Grants HD13527 and AM26741. We thank R. Galyean, R. McClintock, R. Ferenczi, and R. Kaiser for technical assistance and G. L. Swart for manuscript preparation.

Registry No. 1, 89596-94-1; 2, 89618-30-4; 3, 89596-95-2; 4, 89618-31-5; 5, 89596-96-3; 6, 89596-97-4; 7, 89596-98-5; 8, 89596-99-6; 9, 89673-88-1; Ac-Tyr-Met-Gly-Trp-Met-Ser-Phe-NH_2, 89597-00-2; Ac-Tyr-Met-Gly-Trp-Met-Thr-Phe-NH_2, 89597-01-3; Ac-Tyr-Met-Gly-Trp-Met-Hyp-Phe-NH_2, 89597-02-4; Ac-Tyr-Met-D-Ala-Trp-Met-Asp-Phe-NH_2, 89597-03-5; Ac-Tyr-Met-Gly-D-Trp-Met-Asp-Phe-NH_2, 88457-85-6; Ac-Tyr-Met-Gly-Trp-D-Met-Asp-Phe-NH_2, 88495-33-4.

Histamine H_2 Receptor Antagonists. 1. Synthesis of *N*-Cyano and *N*-Carbamoyl Amidine Derivatives and Their Biological Activities

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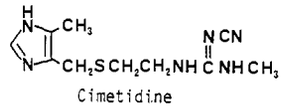
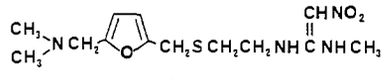
A large number of *N*-cyano amidine derivatives were prepared as potential histamine H_2 receptor antagonists and evaluated for their inhibitory action on histamine-stimulated chronotropic response of isolated right atria from guinea pigs. Several selected compounds were assessed as inhibitors of gastric acid secretion induced by histamine in anesthetized dogs. Of these compounds, furan (**8c**) and [(diaminomethylene)amino]thiazole derivatives (**16c**) were found to be more potent than cimetidine in both assays. In contrast to the guanidine series, methyl substitution at the terminal nitrogen of the cyano amidines was detrimental to the activities. Furthermore, acid hydrolysis of the cyano amidines gave carbamoyl amidines, which proved to be more active than the cyano amidines, the converse of the case for guanidines. 3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]-*N'*-carbamoylpropionamidine (**16d**) was the most potent of all the compounds tested and was approximately 30 times more active in vitro and 50 times more active in vivo than cimetidine.

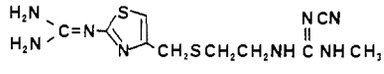
Burimamide was first demonstrated as a histamine H_2 receptor antagonist by Black et al. in 1972.[1] Structural modification of this prototype led to the more potent antagonists, metiamide[2] and cimetidine.[3] Cimetidine is a



Cimetidine



Ranitidine

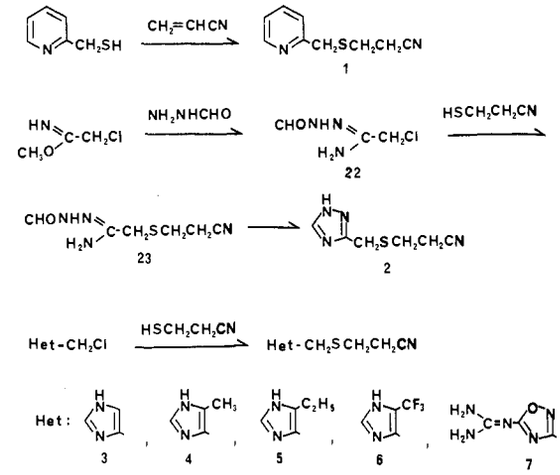


Tiotidine

well-known histamine H_2 receptor antagonist and used widely as an effective inhibitor of gastric acid secretion in the treatment of peptic ulcers and associated gastrointestinal disorders. Recent studies have shown that structurally unique nonimidazole derivatives, such as ranitidine[4] and tiotidine,[5] are more active antagonists than cimetidine.

In general, the structures of these antagonists are composed of three fundamental substructures: substituted heterocyclic components, i.e., methylimidazole, [(dimethylamino)methyl]furan, or [(diaminomethylene)amino]thiazole, connected by a (methylthio)ethyl chain to an essentially neutral end group, such as cyanoguanidine or 1,1-diamino-2-nitroethylene.[6] More recently, a new class of potent histamine H_2 receptor antagonist, in which the end group was replaced by a 3,4-diamino-1,2,5-thiadiazole 1-oxide or 1,1-dioxide, was reported.[6,7]

Scheme I



Our efforts to find a new type of H_2 antagonist focused on replacing the usual cyanoguanidine and 1,1-diamino-2-nitroethylene moieties with the cyano amidine and carbamoyl amidine moieties. We now report in this paper the preparation and the pharmacological profile of the cyano and carbamoyl amidine derivatives as H_2 antihistaminic agents and discuss the structure–activity relationships.

(1) Black, J. W.; Duncan, W. A. M.; Durant, G. J.; Ganellin, C. R.; Parsons, M. E. *Nature (London)* **1972**, *236*, 385.
(2) Black, J. W.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R. *Nature (London)* **1974**, *248*, 65.
(3) Brimblecombe, R. W.; Duncan, W. A. M.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Parsons, M. E. *J. Int. Med. Res.* **1975**, *3*, 86.
(4) Bradshaw, J.; Brittain, R. T.; Clitherow, J. W.; Daly, M. J.; Jack, D.; Price, B. J.; Stables, R. *Br. J. Pharmacol.* **1979**, *66*, 464.
(5) Yellin, T. O.; Buck, S. H.; Gilman, D. J.; Jones, D. F.; Wardleworth, J. M. *Life Sci.* **1979**, *25*, 2001.
(6) Lumma, W. C., Jr.; Anderson, P. S.; Baldwin, J. J.; Bolhofer, W. A.; Habecker, C. N.; Hirshfield, J. M.; Pietruszkiewicz, A. M.; Randall, W. C.; Torchiana, M. L.; Britcher, S. F.; Clineschmidt, B. V.; Denny, G. H.; Hirshmann, R.; Hoffman, J. M.; Phillips, B. T.; Streeter, K. B. *J. Med. Chem.* **1983**, *25*, 207.
(7) Algieri, A. A.; Luke, G. M.; Standridge, R. T.; Brown, M.; Partyka, R. A.; Crenshaw, R. R. *J. Med. Chem.* **1983**, *25*, 210.

