

isothioureia 0.5-sulfate (5 g, 35.92 mmol), and water (50 mL) was stirred at 80 °C for 2 h. The solvent was removed under reduced pressure, and the residue was recrystallized from ethanol and water to yield **17** (4.82 g, 70%): IR (KBr) ν_{\max} (cm⁻¹) 1620, 1660 (guanidine).

4-Amidino-1-(5-isoquinolylsulfonfyl)-1,4-perhydrodiazepine Hydrochloride (33). To an ice-cold aqueous solution (30 mL) of 5-isoquinolinesulfonyl chloride (1.5 g, 5.68 mmol) was added slowly NaHCO₃ (0.48 g, 5.7 mmol) with stirring. The solution was extracted twice with CH₂Cl₂ (40 mL). The CH₂Cl₂ solution was dried with MgSO₄ and evaporated off. THF (40 mL) was added to the residue and this solution was added to an aqueous solution (15 mL) of **17** (2.5 g, 13 mmol) at 0 °C. The solution was stirred at 0 °C for 2 h and then acidified with HCl, and the solvent was removed under reduced pressure. The residue was dissolved in water (10 mL) and filtered. The pH of the filtrate was adjusted to 12.5 with 10 N NaOH. The precipitate was filtered and dissolved in water with a small amount of dilute HCl. The solution, following adjustment of its pH to 5.0 with NaOH, was evaporated off, and the residue was recrystallized from acetone/MeOH to give **33** (851 mg, 41%): IR (KBr) ν_{\max} (cm⁻¹) 1630, 1670 (guanidine), 1330 (S=O); NMR (D₂O) δ 1.7-2.1 (2 H, m, CH₂CH₂CH₂), 3.4-3.8 (8 H, m, CH₂N), 7.86 (1 H, dd, isoquinoline H-7), 8.27-8.80 (4 H, m, isoquinoline H-1); mp 247-249 °C.

Biological Determination.³ Mongrel dogs unselected as to sex (15-26 kg) were anesthetized with pentobarbital sodium (35 mg/kg iv). The trachea was intubated, and ventilation rates (12-16 cycles/min) and tidal volumes were adjusted so as to maintain the arterial blood pH, pCO₂, and pO₂ within physiological limits. The body temperature was maintained at 37-38 °C with a heating pad. Catheters were placed in the right femoral artery and vein, and the heart rate and mean blood pressure were monitored. An electromagnetic flow probe of the extracorporeal type (Nihon Kohden, Model MFV-1200) was inserted into the left femoral artery to evaluate the increase in femoral blood flow.

The test compounds in a volume of 10 μ L were injected with microinjector into a rubber tube connected to the arterial cannula over a period of 5 s. Despite the injections of drugs, neither blood pressure nor heart rate changed. At least three different amounts

of each test compound were injected and the resulting changes in blood flow were assessed. After and before the administrations of three doses of each compound, 100 μ g of trapidil was administered as a relative control. At least three dose-response curves per compound were obtained.

The increment in femoral blood flow by trapidil had a very big difference among individual dogs (183 \pm 85% (SD), *n* = 12). Accordingly the vasodilatory activity was evaluated as an equipotent dose compared to trapidil, which was calculated from the dose-response curves.

Acknowledgment. We thank Masami Yanagita for his assistance in the biological testing, members of the Department of Medicinal Chemistry for their assistance in synthesis work, and Barrett B. Madrigal for his critical reading of the manuscript.

Registry No. 1, 91742-10-8; 1-HCl, 92564-34-6; 4, 27655-40-9; 5, 105627-79-0; 6, 116700-33-5; 7, 116700-34-6; 8, 116700-35-7; 9, 116700-36-8; 10, 116700-37-9; 11, 116700-38-0; 12, 116700-39-1; 13, 116700-40-4; 14, 113276-94-1; 15, 22365-47-5; 16, 92564-61-9; 17, 92586-45-3; 18, 116700-32-4; 18-HCl, 116724-50-6; 19, 116700-49-3; 19-HCl, 116700-41-5; 20, 92564-06-2; 20-HCl, 116700-42-6; 21, 92564-04-0; 21-HCl, 116700-43-7; 22, 116700-50-6; 22-HCl, 116700-44-8; 23, 92564-35-7; 23-2HCl, 116700-45-9; 24, 116700-51-7; 24-2HCl, 116700-46-0; 25, 116700-52-8; 25-2HCl, 116724-51-7; 26, 116700-53-9; 26-2HCl, 116700-47-1; 27, 116700-54-0; 27-2HCl, 116700-48-2; 28, 92564-37-9; 28-2HCl, 92564-09-5; 29, 92564-38-0; 29-2HCl, 92564-10-8; 30, 92564-40-4; 30-2HCl, 92625-77-9; 31, 92564-57-3; 31-HCl, 98646-59-4; 32, 92564-64-2; 32-HCl, 98646-62-9; 33, 92564-62-0; 33-HCl, 98672-47-0; H₂N(C-H₂)₃NH₂, 109-76-2; H₂N(CH₂)₄NH₂, 110-60-1; H₂N(CH₂)₆NH₂, 124-09-4; H₃CSC=NCN(NH₂), 15760-26-6; H₃CSC=NNO₂(NH₂), 2986-25-6; H₃CSC=NCH₃(NH₂), 44387-05-5; H₃CSC=NCH₃(N-HCH₃), 2986-23-4; H₃CSC=NC₆H₅(NHC₆H₅), 5416-30-8; H₃CS-C=N(CH₂)₂NH, 20112-79-2; HN(CH₃)(CH₂)₂OH, 109-83-1; H₂N(CH₂)₂OH, 141-43-5; H₃CSC=NH(NH₂)¹/₂H₂SO₄, 867-44-7; 2-chloropyrimidine, 1722-12-9; piperazine, 110-85-0; 2,5-dimethylpiperazine, 106-55-8; hexahydro-1*H*-1,4-diazepine, 505-66-8.

