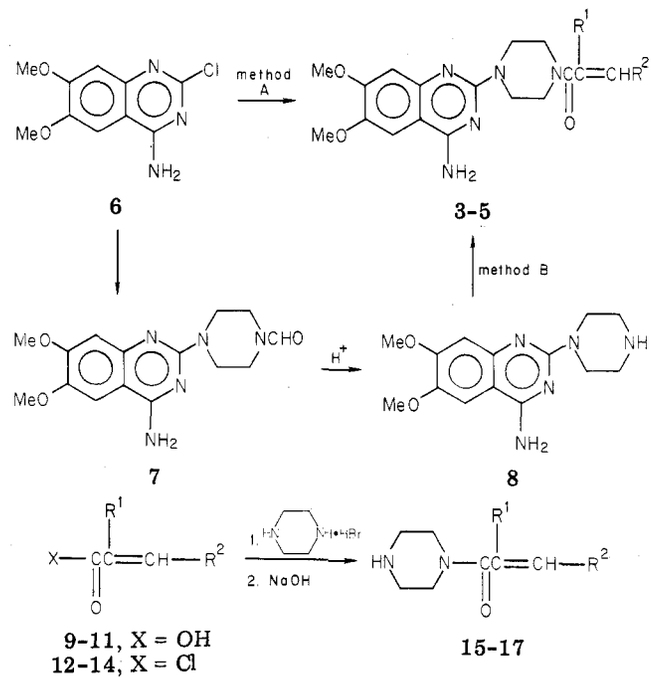


2

piperazino]quinazoline, is known to have an excellent antihypertensive effect resulting from its postsynaptic α-adrenergic blockade;[2] therefore, it is often used in the treatment of hypertension. Compounds structurally related to prazosin, such as trimazosin,[3] E-643,[4] tiodazosin,[5] and terazosin,[6] have also been reported to show hypotensive activity.

In the course of an ongoing program in the development of novel agents for the treatment of hypertension, certain compounds in a series of 4-amino-2-piperazino-5,6-poly(methylene)pyrimidine derivatives previously reported as hypoglycemic agents[7] were examined for antihypertensive activity. Of these derivatives, 4-amino-2-(4-cinnamoyl-

Scheme I[a]



[a] R^1 = H or Me. R^2 = phenyl (**3**, **9**, **12**, and **15**), thienyl (**4**, **10**, **13**, and **16**), or furyl (**5**, **11**, **14**, and **17**); see Table I. For methods A and B, see Experimental Section.

piperazino)-5,6,7,8-tetrahydroquinazoline (**2**) showed an antihypertensive effect when examined in spontaneously

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(1) Part III: T. Sekiya, H. Hiranuma, T. Kanayama, S. Hata, and S. Yamada, *Eur. J. Med. Chem.*, **17**, 75 (1982).

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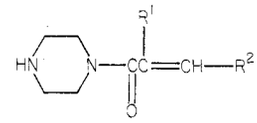
Table I. Acryloylpiperazine Derivatives 15–17



no.	R^1	R^2 [a]	method [b]	yield, %	mp or bp (mmHg), °C	recrystn solvent [c]	formula [d]
15a	H	Ph	C	65	80–81	A	$C_{13}H_{16}N_2O$
15b	H	2-MePh	D	72	179–182 (0.2)		$C_{14}H_{18}N_2O$
15c	H	4-MePh	C	62	90–92	A	$C_{14}H_{18}N_2O$
15d	H	2-MeOPh	D	27	81–86	A	$C_{14}H_{18}N_2O_2$
15e	H	3-MeOPh	C	64	84–86	A	$C_{14}H_{18}N_2O_2$
15f	H	2-EtOPh	D	33	70–73	A	$C_{15}H_{20}N_2O_2$
15g	H	4-*i*-PrOPh	D	47	90–94	B	$C_{16}H_{22}N_2O_2$
15h	H	4-BrPh	D	24	205–208 [e]	C	$C_{13}H_{15}BrN_2O$
15i	Me	Ph	C	40	oil		$C_{14}H_{18}N_2O$
16a	H	2-Th	D	54	107–113	A	$C_{11}H_{14}N_2OS$
16b	Me	2-Th	D	51	oil		$C_{12}H_{16}N_2OS$
16c	H	3-Me-2-Th	D	33	139–140	C	$C_{12}H_{16}N_2OS$
16d	H	5-Me-2-Th	D	63	173–180 [e]	C	$C_{12}H_{16}N_2OS$
17a	H	2-Fu	C	56	61–63	A	$C_{11}H_{14}N_2O_2$
17b	H	5-Me-2-Fu	D	47	66–68	C	$C_{12}H_{16}N_2O_2$

[a] Ph = phenyl, Th = thienyl, and Fu = furyl. [b] Method C: from the isolated acid chlorides; see the synthesis of 15a. Method D: from the corresponding acids; see the synthesis of 17b. [c] A = from oil; B = Et_2O–hexane; C = EtOAc. [d] Mass spectra of the derivatives were consistent with the assigned structures. [e] A hydrochloride salt.

hypertensive rats (SHR); however, the efficacy was not satisfactory when compared with the quinazoline derivatives described above.

The present study was undertaken to prepare 4-amino-2-(4-cinnamoylpiperazino)-6,7-dimethoxyquinazoline (**3a**) and its analogues, which were derived by combination of **1** and **2**. An evaluation of their antihypertensive effect in SHR was also carried out.

Chemistry. Synthesis of 4-amino-2-(4-acryloylpiperazino)-6,7-dimethoxyquinazoline derivatives **3** (R^2 = phenyl), **4** (R^2 = thienyl), and **5** (R^2 = furyl) was carried out by the two methods shown in Scheme I.

