injection of 5 mg/kg of morphine hydrochloride, that was effective (14–15 s) in prolonging the response time to thermal stimulus in 95% of animals. Each compound was administered subcutaneously just before morphine injection. Five mice were used for each dose.

Analgesic and narcotic antagonist ED_{50} values and 95% confidence limits were calculated according to the method of Litchfield and Wilcoxon.[17]

Physical-Dependence Assay. Male mice (19–23 g) of ddN strain received seven subcutaneous administrations of each compound in increasing doses of 8, 16, 25, 50, 100, 100, and 100 mg/kg for 2 days; five doses were given on the first day at 0900, 1000, 1100, 1300, 1500 h, and two were given on the second day at 0900 and 1100 h. Two hours after the last dose, the animals received a single intraperitoneal injection of 50 mg/kg nalorphine hydrochloride, and jumping behavior and other withdrawal signs were observed for 30 min in a separate cylinder (40 cm high and 15 cm in diameter).[18] Ten to 30 mice were used for each dose.

Acknowledgment. We are grateful to Dr. M. Shimizu for valuable discussions and encouragement throughout this work. Thanks are also due to Dr. Y. Nagai and N. Shimokawa for valuable discussions and members of the pharmacological section for pharmacological work and members of the analytical section of these laboratories for elemental analyses and spectral measurements.

Registry No. (–)-1, 57377-70-5; (+)-**2a**, 61310-95-0; (+)-**2a**·2(+)-NTA, 61331-59-7; (–)-**2a**·2HCl, 61310-94-9; (–)-**2a**·2(–)-NTA, 109364-66-1; (±)-**3**·2HCl, 109364-55-8; (+)-**3**·2HCl, 109364-56-9; (–)-**3**·HCl, 109364-57-0; (±)-**4**·2HCl, 109364-58-1; (–)-**4**·2HCl, 109430-82-2; (±)-**5**·2HCl, 61311-32-8; (–)-**5**·2HCl, 109430-83-3; (±)-**6**·2HCl, 109364-59-2; (±)-**7**·2HCl, 109364-60-5; (–)-**7**·2HBr, 109430-84-4; (±)-8·2HBr, 109364-61-6; (±)-**9**·2HBr, 109364-62-7; (–)-**9**·2HCl, 109430-85-5; (±)-**10**·2HCl, 61311-21-5; (+)-**10**·2HCl, 61341-38-6; (–)-**10**·2HCl, 109364-63-8; (±)-11·2HCl, 61311-26-0; (±)-**12**·2HCl, 61311-29-3; (±)-**12**·2HBr, 61311-25-9; (±)-14·HCl, 109364-64-9; (±)-**15**·2HCl, 67279-40-7; (–)-**15**·2HCl, 109430-86-6; (±)-**16**·2HCl, 67279-41-8; (+)-**16**·2HCl, 109364-65-0; (–)-**16**·2HCl, 67279-43-0; (±)-**17**·2HCl, 61311-40-8; (–)-**17**·2HCl, 61311-31-7; (±)-**18**, 83374-58-7; (±)-**18**·2HCl, 61311-22-6; (+)-**18**·2HCl, 61311-23-7; (+)-18·2(+)-NTA, 61311-54-4; (–)-18·2HCl, 61311-01-1; (–)-18·2(–)-NTA, 61311-52-2; (±)-**19**·2HCl, 109364-49-0; (+)-**19**·2HCl, 109364-50-3; (–)-**19**, 83434-62-2; (–)-**19**·2HCl, 109364-51-4; (±)-**20**·2HCl, 61311-63-5; (–)-**20**·2HCl, 109430-79-7; (±)-**21**·2HCl, 109364-52-5; (±)-**22**·2HCl, 61311-75-9; (–)-**22**·2HCl, 109430-80-0; (–)-**23**·2HCl, 109390-25-2; (–)-**24**, 109364-53-6; (–)-**24**·$^5/_2$maleate, 109364-54-7; (–)-**24**·3HCl, 109364-68-3; (–)-**25**·2(–)-NTA, 61311-50-0; (–)-**25**·2HCl, 61311-00-0; (+)-**26b**, 61311-58-8; (–)-**26b**, 65017-62-1; (±)-**26c**, 65017-65-4; (+)-**26c**, 109430-87-7; (+)-**26c**·HCl, 109525-57-7; (+)-**26c**·$^1/_2$(+)-DBT, 109525-58-8; (–)-**26c**, 65017-66-5; (–)-**26c**·HCl, 109525-59-9; (–)-**26c**·$^1/_2$(+)-DBT, 109525-60-2; (±)-**26d**, 109364-67-2; (±)-**26d**·HCl, 109364-48-9; (–)-**26d**, 109430-88-8; (–)-**26d**·$^1/_2$(–)-DBT, 109525-61-3; (±)-**27a**·HCl, 61311-70-4; (±)-**28**, 61311-66-8; (–)-**28**, 109430-81-1; (±)-**31**, 61311-35-1; 2-$MeOC_6H_4NH_2$, 90-04-0; $BrCH_2CH{=}CH_2$, 106-95-6; $Me_2C{=}CHCOCl$, 3350-78-5; c-$C_6H_{11}N((CH_2)_2Cl)_2$·HCl, 879-61-8.

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(18) (a) Saelens, J. K.; Granato, F. R.; Sawyer, W. K. *Arch. Int. Pharmacodyn. Ther.* **1971**, *190*, 213. (b) Nakamura, H.; Yokoyama, Y.; Shimizu, M. *Arch. Int. Pharmacodyn. Ther.* **1983**, *263*, 164.

Studies on Histamine H_2 Receptor Antagonists. 2. Synthesis and Pharmacological Activities of *N*-Sulfamoyl and *N*-Sulfonyl Amidine Derivatives

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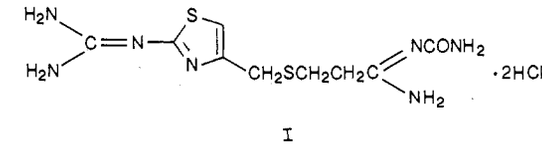
A series of *N*-sulfamoyl and *N*-sulfonyl amidines have been prepared and tested in vitro for H_2 antihistamine activity on guinea pig atrium. In addition, several selected compounds were assessed as inhibitors of gastric acid secretion induced by histamine in anesthetized dogs. Structure–activity relationship studies showed that those compounds containing 2-[(diaminomethylene)amino]thiazole exhibited potent H_2-receptor antagonist activity. Introduction of alkyl or aralkyl groups to the terminal nitrogen of the sulfamoyl moiety reduced biological activities. Sulfamoyl amidines were more potent in both tests than sulfonyl amidines. Of these compounds, 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-N^2-sulfamoylpropionamidine (**2e**, famotidine) showed extremely high potency in both assays and was selected for clinical trials as an antiulcer agent. Acid-catalyzed hydrolysis of famotidine gave the sulfamoyl amide **6** at room temperature and the carboxylic acid **7** at elevated temperatures. ^{15}N NMR spectrum showed that famotidine in solution existed in only one of several possible tautomers derived from the amidine and the guanidine moieties. Nitrosation of famotidine was performed under mild condition and proved to occur on the 5-position of the thiazole ring.