5-Isoquinolinesulfonamide Derivatives. 2. Synthesis and Vasodilatory Activity of *N*-(2-Aminoethyl)-5-isoquinolinesulfonamide Derivatives

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A new series of aromatic sulfonamides, the *N*-(2-aminoethyl)-5-isoquinolinesulfonamide derivatives, **3**, was synthesized from 5-isoquinolinesulfonic acid and shown to possess vasodilatory action. Vasodilatory activity was evaluated in vivo in terms of increases in arterial blood flow in dogs after local injection in the femoral and/or vertebral arteries. When the alkylene group between the two nonaromatic nitrogen atoms was ethylene, the most potent activity was obtained. Alkylations of either of the two nonaromatic nitrogens yielded more active compounds, although bulky or excessively long alkyl groups reduced the potency. Among these derivatives, **27** and **47** were equipotent to diltiazem, which is used clinically as a cardiovascular drug. These two compounds also had antihypertensive and vasodilatory activities when administered intravenously, although the activities were less than that of diltiazem when given by this route.

In the course of our studies with **1**, we found that **2**, a synthetic intermediate that possesses an amino group instead of a guanidino group, also has weak vasodilatory activity. In order to improve the vasodilatory activity of **1** and to find a new series of vasodilators, it was decided

to prepare analogues of **2**. These compounds are represented by the general formula **3**.

In this report, we describe the syntheses and pharmacological evaluation of **2** and its derivatives **3**.

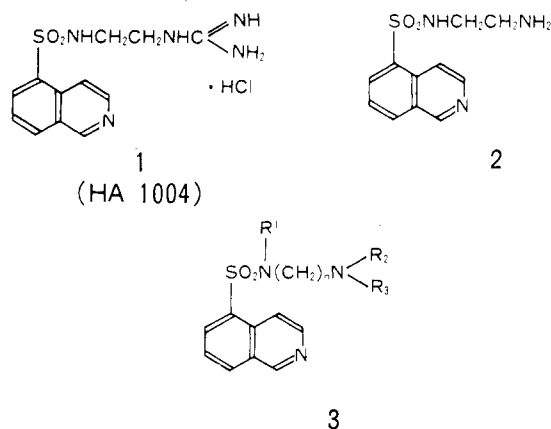
Chemistry

The amines **14**-**17** and **39**-**42** were prepared from the corresponding diamines by treatment with a CH₂Cl₂ solution of the sulfonyl chloride **5** (Scheme I, method A). The secondary amines **18**-**21** were prepared by treatment of **2** with alkyl halide in the presence of K₂CO₃ in EtOH

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(Scheme I, method B). The amines 22–38 were synthesized from the corresponding alcohols (6–13), obtained by sulfonylation of the 2-aminoethanols with 5. The alcohols 6–13 were tosylated with *p*-toluenesulfonyl chloride in pyridine to give the corresponding tosylates, and treatment of the tosylates with primary or secondary amines afforded 22–38 (Scheme I, method C). In method C, however, ammonia afforded only a low yield in comparison with the primary and secondary amines because of its poor reactivity with tosylates. Therefore, we adapted the Mitsunobu reaction¹ for the synthesis of primary amines 43–49. The alcohols 6–13 were treated with triphenylphosphine, diethylazodiformate, and phthalimide in THF at room temperature to yield the corresponding phthalimide derivatives with triphenylphosphine oxide and *N,N'*-bis(ethoxycarbonyl)hydrazine. Elimination of the phthalimide group by hydrazine afforded the corresponding primary amines 43–49 in good yields (Scheme I, method D).

Biology

We used the *in vivo* increasing effect on vertebral and/or femoral artery blood flow in anesthetized dogs following local injection into an artery, as an initial means of screening the compounds. The vasodilatory activity was assessed by recording the dose that increased the blood flow as much as the standard compound, trapidil (5-methyl-7-(diethylamino)[1,2,4]triazolo[1,5-*a*]pyrimidine).^{2,3} These data are expressed in Table II.

The vasodilatory effect of 2 was much less than that of the standard compound, trapidil (Table II). Both reduction and elongation of the alkylene chain between the sulfonamidic and terminal amino nitrogens yielded less active compounds, i.e. 14–17. Consequently, the vasodilatory activities of the ethylenediamine derivatives were examined.

In order to evaluate the relationship between activity and monoalkylation of the terminal amino group, compounds 18–34 were prepared. The activities of 2 and 22–29 suggested that the longer the substituent, the more potent the activity of the derivative. Of the most active compounds, 34 showed increasing effects on the femoral and vertebral blood flows that were approximately 3 times as potent as that of trapidil. Also compound 27 had an increasing effect on femoral blood flow to the same degree as that of diltiazem.