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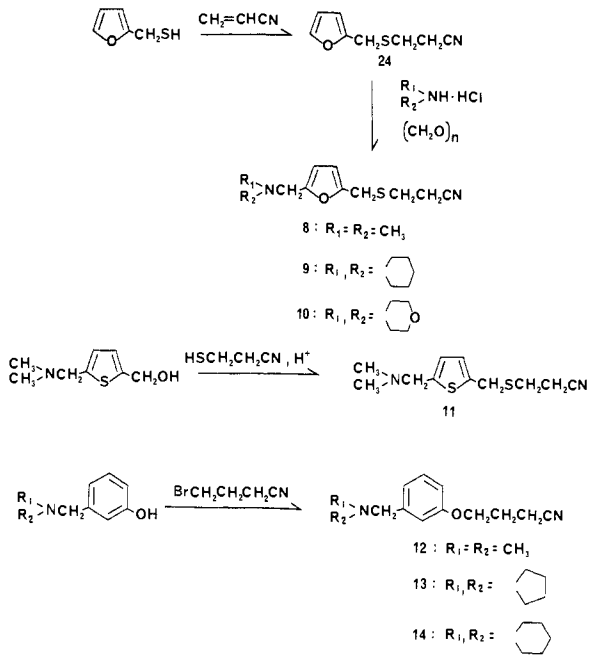
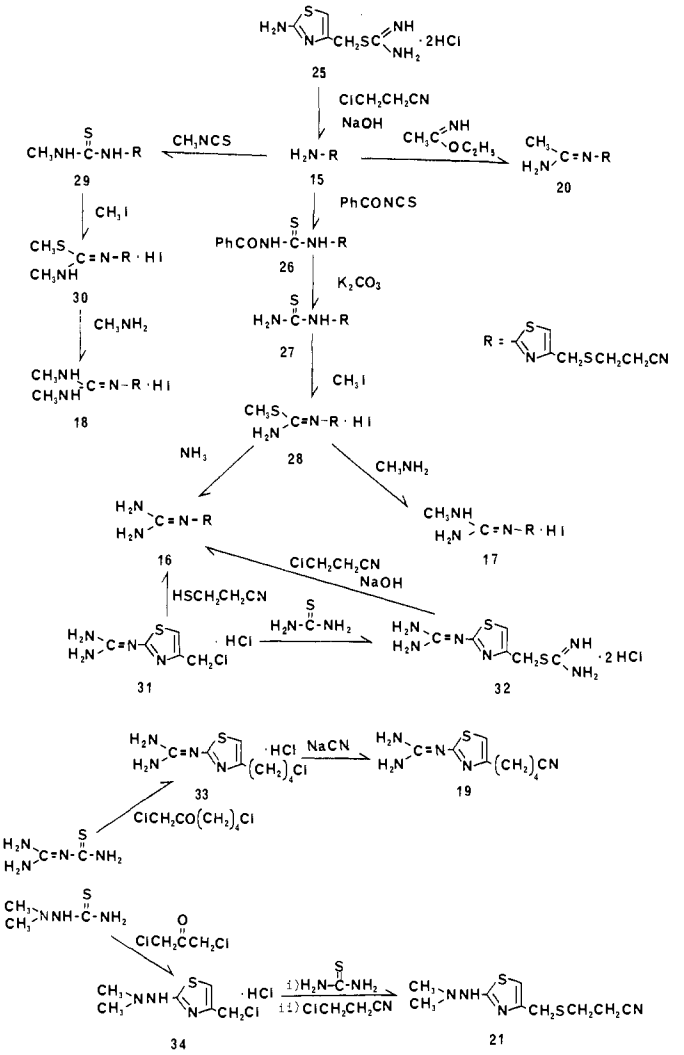
Scheme II

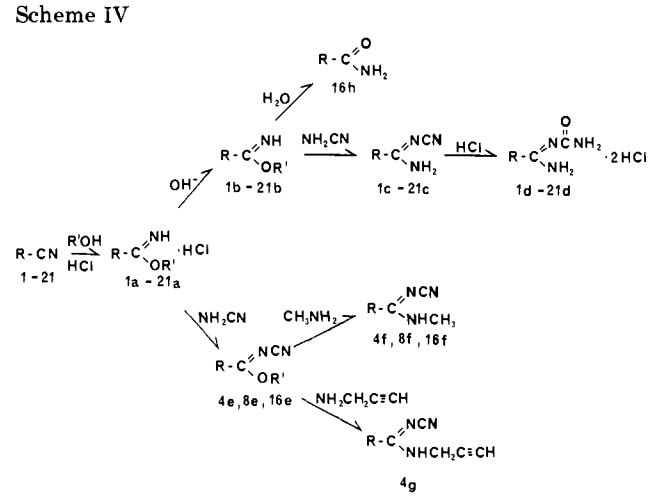


Scheme III



Chemistry. The synthetic routes employed in the preparation of the cyano and carbamoyl amidine derivatives are illustrated in Schemes I–IV. As shown in Scheme I, 3-[(pyridylmethyl)thio]propionitrile (**1**) was prepared from 2-(thiomethyl)pyridine and acrylonitrile by Michael addition. 3-[(Triazolylmethyl)thio]propionitrile (**2**) was obtained from the reaction of *N'*-formyl-2-chloroacetamidrazone **22** and the sodium salt of 3-mercaptopropionitrile, followed by cyclization with heating. Chloromethyl derivatives of the appropriate heterocyclic compounds react readily with the sodium salt of 3-mercaptopropionitrile to afford nitriles **3–7**. Nitriles compounds containing furan, thiophene, or benzene nuclei were prepared according to Scheme II. (Furfurylthio)propionitriles (**8–10**) were synthesized from furfuryl mercaptan and acrylonitrile by Michael addition, followed by treatment of the intermediate propionitrile **24** with the appropriate amines and paraformaldehyde. [(Thienylmethyl)thio]-propionitrile **11** was obtained from the reaction between 5-[(dimethylamino)methyl]-2-thiophenemethanol and 3-mercaptopropionitrile under acidic conditions. Phenoxybutyronitriles **12–14** were prepared from the corresponding phenols and 4-bromobutyronitrile in dimethylformamide. Scheme III shows the preparation of thiazole derivatives. 3-[[(2-Aminothiazolyl)methyl]thio]propionitrile (**15**) was prepared from thiouronium salt **25** and 3-chloropropionitrile under nitrogen. (Thioureido)thiazole **27** was made from aminothiazole **15** and benzoyl isothiocyanate, followed by hydrolysis of the intermediate (benzoylthioureido)thiazole **26**. Compound **27** was then treated with methyl iodide to provide (*S*-methylisothioureido)thiazole **28**, which was allowed to react with ammonium chloride or methylamine to afford [(diaminomethylene)amino]-thiazole **16** or the methyl-substituted compound **17**, respectively. The dimethyl-substituted compound **18** was prepared by an analogous route. Compound **16** was also prepared from 2-[(diaminomethylene)amino]-4-(chloromethyl)thiazole (**31**)[8] and the sodium salt of 3-mercaptopropionitrile or from the reaction of compound **31** and thiourea, followed by treatment with 3-chloropropionitrile as mentioned above. 1,6-Dichloro-2-hexanone was allowed to react with amidinothiourea to provide (chlorobutyl)-thiazole **33**, which was treated with sodium cyanide in dimethyl sulfoxide to afford (cyanobutyl)thiazole **19**. Treatment of **15** with acetimidate gave *N*-(2-thiazolyl)-acetamidine **20**. 3-[[[(Dimethylhydrazino)thiazolyl]-methyl]thio]propionitrile (**21**) was prepared from the reaction of chloromethyl compound **34** and thiourea, followed by treatment with 3-chloropropionitrile.