In the preceding paper[1] we described the synthesis and histamine H_2 receptor antagonist activities of *N*-cyano and *N*-carbamoyl amidine derivatives related to cimetidine, ranitidine, and tiotidine. Structure–activity correlations of the amidine derivatives were different from those of the guanidine derivatives in two important respects, viz. The cyano amidines were less active than the corresponding carbamoyl amidines and introduction of a methyl group to the nitrogen at the terminal amidine moiety reduced the activity, the converse of the case for the guanidine series.[2,3] The most active compound of those derivatives, 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-N^2-carbamoylpropionamidine dihydrochloride (I), when tested in vitro, is 30 times more active than cimetidine. This encouraging result prompted us to prepare



I

compounds structurally related to the carbamoyl amidine to investigate the effect of structural modification on histamine H_2 receptor antagonist activity. It was of in-

(1) Yanagisawa, I.; Hirata, Y.; Ishii, Y. *J. Med. Chem.* **1984**, *27*, 849–857.

(2) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. D.; White, G. R. *J. Med. Chem.* **1977**, *20*, 901–906.

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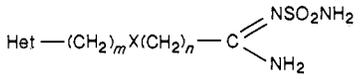
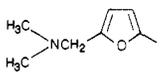
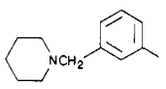
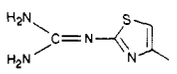
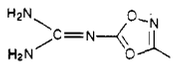
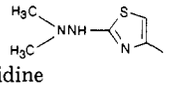
Table I. Structures and H_2-Receptor Antagonist Activities of *N*-Sulfamoyl Amidines



compd	Het	*m*	X	*n*	yield, %	mp, °C	recrystn solvent	formula	H_2-receptor antagonist act. in guinea pig right atrium: ED_{50},[a] M	inhibn of acid output in anesthetized dogs: ED_{50},[b] mg/kg iv
2a		1	S	2	52.2	101–102	EtOH–EtOAc	$C_9H_{14}N_4O_2S_2$	$>10^{-4}$ [e]	
2b		1	S	2	20.4	129–130	EtOH	$C_8H_{15}N_5O_2S_2$	$>10^{-4}$ [e]	
2c		1	S	2	51			$C_{11}H_{20}N_4O_3S_2$ [c]	$(1.7 \pm 0.1) \times 10^{-5}$	
2d		0	0	3	41.2	184–187	MeOH	$C_{16}H_{26}N_4O_3S \cdot 2HCl$	$(1.4 \pm 0.2) \times 10^{-6}$	
2e		1	S	2	54.7	163–164	DMF–H_2O	$C_8H_{15}N_7O_2S_3$	$(2.7 \pm 0.3) \times 10^{-7}$	0.0087 ± 0.0005
2f		1	S	2	47	166–169	EtOH	$C_7H_{14}N_8O_3S_2$	$>10^{-4}$ [e]	
2g		1	S	2	29.5	153–154	acetone	$C_9H_{18}N_6O_2S_3 \cdot C_4H_4O_4$ [d]	$>10^{-4}$ [e]	
cimetidine									$(2.7 \pm 0.3) \times 10^{-6}$	0.33 ± 0.42

[a] Doses representing 50% inhibition (ED_{50}, means ± SE) of chronotropic response to histamine (5×10^{-6} M) were determined from dose–response curves. [b] ED_{50} values for reduction in acid response to histamine [160 μg/(kg h)] were calculated from dose–response curves in anesthetized dogs with an acute gastric fistula. [c] Viscous oil. ^1H NMR (DMSO-d_6) 2.14 (s, 6 H), 2.3–2.8 (m, 4 H), 3.37 (s, 2 H), 3.78 (s, 2 H), 6.20 (m, 2 H); mass spectrum (FD method), *m/z* 321 ($M^+ + 1$). [d] Maleate salt. [e] 50% inhibition of the response to histamine was not observed at 10^{-4} M of test compound.

terest to explore the *N*-sulfamoyl and *N*-sulfonyl amidines as bioisosteres of the carbamoyl amidine.

In this paper we report the synthesis and the results of a preliminary evaluation of *N*-sulfamoyl and *N*-sulfonyl amidine derivatives and discuss the structure–activity correlations among these compounds. In addition, the chemical and physicochemical properties of the most active compound (**2e**, famotidine) of these series are also described.

Chemistry

The synthesis of all compounds evaluated in this study is shown in Scheme I. Imidates **1** were prepared from nitriles according to procedures described in the preceding paper of this series.[1] Imidates were allowed to react with sulfamides, sulfonamides, or sulfonyl hydrazides to afford sulfamoyl amidines **2**, sulfonyl amidines **3**, or sulfonyl amidrazones **4**, respectively. In the case of sulfamide ($R_2 = R_3 = H$), dimer **5** was obtained as a byproduct (see the Experimental Section).

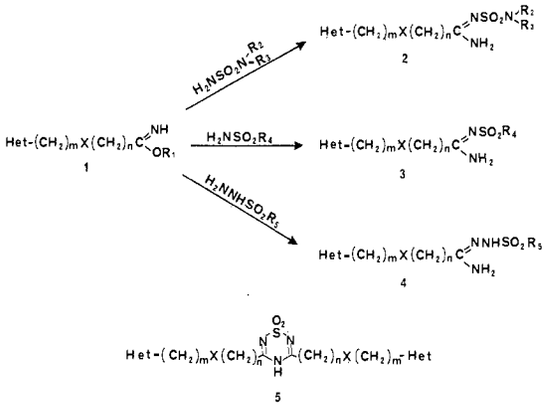
Results and Discussion

The *N*-sulfamoyl and *N*-sulfonyl amidine derivatives were evaluated as antagonists of the positive chronotropic action of histamine (5×10^{-6} M) in the isolated guinea pig right atrium. Additionally several selected compounds were assessed as inhibitors of gastric acid secretion in the anesthetized dogs under histamine stimulation (160 μg/kg h) as previously described.[1]

The compounds presented in this work have been divided into three tables in order to facilitate discussions on the structure–activity relationships. Table I lists the sulfamoyl amidines that contain various aromatic nuclei. It is interesting to note that cimetidine analogue **2b** was found to be inactive up to 10^{-4} M, whereas the *N*-carbamoyl amidine compound that contains the same imidazole ring produced nearly the same potency as cimetidine.[1] This result clearly indicates that in the imidazole series a sulfamoyl group does not function as a bioisostere of the carbamoyl group. This may be attributed to the electronic effects of these substituents. σ constants of SO_2NH_2 ($\sigma_m = 0.46$, $\sigma_p = 0.57$) is close to that of CN ($\sigma_m = 0.56$, $\sigma_p = 0.66$) rather than that of $CONH_2$ ($\sigma_m = 0.28$, $\sigma_p = 0.36$)[4] and the cyano amidine analogue of cimetidine has been shown previously to be inactive.[1]