Substitution on the terminal nitrogen with bulky alkyl groups gave less potent compounds, 20, 30, and 38, than with nonbulky alkyl groups. The vasodilatory activities

Table I. *N*-(Hydroxyethyl)-5-isoquinolinesulfonamide Derivatives

no.	R ¹	yield, %	mp, °C	recrystn solv ^a	formula
6	H	78	144–145	E	C ₁₁ H ₁₂ O ₃ N ₂ S
7	CH ₃	87	121–122	E	C ₁₂ H ₁₄ O ₃ N ₂ S
8	C ₂ H ₅	84	88–89	E	C ₁₃ H ₁₆ O ₃ N ₂ S
9	<i>i</i> -C ₃ H ₇	90	76–79	E	C ₁₄ H ₁₈ O ₃ N ₂ S
10	<i>n</i> -C ₄ H ₉	79	62–64	A	C ₁₅ H ₂₀ O ₃ N ₂ S
11	<i>n</i> -C ₆ H ₁₃	85	95–97	A	C ₁₇ H ₂₄ O ₃ N ₂ S
12	<i>n</i> -C ₈ H ₁₇	54	oil		C ₁₉ H ₂₈ O ₃ N ₂ S
13	C ₆ H ₅ CH ₂	63	108–110	A/M	C ₁₈ H ₁₈ O ₃ N ₂ S

^a E, ethanol; A, acetone; M, methanol.

of 18–21 and 31–34, which are substituted benzylamine derivatives, suggested that the introduction of electron-donating groups to the aromatic ring produces compounds of greater potency. However, structure 33, which has the strongest electron donor in the molecule, had only little activity.

Dialkylation of the terminal amino group did not afford potent compounds 35–39.

Analogues 40–49, in which the sulfonamidic nitrogen is substituted, generally produced strong increases in arterial blood flow. Similar to the case of alkylation on the terminal amino nitrogen, it is thought that the longer the alkyl group bonded to the sulfonamidic nitrogen, the more potent its vasodilatory effect. However, in the case of substitution on the sulfonamidic nitrogen, excessive elongation of the alkyl group diminished the vasodilatory effects, as shown by 48. The low activities of 45 and 49 may have been caused by the substitution of bulky alkyl groups on the sulfonamidic nitrogens. This decrease in activity by bulky groups is analogous to the case of substitution on the terminal amino group. The most active compound, 47, possessed a vasodilatory effect on the vertebral artery that was as potent as that of diltiazem.^{4–6}

These results suggest that both the lipophilicity and the steric environment of the sulfonamidic side chain in the 5-isoquinolinesulfonamide derivatives influence the vasodilatory activity.

The above consideration of the vasodilatory activities of 5-isoquinolinesulfonamide compounds is based on the biological effect of the local injection into the artery. Intraarterial injection had no influence on cardiovascular parameters such as blood pressure and heart rate. We evaluated the effects of the most active compounds of this series, 47 and 27, on heart rate, blood pressure, vertebral artery blood flow, and coronary blood flow when administered intravenously. As shown in Table III, 47 and 27 also had an antihypertensive activity when intravenously administered, but their activities were less potent than that of diltiazem. Although diltiazem reduced heart rate, the former two compounds accelerated it. This fact suggests that there is a difference between the effects of diltiazem and 5-isoquinolinesulfonamide derivatives on the heart.

It has already been reported that 1 has an inhibitory effect on protein kinase C and that it may be an intra-

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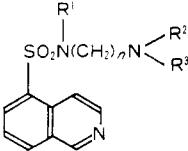
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Table II. *N*-(2-Aminoethyl)-5-isoquinolinesulfonamides