Condensation of 4-amino-2-chloro-6,7-dimethoxyquinazoline (**6**), prepared by the method described by Althuis,[8] with acryloylpiperazine derivatives **15** (R^2 = phenyl), **16** (R^2 = thienyl), and **17** (R^2 = furyl) when refluxed in isoamyl alcohol gave 2-piperazinoquinazoline derivatives **3–5** (method A). Acryloylpiperazine derivatives **15–17** were synthesized by acylation of piperazine hydrobromide with acryloyl chlorides **12** (R^2 = phenyl), **13** (R^2 = thienyl), and **14** (R^2 = furyl). The results are shown in Table I.

Compounds **3–5** were also produced by selective acylation of 4-amino-2-piperazino-6,7-dimethoxyquinazoline (**8**) with mixed anhydrides prepared from acrylic acid derivatives **9** (R^2 = phenyl), **10** (R^2 = thienyl), and **11** (R^2 = furyl) and ethoxycarbonyl chloride (method B). Compound **8** was synthesized from **6** via 4-amino-2-(4-formylpiperazino)-6,7-dimethoxyquinazoline (**7**), which was prepared by condensation of **6** with formylpiperazine. Treatment of **7** with hydrochloric acid, followed by neutralization with sodium hydroxide, gave **8**. All the acrylic acid derivatives **9–11** have been reported previously,[9–15] except 3-(2-thienyl)-2-methylacrylic acid (**10**, R^1 = Me; R^2 = 2-thienyl) which was synthesized from 2-thiophenecarboxaldehyde and propionic anhydride in the presence of sodium propionate. The results of syntheses by methods A and B are given in Table II.

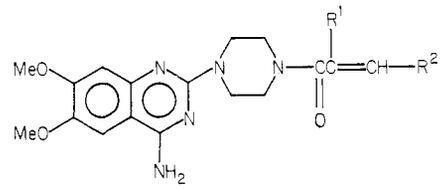
Pharmacological Results and Discussion

Antihypertensive effects of the prepared compounds were examined in SHR as follows: compounds **3a–s**, **4a–f**, and **5a–e** were evaluated orally at doses of 0.3, 1, 3, and 10 mg/kg in conscious SHR with an indwelling catheter for continuous monitoring of blood pressure and heart rate. Table II shows the mean blood pressure measured at four different intervals and the maximum effect observed.

Compounds **3a,b,h,j**, **4a–d**, and **5a,c** showed potent antihypertensive effects at 1 mg/kg dosage comparable to that of prazosin. On the other hand, compounds **3e,f,i,-l,o,q,r** did not produce any hypotension at 10 mg/kg dosage. In the series of cinnamoyl derivatives of **3a**, antihypertensive potency was optimal in **3a** (R^1 = H; R^2 = Ph), **3b** (H, 2-MePh), **3h** (H, 4-MeOPh), and **3j** (H, 4-EtOPh). Strongly electron-withdrawing substituents, as in **3o** (H, 3,4-Cl_2Ph), **3q** (H, 3-NO_2Ph), and **3r** (H, 3-CF_3Ph), eliminated activity. In addition, many of the derivatives of **4** and **5** showed activity similar to prazosin. The electron-rich nature of the thiophene and furan rings may be important in the antihypertensive activity of this series. On the other hand, compounds **3f** (R^2 = 2-MeOPh)

(2) (a) H. J. Hess, British Patent 1 156 973 (1969); *Chem. Abstr.*, **71**, 91519*f* (1969). (b) R. N. Brogden, R. C. Heel, T. M. Speight, and G. S. Avery, *Drugs*, **14**, 163 (1977).
(3) D. DeGuia, M. Mendolowitz, C. Russo, N. D. Vlachakis, and S. Antram, *Curr. Ther. Res.*, **15**, 339 (1973).
(4) T. Igarashi, Y. Nakajima, and S. Ohtake, *Jpn. Cir. J.*, **41**, 903 (1977).
(5) J. E. Schurig, R. L. Cavanagh, L. E. Roebel, and J. P. Buyniski, *Pharmacologist*, **19**, 213, Abstr 485 (1977).
(6) J. J. Kynel, R. E. Hollinger, K. W. Oheim, and M. Winn, *Pharmacologist*, **22**, 272, Abstr 616 (1980).
(7) T. Sekiya, H. Hiranuma, T. Kanayama, and S. Hata, *Eur. J. Med. Chem.*, **15**, 317 (1980).
(8) T. H. Althuis and H. J. Hess, *J. Med. Chem.*, **20**, 146 (1977).
(9) F. K. Thayer, "Organic Syntheses", Collect. Vol. I, A. H. Blatt, Ed., Wiley, New York, 1956, pp 398–399.
(10) M. L. Mihailovic and M. Tot, *J. Org. Chem.*, **22**, 652 (1957).
(11) W. J. King and F. F. Nord, *J. Org. Chem.*, **14**, 405 (1949).
(12) S. Ashida and Y. Shimizu, *Shigen Gijutsu Shikensho Hokoku*, **56**, 1 (1962).
(13) Y. K. Yur'ev, G. B. Elyakov, and A. N. Uysokosov, *Zh. Obshch. Khim.*, **28**, 1554 (1953).
(14) R. Lukeš and V. Dienstbierová, *Chem. Listy*, **48**, 280 (1954).
(15) Z. N. Nazalova and M. I. Pimenova, *Zh. Obshch. Khim.*, **27**, 2842 (1957).