Scheme IV



As shown in Scheme IV, all nitrile compounds (**1–21**) were then treated with alcohol and hydrogen chloride in

(8) Yellin, T. O.; Gilman, D. J. British Patent 2001-624, April 20, 1977.

a suitable diluent at low temperature to afford imidates hydrochlorides (**1a–21a**), which were basified and converted, without purification, to cyano amidines (**1c–21c**) by treatment with cyanamide.[9] Carbamoyl amidines (**1d–21d**) were obtained by hydrolysis of the cyano amidines at low temperature.[9]

N-Cyano-*N'*-substituted amidines (**4f**, **8f**, **16f**, and **4g**) were prepared through *N*-cyano imidates (**4e**, **8e**, and **16e**), which were obtained by treatment of the imidate hydrochlorides (**4a**, **8a**, and **16a**) with cyanamide.[10] Amide **16h** was prepared by hydrolysis of the free imidate **16b** (see the Experimental Section).

Results and Discussion

The *N*-cyano and *N*-carbamoyl amidine derivatives listed in Tables I–III were evaluated as antagonists of the positive chronotropic action of histamine (5×10^{-6}M) in the isolated guinea pig right atrium, which is a standard assay for histamine H_2 receptor antagonists, and several selected compounds were assessed as inhibitors of gastric acid secretion in the anesthetized dogs when administered intravenously under histamine stimulation [160 μg/(kg hr)]. Table I lists the *N*-cyano amidines that contain a pyridine, imidazole, furan, thiophene, or benzene nucleus. Among these compounds, imidazole compound **4c**, viz., cimetidine analogue, was unexpectedly found to be inactive, and the incorporation of a methyl or propargyl group at the terminal amidine nitrogen of **4c**, as in **4f** or **4g**, respectively, failed to restore the activity. This finding suggests that in the series of the imidazole derivatives the cyano amidine moiety is not pharmacophorically equivalent to the cyano guanidine moiety present in cimetidine. On the other hand, it should be noted that significant activities in both assays were observed in the furan compound **8c**, viz., ranitidine analogue. The introduction of a methyl group at the terminal amidine nitrogen of **8c**, as in **8f**, and the substitution of a piperidino or morpholino group in place of the dimethylamino group, as in **9c** or **10c**, all failed to enhance the potency of the parent compound **8c**.

Thiophene compound **11c** showed only weak activity. The most active compound in the series of the benzene derivatives was **14c**, whose potency was slightly less than furan compound **8c**. In contrast to the series of the furan derivatives, the (dimethylamino)methyl compound **12c** was less potent than the piperidinomethyl compound **14c**. Table II shows those compounds in which the heterocycles are thiazoles or thiadiazoles. 2-Aminothiazole compound **15c** was found to be inactive, whereas the replacement of the aminothiazole moiety by the [(diaminomethylene)-amino]thiazole moiety resulted in compound **16c**, which showed a greatly enhanced potency in both assays. A methyl substitution at the terminal amidine nitrogen of **16c**, as in **16f**, significantly reduced potency, when compared with the unsubstituted compound **16c**. This finding is similar to the fact recently reported for 3,4-diamino-1,2,5-thiadiazole 1-oxide or 1,1-dioxide derivatives, in which the primary amino compounds are generally more active than the corresponding substituted amines.[6,7] From the results described above it can be concluded that the cyano amidine moiety behaves as a bioisostere of the cyano guanidine moiety present in the tiotidine series or the 1,1-diamino-2-nitroethylene moiety present in the ranitidine series. On the other hand, in the imidazole series the cyano amidine moiety does not behave as a bioisostere of the cyano guanidine moiety present in cimetidine as mentioned above. This fact indicates that the affinity to the H_2 receptor is a result of cooperative and dependent interactions of the molecular substructures with the receptor.[6] The analogue **19c**, in which the heterocycle is attached to the amidine function by four methylene units, was also prepared and found to retain nearly the same potency as **16c**. This result contrasted with the imidazole derivatives, in which the thioether compounds are approximately ten times more active than the methylene compounds,[11] probably due to the existence of tautomerism in the imidazole ring. The introduction of methyl groups to the guanidine nitrogen of **16c**, as in **17c** or **18c**, resulted in reduced potency, especially disubstituted compound **18c** led to drastic reduction of the activity. These are probably a result of unfavorable steric interactions. (Aminoethylidene)thiazole **20c**, hydrazinothiazole **21c**, and [(diaminomethylene)amino]oxadiazole **7c** were all less active than the tiotidine analogue **16c**, suggesting that the [(diaminomethylene)amino]thiazole moiety possesses exceptionally high affinity to the H_2 receptor. Even amide **16h** was found to retain nearly the same activity as cimetidine. Table III shows the *N*-carbamoyl amidine derivatives. We were surprised at finding that the carbamoyl amidine compounds that contain pyridine (**1d**), triazole (**2d**), 5-methylimidazole (**4d**), and [(diaminomethylene)amino]-oxadiazole (**7d**) exhibited detectable blocking activities in both assays, while no effects were observed in the corresponding cyano amidine compounds (**1c**, **2c**, **4c**, and **7c**), as shown in Table I. It is clear from this finding that the carbamoyl amidine derivatives are superior to the corresponding cyano amidine derivatives as specific H_2 receptor antagonists. This result observed in the amidine derivatives interestingly contrasts to the fact reported for the guanidine derivatives, in which the carbamoyl guanidine analogue of cimetidine was less potent than cimetidine in the in vitro test.[11] 5-Methylimidazole derivative **4d** was slightly more active than cimetidine in both tests. Unsubstituted imidazole **3d** and 5-ethylimidazole **5d** were slightly less active than **4d**. 5-(Trifluoromethyl)imidazole **6d** was found to be much less active, probably because the electron-withdrawing property of the trifluoromethyl substituent is enough to reduce the basicity of the imidazole ring. [(Diaminomethylene)amino]thiazole derivative **16d** was also prepared and found to be the most active agent of this amidine series of compounds.

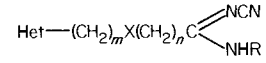
In summary, the results presented here lead us to conclude that the cyano and carbamoyl amidines are novel bioisosteres of the usual cyanoguanidine and 1,1-diamino-2-nitroethylene moieties for selective H_2-receptor antagonist activity. In contrast to the guanidine series, the *N*-carbamoyl derivatives are superior to the *N*-cyano derivatives in the amidine series as H_2-receptor antagonists. Compound **16d** is the most active compound amongst all of the compounds tested. This compound was approximately 30 times more active in vitro and 50 times more active in vivo than cimetidine. Further investigations of amidine derivatives are in progress, and the results will be published in forthcoming papers.