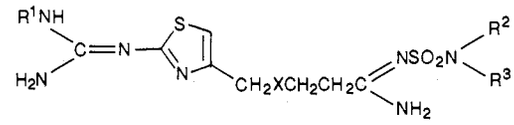
Pyridine **2a**, [(diaminomethylene)amino]oxadiazole **2f**, and hydrazinothiazole **2g** were also virtually devoid of activity in vitro. Although the furan **2c**, which is a ranitidine analogue, and the benzene compound **2d** showed only weak activity, 2-[(diaminomethylene)amino]thiazole compound **2e**, viz. tiotidine analogue, proved to have ex-

Scheme I



(4) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207–1216.

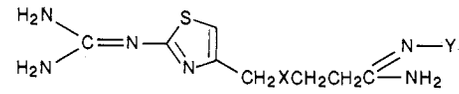
Table II. Structures and H_2-Receptor Antagonist Activities of *N*-Sulfamoyl Amidine Derivatives



compd	X	R^1	R^2	R^3	yield, %	mp, °C	recrystn solvent	formula	H_2-receptor antagonist act. in guinea pig right atrium: ED_{50},[a] M	inhibn of acid output in anesthetized dogs: ED_{50},[b] mg/kg iv
2h	CH_2	H	H	H	43	156–157	H_2O	$C_9H_{17}N_7O_2S_2$	$(2.3 \pm 0.2) \times 10^{-7}$	0.0089 ± 0.0005
2i	SO	H	H	H	68	176–177	DMF–acetone	$C_8H_{15}N_7O_3S_3 \cdot C_4H_4O_4$[c]	$(7.3 \pm 1.6) \times 10^{-5}$	
2j	S	CH_3	H	H	59	163–164	MeOH	$C_9H_{17}N_7O_2S_3$	$(4.8 \pm 0.8) \times 10^{-7}$	0.0518 ± 0.0060
2k	S	H	CH_3	H	63	181–184	acetone	$C_9H_{17}N_7O_2S_3 \cdot C_4H_4O_4$[c]	$(8.6 \pm 3.2) \times 10^{-7}$	0.0366 ± 0.0061
2l	S	H	CH_3	CH_3	68	183–186	acetone	$C_{10}H_{19}N_7O_2S_3 \cdot C_4H_4O_4$[c]	$(1.4 \pm 0.3) \times 10^{-6}$	0.2770 ± 0.0391
2m	CH_2	H	*n*-C_3H_7	H	58	173–175	EtOH	$C_{12}H_{23}N_7O_2S_2$	$(5.6 \pm 1.3) \times 10^{-7}$	0.0266 ± 0.0008
2n	CH_2	H	c-C_6H_{11}	H	54	130–131	EtOH	$C_{15}H_{27}N_7O_2S_2 \cdot C_4H_4O_4$[c]	$(1.3 \pm 0.2) \times 10^{-6}$	
2o	S	H	$C_6H_5CH_2$	H	60	160–162	acetone	$C_{15}H_{21}N_7O_2S_3 \cdot C_4H_4O_4$[c]	$(1.1 \pm 0.2) \times 10^{-6}$	0.0396 ± 0.0061

[a] Same as for Table I. [b] Same as for Table I. [c] Maleate salt.

Table III. Structures and H_2-Receptor Antagonist Activities of *N*-Sulfonyl Amidine Derivatives



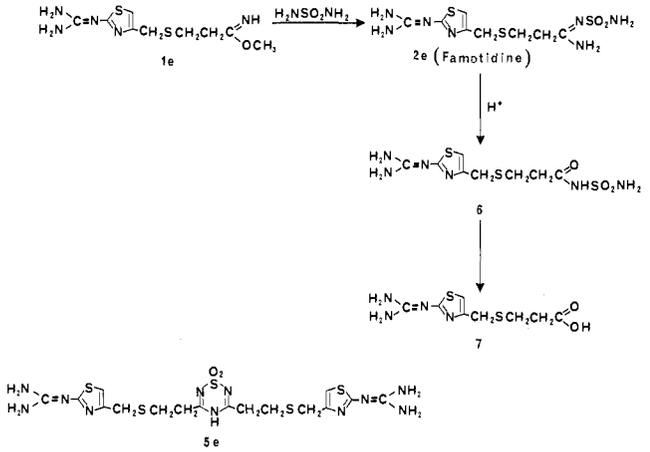
compd	X	Y	yield, %	mp, °C	recrystn solvent	formula	H_2-receptor antagonist act. in guinea pig right atrium: ED_{50},[a] M	inhibn of acid output in anesthetized dogs: ED_{50},[b] mg/kg iv
3a	S	SO_2CH_3	56.9	117–118	EtOH	$C_9H_{16}N_6O_2S_3$[d]	$(5.1 \pm 0.9) \times 10^{-7}$	0.0191 ± 0.0024
3b	S	$SO_2C_6H_5$	53.5	152–153	EtOH	$C_{14}H_{18}N_6O_2S_3$	$(7.0 \pm 1.9) \times 10^{-7}$	0.0568 ± 0.0024
3c	S	$SO_2C_6H_4$-4-NH_2	80	198–200	acetone	$C_{14}H_{19}N_7O_2S_3 \cdot C_4H_4O_4$[c]	$(4.5 \pm 0.3) \times 10^{-7}$	0.0300 ± 0.0025
3d	CH_2	$SO_2CH_2CH_3$	43	115–116	MeOH	$C_{11}H_{20}N_6O_2S_2$	$(6.0 \pm 1.1) \times 10^{-7}$	0.0244 ± 0.0015
3e	CH_2	$SO_2C_6H_5$	52	162–164	MeOH	$C_{15}H_{20}N_6O_2S_2 \cdot C_4H_4O_4$[c]	$(5.8 \pm 0.3) \times 10^{-7}$	0.0194 ± 0.0011
3f	CH_2	$SO_2C_6H_4$-4-NH_2	40	143–146	MeOH–Et_2O	$C_{15}H_{21}N_7O_2S_2 \cdot C_4H_4O_4$[c]	$(3.5 \pm 2.5) \times 10^{-7}$	0.0101 ± 0.0006
4a	S	$NHSO_2C_6H_5$	40	159.5–161	EtOH	$C_{14}H_{19}N_7O_2S_3$	$(8.3 \pm 0.6) \times 10^{-6}$	
4b	CH_2	$NHSO_2C_6H_5$	52	206–207	MeOH	$C_{15}H_{21}N_7O_2S_2$	$(2.3 \pm 0.7) \times 10^{-5}$	