no.	<i>n</i>	R ¹	R ²	R ³	formula (C, H, O, N, S)	method (×)	yield, %	recrystn solv ^a	mp, °C	FBF ^b	VBF ^b
2	2	H	H	H	C ₁₁ H ₁₃ O ₂ N ₃ S·HCl	A	71	H ₂ O	253–254	2.0 ± 0.3	1.8 ± 0.3
14	0	H	H	H	C ₉ H ₉ O ₂ N ₃ S·2HCl	A	45	H ₂ O	240–241	ND	>100
15	3	H	1H	H	C ₁₂ H ₁₅ O ₂ N ₃ S·HCl	A	76	H ₂ O	246–248	3.6 ± 0.1	5.1 ± 0.3
16	4	H	H	H	C ₁₃ H ₁₇ O ₂ N ₃ S·HCl	A	58	H ₂ O	220–222	2.7 ± 0.2	4.2 ± 0.08
17	6	H	H	H	C ₁₅ H ₂₁ O ₂ N ₃ S·HCl	A	23	H ₂ O	205–207	2.4 ± 0.1	1.4 ± 0.4
22	2	H	CH ₃	H	C ₁₂ H ₁₅ O ₂ N ₃ S·HCl	C	46	A/MA	221–222	1.7 ± 0.2	3.7 ± 0.2
23	2	H	C ₂ H ₅	H	C ₁₃ H ₁₇ O ₂ N ₃ S·HCl	C	43	A	151–152	2.7 ± 0.3	4.2 ± 0.3
24	2	H	<i>n</i> -C ₃ H ₇	H	C ₁₄ H ₁₉ O ₂ N ₃ S·HCl	C	56	A	155–156	1.6 ± 0.2	2.7 ± 0.3
25	2	H	<i>n</i> -C ₄ H ₉	H	C ₁₅ H ₂₁ O ₂ N ₃ S·HCl	C	59	A	177–178	1.3 ± 0.1	4.6 ± 0.5
26	2	H	<i>n</i> -C ₆ H ₁₃	H	C ₁₇ H ₂₅ O ₂ N ₃ S·HCl	C	68	A	118–120	0.23 ± 0.02	2.4 ± 0.2
27	2	H	<i>n</i> -C ₈ H ₁₇	H	C ₁₉ H ₂₉ O ₂ N ₃ S·2HCl	C	17	A	132–133		0.17 ± 0.06
28	2	H	<i>n</i> -C ₁₀ H ₂₁	H	C ₂₁ H ₃₃ O ₂ N ₃ S·2HCl	C	66	A	138–142		0.53 ± 0.08
29	2	H	<i>n</i> -C ₁₀ H ₂₁	H	C ₂₁ H ₃₃ O ₂ N ₃ S·2HCl	C	66	A	138–142		0.49 ± 0.10
30	2	H	<i>c</i> -C ₆ H ₁₁	H	C ₁₇ H ₂₅ O ₂ N ₃ S·HCl	C	65	A	199–200		1.4 ± 0.2
31	2	H	C ₆ H ₅ CH ₂	H	C ₁₈ H ₁₉ O ₂ N ₃ S·2HCl	C	60	A	217–220		0.57 ± 0.1
32	2	H	4-MeOC ₆ H ₄ CH ₂	H	C ₁₉ H ₂₁ O ₂ N ₃ S·2HCl	C	67	EA	146–149	0.43 ± 0.08	0.38 ± 0.07
33	2	H	3,4-(MeO) ₂ C ₆ H ₃ CH ₂	H	C ₂₀ H ₂₃ O ₂ N ₃ S·2HCl	C	38	EA	188–191	3.7 ± 0.4	4.3 ± 0.5
34	2	H	C ₆ H ₅ CH ₂ CH ₂	H	C ₁₉ H ₂₁ O ₂ N ₃ S·2HCl	C	41	A	138–142	0.32 ± 0.07	0.31 ± 0.04
18	2	H	4-ClC ₆ H ₄ CH ₂	H	C ₁₈ H ₁₈ O ₂ N ₃ SCl·2HCl	B (Br)	20	EA/EE	246–247	1.0 ± 0.11	0.25 ± 0.02
19	2	H	3-ClC ₆ H ₄ CH ₂	H	C ₁₈ H ₁₈ O ₂ N ₃ SCl·2HCl	B (Cl)	34	EA/EE	218–220	0.83 ± 0.03	0.26 ± 0.01
20	2	H	2-ClC ₆ H ₄ CH ₂	H	C ₁₈ H ₁₈ O ₂ N ₃ SCl·2HCl	B (Cl)	18	EA/EE	223–227	2.6 ± 0.2	1.5 ± 0.1
21	2	H	4-NO ₂ C ₆ H ₄ CH ₂	H	C ₁₈ H ₁₈ O ₄ N ₄ S·2HCl	B (Br)	72	H ₂ O	207–208	2.5 ± 0.3	1.5 ± 0.3
35	2	H	CH ₃	<i>c</i> -C ₆ H ₁₁	C ₁₈ H ₂₅ O ₂ N ₃ S·2HCl	C	58	EA/EE	145–148	0.83 ± 0.08	1.7 ± 0.3
36	2	H	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	C ₂₀ H ₃₁ O ₂ N ₃ S·HCl	C	56	A	135–137	1.9 ± 0.10	1.7 ± 0.2
37	2	H	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₆ H ₁₃	C ₂₃ H ₃₇ O ₂ N ₃ S·HCl	C	53	A	120–125	1.2 ± 0.12	0.48 ± 0.09
38	2	H	<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	C ₁₇ H ₂₅ O ₂ N ₃ S·HCl	C	27	H ₂ O	232–233		2.7 ± 0.2
39	2	H	CH ₃	CH ₃	C ₁₃ H ₁₇ O ₂ N ₃ S·HCl	A	79	EA/H ₂ O	227–228		1.4 ± 0.2
40	2	CH ₃	CH ₃	H	C ₁₃ H ₁₇ O ₂ N ₃ S·HCl	A	32	EA/H ₂ O	209–212	1.5 ± 0.09	1.3 ± 0.1
41	2	C ₂ H ₅	C ₂ H ₅	H	C ₁₅ H ₂₁ O ₂ N ₃ S·HCl	A	36	EA/H ₂ O	221–222	1.1 ± 0.05	0.78 ± 0.04
42	2	C ₆ H ₅ CH ₂	C ₆ H ₅ CH ₂	H	C ₂₅ H ₂₅ O ₂ N ₃ S·HCl	A	47	MA/H ₂ O	108–109		1.8 ± 0.2
43	2	CH ₃	CH ₃	H	C ₁₂ H ₁₅ O ₂ N ₃ S·HCl	D	67	EA/H ₂ O	223–225		1.6 ± 0.3
44	2	C ₂ H ₅	H	H	C ₁₃ H ₁₇ O ₂ N ₃ S·HCl	D	56	EA/H ₂ O	238–240		1.3 ± 0.2
45	2	<i>i</i> -C ₃ H ₇	H	H	C ₁₄ H ₁₉ O ₂ N ₃ S·HCl	D	51	EA/H ₂ O	258		3.3 ± 0.5
46	2	<i>n</i> -C ₄ H ₉	H	H	C ₁₅ H ₂₁ O ₂ N ₃ S·HCl	D	54	EA/H ₂ O	245–246		0.27 ± 0.01
47	2	<i>n</i> -C ₆ H ₁₃	H	H	C ₁₇ H ₂₅ O ₂ N ₃ S·HCl	D	47	EA/A	189–191		0.12 ± 0.007
48	2	<i>n</i> -C ₈ H ₁₇	H	H	C ₁₉ H ₂₉ O ₂ N ₃ S·HCl	D	43	EA/A	171–175		0.92 ± 0.1
49	2	C ₆ H ₅ CH ₂	H	H	C ₁₈ H ₁₉ O ₂ N ₃ S·HCl	D	58	EA/H ₂ O	142–145		1.92 ± 0.3
diltiazem										0.21 ± 0.009	0.15 ± 0.008