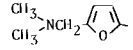
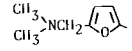
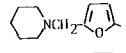
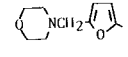
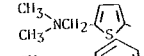
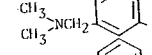
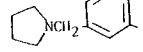
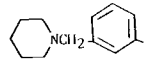
Experimental Section

Chemistry. All melting points and boiling points are uncorrected. The structures of all compounds were confirmed by their IR, NMR, and mass spectra. The IR spectra were measured on a Hitachi 215 spectrophotometer, the NMR spectra were measured on a JEOL MH100 with Me_4Si as an internal standard, and the

(9) Huffman, K. R.; Schaefer, F. C. *J. Org. Chem.* **1963**, *28*, 1812.
(10) Huffman, K. R.; Schaefer, F. C. *J. Org. Chem.* **1963**, *28*, 1816.
(11) 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.

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



compd	Het	*m*	X	*n*	R	yield, %	mp, °C	recrystn solvent	formula	H_2-receptor antagonist act. in guinea pig atrium: ED_{50}, M[a]	inhibn of acid output in anesthetized dogs: ED_{50}, mg/kg iv[b]
1c		1	S	2	H	46	110–112	EtOAc–ether	$C_{10}H_{12}N_4S$	$>10^{-4}$ [e]	
2c		1	S	2	H	78	108–110	EtOH	$C_7H_{10}N_6S$	$>10^{-4}$ [e]	
		1	S	2	H	57	147–149	*i*-PrOH–EtOAc	$C_9H_{13}N_5S$	$>10^{-4}$ [e]	
4f		1	S	2	CH_3	82	179–180	EtOH	$C_{10}H_{15}N_5S$	$>10^{-4}$ [e]	
4g		1	S	2	$CH_2C{\equiv}CH$	80	130–131	EtOH	$C_{12}H_{15}N_5S$	$>10^{-4}$ [e]	
8c		1	S	2	H	55	70–72	EtOAc–ether	$C_{12}H_{18}N_4OS$	$(2.1 \pm 0.2) \times 10^{-6}$	0.28 ± 0.06
8f		1	S	2	CH_3	40			$C_{13}H_{20}N_4OS$[c]	$(1.7 \pm 0.14) \times 10^{-4}$	>10
9c		1	S	2	H	56	102–103	EtOAc	$C_{15}H_{22}N_4OS$	$(3.5 \pm 1.0) \times 10^{-5}$	
10c		1	S	2	H	63			$C_{14}H_{20}N_4O_2S$[d]	$>10^{-4}$ [e]	
11c		1	S	2	H	78	135–136	EtOAc	$C_{12}H_{18}N_4S_2$	$(1.3 \pm 0.2) \times 10^{-5}$	4.4 ± 0.8
12c		0	O	3	H	72	135–136	MeOH–ether	$C_{14}H_{20}N_4O$	$(2.0 \pm 0.4) \times 10^{-5}$	9.0 ± 1.0
13c		0	O	3	H	80	166–167	MeOH	$C_{16}H_{22}N_4O$	$(1.3 \pm 0.3) \times 10^{-5}$	3.5 ± 0.8
14c		0	O	3	H	85	179–182	MeOH	$C_{17}H_{24}N_4O$	$(4.7 \pm 1.1) \times 10^{-6}$	2.3 ± 0.5
Cimetidine										$(2.7 \pm 0.3) \times 10^{-6}$	0.33 ± 0.42

[a] Doses representing 50% inhibition (ED_{50}, means ± SE) of positive 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. ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 6 H), 2.6–2.9 (m, 4 H), 2.84 (s, 3 H), 3.40 (s, 2 H), 3.74 (s, 2 H), 6.16 (m, 2 H); IR (neat) ν_{max} 2150 cm^{-1}; mass spectrum, *m/z* 280 (M^+), 265. [d] Viscous oil. ^{1}H NMR ($CDCl_3$) δ 2.4–2.9 (m, 8 H), 3.48 (s, 2 H), 3.60–3.61 (m, 4 H), 3.73 (s, 2 H), 6.14 (s, 2 H); IR (neat) ν_{max} 2160 cm^{-1}; mass spectrum, *m/z* 308 (M^+), 266, 213. [e] 50% inhibition of the response to histamine was not observed at 10^{-4} M of test compound.

mass spectra were taken on a Hitachi RMU-6Mg double-focusing 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.

General Procedure for the Preparation of Imidates. The nitrile was dissolved in either alcohol alone or slightly excess amounts of alcohol with appropriate solvent as a diluent. The resultant solution was cooled to 0–10 °C, and this temperature was maintained during the addition of dry HCl. Following addition of the HCl, the mixture was allowed to stand at 4 °C for 2–7 days and then concentrated under reduced pressure to afford imidate hydrochlorides as a crystalline solid. Free imidates were obtained by adding the reaction mixture into ice-cooled water containing excess potassium carbonate and extracting with appropriate solvent. The imidates were directly converted to *N*-cyano amidines without further purification.

Ethyl 3-[[(5-Methyl-4-imidazolyl)methyl]thio]propionimidate Dihydrochloride (4a). To a solution of 3-[[(5-methyl-4-imidazolyl)methyl]thio]propionitrile **4** (10.0 g, 55.2 mmol) in absolute EtOH (150 mL) was added dry HCl (4.8 g, 55.2 mmol) at 0–5 °C and the mixture was allowed to stand for 1 week in a refrigerator. The solvent was evaporated and the residual solid was collected and washed with EtOH–diethyl ether to afford 12.0 g (72.4%) of **4a** as a crystalline solid.

Ethyl 3-[[(5-Methyl-4-imidazolyl)methyl]thio]-*N*-cyanopropionimidate (4e). To an ice-cooled solution of compound **4a** (10.0 g, 33.3 mmol) in absolute EtOH (60 mL) was added a solution of triethylamine (3.36 g, 33.3 mmol) in absolute EtOH (10 mL) and a solution of cyanamide (1.4 g, 33.3 mmol) in absolute EtOH (10 mL). The mixture was stirred for 1.5 h at room temperature and evaporated. To the residue was added H_2O (50 mL), and the mixture was extracted with chloroform. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated to afford 6.2 g (73.8%) of **4e** as an oil.

Ethyl 3-[[5-[(Dimethylamino)methyl]furfuryl]thio]propionimidate (8b). To a solution of 3-[[5-[(dimethylamino)methyl]furfuryl]thio]propionitrile (**8**; 19.8 g, 88.4 mmol) in absolute EtOH (4.5 g, 97.8 mmol) and dry chloroform (60 mL) was added dry HCl (6.5 g, 178.1 mmol) at 0–5 °C. The reaction mixture was allowed to stand for 1 week in a refrigerator and then poured into ice-cooled water containing excess potassium carbonate. The product was extracted with chloroform, and the organic layer was dried (K_2CO_3) and evaporated to afford 23.0 g (96.4%) of **8b** as an oil.

Methyl 3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionimidate (16b). To a solution of 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionitrile (**16**; 10.0 g, 41.5 mmol) in dry DMF (20 mL) and absolute MeOH (20 mL) was added dry HCl (20 g, 547.9 mmol) at 0–5 °C. The reaction mixture was allowed to stand for 48 h at 4 °C and poured into ice-cooled water containing excess potassium carbonate, followed by stirring for 2 h in an ice bath. The resulting crystalline precipitate was collected to afford 9.27 g (81.8%) of **16b**.