[a] Same as for Table I. [b] Same as for Table I. [c] Maleate salt. N: calcd, 19.17; found, 18.67. [d] N: calcd, 24.98; found, 24.43.

tremely high potency in both assays. Therefore, we prepared a further number of structurally related analogues of **2e** in an attempt to search for more effective ones. Those compounds are shown in Table II. Replacement of sulfur by a methylene group resulted in compound **2h**, which retained essentially the same potency as compound **2e** in both assays. Sulfoxide compound **2i** showed markedly reduced potency. Incorporation of a methyl group at the guanidine nitrogen to give **2j** led to a decrease in potency, especially in vivo. The effects of substituents on the nitrogen of the sulfamoyl function were also surveyed. The monomethyl-substituted compound **2k** was approximately one-third as active in vitro as the parent **2e**. N,N-Disubstituted compound **21** was significantly less active than the monosubstituted compound **2k** in both assays. Introduction of bulkier and more lipophilic substituents, e.g., *n*-propyl **2m**, cyclohexyl **2n**, and benzyl **2o**, also resulted in a decreased potency. Thus, **2e** was 4–5 times more potent in vivo than monosubstituted compounds **2k**, **2m**, and **2o**. These findings indicate that a free sulfamoyl NH_2 is the most desirable for affinity to the H_2 receptor. Table III shows the sulfonyl amidine derivatives that contain the 2-[(diaminomethylene)amino]thiazole ring. Methylsulfonyl amidine **3a**, benzenesulfonyl amidine **3b**, and *p*-aminobenzenesulfonyl amidine **3c** showed relatively high potency. Alkylsulfonyl amidines were virtually equipotent with arylsulfonyl amidines in both tests, suggesting that these compounds have similar affinities for the H_2 receptor. Analogues in which sulfur replaced the methylene group, **3d–f**, were also found to have nearly the same potency as the parent in both assays. However, none of these compounds listed in Table III exceeded sulfamoyl amidine compound **2e** in biological activity. Amidrazone derivatives, **4a** and **4b**, showed only weak potency. In summary, our studies show that the sulfamoyl amidine group behaves as a bioisostere of the carbamoyl amidine group present in compound I in the [(diaminomethylene)amino]thiazole series. On the other hand, in the imidazole series the former does not function as a bioisostere of the latter. Sulfamoyl amidines were more potent than sulfonyl amidines and sulfonyl amidrazones. The presence of alkyl or aralkyl groups on the nitrogen of sulfamoyl group reduced biological activities. On the basis of the screening data described above and additional pharmacological, toxicological, and physicochemical studies,[5] **2e**, namely, famotidine,[6] was selected for evaluation

(5) The carbamoyl amidine analogue I (or **16d** in ref 1) was slightly more potent in vitro and in vivo than the sulfamoyl amidine analogue **2e**. However, I unfortunately has liabilities as a potential therapeutic agent, including labile nature and somewhat high acute toxicity.

Scheme II



in humans as an antiulcer agent.

Famotidine differs from previously described H_2 antagonists in possessing a sulfamoyl amidine function. Further pharmacological studies with famotidine suggest its potential utility in the treatment of gastrointestinal disorders. On the guinea pig isolated atrium, famotidine antagonized the positive chronotropic action of histamine (Table I) and was also an antagonist of H_2 receptors in the isolated rat uterus with a ED_{50} of $(1.7 \pm 0.4) \times 10^{-7}$ M, which corresponded to 54 times the potency of cimetidine with a ED_{50} of $(9.3 \pm 1.8) \times 10^{-6}$ M. On gastric mucosal histamine-sensitive adenylate cyclase from guinea pig, famotidine inhibited competitively the stimulation by histamine.[7] Gastric antisecretory activity of famotidine was determined in the anesthetized dog (Table I), the Heidenhain pouch dog[8,9] and the pylorus-ligated rat.[10] Famotidine was 42 times more potent iv and 39 times more potent po than cimetidine in the histamine-stimulated Heidenhain pouch dog.[8] Since the ratio of ED_{50} (po) to ED_{50} (iv) was 2.9,[8] famotidine proved to be a well-adsorbed drug. When administered intraduodenally to the pylorus-ligated rat, famotidine was found to be 50 times more potent in inhibiting the acid output than cimetidine.[10] Thus famotidine is a potent histamine H_2 receptor antagonist and a powerful inhibitor of gastric acid secretion.

Extensive clinical studies have been conducted with famotidine and its therapeutic efficacy has been demonstrated in the treatment of peptic ulcers and related conditions.[11-14]

Chemistry of Famotidine

As shown in Scheme II, famotidine is synthesized from the reaction between methyl 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionimidate (**1e**) and sulfamide. A small amount of dimer **5e** is also obtained as a byproduct.[15] Compound **5e** is an H_2 receptor antagonist with an ED_{50} of $(1.7 \pm 1.1) \times 10^{-6}$ M. Famotidine is relatively susceptible to acid-catalyzed hydrolysis. It is hydrolyzed in the presence of excess hydrochloric acid to afford sulfamoyl amide **6** and furthermore converted at elevated temperatures to carboxylic acid **7**. Compound **6** and **7** have only weak antagonist potency and neither of these acid decomposition products is found to a significant extent in the metabolites of famotidine, although it is possible that famotidine could be hydrolyzed in vivo when administered orally. Famotidine is excreted largely in unchanged form, together with a small amount of the sulfoxide **2i**.[16,17]

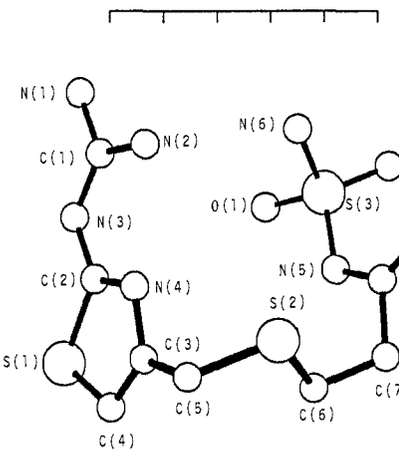


Figure 1. The X-ray-determined crystal structure of famotidine.

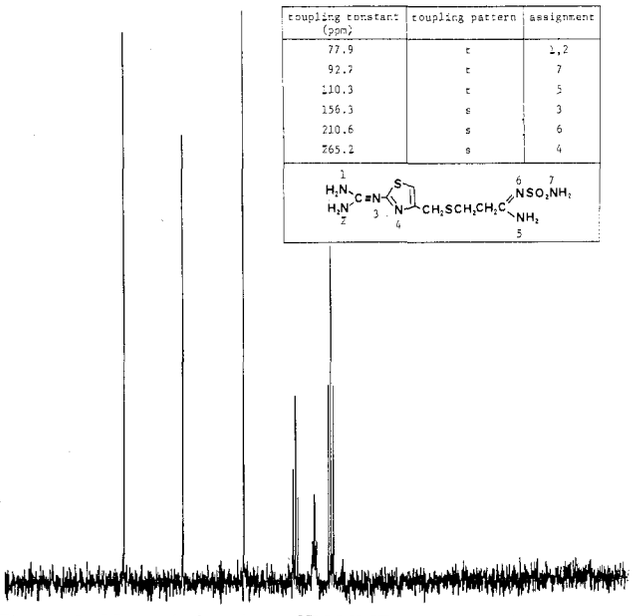


Figure 2. Natural-abundance ^{15}N NMR spectrum of famotidine in DMSO-d_6 with no proton decoupling.