^a EA, ethanol; MA, methanol; EE, diethyl ether. ^b Increasing effect on femoral or vertebral blood flow. FBF and VBF: mean femoral and vertebral arteries, respectively. These values are expressed as equipotent dose ratios compared to trapidil.

Table III. Hemodynamic Effects Given Intravenously to Anesthetized Dogs

entry	% of changes from control ^a			
	HR ^b	MBP ^c	VBF ^d	CBF ^e
27	3.9 ± 0.9	-16.8 ± 2.6	93.7 ± 40.0	45.7 ± 21.4
47	2.8 ± 1.7	-11.4 ± 1.9	91.4 ± 28.3	53.6 ± 16.6
diltiazem	-8.0 ± 4.4	-28.9 ± 4.9	180 ± 43	91.3 ± 21.1

^a The data used to calculate the percentage of changes were the maximum observed changes. Each result is the mean ± SE.

^b Heart rate (*n* = 12). ^c Mean blood pressure (*n* = 12). ^d Vertebral blood flow (*n* = 6). ^e Coronary blood flow (*n* = 6).

cellular calcium antagonist.⁷ The new vasodilators described above have quite similar chemical structures to that of 1, but it is unclear whether they have the same effect as 1, and further research will therefore be necessary in order to define the mechanism of action of these compounds.

Experimental Sections

Melting points were determined in open capillary tubes on a Büchi apparatus and have not been corrected. Compounds gave

satisfactory IR and NMR spectral data and were obtained respectively on a Hitachi 260-10 IR spectrophotometer and a JEOL JNM-PMX-60 NMR spectrophotometer. Elemental analyses were performed by the analytical department at the Nobeoka plant, Asahi Chemical Industry Co., Ltd., and were within ±0.4% of the calculated values.

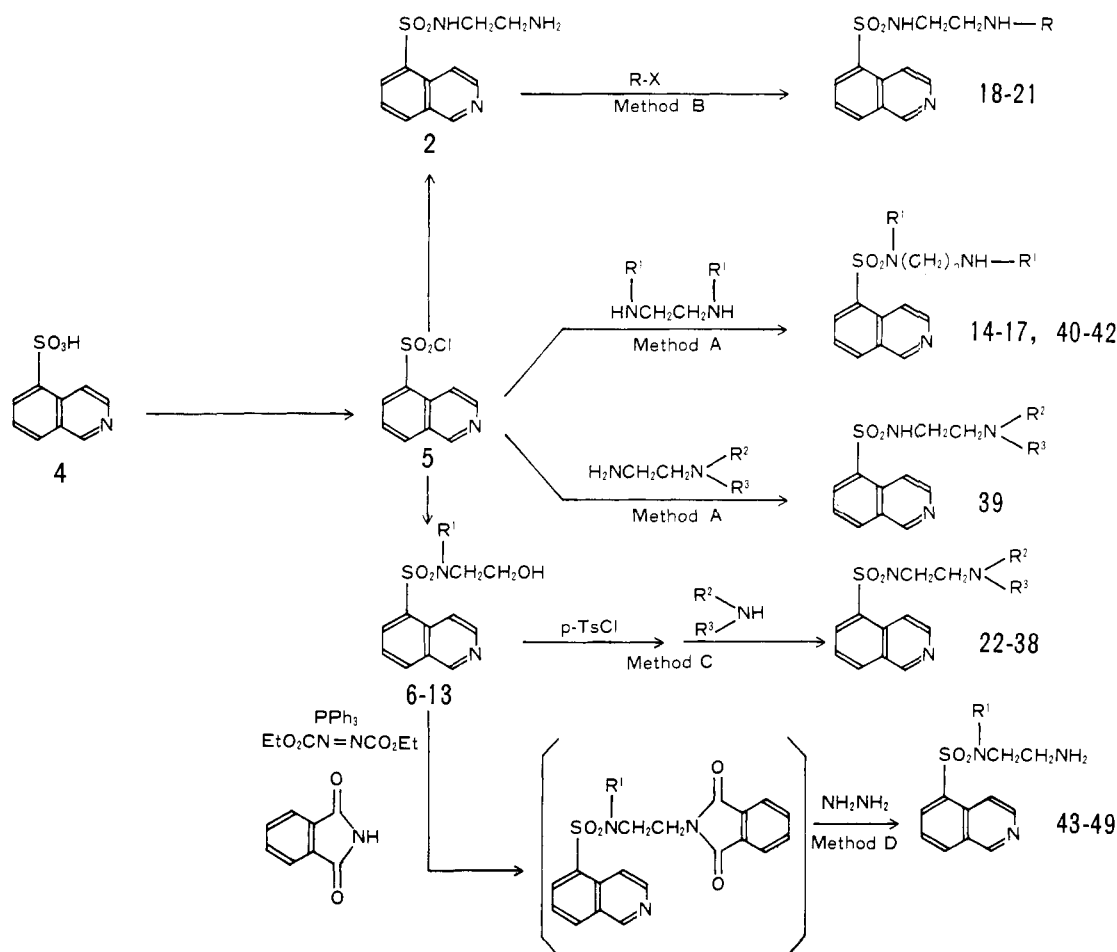
5-Isoquinolinesulfonyl Chloride Hydrochloride (5). A mixture of 5-isoquinolinesulfonic acid (100 g), SOCl₂ (750 g), and DMF (2 mL) was refluxed for 2 h, and the resulting solution was evaporated to remove the SOCl₂. The residue was suspended with CHCl₃ (300 mL), filtered, and washed with two portions of CHCl₃ (200 mL). The precipitate was collected and dried under reduced pressure to remove the solvent, yielding crude crystalline 5-isoquinolinesulfonyl chloride hydrochloride (6) (123.13 g, 91%). As this compound is not stable, it was used for the subsequent syntheses without further purification.