Table II. 2-(4-Acryloylpiperazino)-4-amino-6,7-dimethoxyquinazoline Derivatives 3-5



no.	R^1	R^2 [a]	method [b]	yield, %	mp, °C	recrystn solvent [c]	formula [d]	po dose, mg/kg	act. rating in SHR [e] at the following hours postdose: 1 h	3 h	6 h	24 h	max % [f]
1 (prazosin)								3	2	1	1	0	27 (1)
								1	2	2	1	0	25 (1)
								0.3	1	1	1	0	19 (1)
3a	H	Ph	A	76	291-293	A [g]	$C_{23}H_{25}N_5O_3 \cdot HCl$	3	2	1	1	0	22 (1)
								1	1	1	1	0	14 (6)
								0.3	0	0	1	0	10 (6)
3b	H	2-MePh	A	86	251-253	B	$C_{24}H_{27}N_5O_3 \cdot 0.5H_2O$	10		2	2	0	23 (3)
								3	1	1	1	0	18 (3)
								1	1	0	0	0	12 (1)
3c	H	3-MePh	B	45	240-241	B	$C_{24}H_{27}N_5O_3 \cdot H_2O$	10	0	1	1	0	18 (3)
3d	H	4-MePh	A	88	285-286	B	$C_{24}H_{27}N_5O_3 \cdot HCl \cdot 2H_2O$ [h]	3	0	1	0	0	10 (3)
3e	H	4-*i*-PrPh	B	52	237-238	C	$C_{26}H_{31}N_5O_3$	10		0	0		
3f	H	2-MeOPh	A	82	286-287	D	$C_{24}H_{27}N_5O_4 \cdot HCl \cdot 0.75H_2O$	10		0	0		
3g	H	3-MeOPh	A	52	184-185	D	$C_{24}H_{27}N_5O_4 \cdot HCl \cdot 1.5H_2O$	10		1	1	0	12 (6)
3h	H	4-MeOPh	B	45	265-267	A	$C_{24}H_{27}N_5O_4$	10	1	2	2	0	23 (6)
								3	0	1	2	0	20 (6)
								1	0	1	1	0	15 (6)
3i	H	2-EtOPh	A	90	291-293	D	$C_{25}H_{29}N_5O_4 \cdot HCl \cdot H_2O$	10	0	0			
3j	H	4-EtOPh	B	62	277-278	A	$C_{25}H_{29}N_5O_4$	3	0	1	2	0	24 (6)
								1	0	1	2	0	21 (6)
								0.3	0	0	0	1	13 (6)
3k	H	4-*i*-PrOPh	A	89	251-253	D	$C_{26}H_{31}N_5O_4 \cdot HCl \cdot H_2O$	10	0	1	1	0	19 (6)
3l	H	3,5-$(MeO)_2$Ph	B	43	132-135	C	$C_{25}H_{29}N_5O_5 \cdot CH_3OH$	10	0	0	0	0	
3m	H	2,3,4-$(MeO)_3$Ph	B	40	263-264	C	$C_{26}H_{31}N_5O_6$	10	0	1	1	0	16 (3)
3n	H	4-ClPh	B	88	267-269	D	$C_{23}H_{24}ClN_5O_3 \cdot HCl \cdot 0.75H_2O$	10		0	1		10 (6)
3o	H	3,4-Cl_2Ph	B	61	196-198	C	$C_{23}H_{23}Cl_2N_5O_3$	10		0	0		
3p	H	4-BrPh	A	84	227-229	D	$C_{23}H_{24}BrN_5O_3 \cdot HCl \cdot 1.5H_2O$	10	0	1	1	0	12 (3)
3q	H	3-NO_2Ph	B	58	245-248	A	$C_{23}H_{24}N_6O_5 \cdot HCl \cdot H_2O$ [i]	10		0	0		
3r	H	3-CF_3Ph	B	47	225-227	C	$C_{24}H_{24}F_3N_5O_3 \cdot 0.5H_2O$	10		0	0		
3s	Me	Ph	A	77	188-190	A	$C_{24}H_{27}N_5O_3 \cdot HCl \cdot H_2O$	3	1	0	1	0	16 (1)
								1	0	0	1	0	12 (6)
4a	H	2-Th	A	85	233-234	A	$C_{21}H_{23}N_5O_3S \cdot 0.75H_2O$	3	2	1	2	0	24 (1)
								1	1	1	1	0	14 (1)
								0.3	0	0	1	0	10 (6)
4b	H	3-Th	B	54	238-241	B	$C_{21}H_{23}N_5O_3S \cdot 0.75H_2O$	3	2	1	1	0	25 (1)
								1	1	1	1	0	19 (6)
								0.3	1	1	1	0	11 (6)
4c	Me	2-Th	A	74	256-258	D	$C_{22}H_{25}N_5O_3S \cdot HCl$	3	3	1	1	0	34 (1)
								1	1	1	0	0	14 (1)
4d	H	3-Me-2-Th	A	95	170-180	A	$C_{22}H_{25}N_5O_3S \cdot HCl \cdot H_2O$	10	2	2	2	1	25 (6)
								1	1	1	1	0	10 (1)
4e	H	5-Me-2-Th	A	84	273-275	D	$C_{22}H_{25}N_5O_3S \cdot HCl \cdot H_2O$	3	0	1	0	0	14 (3)
4f	H	5-Cl-2-Th	B	53	202-205	D	$C_{21}H_{22}ClN_5O_3S \cdot HCl \cdot 3H_2O$	10	1	1	1		12 (1)
5a	H	2-Fu	A	77	245-247	E	$C_{21}H_{23}N_5O_4 \cdot HCl \cdot H_2O$	3	3	2	2	0	41 (1)
								1	2	1	2	0	28 (1)
								0.3	1	1	1	0	15 (3)
5b	H	3-Fu	B	59	252-253	D	$C_{21}H_{23}N_5O_4$	3	1	1	1	0	19 (6)
5c	Me	2-Fu	B	52	273-275	D	$C_{22}H_{25}N_5O_4 \cdot HCl \cdot H_2O$	3	1	0	1	0	16 (1)
								1	0	0	1	0	15 (6)
5d	H	5-Me-2-Fu	A	81	243-247	E	$C_{22}H_{25}N_5O_4 \cdot HCl \cdot H_2O$	10	1	2	1	0	22 (3)
								1	0	0	0	0	
5e	H	5-Cl-2-Fu	B	45	188-191	D	$C_{21}H_{22}ClN_5O_4 \cdot HCl \cdot H_2O$ [j]	3	1	1	1	0	17 (6)