As shown in Figure 1, single-crystal X-ray determination of famotidine showed it to be in a strongly folded conformation with intramolecular hydrogen bonding between guanidino nitrogen N(2) and sulfamoyl nitrogen N(6) and between guanidino nitrogen N(2) and thiazole nitrogen N(4).[18] It is of interest that this folded conformation is

(6) The WHO recommended international nonproprietary name for **2e** is famotidine.
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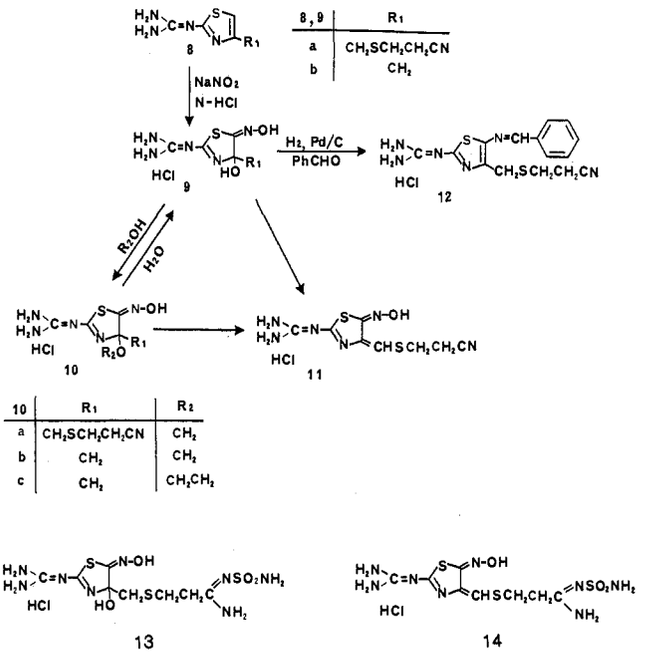
common among other H_2 receptor antagonists, cimetidine[19] and ranitidine,[20] although this geometry may not represent an actual conformation bound at the H_2 receptor.[21]

The ^{15}N NMR spectrum of famotidine in DMSO-d_6 at 400 MHz showed three triplet signals (77.9 MHz, 2N; 92.7 MHz, 1 N; 110.3 MHz, 1 N) and three singlet signals (156.3 MHz, 1 N; 210.6 MHz, 1 N; 265.2 MHz, 1 N) as shown in Figure 2.[22] In comparison with the studies on sulfaguanidine by Sullivan et al.,[23] the first triplet signal was assigned to two nitrogens of the guanidino group. The next triplet signal was assigned to the amidine nitrogen and the third triplet signal to the sulfamoyl nitrogen. This result clearly indicates that famotidine in solution exists in only one tautomer as illustrated in Figure 2, although there are several possible tautomers derived from the guanidine and amidine moieties of famotidine. It coincides with the recent publication on the tautomeric preference in the heterocyclic guanidines as histamine H_2 receptor antagonists,[24] in which the dominant arylimino tautomer is considered as a candidate for interaction at the H_2 receptor.

Nitrosamines have recently received much attention as possible products of in vivo nitrosation of several H_2 antagonists since the discovery of their carcinogenic and mutagenic properties. It was reported that cimetidine[25-28] and ranitidine[29,30] were treated with sodium nitrite in the presence of hydrochloric acid to yield isolatable nitroso compounds. Nitrosocimetidine proved to be mutagenic.[31] Therefore we also attempted to investigate the nitrosation reaction of famotidine and study the biological activities of its nitroso derivative. Under the nitrosation conditions recommended by WHO,[32] namely, physiological conditions, famotidine decomposed and gave no isolatable products and the reaction mixture was not mutagenic.[33] However,

Scheme III



under mild conditions using 1–2 equiv of sodium nitrite at a reaction temperature range of 0–5 °C, famotidine proved to yield two nitrosated products observable by HPLC analysis. HPLC analysis of the reaction mixture indicated that one peak at first appeared and this peak gradually decreased and another peak appeared (see the Experimental Section). In order to elucidate this reaction, we attempted to consider the nitrosation reaction of compound 8 as a model compound, which lacked the sulfamoyl amidine moiety of famotidine. Compounds **8a** and **8b** were treated with 2 equiv of sodium nitrite in 1 N HCl to afford 2-[(diaminomethylene)amino]-4-hydroxy-5-(hydroxyimino)thiazoline derivatives, **9a** and **9b**, as crystalline products, in which nitrosation occurred at the 5-position of the thiazole ring.[34] This structure was confirmed through the hydrogenation of **9a** followed by treatment with benzaldehyde to afford the Shiff base **12**. When dissolved in methanol or ethanol, nitroso compound **9** converted rapidly to product **10**, in which water was eliminated and methanol or ethanol was added. Compound **9a** or **10a** was dissolved in dipolar aprotic solvents, such as DMSO and DMF, to give the exo methine product **11** through the elimination of water or alcohol. The nitrosation reaction of compound 8 is summarized in Scheme III. All products were isolated as crystalline materials. The nitroso compounds were dissolved in more bulkier alcohols, such as 2-propanol, to afford 4-alkoxy derivatives, but this product was only detected by HPLC analysis and could not be isolated in pure form.