General Procedure for the Preparation of *N*-Cyano Amidines. *N*-Cyano amidines were prepared according to the method reported by Huffman and Schaefer.[9] To a solution of an appropriate imidate in alcohol was added an equivalent amount of cyanamide, and the mixture was stirred for 15–30 min at room temperature. Evaporation of the solvent and chromatographic purification (SiO_2; chloroform–MeOH) of the residue gave the corresponding *N*-cyano amidine. An example procedure follows.

3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]-*N'*-cyanopropionamidine (16c). To a solution of methyl 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionimidate (**16b**; 5.1 g, 18.7 mmol) in MeOH (35 mL) was added cyanamide (0.9 g, 21.4 mmol), followed by stirring at room temperature for 30 min. Following concentration, the residue was chromatographed (SiO_2; chloroform–MeOH), and the product obtained was recrystallized from MeOH–diethyl ether to afford 4.15 g (70.7%) of **16c**: mp 102.5–104 °C. Anal. ($C_9H_{13}N_7S_2$) C, H, N.

General Procedure for the Preparation of *N*-Carbamoyl Amidines. *N*-Carbamoyl amidines were also prepared according to the method reported by Huffman and Schaeffer.[9] To a solution of an appropriate *N*-cyano amidine in suitable solvents was added excess dry HCl, while cooling in an ice bath, followed by concentration under reduced pressure to afford the *N*-carbamoyl amidine hydrochloride as a crystalline product. An example procedure follows.

3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]-*N'*-carbamoylpropionamidine Dihydrochloride (16d). To a solution of compound **16c** (0.5 g, 1.7 mmol) in EtOH (15 mL) and chloroform (10 mL) was added dry HCl over 1.5 h while maintaining the temperature at 0–5 °C. The resultant mixture was evaporated under reduced pressure, and the residue was recrystallized from EtOH–diethyl ether to afford 0.55 g (83.3%) of **16d**, mp 171–173 °C. Anal. ($C_9H_{17}N_7S_2OCl_2$) C, H, N.

Preparation of Nitriles. 3-[[(2-Pyridyl)methyl]thio]propionitrile (1). To 2-(thiomethyl)pyridine (30.0 g, 240 mmol) containing sodium methoxide (0.2 g, 3.7 mmol) was added gradually acrylonitrile (12.7 g, 240 mmol) while maintaining the temperature at 40–50 °C. The reaction mixture was distilled after neutralization with acetic acid (0.22 g, 3.7 mmol) to afford 41.1 g (95.5%) of **1** as a pale yellow oil: bp 124–125 °C (0.4 mm): mass spectrum, m/z 179 ($M^+ + 1$).

3-[[(3-Triazolyl)methyl]thio]propionitrile (2). A. To an ice-cooled solution of chloroacetonitrile (10.0 g, 132.4 mmol) in absolute MeOH (50 mL) was added sodium methoxide (0.2 g, 3.7 mmol), and the solution was stirred for 0.5 h at room temperature. The solution was neutralized with acetic acid (0.22 g, 3.7 mmol), and formic acid hydrazide (7.9 g, 131.7 mmol) was added, followed by stirring for 15 min at room temperature. The resultant solution was concentrated to afford 12.0 g (66.9%) of *N*-formyl-2-chloroacetamidrazone **22**: mp 124–126 °C dec.

B. In absolute EtOH (250 mL) was dissolved sodium (4.5 g, 195.6 mmol) under nitrogen, and a solution of 3-mercaptopropionitrile (17.0 g, 195.4 mmol) in absolute EtOH (30 mL) was added to the solution at 0–5 °C, followed by stirring for 1 h. To the mixture was added compound **22** (26.5 g, 195.6 mmol), followed by stirring at room temperature for 20 h. The salt was filtered off, and the solvent was removed under reduced pressure to afford 34.9 g (95.9%) of *N*-formyl-2-[(2-cyanoethyl)thio]acetamidrazone **23**: mp 102.5–103.5 °C; mass spectrum m/z 168 ($M^+ - 18$).

C. Compound **23** (20.0 g, 107.5 mmol) was heated at 120 °C for 10 min with stirring. The crude product was recrystallized from EtOH–diethyl ether to afford 17.1 g (94.7%) of **2**: mp 109–110 °C; mass spectrum m/z 168 (M^+), 128, 114.

3-[[(5-Methyl-4-imidazolyl)methyl]thio]propionitrile (4). In absolute EtOH (1000 mL) was dissolved sodium (12.2 g, 0.53 mol) under nitrogen, and a solution of 3-mercaptopropionitrile (23.1 g, 0.26 mol) in absolute EtOH (50 mL) was added to the solution at 0–5 °C, followed by stirring for 1 h. To the mixture was added a solution of 5-methyl-4-(chloromethyl)imidazole hydrochloride (44.4 g, 0.26 mol) in absolute EtOH (800 mL), and the mixture was allowed to react for 2 h at 0–5 °C, followed by further stirring for 18 h at room temperature. The salt was filtered off, and the solvent was evaporated. The residue was recrystallized from EtOH–diethyl ether to afford 46.8 g (97.3%) of **4**: mp 103–104 °C. Anal. ($C_8H_{11}N_3S$) C, H, N.

Compounds 3 and 5–7 were prepared from the appropriate chloromethyl derivatives by the same procedure.

3-[[(4-Imidazolyl)methyl]thio]propionitrile (3): mp 82–83 °C (EtOH–EtOAc). Mass spectrum, m/z 167 (M^+), 81. Anal. ($C_7H_9N_3S$) C, H, N.

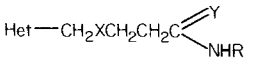
3-[[(5-Ethyl-4-imidazolyl)methyl]thio]propionitrile (5): mp 106–108 °C (EtOH–EtOAc).

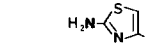
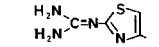
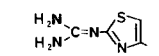
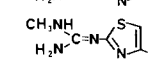
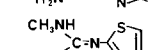
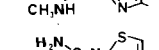
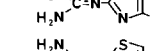
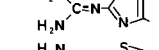
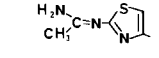
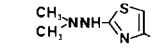
3-[[[5-(Trifluoromethyl)-4-imidazolyl]methyl]thio]propionitrile (6): mp 102–103 °C (EtOH–diethyl ether); mass spectrum, m/z 235 (M^+), 149.

3-[[[5-[(Diaminomethylene)amino]-1,2,4-oxadiazol-3-yl]methyl]thio]propionitrile (7): mp 138–140 °C (*i*-PrOH); mass spectrum, m/z 226 (M^+), 172. Anal. ($C_7H_{10}N_6OS$) C, H, N.