[a] Ph = phenyl; Th = thienyl; Fu = furyl. [b] See Experimental Section. [c] Solvent: A = EtOH; B = EtOAc; C = MeOH; D = aqueous EtOH; E = aqueous MeOH. [d] Elemental analytical data of all compounds were obtained within ±0.4% errors of the theoretical values for C, H, and N except where specifically noted. [e] Activity ratings: all results were analyzed for statistically significant differences from predose control values by Student's *t* test. Compounds producing a significant ($p < 0.05$) blood pressure reduction (BPR) were rated as follows: BPR ≥ 30, 3; 30 > BPR ≥ 20, 2; 20 > BPR ≥ 10, 1. Those producing no significant reduction were rated 0. [f] The maximum percent decrease observed is given, followed by the hour postdose at which it was first attained in parentheses. [g] The crystallines were refluxed in isoamyl alcohol after recrystallization from EtOH. [h] H: calcd, 6.38; found, 5.68. [i] C: calcd, 53.23; found, 53.84. [j] C: calcd, 50.69; found, 51.49.

Table III. Effect of Quinazoline Derivatives on BP in Renal Hypertensive Rats[a]

compd	dose, mg/kg, po	n	mean blood pressure, mmHg initial	1 h	3 h	6 h	12 h	24 h
control		4	210 ± 6	0.1 ± 1.9	1.9 ± 1.9	4.3 ± 1.6	1.9 ± 1.9	0.7 ± 4.8
prazosin	3	6	197 ± 7	−17.9 ± 2.2[b]	−15.5 ± 2.1[b]	−14.5 ± 3.1[b]		−3.3 ± 2.4
	10	5	187 ± 5	−25.6 ± 3.2[b]	−17.6 ± 2.6[b]	−14.7 ± 4.2[b]		−8.9 ± 2.7
3a	3	5	195 ± 4	−3.7 ± 3.1	−6.8 ± 3.4	−7.2 ± 2.1[b]		−0.1 ± 2.1
	10	5	199 ± 6	−12.6 ± 3.6[c]	−14.1 ± 3.1[b]	−15.9 ± 2.5[b]		−14.1 ± 0.9[b]
3j	3	5	203 ± 10	−4.0 ± 3.6	−11.7 ± 4.9	−14.5 ± 3.6[b]	−10.6 ± 2.5[b]	−2.6 ± 1.7
	10	5	204 ± 12	−6.2 ± 5.2	−16.3 ± 3.9[b]	−19.1 ± 5.6[b]	−15.5 ± 5.5[c]	−10.4 ± 3.8
5a	3	4	193 ± 9	−17.1 ± 2.7[b]	−16.9 ± 1.2[b]	−18.3 ± 1.2[b]		−5.2 ± 6.1
	10	5	181 ± 7	−17.9 ± 2.4[b]	−16.3 ± 3.1[b]	−17.4 ± 2.5[b]		−11.7 ± 4.9

[a] One-kidney, one clip. [b] $p < 0.01$. [c] $p < 0.05$.

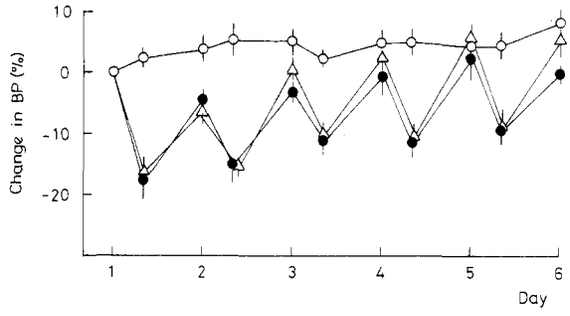


Figure 1. Effect of 5-day consecutive administration of **3a** and **3j** on mean blood pressure in SHR. Blood pressure was measured at 3 and 24 h after each administration. Vertical bars indicate the standard errors of the means: (○) control, $n = 6$, initial mean BP (mmHg) = 170 ± 3; (△) **3a**, 3 (mg/kg)/day, $n = 5$, initial mean BP (mmHg) = 175 ± 3; (●) **3j**, 3 (mg/kg)/day, $n = 4$, initial mean BP (mmHg) = 178 ± 5.

and **3i** (R^2 = 2-EtOPh) were inactive, whereas compounds **3h** (R^2 = 4-MeOPh) and **3j** (R^2 = 4-EtOPh), each of which had the same lipophilicity and electronic effect, showed good potency. For an understanding of these findings, other factors, such as the ortho effect of 2-alkoxy groups, will have to be examined.

Compounds **3a** (R^1 = H; R^2 = Ph), **3j** (R^1 = H; R^2 = 4-EtOPh), and **5a** (R^1 = H; R^2 = 2-furyl), which showed enhanced activity in SHR, were examined for development of tolerance to their antihypertensive effects and were tested for hypotension in renal hypertensive rats.

Five-day consecutive oral administration of **3a** and **3j** in SHR did not affect efficiency in reducing the mean blood pressure, as shown in Figure 1.

Table III shows that in renal hypertensive rats the effect of **3a**, **3j**, and **5a** was revealed to be similar to that in SHR. These compounds caused dose-related decreases in blood pressure with doses of 3 and 10 mg/kg. These results suggest that **3a**, **3j**, and **5a** would be effective as antihypertensive agents in humans.

To elucidate the mode of action of **3a**, **3j**, and **5a**, we studied α-adrenoceptor blocking activities in isolated rat aortas. These compounds antagonized norepinephrine contraction in the isolated rat aortas similar to prazosin, as shown in Table IV. On the basis of these findings, the antihypertensive effect of this series of compounds may be attributed to α-adrenoceptor blocking action.