In the case of famotidine, the nitrosation reaction occurred on the thiazole ring and initially produced 4-hydroxythiazoline derivative **13**, which was found to convert gradually to the exo methine compound **14** in the reaction mixture. However, the *C*-nitroso famotidine **13** and **14** could not be crystallized and were obtained as a crude mixture by lyophilization. We investigated famotidine, the mixture of nitroso famotidine **13** and **14**, and nitroso famotidine **14** (purity: 72% by HPLC) for mutagenecity. Neither famotidine nor its nitroso compounds possessed significant mutagenic activity in microorganisms

(18) Furuya, T., Yamanouchi Pharmaceutical Co., Ltd., unpublished results. Crystals grown in DMF–H_2O are monoclinic with cell dimensions a = 17.057 (3) Å, b = 5.335 (1) Å, c = 17.776 (3) Å, β = 116.6 (2)°, and space group $P2_1/n$. The final R was 0.040 for $F_o > 3(F_o)$.
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commonly used in the Ames test.[33]

Experimental Section

Chemistry. All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The structure of all compounds were confirmed by their IR, NMR, and mass spectra. The IR spectra were measured on a Hitachi 215 spectrophotometer. The ^1H NMR spectra were measured on a JEOL MH 100 instrument with Me_4Si as an internal standard, and natural-abundance ^{15}N NMR spectrum of famotidine without proton decoupling was recorded in DMSO-d_6 solution in a 15-mm sample tube on a JEOL FX 400 NMR system with nitromethane (380.23 ppm) as an external standard. The operating conditions employed a pulse width of 32 μs (45° flip angle) and a pulse dalay of 6–10 s. The mass spectra were taken on a Hitachi RMU-6Mg double-focusing mass spectrometer and a JEOL JMS-DX 300 (HF) mass spectrometer. Microanalyses for the elements indicated are within 0.4% of theoretical values, unless stated otherwise. Melting points and recrystallization solvents of final products are indicated in Tables I–III. The synthetic methods of all imidates described below were reported in a preceding paper[1] of this series.

General Procedure for the Preparation of Sulfamoyl and Sulfonyl Amidines and Sulfonyl Amidrazones. To a solution of imidate in alcohol such as MeOH or EtOH was added a solution of sulfamide (2–4 equiv), sulfonamide (1–1.2 equiv), or sulfonyl hydrazide (1–1.2 equiv) in alcohol followed by stirring for 24–48 h at room temperature. Evaporation of the solvent and chromatographic purification (SiO_2, $CHCl_3$–MeOH) of the residue gave the corresponding sulfamoyl or sulfonyl amidine or sulfonyl amidrazone. Example procedures follow.

3-[(2-Pyridylmethyl)thio]-N^2-sulfamoylpropionamidine (2a). To a solution of ethyl 3-[(2-pyridylmethyl)thio]propionimidate (7.2 g, 32.1 mmol) in MeOH (30 mL) was added a solution of sulfamide (12.3 g, 128.1 mmol) in MeOH (40 mL), followed by stirring for 24 h at room temperature. Following evaporation of the solvent under reduced pressure, the residue was chromatographed (SiO_2, $CHCl_3$–MeOH) and the product obtained was recrystallized from EtOH–EtOAc to afford 4.6 g (52.2%) of **2a**: mp 101–102 °C. Anal. ($C_9H_{14}N_4O_2S_2$) C, H, N.

3-[[(5-Methyl-4-imidazolyl)methyl]thio]-N^2-sulfamoylpropionamidine (2b). To a solution of ethyl 3-[[(5-methyl-4-imidazolyl)methyl]thio]propionimidate (7.0 g, 30.8 mmol) in MeOH (30 mL) was added a solution of sulfamide (8.9 g, 92.7 mmol) in MeOH (30 mL), followed by stirring for 24 h at room temperature. Following evaporation of the solvent under reduced pressure, the residue was chromatographed (SiO_2, $CHCl_3$–MeOH) and the product obtained was recrystallized from EtOH to afford 1.74 g (20.4%) of **2b**: mp 129–130 °C. Anal. ($C_8H_{15}N_5O_2S_2$) C, H, N.

3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]-N^2-sulfamoylpropionamidine (2e). Sulfamide (619 g, 6.4 mol) was dissolved in MeOH (2000 mL) with heating. To the resultant solution was added methyl 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionimidate (400 g, 1.46 mol) at 30–35 °C followed by stirring at room temperature. After 7 h, imidate (400 g, 1.46 mol) was added again to the reaction mixture, which already deposited the crystal of **2e**, followed by stirring at room temperature for 40 h. The crystals were collected and recrystallized from DMF–H_2O to give 540 g (54.7 %) of **2e**: mp 164–165 °C. Anal. ($C_8H_{15}N_7O_2S_3$) C, H, N, S.

3,5-Bis[2-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]ethyl]-4*H*-1,2,4,6-thiatriazine 1,1-Dioxide Dimaleate (5e). A solution of methyl 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionimidate (13 g, 47.6 mmol) and sulfamide (1.75 g, 18.2 mmol) in MeOH (100 mL) was refluxed for 2 h. The solvent was removed in vacuo and the residue was chromatographed (SiO_2, $CHCl_3$–MeOH) to afford 5.0 g (37.4%) of **5e** as an oily product, which was treated with maleic acid (2.1 g, 18.1 mmol) in MeOH (90 mL) to give 6.4 g of maleate, mp 172–174 °C. Anal. ($C_{24}H_{31}N_{11}O_{10}S_5$) C, H, N, S.

4-[3-(Piperidinomethyl)phenoxy]-N^2-sulfamoylbutyramidine Dihydrochloride (2d). To a solution of ethyl 4-[3-(piperidinomethyl)phenoxy]butyrimidate (48 g, 157.9 mmol) in MeOH (100 mL) was added a solution of sulfamide (33.8 g, 351.7 mmol) in MeOH (200 mL), followed by stirring for 48 h at room temperature. Following evaporation of the solvent under reduced pressure, the residue was chromatographed (SiO_2, EtOAc–MeOH) and the product obtained was treated with cold HCl in EtOH and recrystallized with MeOH to afford 27.7 g (41.2%) of **2d**: mp 184–187 °C. Anal. ($C_{16}H_{28}N_4O_3SCl_2$) C, H, N, S, Cl.

Simultaneously, the dimer 3,5-bis[3-[3-(piperidinomethyl)-phenoxy]propyl]-4*H*-1,2,4,6-thiatriazine 1,1-dioxide (**5d**) (6.9 g, 14.7%) was also obtained: mp 103–104 °C from EtOAc. Anal. ($C_{32}H_{45}N_5O_4S$) C, H, N, S. Mass spectrum, m/z 595 (M^+), 512.

3-[[[2-(2,2-Dimethylhydrazino)-4-thiazolyl]methyl]thio]-N^2-sulfamoylpropionamidine Maleate (2g). Ethyl 3-[[[2-[2,2-dimethylhydrazino]-4-thiazolyl]methyl]thio]propionimidate (4.3 g, 14.9 mmol) and sulfamide (2.17 g, 22.6 mmol) were dissolved in MeOH (20 mL). The resultant solution was stirred for 48 h at room temperature, followed by evaporation of the solvent under reduced pressure. The residue was chromatographed (SiO_2, $CHCl_3$–MeOH) and the product obtained was treated with maleic acid in acetone to afford 2.0 g (29.5%) of **2g**: mp 153–154 °C. Anal. ($C_{13}H_{22}N_6O_6S_3$) C, H, N.

Simultaneously, dimer 3,5-bis[2-[[[2-[2,2-dimethylhydrazino]-4-thiazolyl]methyl]thio]ethyl]-4*H*-1,2,4,6-thiatriazine 1,1-dioxide (**5g**) (0.4 g, 5.2%) was also obtained: mp 186–187 °C from MeOH. Anal. ($C_{18}H_{29}N_9O_2S_5$) C, H, N. Mass spectrum (FD method), m/z 512 ($M^+ + 1$).