***N*-(2-Hydroxyethyl)-5-isoquinolinesulfonamide (7).** To an ice-cold aqueous solution (100 mL) of crude 6 (50 g, 189 mmol) was added slowly NaHCO₃ (25.89 g, 189 mmol) with stirring. The resulting solution was extracted twice with CHCl₃ (100 mL × 2). The CHCl₃ solution was dried (MgSO₄) and added dropwise to a CHCl₃ solution (100 mL) of 2-aminoethanol (34.63 g, 567 mmol) at 0 °C. The solution was stirred for 1 h at room temperature, washed with water, and evaporated off. The residue was recrystallized from ethanol to give 7 (37.2 g, 78%): mp 144–145 °C.

Method A. *N*-Ethyl-*N*-[2-(ethylamino)ethyl]-5-isoquinolinesulfonamide Hydrochloride (41). To a mixture of

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Scheme I



crude **5** (5.28 g, 20 mmol) and water (100 mL) was added slowly NaHCO_3 (1.68 g, 20 mmol) with ice-cooling and stirring. The resulting solution was extracted twice with CH_2Cl_2 (50 mL \times 2). The organic layer was dried (MgSO_4) and added dropwise to an ice-cold solution of N,N' -diethylethylenediamine (3.48 g, 30 mmol) and CH_2Cl_2 (60 mL). The solution was stirred for 1 h at room temperature, washed with water, and extracted with 6 N HCl. Neutralization of the aqueous layer with NaHCO_3 precipitated crude crystalline of **41**. Recrystallization with ethanol/water afforded **41** (2.48 g, 36%): mp 221–222 °C.

Method B. *N*-[2-[(*p*-Nitrobenzyl)amino]ethyl]-5-isoquinolinesulfonamide Dihydrochloride (**21**). A mixture of **2** (12.9 g, 45 mmol), *p*-nitrobenzyl bromide (3.24 g, 15 mmol), K_2CO_3 (9.9 g, 100 mmol), and THF (150 mL) was stirred overnight, and the solvent was removed. The residue was extracted with CH_2Cl_2 (100 mL) and washed with water. The amine was extracted from the organic layer with 2 N HCl (80 mL). The aqueous layer was condensed to 40 mL under reduced pressure to give a precipitate. This precipitate was recrystallized from water to yield **21** (4.95 g, 72%): mp 207–208 °C.

Method C. *N*-[2-(Hexylamino)ethyl]-5-isoquinolinesulfonamide Hydrochloride (**27**). A mixture of the alcohol **6** (5.05 g, 20 mmol), *p*-toluenesulfonyl chloride (4.19 g, 22 mmol), and dry pyridine (20 mL) was heated at 50 °C for 1 h. After cooling, the precipitate was filtered off, and the filtrate was evaporated off under reduced pressure. To the residue was added a THF (40 mL) solution of *n*-hexylamine (8.10 g, 80 mmol), and the mixture was heated in an autoclave at 80 °C for 6 h and evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (40 mL) and washed with water. The amine was extracted from the organic layer with 1 N HCl and extracted again with CH_2Cl_2 (20 mL \times 2) from the basic aqueous layer. The organic layer was dried (Na_2SO_4) and chromatographed on a silica gel column, eluted with CHCl_3 and 1% v/v MeOH/ CHCl_3 . The 1% v/v MeOH/ CHCl_3 fraction was evaporated under reduced pressure and treated in the same way as for method A. The

hydrochloride of **27** was obtained by recrystallization from acetone (5.06 g, 68%): mp 159–161 °C.

Method D. *N*-(2-Aminoethyl)-*N*-hexyl-5-isoquinolinesulfonamide Hydrochloride (**47**). To the mixture of **11** (3.36 g, 11 mmol), phthalimide (2.62 g, 11 mmol), and dry THF (20 mL) was added dropwise a THF solution (5 mL) of diethyl azodicarboxylate (1.915 g, 11 mmol) at room temperature. The solution was stirred overnight and evaporated under reduced pressure, and diethyl ether (30 mL) was added. The precipitate (N,N' -bis(ethoxycarbonyl)hydrazine) was filtered off and washed with a small amount of ether (20 mL \times 2). The filtrate was evaporated off and dissolved in EtOH (20 mL). To the ethanol solution was added hydrazine hydrate (1.50 g, 30 mmol), and the solution was refluxed for 2 h. After cooling, the precipitate (phthalhydrazide) was filtered off and washed with two portions of CHCl_3 (20 mL \times 2). The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column, which was eluted with CHCl_3 and 5% v/v MeOH/ CHCl_3 . The 5% v/v MeOH/ CHCl_3 fraction was evaporated and dissolved in water (5 mL) with a small amount of dilute HCl. The pH of the aqueous solution was 6.0. The resulting solution was evaporated and the residue was recrystallized from EtOH/acetone to yield **47** (1.75 g, 47.1%): mp 189–191 °C.