Conclusion

Most of prepared compounds, especially **3a,j**, **4a,b**, and **5a**, showed potent activity in SHR at oral doses of 0.3–10 mg/kg. In consideration of structure–activity relationships, the activity of the derivatives in this series seems to be mainly concerned with the electronic effects of the derivatives; however, other factors are necessary to explain the activity of some compounds. Compounds **3a,j** and **5a** were also found to be effective in renal hypertensive rats, and no tolerance to the antihypertensive action of **3a,j** in SHR was observed. Compounds **3a,j** and **5a** antagonized norepinephrine contraction of isolated rat aortas in the same way as prazosin. These findings indicate that the hypotensive effect of these compounds may be the result of α-adrenoceptor blocking action. Further studies are now in progress to determine the mechanism of action of **3a,j** and **5a**.

Table IV. α-Adrenoceptor Blocking Activity in the Rat Thoracic Aorta

compd	PA_2[a]	potency ratio
3a	9.14 ± 0.06	0.07
3j	8.66 ± 0.08	0.02
5a	9.85 ± 0.06	0.4
prazosin	10.29 ± 0.11	1
phentolamine	8.07 ± 0.02	0.006

[a] $n = 5$.

Experimental Section

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Analyses were performed by a Perkin-Elmer Model 240 elemental analyzer. Infrared (IR) spectra were obtained for all compounds with a JASCO IRA-1 grating infrared spectrophotometer and were consistent with the assigned structures. Nuclear magnetic resonance (NMR) spectra were measured with a Hitachi R-24B high-resolution NMR spectrometer; chemical shifts are expressed in parts per million downfield from Me_4Si as an internal standard. Mass spectra (MS) were taken with a Shimadzu LKB-900 GC/MS machine; mass numbers are given in m/e, followed by relative intensity (percent) in parentheses.

4-Amino-6,7-dimethoxy-2-(4-formylpiperazino)quinazoline Hydrochloride (7). A mixture of 4-amino-2-chloro-6,7-dimethoxyquinazoline (**6**;[8] 24.0 g, 0.1 mol) and formylpiperazine (11.4 g, 0.1 mol) in isoamyl alcohol (100 mL) was refluxed for 1 h and cooled. The product was filtered off and washed with ethyl alcohol to give 33.4 g of **7**: mp 266–271 °C; ^1H NMR (Me_2SO-d_6 and D_2O) δ 3.4–4.0 (m, 14 H, 6,7-OMe and piperazine), 6.65 (s, 1 H, 5-H), 6.95 (s, 1 H, 8-H), 8.03 (s, 1 H, CHO). Compound **7** was used without further purification.

4-Amino-6,7-dimethoxy-2-piperazinoquinazoline Hydrochloride (8). A suspension of **7** (34.3 g, 0.2 mol) in 10% hydrochloric acid (200 mL) was refluxed for 1.5 h and allowed to stand overnight. The product was filtered and washed with EtOH to give **8**: mp 270–275 °C (lit.[8] mp 285–287 °C). An analytical sample was obtained by the following procedure: The salt (0.5 g) was suspended in 2 N NaOH (10 mL) with stirring for 30 min, and the product was filtered to yield free **8**, which was recrystallized from 95% EtOH to give 0.2 g of **8**: mp 230–232 °C (once melted at 120–130 °C); ^1H NMR (Me_2SO-d_6 and D_2O) δ 1.07 (t, 3 H, J = 7 Hz, CH_3CH_2OH), 2.6–2.9 (m, 4 H, piperazine), 3.45 (q, 2 H, J = 7 Hz, CH_3CH_2OH), 3.5–3.7 (m, 4 H, piperazine), 3.75 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 6.72 (s, 1 H, 5-H), 7.34 (s, 1 H, 8-H). Anal. ($C_{14}H_{19}N_5O_2 \cdot C_2H_5OH$) C, H, N.

Cinnamic Acids 9a–s. Compounds **9a** (R^1 = H, substituent of R^2 = H), **9d** (H, 4-Me), **9f** (H, 2-OMe), **9g** (H, 3-OMe), **9h** (H,

4-OMe), **9n** (H, 4-Cl), and **9q** (H, 3-NO_2) were obtained from Tokyo Chemical Inc. Co., Ltd. Compounds **9l** (H, 3,5-OMe_2), **9o** (H, 3,4-Cl_2), **9r** (H, 3-CF_3), and **9s** (Me, H) were obtained from Aldrich Chemical Co., Inc. Compounds **9b** (H, 2-Me), **9c** (H, 3-Me), **9e** (H, 4-*i*-Pr), **9i** (H, 2-OEt), **9j** (H, 4-OEt), **9k** (H, 4-O-*i*-Pr), **9m** [H, 2,3,4-$(OMe)_3$] and **9p** (H, 4-Br) were prepared from their corresponding benzaldehydes and acetic anhydride by the standard method.[9]

3-(2-Thienyl)- or 3-(3-Thienyl)acrylic Acids 10a–f. Compound **10a** [R^1 = H, R^2 = 2-thienyl (Th)] was obtained from Aldrich Chemical Co., Inc., and acids **10b** (H, 3-Th),[10] **10d** (H, 3-Me-2-Th),[11] **10e** (H, 5-Me-2-Th),[11] and **10f** (H, 5-Cl-2-Th)[11] were prepared by the methods previously reported.

3-(2-Furyl)- or 3-(3-Furyl)acrylic Acids 11a–e. Compound **11a** [R^1 = H, 2-furyl (Fu)] was obtained from Aldrich Chemical Co., Inc., and acids **11b** (H, 3-Fu),[12] **11c** (Me, 2-Fu),[13] **11d** (H, 5-Me-2-Fu),[14] and **11e** (H, 5-Cl-2-Fu)[15] were prepared by the methods previously reported.