3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]-N^2-(methylsulfonyl)propionamidine (3a). Methyl 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-propionimidate (1.0 g, 3.66 mmol) and methanesulfonamide (0.38 g, 4.0 mmol) were dissolved in MeOH (10 mL), followed by stirring at room temperature for 48 h. The solvent was evaporated under reduced pressure and the residue was recrystallized from EtOH to give 0.7 g (56.9%) of **3a**: mp 117–118 °C. Anal. ($C_9H_{16}N_6O_2S_3$) C, H, S; N: calcd, 24.98; found, 24.43.

3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]-N^2-(phenylsulfonyl)propionamidine (3b). Methyl 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-propionimidate (10 g, 36.6 mmol) and benzenesulfonamide (6.9 g, 43.9 mmol) was dissolved in MeOH (30 mL), followed by stirring for 48 h. Following concentration under reduced pressure, the residue was chromatographed (SiO_2, $CHCl_3$–MeOH) and the product obtained was recrystallized from EtOH to afford 7.8 g (53.5%) of **3b**: mp 152–153 °C. Anal. ($C_{14}H_{18}N_6O_2S_3$) C, H, N, S.

3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]-N^3-(phenylsulfonyl)propionamidrazone (4a). Methyl 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-propionimidate (2.0 g, 7.3 mmol) and benzenesulfonohydrazide (1.21 g, 7.0 mmol) was dissolved in MeOH (40 mL), followed by stirring at room temperature for 24 h. Following concentration under reduced pressure, the residue was chromatographed (SiO_2, $CHCl_3$–MeOH) and the product obtained was recrystallized from EtOH to afford 1.2 g (40.0%) of **4a**: mp 159.5–161 °C. Anal. ($C_{14}H_{19}N_7O_2S_3$) C, H, N.

Preparation of 3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]sulfinyl]-N^2-sulfamoylpropionamidine Maleate (2i). To a stirred solution of compound **2e** (30 g, 89.0 mmol) in H_2O (2600 mL) and MeOH (440 mL) was added sodium metaperiodate (20 g, 93.5 mmol), followed by stirring at room temperature for 1 h. The solvent was evaporated under reduced pressure and the residue was extracted with 50% MeOH in $CHCl_3$ (4 × 500 mL) under reflux. The combined extract was concentrated and the residue was chromatographed (SiO_2, $CHCl_3$–MeOH). The product obtained was treated with maleic acid in acetone to afford 28.5 g (68.2%) of **2i**: mp 165 °C dec. Anal. ($C_{12}H_{19}N_7O_7S_3$) C, H, N, S.

Acid Hydrolysis of Famotidine. [3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionyl]sulfamide Hydrochloride (6). A solution of compound **2e** (5.0 g, 14.8 mmol) in 1 N HCl (50 mL) was allowed to stand for 64 h at room temperature. The crystals that precipitated were collected and recrystallized from MeOH to afford 4.6 g (83.6%) of **6**: mp 166–167 °C. Anal. ($C_8H_{15}N_6O_3S_3Cl$) C, H, N, S, Cl.

3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionic Acid (7). A solution of **2e** (5.0 g, 14.8 mmol) in concentrated HCl (50 mL) was heated at reflux for 2 h. The resultant solution was basified with 20% K_2CO_3 solution to pH

8. The precipitate was collected and washed with H_2O to afford 2.9 g (75.3%) of **7**: mp 256 °C dec. Anal. ($C_8H_{12}N_4O_2S_2$) C, H, N, S.

Nitrosation of 3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionitrile (8a). 3-[[[2-[(Diaminomethylene)amino]-4-hydroxy-5-(hydroxyimino)thiazolin-4-yl]methyl]thio]propionitrile Hydrochloride (9a). To a stirred solution of **8a** (2.0 g, 8.3 mmol) in 1 N HCl (83 mL) was added slowly sodium nitrite (1.14 g, 16.5 mmol), followed by stirring at room temperature for 1 h. The precipitated product was collected and washed with a small amount of cold H_2O to afford 1.92 g (71.4%) of **9a**: mp 163–164 °C dec. Anal. ($C_8H_{13}N_6O_2S_2Cl$) C, H, N, S, Cl. Mass spectrum (FAB), m/z 289 ($M^+ + 1$).

3-[[[2-[(Diaminomethylene)amino]-4-methoxy-5-(hydroxyimino)thiazolin-4-yl]methyl]thio]propionitrile Hydrochloride (10a). Compound **9a** (7.0 g, 21.5 mmol) was dissolved in MeOH (300 mL) followed by stirring at room temperature for 1 h. The solvent was removed in vacuo below 20 °C and the residue was recrystallized from MeOH to afford 1.2 g (16.4%) of **10a**: mp 143–145 °C dec. Anal. ($C_9H_{15}N_6O_2S_2Cl$) C, H, N, S, Cl. Mass spectrum (FAB), m/z 303 ($M^+ + 1$).

3-[[[2-[(Diaminomethylene)amino]-5-(hydroxyimino)thiazolin-4-ylidene]methyl]thio]propionitrile Hydrochloride (11). Compound **9a** (1.0 g, 3.07 mmol) was dissolved in DMF (4 mL) and allowed to stand for 1 h at room temperature. To the resultant solution was added acetonitrile (35 mL) and diethyl ether (30 mL), followed by stirring at room temperature to afford 0.93 g (98.9%) of **11** as a crystalline product: mp 175–177 °C dec. Anal. ($C_8H_{11}N_6OS_2Cl$) C, H, S, Cl; N: calcd, 11.56; found, 12.08. Mass spectrum (FAB), m/z 271 ($M^+ + 1$).

3-[[[2-[(Diaminomethylene)amino]-5-(benzylideneamino)-4-thiazolyl]methyl]thio]propionitrile Hydrochloride (12). A solution of compound **9a** (5.0 g, 15.4 mmol) in MeOH (500 mL) containing 3.0 g of 10% Pd/C was hydrogenated. Following filtration and addition of benzaldehyde (2.0 g, 18.8 mmol), the reaction mixture was allowed to stand at room temperature for 48 h. The solvent was removed under reduced pressure and the residue was recrystallized from MeOH to afford 0.65 g (11.1%) of **12**: mp 219–220 °C dec. Anal. ($C_{15}H_{17}N_6S_2Cl$) C, H, N, S, Cl. Mass spectrum, m/z 344 (M^+), 302, 258.