3-[[5-[(Dimethylamino)methyl]furfuryl]thio]propionitrile (8). A. To furfuryl mercaptan (95.0 g, 0.83 mol) containing sodium methoxide (0.2 g, 3.7 mmol) was added gradually acrylonitrile (53.0 g, 1.0 mol) while maintaining the temperature at 40–50 °C. The reaction mixture was distilled after neutralization with acetic acid (0.22 g, 3.7 mmol) to afford 135.5 g (97.4%) of 3-(furfurylthio)propionitrile **24**: bp 92–93 °C (0.1 mm); mass spectrum, m/z 167 (M^+), 81.

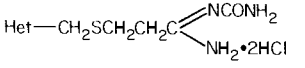
Table II. Structures and H_2-Receptor Antagonist Activities of Amidine Derivatives



compd	Het	X	Y	R	yield, %	mp, °C	recrystn solvent	formula	H_2-receptor antagonist act. in guinea pig atrium: ED_{50}, M[a]	inhibn of acid output in anesthetized dogs: ED_{50}, mg/kg iv[a]
15c		S	NCN	H	68	136–137	EtOH	$C_8H_{11}N_5S_2$ [b]	$>10^{-4}$ [f]	
16c		S	NCN	H	70	102.5–104	MeOH–ether	$C_9H_{13}N_7S_2$	$(1.8 \pm 0.3) \times 10^{-7}$	0.018 ± 0.007
16f		S	NCN	CH_3	42	159–161	MeOH	$C_{10}H_{15}N_7S_2 \cdot 1.5C_4H_4O_4 \cdot 0.5H_2O$ [c]	$(9.8 \pm 1.5) \times 10^{-7}$	0.39 ± 0.17
17c		S	NCN	H	33	144–145	EtOH	$C_{10}H_{15}N_7S_2$	$(1.2 \pm 0.2) \times 10^{-6}$	
18c		S	NCN	H	74	115–117	EtOH	$C_{11}H_{17}N_7S_2 \cdot 0.25H_2O$	$>10^{-4}$ [f]	
16h		S	O	H	68	193–194	MeOH	$C_8H_{13}N_5OS_2$	$(1.0 \pm 0.5) \times 10^{-6}$	
19c		CH_2	NCN	H	77	195–196	DMF–H_2O	$C_{10}H_{15}N_7S$	$(1.2 \pm 0.2) \times 10^{-7}$	0.022 ± 0.011
20c		S	NCN	H	52	86–88	EtOH–EtOAc	$C_{10}H_{14}N_6S_2 \cdot 0.5H_2O$	$(9.1 \pm 2.5) \times 10^{-6}$	
21c		S	NCN	H	96	121–122	MeOH	$C_{10}H_{16}N_6S_2 \cdot C_4H_4O_4$ [e]	$>10^{-4}$ [f]	
7c		S	NCN	H	95	177–179	MeOH	$C_8H_{12}N_8OS$	$>10^{-4}$ [f]	

[a] Same as for Table I. [b] N: calcd, 29.02; found, 28.61. [c] Maleate salt. [d] Maleate salt. [e] Maleate salt. [f] Same as for Table I.

Table III. Structures and H_2-Receptor Antagonist Activities of *N*-Carbamoyl Amidines



compd	Het	yield, %	mp, °C	recrystn solvent	formula[b]	H_2-receptor antagonist act. in guinea pig atrium: ED_{50}, M[a]	inhibn of acid output in anesthetized dogs: ED_{50}, mg/kg iv[a]
1d		97	136–141	EtOH–ether	$C_{10}H_{16}N_4OSCl_2$ [c]	$(1.2 \pm 0.3) \times 10^{-5}$	2.5 ± 0.4
2d		42	147–151	EtOH	$C_7H_{14}N_6OSCl_2$	$(4.1 \pm 0.9) \times 10^{-5}$	6.9 ± 2.6
3d		65	169–171	EtOH	$C_8H_{15}N_5OSCl_2$	$(5.3 \pm 1.1) \times 10^{-6}$	1.3 ± 0.2
4d		71	169–172.5	EtOH	$C_9H_{17}N_5OSCl_2 \cdot 0.25H_2O$	$(9.0 \pm 1.2) \times 10^{-7}$	0.22 ± 0.04
5d		86	164–167	EtOH	$C_{10}H_{19}N_5OSCl_2$	$(2.0 \pm 0.5) \times 10^{-6}$	0.33 ± 0.03

6d		60	109–112	EtOH	$C_9H_{14}N_5OSF_3Cl_2$	$>10^{-4}$ [a]	
16d		79	171–173	EtOH–ether	$C_9H_{17}N_7OS_2Cl_2$	$(7.4 \pm 0.7) \times 10^{-8}$	0.0064 ± 0.0006
17d		92	180–182	EtOH	$C_{10}H_{19}N_7OS_2Cl_2$	$(3.2 \pm 0.8) \times 10^{-7}$	0.046 ± 0.007
20d		98	135–138 dec	EtOH	$C_{10}H_{18}N_6OS_2Cl_2 \cdot 0.2H_2O$	$(2.5 \pm 0.7) \times 10^{-6}$	
7d		85	125–130	EtOH	$C_8H_{16}N_8O_2SCl_2 \cdot H_2O$	$(2.6 \pm 1.8) \times 10^{-5}$	

[a] Same as for Table I. [b] All compounds were dihydrochloride salts. [c] N: calcd, 18.00; found, 17.25.

B. A suspension of compound **24** (40.0 g, 239.5 mmol), dimethylamine hydrochloride (39.0 g, 478.5 mmol), and paraformaldehyde (16.7 g, 556.6 mmol) in EtOH (600 mL) was stirred under reflux for 24 h; to the solution were added dimethylamine hydrochloride (39.0 g, 478.5 mmol) and paraformaldehyde (16.7 g, 556.6 mmol), and the solution was then stirred under reflux for 24 h. Following evaporation, H_2O (300 mL) was added, and the mixture was basified with potassium carbonate and extracted with EtOAc. The extract was dried (K_2CO_3) and distilled to afford 41.6 g (77.5%) of **8**: bp 131–137 °C (0.25 mm); mass spectrum, m/z 224 (M^+), 180, 138.

Compounds **9** and **10** were also prepared from the appropriate amines by the same procedure.

3-[[5-(Piperidinomethyl)furfuryl]thio]propionitrile (9): bp 150–153 °C (0.2 mm); mass spectrum, m/z 264 (M^+).

3-[[5-(Morpholinomethyl)furfuryl]thio]propionitrile (10): bp 152–160 °C (0.1–0.25 mm); mass spectrum, m/z 266 (M^+), 180.

3-[[[5-[(Dimethylamino)methyl]-2-thienyl]methyl]thio]propionitrile (11). To concentrated HCl (25 mL) was added 3-mercaptopropionitrile (4.6 g, 52.8 mmol) and 5-[(dimethylamino)methyl]-2-thiophenemethanol (6.0 g, 35.1 mmol) below 0 °C, and the mixture was allowed to stand for 20 h at 5 °C. The reaction mixture was poured into ice–water containing sodium hydroxide (10 g, 250 mmol) and was extracted with methylene chloride. The organic layer was dried (K_2CO_3) and evaporated. The residual oil was chromatographed (SiO_2; chloroform–MeOH) to afford 5.5 g (85.3%) of **11** as an oil: mass spectrum, m/z 240 (M^+).