2-Methyl-3-(2-thienyl)acrylic Acid (10c). A mixture of 2-thiophenecarboxaldehyde (5.82 g, 50 mmol), propionic anhydride (6.76 g, 55 mmol), and sodium propionate (6.76 g, 70 mmol) was heated at 150 °C for 7.5 h. The reaction mixture was poured into ice–water (30 mL) and allowed to stand overnight. The precipitate was filtered and washed with water and then with *n*-hexane to give 5.72 g (65%) of **10c**: mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3 H, 2-Me), 7.05 (t, J = 5 Hz, 1 H, 4′-H), 7.25 (d, J = 5 Hz, 1 H, 3′-H), 7.47 (d, J = 5 Hz, 1 H, 5′-H), 7.93 (s, 1 H, 3-H), 11.15 (s, 1 H, COOH). Anal. ($C_8H_8O_2S$) C, H, N.

3-(5-Methyl-2-furyl)acryloylpiperazine (17b). A mixture of 3-(5-methyl-2-furyl)acrylic acid (3.04 g, 20 mmol) and thionyl chloride (3.57 g, 30 mmol) in benzene (10 mL) was refluxed for 3 h and concentrated to give the acid chloride **14** (R^1 = H; R^2 = 5-Me-2-furyl). The acid chloride was then dissolved in THF (10 mL), and this solution was added dropwise to a mixture of piperazine hexahydrate (7.78 g, 40 mmol), 47% hydrobromic acid (6.89 g, 40 mmol), and EtOH (30 mL) below 10 °C for 45 min. The mixture was refluxed for 2 h. After the reaction mixture was kept at room temperature overnight, the precipitate was removed by filtration, and the filtrate was concentrated. The residue was dissolved in 2 N HCl (20 mL), and the solution was washed with EtOAc and then alkalized with 2 N NaOH and extracted with EtOAc. The organic solution was dried over anhydrous $MgSO_4$ and concentrated to give **17b** (2.09 g, 47%): ^{1}H NMR (Me_2SO-d_6) δ 2.30 (s, 3 H, 5′-Me), 2.40–2.85 (m, 4 H, piperazine), 3.12 (s, 1 H, NH), 3.30–3.70 (m, 4 H, piperazine), 6.16 (d, J = 4 Hz, 1 H, 4′-H), 6.65 (d, J = 4 Hz, 1 H, 3′-H), 6.65 (d, J = 18 Hz, 1 H, β-H), 7.22 (d, J = 18 Hz, 1 H, α-H); MS, m/e 220 (42, M^+), 85 (100). Anal. ($C_{12}H_{16}N_2O_2$) C, H, N. Other data are given in Table I.

Most of acryloylpiperazine derivatives (**15b–d**, **15f–i**, and **16a–d**) were prepared in a manner similar to **17b**, and their data are given in Table I. Acryloylpiperazine derivatives **15e** and **17a** were prepared in a manner similar to that of **15a**, where the isolated acid chloride was used.

Cinnamoylpiperazine (15a). A solution of cinnamoyl chloride (3.33 g, 20 mmol) in THF (10 mL) was added dropwise to a solution of piperazine hexahydrate (7.78 g, 40 mmol) and 47% HBr (6.89 g, 40 mmol) in EtOH at room temperature. The reaction mixture was treated in a manner similar to that of **17b** to yield 2.80 g (65%) of **15a**: ^{1}H NMR (Me_2SO-d_6) δ 2.30–3.00 (m, 4 H, piperazine), 2.94 (s, 1 H, NH), 3.20–3.80 (m, 4 H, piperazine), 6.85–7.85 (m, 7 H, cinnamoyl); MS, m/e 216 (17, M^+), 69 (100). An analytical sample was obtained by distillation: bp 181–184 °C (2 mmHg). Anal. ($C_{13}H_{16}N_2O$) C, H, N. Other data are given in Table I.

Method A. Compounds **3b,d,f–g,i,k,p,s**, **4a,c–e**, and **5a,d** were prepared in a manner similar to that of **3a**.

4-Amino-2-(4-cinnamoylpiperazino)-6,7-dimethoxyquinazoline Hydrochloride (3a). A mixture of 4-amino-2-chloro-6,7-dimethoxyquinazoline (2.40 g, 10 mmol) and cinnamoylpiperazine (2.16 g, 10 mmol) in isoamyl alcohol (100 mL) was refluxed for 3 h, and allowed to cool overnight. The product was filtered and then washed with Et_2O to give a white powder, **3a** (3.80 g). A sample of **3a** was recrystallized from EtOH to give a hydrochloride (mp 259–260 °C), which was refluxed in isoamyl alcohol for 1 h to yield **3a**: mp 290–293 °C; ^{1}H NMR (Me_2SO-d_6, free base **3a**) δ 3.40–4.10 [m, 14 H, piperazine, 6,7-$(OMe)_2$], 6.72 (s, 1 H, 5-H), 7.07 (br s, 2 H, 4-NH_2), 7.27–7.80 (m, 8 H, cinnamoyl and 8-H); MS, m/e 419 (52, M^+), 233 (100). Other data are given in Table II.

Compounds **3b** and **4a** were converted to free bases by the following procedure: A suspension of the hydrochloride of **3b** (or **4a**) (100 mg) in EtOAc (10 mL) and 10% aqueous K_2CO_3 solution was stirred for 30 min at room temperature. The product was filtered and recrystallized from EtOAc to give free **3b** (or **4a**). The data are given in Table II.

Method B. Compounds **3c,e,h,l–o,q–r**, **4b,f**, and **5b,c,e** were prepared in a manner similar to that of **3j**.