Nitrosation of 2-[(Diaminomethylene)amino]-4-methylthiazole (8b). 2-[(Diaminomethylene)amino]-4-methyl-4-hydroxy-5-(hydroxyimino)-2-thiazoline Hydrochloride (9b). To a stirred solution of **8b**·HCl (5.0 g, 25.97 mmol) in 1 N HCl (60 mL) was added slowly sodium nitrite (3.5 g, 50.7 mmol) at 0–5 °C, followed by stirring for 0.5 h. The precipitated product was collected and washed with a small portion of cold H_2O to afford 4.8 g (77.2%) of **9b**. Compound **9b** turned to a black color above 200 °C and did not show a clear melting point. Anal. ($C_5H_{10}N_5O_2SCl$) C, H, N, S, Cl. Mass spectrum (FAB), m/z 204 ($M^+ + 1$).

2-[(Diaminomethylene)amino]-4-methyl-4-methoxy-5-(hydroxyimino)thiazoline Hydrochloride (10b). 2-[(Diaminomethylene)amino]-4-methyl-4-ethoxy-5-(hydroxyimino)thiazoline Hydrochloride (10c). A solution of **9b** (1.5 g, 6.2 mmol) in MeOH (50 mL) was allowed to stand for 1 h at room temperature. The solution was concentrated and the residue was recrystallized from MeOH–diethyl ether to afford 0.9 g (56.9%) of **10b**. Anal. ($C_6H_{12}N_5O_2SCl$) C, H, N, S, Cl. Mass spectrum (FAB), m/z 218 ($M^+ + 1$). Compound **10c** was also prepared, using EtOH instead of MeOH, by the same procedure. Anal. ($C_7H_{14}N_5O_2SCl$) C, H, N. Mass spectrum (FAB), m/z 232 ($M^+ + 1$). Compound **10b** and **10c** did not show clear melting points.

Nitrosation of 3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]-N^2-sulfamoylpropionamidine (2e). 3-[[[2-(Diaminomethylene)amino]-5-(hydroxyimino)thiazolin-4-ylidene]methyl]thio]-N^2-sulfamoylpropionamidine Hydrochloride (14). To a solution of sodium nitrite (2.0 g, 28.9 mmol) in 1 N HCl (45 mL) and H_2O (5 mL) at 0 °C was added slowly **2e** (5.0 g, 14.8 mmol) with stirring. Stirring was continued for 1 h at 5–10 °C and the reaction mixture was lyophilized to afford the crude nitroso compound (7.8 g), which was found to contain **13** (45%) and **14** (32%) by HPLC analyses (column, SI-100, 4.6 mm × 300 mm; solvent, *n*-hexane–EtOH–H_2O *i*-$PrNH_2$ = 65:35:1:1; flow rate, 1.5 mL/min). The crude nitroso compound (3.0 g) was dissolved in DMF (1 mL) and allowed to stand for 1 h at room temperature. The resultant solution was diluted with H_2O (4 mL) and purified by column chromatography on polyamide with H_2O as eluent, followed by lyophilization of the eluate to afford 0.8 g of **14** (purity, 72% by HPLC). ^1H NMR (Me_2SO-d_6) δ 2.50–2.80 (m, 2 H), 2.90–3.30 (m, 2 H), 6.89 (s, 1 H), (D_2O) 2.60–2.84 (7, 2 H), 3.04–3.30 (m, 2 H), 6.88 (s, 1 H), (CD_3OD) 2.58–2.84 (m, 2 H), 3.05–3.34 (m, 2 H), 6.92 (s, 1 H). Mass spectrum (FD), m/z 367 ($M^+ + 1$).

Pharmacology. Isolated Guinea Pig Atrium. The atrium isolated from a guinea pig was mounted in a 30-mL bath containing oxygenated Krebs–Henseleit solution at 36 °C. Atrial rate was recorded through a force-displacement transducer on a polygraph (Nihon Koden, RM-6200). The inhibitory effect of test compounds on the histamine-induced increase in atrial rate was determined with three to four concentrations for each compound. The test compound was added 10 min before treatment with histamine (5×10^{-6} M). The dose producing 50% inhibition of atrial response to histamine was calculated from the dose–response curve, in which inhibitory percentage was plotted against log concentration of test compound.

Gastric Acid Secretion in Anesthetized Dogs. Mongrel dogs weighing 8–10 kg were deprived of food for 24 h and anesthetized by intravenous administration of pentobarbital (30 mg/kg). A stainless steel cannula was introduced through the ventral wall of the stomach after ligation of the pylorus and esophagus.[35] The gastric juice was collected from the gastric cannula by gravity drainage every 15 min. Test compounds were given intravenously after gastric secretion, induced by a continuous intravenous infusion of histamine (160 g/kg h), reached a steady state. The acidity of gastric juice was measured by titration with 0.05 N NaOH with an automatic titrator (Kyoto Electronics Manufacturing Co., AT-107). The percent inhibition of gastric secretion by each dose of drugs was calculated from the difference between the predrug acid output and the minimum acid output that was usually obtained within 45 min after drug administration. The dose producing 50% inhibition of the acid output was obtained from the dose–response curve in which the inhibition was semilogarithmically plotted against dose. For each compound two to four animals were used.

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Registry No. **1a**, 81814-12-2; **1b**, 101187-64-8; **1d**, 82840-73-1; **1e**, 76823-94-4; **1g**, 81814-09-7; **2a**, 81813-97-0; **2b**, 81813-98-1; **2c**, 81814-01-9; **2d**, 91287-04-6; **2d**·2HCl, 100846-35-3; **2e**, 76824-35-6; **2f**, 81814-06-4; **2g**, 81814-03-1; **2g**·$C_4H_4O_4$, 81814-04-2; **2h**, 77219-67-1; **2i**, 90237-03-9; **2i**·$C_4H_4O_4$, 109467-06-3; **2j**, 77226-65-4; **2k**, 77219-65-9; **2l**, 77219-61-5; **2m**, 77219-68-2; **2n**, 77219-74-0; **2o**, 77219-59-1; **3a**, 77219-53-5; **3b**, 77219-55-7; **3c**, 109467-07-4; **3d**, 77219-75-1; **3e**, 77219-72-8; **3f**, 77219-70-6; **4a**, 76824-05-0; **4b**, 76824-30-1; **5d**, 109467-09-6; **5e**, 89268-62-2; **5e**·$C_4H_4O_4$, 109467-08-5; **5g**, 81814-05-3; **6**·HCl, 76824-17-4; **7**, 107880-74-0; **8a**, 76823-93-3; **8b**·HCl, 7120-01-6; **9a**·HCl, 109467-10-9; **9b**·HCl, 109467-11-0; **10a**, 109467-12-1; **10b**, 109467-15-4; **10c**, 109467-16-5; **11**, 109467-13-2; **12**, 109467-14-3; **13**, 109467-18-7; **14**, 109467-17-6; $H_2NSO_2NH_2$, 7803-58-9; $H_2NSO_2CH_3$, 3144-09-0; $H_2NSO_2C_6H_5$, 98-10-2; $C_6H_5SO_2NHNH_2$, 80-17-1; cimetidine, 51481-61-9.

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