4-[3-[(Dimethylamino)methyl]phenoxy]butyronitrile (12). To an ice-cooled solution of 3-[(dimethylamino)methyl]phenol (22.65 g, 150 mmol) in DMF (150 mL) was added sodium hydride (7.9 g at 50% in mineral oil, 164.5 mmol). 4-Bromobutyronitrile (22.2 g, 150 mmol) was added to the mixture, followed by stirring for 18 h at room temperature. 4-Bromobutyronitrile (10 g, 67.5 mmol) was added, and stirring was continued at 50 °C for 3.5 h. The reaction mixture was poured into ice–water and extracted with EtOAc. The organic layer was washed with dilute sodium hydroxide solution and H_2O and extracted with dilute hydrochloric acid. The aqueous layer was basified with potassium carbonate and extracted with EtOAc. The organic layer was dried (K_2CO_3) and distilled to afford 22.0 g (67.3%) of **12**, bp 135–150 °C (0.2 mm).

Compounds **13** and **14** were also prepared from the appropriate phenols by the same procedure. These compounds were purified by column chromatography on silica gel with chloroform–MeOH as an eluent.

4-[3-(1-Pyrrolidinylmethyl)phenoxy]butyronitrile (13): mass spectrum, m/z 244 (M^+), 175.

4-[3-(Piperidinomethyl)phenoxy]butyronitrile (14): mass spectrum, m/z 258 (M^+), 175.

3-[[(2-Amino-4-thiazolyl)methyl]thio]propionitrile (15). To a solution of *S*-[(2-amino-4-thiazolyl)methyl]isothiourea dihydrochloride (98.1 g, 0.37 mol) and 3-chloropropionitrile (37.0 g, 0.41 mol) in H_2O (490 mL) and EtOH (320 mL) was added gradually under nitrogen a solution of sodium hydroxide (45.1 g, 1.12 mol) in H_2O (450 mL) at 0–10 °C, followed by stirring for 1 h at 0–10 °C and for an additional 1 h at room temperature. The product was extracted with chloroform, and the organic layer was washed with H_2O and dried ($MgSO_4$), followed by evaporation and recrystallization from EtOAc to afford 47.2 g (63.1%) of **15**: mp 104–106 °C; mass spectrum, m/z 199 (M^+), 114.

3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionitrile (16). **A.** A solution of compound **15** (50.0 g, 0.25 mol) and benzoyl isothiocyanate (45.0 g, 0.27 mol) in acetone (500 mL) was stirred under reflux for 5 h. The solvent was removed to afford 79.4 g (87.3%) of 3-[[[2-(3-benzoylthioureido)-4-thiazolyl]methyl]thio]propionitrile (**26**) as colorless needles: mp 158–160 °C; mass spectrum, m/z 362 (M^+), 277, 218.

B. To a solution of compound **26** (80.0 g, 0.22 mol) in acetone (1400 mL) and MeOH (350 mL) was added a solution of potassium carbonate (20 g, 0.14 mol) in H_2O (300 mL), and the solution was stirred for 5 h at 50 °C. Following concentration and addition of ice–water (2000 mL), the mixture was stirred for 24 h. The product was gradually solidified and collected, followed by recrystallization from EtOH to afford 53.3 g (93.5%) of 3-[[(2-thioureido-4-thiazolyl)methyl]thio]propionitrile (**27**): mp 135–137

°C; mass spectrum, m/z 258 (M^+).

C. A solution of compound **27** (15.0 g, 58.1 mmol) and methyl iodide (12.4 g, 87.3 mmol) in EtOH (200 mL) was refluxed for 1 h, and the solvent was concentrated to afford 20.9 g (89.9%) of 3-[[[2-(*S*-methylisothioureido)-4-thiazolyl]methyl]thio]-propionitrile hydriodide **28**: mp 148–149 °C; mass spectrum, m/z 272 (M^+), 225, 187.

D. In MeOH (200 mL) containing ammonia (17.0 g, 1.0 mol) were dissolved compound **28** (20 g, 0.05 mol) and ammonium chloride (2.68 g, 0.05 mol). The solution was heated in a sealed stainless-steel bomb at 80–90 °C for 15 h. After the solution was cooled and the solvent was removed, H_2O (200 mL) was added, and the solution was basified with saturated aqueous potassium carbonate. The brown solid obtained was recrystallized from acetone to afford 6.2 g (51.45%) of **16**: mp 132 °C. Anal. ($C_8H_{11}N_5S_2$) C, H, N.

3-[[[2-[(Methylamino)aminomethylene]amino]-4-thiazolyl]methyl]thio]propionitrile Hydriodide (17). A solution of compound **28** (20.9 g, 52.2 mmol) in 40 wt % methanolic methylamine (200 mL) was refluxed for 20 h. Following concentration, the residue was chromatographed (SiO_2; chloroform–MeOH) and recrystallized from MeOH–EtOAc to afford 5.5 g (27.5%) of **17**: mp 161–163 °C; mass spectrum, m/z 255 (M^+), 170. Anal. ($C_9H_{13}N_5S_2$·HI) C, H, N.

3-[[[2-[[Bis(Methylamino)methylene]amino]-4-thiazolyl]methyl]thio]propionitrile Hydriodide (18). A. To a solution of compound **15** (9.0 g, 45.2 mmol) in EtOH (90 mL) was added methyl isothiocyanate (3.6 g, 49.3 mmol), and the mixture was refluxed for 24 h, followed by concentration and recrystallization from EtOH, to afford 4.5 g (37.5%) of 3-[[[2-(3-methylthioureido)-4-thiazolyl]methyl]]thio]propionitrile (**29**): mp 172–173 °C; mass spectrum, m/z 272 (M^+). Anal. ($C_9H_{12}N_4S_3$) C, H, N.

B. To a solution of compound **29** (10.0 g, 36.7 mmol) in EtOH (400 mL) was added methyl iodide (7.8 g, 54.9 mmol), and the mixture was refluxed for 1 h, followed by evaporation to afford 15.0 g (98.5%) of 3-[[[2-(*N*,*S*-dimethylisothioureido)-4-thiazolyl]methyl]thio]propionitrile hydriodide (**30**) as an oil.

C. Compound **30** (15.0 g, 36.2 mmol) was dissolved in 40 wt % methanolic methylamine (100 mL), and the solution was refluxed for 20 h. Following concentration, the residue was chromatographed (SiO_2; chloroform–EtOAc) to afford 5.1 g (52.3%) of **18** as an oil: mass spectrum, m/z 269 (M^+), 184.