4-Amino-2-[4-(4-ethoxycinnamoyl)piperazino]-6,7-dimethoxyquinazoline (3j). Ethyl chlorocarbonate (195 mg, 1.8 mmol) was added dropwise to a mixture of 4-ethoxycinnamic acid (346 mg, 1.8 mmol) and triethylamine (202 mg, 2 mmol) in an ice–water bath. The reaction mixture was stirred for 3.5 h, and then 4-amino-6,7-dimethoxy-2-piperazinoquinazoline hydrochloride (543 mg, 1.5 mmol) and triethylamine (364 mg, 3.6 mmol) were added to the mixture. It was stirred at room temperature overnight. The product was filtered and washed with water and EtOH to give **3j** (430 mg, 62%), which was recrystallized from EtOH to yield pure **3j**: ^{1}H NMR (Me_2SO-d_6) δ 1.33 (t, J = 7 Hz, 3 H, CH_2CH_3), 3.40–4.50 [m, 16 H, piperazine, 6,7-$(OMe)_2$, 4′-OCH_2CH_3], 6.70 (s, 1 H, 5-H), 6.89 (d, J = 8 Hz, 2 H, 2′- and 6′-H), 7.05 (br s, 2 H, 4-NH_2), 7.05 (d, J = 15 Hz, 1 H, β-H), 7.36 (s, 1 H, 8-H), 7.43 (d, J = 15 Hz, 1 H, α-H), 7.57 (d, J = 8 Hz, 2 H, 3′- and 5′-H); MS, m/e 463 (40, M^+), 233 (100). Other data are given in Table II.

Compounds **3n,q**, **4f**, and **5c,e** were converted to the hydrochloride salts by the following procedure: A free compound (100 mg) was dissolved in EtOH (10 mL), and then 2 N HCl (1 mL) was added. The product was filtered and washed with EtOH to yield the hydrochloride. The data are given in Table II.

Pharmacological Methods. Antihypertensive Effects. Experiments were performed on spontaneously hypertensive rats (SHR, Okamota and Aoki strain),[16] supplied by Jichi medical school, and renal hypertensive rats (one-kidney, one clip). Male animals were used.

SHR were F-35, 23–28 weeks of age, weighing 300–400 g, and their mean blood pressures (BP) ranged from 160 to 200 mmHg. We induced renal hypertension by clipping the left renal artery with a silver ribbon and removing the right kidney a week later in rats of Wister strain, weighing 180–200 g.[17] They were used 12 to 14 weeks after being clipped. Body weight ranged from 350 to 450 g, and BP ranged from 170 to 220 mmHg.

BP and heart rate (HR) were measured, without anesthesia or restraint, through an aortic catheter by a recording system (pressure transducer MPU-0.5, carrier amplifier AP-620G, heart rate counter AT-600G, RM-6008, recorder W-681G, Nihon Kohden) as described previously.[18] BP and HR were determined 30 min prior to, and at intervals of 1, 3, 6, 12, and 24 h after, the administration. The test compounds were suspended with a 1% tragacanth mucilage at the required concentration and given orally in a volume of 5 mL/kg.

For the studies of 5-day consecutive oral administrations, the test compounds in a dose of 1 mg/kg were given orally once a day for 5 consecutive days. BP and HR were measured at 3 and 24 h after each administration.

α-Adrenoceptor Blocking Activity in Isolated Aortas of Rats. Male Wister rats weighing 200–300 g were used. Animals were killed by a blow on the head, and the thoracic aortas were removed. The aortas were helically cut at a length of 40 mm and mounted in a incubation bath at 37 °C with a resting tension of 1 g. They were allowed to equilibrate for 90 min to renew the fluids and then tested 15 min later. Contraction of aortas was measured isometrically by a recording system (force-displacement transducer SB-1T, carrier amplifier RP-5, recorder RM-25, Nihon Koden). The bath was of 20 mL working volume and contained a modified Krebs' solution resulting from bubbling 95% O_2 and 5% CO_2 through the following mixture (mM): NaCl, 133; KCl,

(16) K. Okamoto and K. Aoki, *Jpn. Circ. J.*, **27**, 282 (1963).
(17) C. Wilson and F. B. Byron, *Lancet*, **1**, 136, (1939).
(18) S. Mizogami, F. Shibayama, H. Kikuchi, and H. Sokabe, *Jpn. J. Const. Med.*, **32**, 59 (1969).

4.5; $NaHCO_3$, 25; $MgCl_2$, 1.25; dextrose, 10; (Ca/Na_2) EDTA, 0.025. After a cumulative dose–response curve was obtained for 1-norepinephrine bitartrate (NE), the test compound was added in a volume of between 0.01 and 0.1 mL, and the cumulative dose–response curve for NE was again determined in the presence of the test compound incubated for 10 min. The test compounds and prazosin hydrochloride (PZ) were dissolved in dimethyl sulfoxide. Phentolamine mesylate (PT) and NE were diluted with saline. PA_2 values were determined according to the method of Van Rossam.[19]

Acknowledgment. The authors thank Drs. Y. Masuda and T. Kobayashi for their continuing interest and encouragement during this work.