Biological Determination.^{8,9} **Intraarterial Injection.** Mongrel dogs unselected as to sex (15–26 kg) were anesthetized with pentobarbital sodium (35 mg/kg iv). The trachea was intubated, and ventilation rates (12–16 cycles/min) and tidal volumes (22–27 mL/kg) were adjusted so as to maintain the arterial blood pH, pCO_2 , and pO_2 within physiological limits. Catheters were placed in the right femoral artery to measure the pulsatile arterial blood flow. Heart rate was monitored with a

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cardiotachometer (Sanei, 2336A) triggered by a lead II electrocardiogram. Mean blood pressure was measured with a pressure transducer (Sanei, 45266). The body temperature was maintained at 37–38 °C with a heating pad.

When the vertebral arterial blood flow was measured, arterial blood taken from the left femoral artery was led to the right vertebral artery. An electromagnetic flow probe (Nihon Kohden, Model MFV-1200) of the extracorporeal type was inserted into this circuit.

In the case of femoral blood flow, an electromagnetic flow probe of extracorporeal type (Nihon Kohden, Model MFV-1200) was inserted into the left femoral artery.

Compounds in a volume of 10 μ L were injected with a microinjector into a rubber tube connected to the arterial cannula over a period of 5 s. Despite drug injections, neither blood pressure nor heart rate changed. At least three different amounts of each test compound were injected and the changes in blood flow were assessed. After and before the administration of three doses of each compound, 100 μ g of trapidil was administered as a relative control. At least three dose-response curves per compound were obtained. From these dose-response curves, the dose that gave the same increasing effect on the femoral arterial blood flow as 100 μ g of trapidil was calculated.

The increments in femoral and vertebral blood flow by trapidil were $165 \pm 73\%$ (SD) ($n = 30$) and $130 \pm 78\%$ (SD) ($n = 30$), respectively.

Intravenous Injection. In order to monitor the vertebral or coronary arterial blood flow, arterial blood of an anesthetized mongrel dog taken from the left femoral artery was led to the right vertebral or coronary artery. An electromagnetic flow probe was inserted into the circuit. Heart rate and mean blood pressure were monitored with a cardiotachometer and pressure transducer in a manner similar to that for intraarterial injection. Compounds in a volume of 100 μ L were injected (0.3 mg/kg). Changes in cardiovascular parameters, heart rate, mean blood pressure, and femoral or vertebral blood flow were monitored and evaluated as a percentage.