Registry No. **3a**, 84050-18-0; **3a** (base), 70842-66-9; **3b**·HCl, 84050-26-0; **3b** (base), 84050-25-9; **3c**, 84050-28-2; **3d**, 84050-29-3; **3d** (base), 84050-45-3; **3e**, 70842-70-5; **3f**, 84050-30-6; **3f** (base), 84050-46-4; **3g**, 84050-31-7; **3g** (base), 84050-47-5; **3h**, 70842-73-8; **3i**, 84050-32-8; **3i** (base), 84050-48-6; **3j**, 70842-75-0; **3k**, 84050-33-9; **3k** (base), 84050-49-7; **3l**, 70842-78-3; **3m**, 70842-79-4; **3n**, 84050-34-0; **3n** (base), 84050-50-0; **3o**, 70842-85-2; **3p**, 84050-35-1; **3p** (base), 70842-86-3; **3q**, 84050-36-2; **3q** (base), 84050-51-1; **3r**, 70842-87-4; **3s**, 84056-88-2; **3s** (base), 84050-52-2; **4a**·HCl, 84050-27-1; **4a** (base), 84050-19-1; **4b**, 84050-37-3; **4c**, 84050-38-4; **4c** (base), 84050-53-3; **4d**, 84050-39-5; **4d** (base), 70843-21-9; **4e**, 84050-40-8; **4e** (base), 84050-54-4; **4f**, 84050-41-9; **4f** (base), 84050-55-5; **5a**, 84050-20-4; **5a** (base), 84050-56-6; **5b**, 70842-93-2; **5c**, 84050-42-0; **5c** (base), 84050-57-7; **5d**, 84050-43-1; **5d** (base), 84050-58-8; **5e**, 84050-44-2; **5e** (base), 84050-59-9; **6**, 23680-84-4; **7**·HCl, 84050-21-5; **8**·HCl, 84050-22-6; **8** (base), 60547-97-9; **9a**, 621-82-9; **9b**, 2373-76-4; **9c**, 3029-79-6; **9d**, 17451-22-8; **9e**, 3368-21-6; **9f**, 6099-03-2; **9g**, 6099-04-3; **9h**, 830-09-1; **9i**, 69038-81-9; **9j**, 2373-79-7; **9k**, 20718-97-2; **9l**, 16909-11-8; **9m**, 33130-03-9; **9n**, 1615-02-7; **9o**, 1202-39-7; **9p**, 1200-07-3; **9q**, 555-68-0; **9r**, 779-89-5; **9s**, 1199-77-5; **10a**, 1124-65-8; **10b**, 1195-52-4; **10c**, 40527-55-7; **10d**, 77741-66-3; **10e**, 14770-88-8; **10f**, 41914-51-6; **11a**, 539-47-9; **11b**, 39244-10-5; **11c**, 84050-60-2; **11d**, 14779-25-0; **11e**, 75426-52-7; **14**, 84050-23-7; **15a**, 55486-27-6; **15b**, 70842-48-7; **15c**, 70842-53-4; **15d**, 70842-55-6; **15e**, 70842-49-8; **15f**, 70842-56-7; **15g**, 70842-57-8; **15h**, 70842-64-7; **15i**, 84050-62-4; **16a**, 58955-26-3; **16b**, 70843-15-1; **16c**, 70843-13-9; **16d**, 84050-63-5; **17a**, 84050-24-8; **17b**, 84050-61-3; cinnamoyl chloride, 102-92-1; acryloyl chloride, 814-68-6; formylpiperazine, 7755-92-2; 2-thiophenecarboxaldehyde, 98-03-3; propionic anhydride, 123-62-6; piperazine hydrobromide, 14007-05-7; ethyl chlorocarbonate, 541-41-3; 4-ethoxycinnamic acid, 2373-79-7.

(19) J. M. Van Rossam, *Arch. Int. Pharmacodyn. Ther.*, **143**, 229 (1963).

Synthesis and Antihypertensive Activity of 2-Sulfonamido- and 2-Sulfamido-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizines

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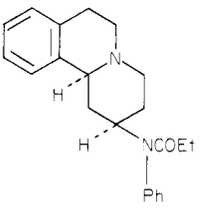
The synthesis of a series of 2-sulfonamido- and 2-sulfamido-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizines is reported. Compounds in which the 2-substituent is equatorial were synthesized stereoselectively and shown to possess greater antihypertensive activity than the 2-axial isomers. *N*-(1,3,4,6,7,11bα-Hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)methanesulfonamide (**5**) was shown to possess antihypertensive activity in the DOCA rat at 10–50 mg/kg, and its pharmacology was examined in detail.

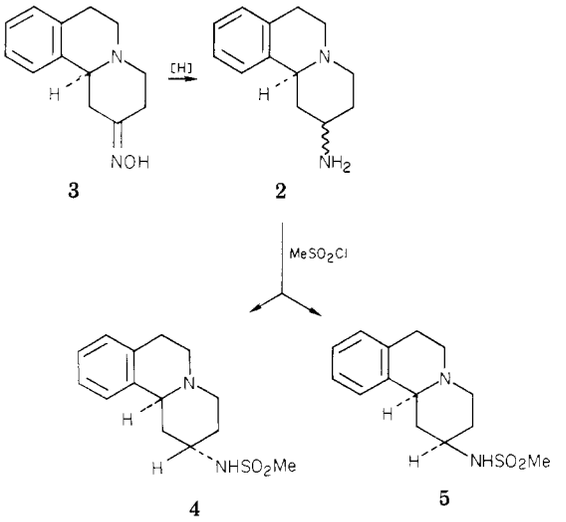
Some years ago, a series of amide derivatives of 2-aminobenzoquinolizine was reported and examined for antihypertensive activity.[1] Of particular interest from this series was compound **1**, which showed vasodilating activity



1

and was chosen for further evaluation.[2] Despite this interest in amides of 2-aminobenzoquinolizine, the related sulfonamides remained unexplored. We were therefore prompted to prepare a series of 2-sulfonamidobenzoquinolizines for evaluation as antihypertensive agents. A number of these sulfonamides have shown marked antihypertensive activity.

Scheme I



3 **2** **4** **5**

Chemistry. In initial experiments, the required intermediate, 2-aminobenzoquinolizine (**2**), was prepared by reduction of the oxime **3** over Raney nickel (Scheme I). Treatment of **2**, prepared in this way, with methane-

(1) Van Dyke, J. W. Jr.; Havera, H. J.; Johnson, R. D.; Vidrio, H.; Viveros, A. *J. Med. Chem.* **1972**, *15*, 91.
(2) Vargas, R.; Vidrio, H.; Viveros, A. *Arzeim.-Forsch.* **1972**, *21*, 941. Fonseca, E. H.; Hartnagel, R. E.; Kowalski, R. L.; Kraus, P. J.; Phillips, B. M. *Toxicology*, **1975**, *4*, 215. Johnson, N., Jr.; Leeling, J. L.; Muni, I. A.; Phillips, B. M. *Toxicol. Appl. Pharmacol.* **1978**, *46*, 77.

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