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Registry No. 2, 84468-17-7; 2-HCl, 116970-50-4; 6, 116700-33-5; 7, 116700-34-6; 8, 111541-58-3; 9, 116970-51-5; 10, 116970-52-6; 11, 111541-55-0; 12, 116970-53-7; 13, 116970-54-8; 14, 92564-42-6; 14-2HCl, 116700-35-7; 15, 84468-18-8; 15-HCl, 116970-55-9; 16, 84468-16-6; 16-HCl, 116970-56-0; 17, 84477-66-7; 17-HCl, 116970-57-1; 18, 116971-01-8; 18-2HCl, 116970-58-2; 19, 117254-10-1; 19-2HCl, 116970-59-3; 20, 116971-02-9; 20-2HCl, 116970-60-6; 21, 116971-03-0; 21-2HCl, 116970-61-7; 22, 84478-11-5; 22-HCl, 116970-62-8; 23, 116970-89-9; 23-HCl, 116970-63-9; 24, 116970-90-2; 24-HCl, 116970-64-0; 25, 116970-91-3; 25-HCl, 116970-65-1; 26, 116970-92-4; 26-HCl, 116970-66-2; 27, 116970-93-5; 27-HCl, 116970-67-3; 28, 116970-94-6; 28-2HCl, 116970-68-4; 29, 116970-95-7; 29-2HCl, 116970-69-5; 30, 116970-96-8; 30-HCl, 116970-70-8; 31, 116970-97-9; 31-2HCl, 116970-71-9; 32, 116970-98-0; 32-2HCl, 116970-72-0; 33, 116970-99-1; 33-2HCl, 116970-73-1; 34, 116971-00-7; 34-2HCl, 116970-74-2; 35, 116971-04-1; 35-2HCl, 116970-75-3; 36, 116971-05-2; 36-HCl, 116970-76-4; 37, 116971-06-3; 37-HCl, 116970-77-5; 38, 116971-07-4; 38-HCl, 116970-78-6; 39, 116971-08-5; 39-HCl, 116970-79-7; 40, 111541-20-9; 40-HCl, 116970-80-0; 41, 111541-21-0; 41-HCl, 116970-81-1; 42, 111541-25-4; 42-HCl, 116970-82-2; 43, 111540-96-6; 43-HCl, 116970-83-3; 44, 116971-09-6; 44-HCl, 116970-84-4; 45, 111540-97-7; 45-HCl, 116970-85-5; 46, 111540-98-8; 46-HCl, 116970-86-6; 47, 111540-99-9; 47-HCl, 111541-46-9; 48, 111541-00-5; 48-HCl, 116970-87-7; 49, 111541-01-6; 49-HCl, 116970-88-8; $\text{NH}_2(\text{CH}_2)_2\text{OH}$, 141-43-5; $\text{CH}_3\text{NH}(\text{CH}_2)_2\text{OH}$, 109-83-1; $\text{CH}_3\text{CH}_2\text{NH}(\text{CH}_2)_2\text{OH}$, 110-73-6; $(\text{CH}_3)_2\text{CHNH}(\text{CH}_2)_2\text{OH}$, 109-56-8; $\text{CH}_3(\text{CH}_2)_3\text{NH}(\text{CH}_2)_2\text{OH}$, 111-75-1; $\text{CH}_3(\text{CH}_2)_5\text{NH}(\text{CH}_2)_2\text{OH}$, 54596-69-9; $\text{CH}_3(\text{CH}_2)_7\text{NH}(\text{CH}_2)_2\text{OH}$, 32582-63-1; $\text{C}_6\text{H}_5\text{CH}_2\text{NH}(\text{CH}_2)_2\text{OH}$, 104-63-2; $\text{CH}_3\text{CH}_2\text{NH}(\text{CH}_2)_2\text{NHC}_6\text{H}_5$, 111-74-0; $\text{NH}_2(\text{CH}_2)_3\text{NH}_2$, 109-76-2; $\text{NH}_2(\text{CH}_2)_4\text{NH}_2$, 110-60-1; $\text{NH}_2(\text{CH}_2)_6\text{NH}_2$, 124-09-4; $\text{NH}_2(\text{CH}_2)_2\text{NHCH}_3$, 108-00-9; $\text{CH}_3\text{NH}(\text{CH}_2)_2\text{NHCH}_3$, 110-70-3; $\text{C}_6\text{H}_5\text{CH}_2\text{NH}(\text{CH}_2)_2\text{NHCH}_2\text{C}_6\text{H}_5$, 140-28-3; *o*- $\text{ClC}_6\text{H}_4\text{CH}_2\text{Cl}$, 611-19-8; *m*- $\text{ClC}_6\text{H}_4\text{CH}_2\text{Cl}$, 620-20-2; *p*- $\text{ClC}_6\text{H}_4\text{CH}_2\text{Cl}$, 622-95-7; $\text{CH}_3(\text{CH}_2)_6\text{NH}_2$, 111-26-2; $\text{CH}_3(\text{CH}_2)_4\text{NH}_2$, 110-58-7; $\text{CH}_3(\text{CH}_2)_7\text{NH}_2$, 111-86-4; $\text{CH}_3(\text{CH}_2)_9\text{NH}_2$, 2016-57-1; *c*- $\text{C}_6\text{H}_{11}\text{NH}_2$, 108-91-8; $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$, 100-46-9; *p*- $\text{CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{NH}_2$, 2393-23-9; 3,4- $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\text{CH}_2\text{NH}_2$, 5763-61-1; $\text{C}_6\text{H}_5(\text{CH}_2)_2\text{NH}_2$, 64-04-0; *c*- $\text{C}_6\text{H}_{11}\text{NHCH}_3$, 100-60-7; $\text{CH}_3(\text{CH}_2)_5\text{NH}(\text{CH}_2)_2\text{CH}_3$, 20193-73-1; $[\text{CH}_3(\text{CH}_2)_5]_3\text{N}$, 143-16-8; *p*- $\text{NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{Br}$, 100-11-8; isoquinolinesulfonic acid, 27655-40-9; 5-isoquinolinesulfonyl chloride hydrochloride, 105627-79-0.

Structure-Activity Relationships in Prazosin-Related Compounds. Effect of Replacing a Piperazine Ring with an Alkanediamine Moiety on α_1 -Adrenoreceptor Blocking Activity

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Several prazosin-related compounds were synthesized in which the piperazine ring of prazosin (1) was replaced by an alkanediamine chain and were evaluated for their blocking activity on α_1 - and α_2 -adrenoreceptors in isolated rat vas deferens. All the compounds investigated proved highly selective toward the α_1 -adrenoreceptor owing to a very low affinity for α_2 -adrenoreceptors. Furthermore, compounds 2, 9, and 13 were also investigated in vivo to determine their hypotensive effect on anesthetized rats, which were compared with that of prazosin (1). It was confirmed that the piperazine moiety of 1 is not essential for potency. However, optimum activity depends on two parameters: carbon-chain length of the alkanediamine moiety and N-methylation of both the amide and the 2-amino functions. In the desmethyl series, optimum activity was associated with the lower homologues (2–4) bearing a chain of two to four methylenes whereas in the *N,N'*-dimethyl series peak potency was observed with a six-carbon chain as in 13. Compound 13 proved the most active of the series and was more potent than prazosin (1) in both in vivo and in vitro assays. It is hypothesized that the α_1 -adrenoreceptor incorporates a lipophilic area that is located between the binding sites for the quinazoline and the furoyl moieties and is able to accommodate a polymethylene chain.

Prazosin (1) is a potent and highly selective α_1 -adrenoreceptor antagonist.¹ At clinically relevant concentrations, it acts as a peripheral vasodilator by competitively anta-

gonizing the vascular postsynaptic α_1 -adrenoreceptor and is used to treat patients with hypertension and congestive

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