2-[(Diaminomethylene)amino]-4-(4-cyanobutyl)thiazole (19). A. To a solution of diazomethane prepared from *p*-tosyl-*N*-methyl-*N*-nitrosoacetamide (43 g, 200 mmol) in diethyl ether (300 mL) was added a solution of 5-chlorovaleryl chloride (8.0 g, 51.6 mmol) in diethyl ether (30 mL) at −5 to 0 °C, and the mixture was allowed to stand at the same temperature for 2 h. Dry HCl was passed through at 0 °C for 30 min, followed by the addition of H_2O (100 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined ether layer was dried ($MgSO_4$) and evaporated. The residue was distilled to afford 8.2 g (94.0%) of 1,6-dichloro-2-hexanone: bp 120–125 °C (14 mm).

B. A solution of 1,6-dichloro-2-hexanone (23.5 g, 139 mmol) and amidinothiourea (16.4 g, 139 mmol) in acetone (200 mL) was stirred at room temperature for 48 h. Following concentration, the residue was chromatographed (SiO_2; chloroform–MeOH) and recrystallized from EtOH–diethyl ether to afford 24.6 g (65.8%) of 2-[(diaminomethylene)amino]-4-(4-chlorobutyl)thiazole hydrochloride **33**: mp 113–114 °C. This hydrochloride (24.5 g, 91 mmol) was basified by the usual manner. The product obtained was recrystallized from diethyl ether–*n*-hexane to afford 20.0 g (94.5%) of free base: mp 83–84 °C.

C. To a stirred suspension of sodium cyanide (4.9 g, 100 mmol) in dimethyl sulfoxide (24 mL) was added the free base of compound **32** (19.5 g, 83.8 mmol) at 70–75 °C, and stirring was continued at the same temperature for 3 h. To the solution was added chloroform (100 mL), and the undissolved material was filtered off, followed by concentration and purification by chromatography (SiO_2; chloroform–MeOH). The product obtained was recrystallized from EtOAc–*n*-hexane to afford 15.0 g (80.2%) of **19**: mp 104–105 °C.

3-[[[2-[(1-Aminoethylidene)amino]-4-thiazolyl]methyl]thio]propionitrile (20). To a solution of compound **15** (10.0 g, 50.2 mmol) in EtOH (100 mL) was added ethyl acetimidate (17.5 g, 201 mmol), and the mixture was refluxed for 18 h. Ethyl acetimidate (17.5 g, 201 mmol) was added, and refluxing was continued for 24 h, followed by concentration to afford 8.8 g (73.3%) of **20**: mp 87.5–88.5 °C; mass spectrum, m/z 240 (M^+), 155. Anal. ($C_9H_{12}N_4S_2$) C, H, N.

3-[[[2-(2,2-Dimethylhydrazino)-4-thiazolyl]methyl]thio]-propionitrile (21). A. 1,1-Dimethylthiosemicarbazide (10.0 g, 84.0 mmol) was added to a solution of dichloroacetone (10.67 g, 84.0 mmol) in acetone (50 mL) at 0–4 °C. The mixture was stirred at the same temperature for 4 days, and stirring was continued for an additional 24 h at room temperature. The precipitate was collected and washed with acetone to afford 11.8 g (61.6%) of 2-(2,2-dimethylhydrazino)-4-(chloromethyl)thiazole hydrochloride (**34**), mp 119–122 °C.

B. A mixture of compound **34** (11.5 g, 50 mmol) and thiourea (3.8 g, 50 mmol) in EtOH (50 mL) was refluxed for 15 min. To this mixture was added EtOH (25 mL), water (100 mL), and 3-chloropropionitrile (5.0 g, 5.8 mmol). The resultant solution was cooled to 0–10 °C, and a solution of sodium hydroxide (7.2 g, 180 mmol) in H_2O (70 mL) was added dropwise under nitrogen at 0–10 °C, followed by stirring for 1 h at the same temperature and for an additional 3 h at room temperature. The precipitate was collected and washed with H_2O to afford 7.7 g (63.1%) of **21**: mp 80–81 °C; mass spectrum, m/z 242 (M^+). Anal. ($C_9H_{14}N_4S_2$) C, H, N.

3-[[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl]-thio]propionamide (16h). A solution of compound **16b** (5.0 g, 18.3 mmol) in a mixed solvent of EtOH (30 mL) and H_2O (30 mL) was stirred at 40 °C for 20 h. Following evaporation, the residue was chromatographed (SiO_2; chloroform–MeOH) and recrystallized from MeOH to afford 3.2 g (67.5%) of **16h**: mp 193–194 °C dec. Anal. ($C_8H_{13}N_5OS_2$) C, H, N.

Pharmacology. Isolated Guinea Pig Atrium. The atrium isolated from 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 Kohden, RM-6200). The inhibitory effect of test compounds on the histamine-induced increase in atrial rate was determined with three to four preparations 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 to 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.[12] 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 μg/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, which 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. 1, 70296-26-3; **1c**, 70296-28-5; **1d**, 89378-89-2; **1d**·2HCl, 70296-30-9; **2**, 89378-66-5; **2c**, 89378-80-3; **2d**, 89378-90-5; **2d**·2HCl, 89378-85-8; **3**, 89378-67-6; **3d**, 89378-91-6; **3d**·2HCl, 89378-86-9; **4**, 70296-65-0; **4a**, 70296-66-1; **4c**, 70296-67-2; **4d**, 89378-92-7; **4d**·2HCl, 70296-71-8; **4e**, 89378-79-0; **4f**, 89378-81-4;

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4g, 89378-82-5; 5, 89378-68-7; 5d, 89378-93-8; 5d·2HCl, 89378-87-0; 6, 89378-69-8; 6d, 89378-94-9; 6d·2HCl, 89378-88-1; 7, 81814-10-0; 7c, 81821-03-6; 7d, 89378-97-2; 7d·2HCl, 81821-04-7; 8, 70296-73-0; 8b, 70296-74-1; 8c, 70296-69-4; 8f, 76683-79-9; 9, 89397-94-4; 9c, 76661-71-7; 10, 89397-95-5; 10c, 76661-72-8; 11, 89378-70-1; 11c, 76661-70-6; 12, 89378-71-2; 12c, 76506-38-2; 13, 89378-72-3; 13c, 76506-40-6; 14, 73279-30-8; 14c, 76506-41-7; 15, 76823-89-7; 15c, 89378-83-6; 16, 76823-93-3; 16b, 76823-94-4; 16c, 76823-97-7; 16d, 76824-37-8; 16d·2HCl, 76824-02-7; 16f, 76824-10-7; 16h, 76824-16-3; 17, 89378-73-4; 17c, 76824-03-8; 17d, 89378-95-0; 17d·2HCl, 76824-04-9; 18, 89378-74-5; 18c, 89378-84-7; 19, 76824-22-1; 19c, 76824-18-5; 20, 81821-08-1; 20c, 81821-05-8; 20d, 89378-96-1; 20d·2HCl, 81821-06-9; 21, 81814-08-6; 21c, 81821-01-4; 22, 89378-75-6; 23, 89378-76-7; 24, 70296-72-9; 26, 76823-90-0; 27, 76823-91-1; 28, 76823-92-2; 29, 89378-77-8; 30, 89378-78-9; 33, 81152-53-6; 33·HCl, 69014-12-6; 34, 81814-07-5; sodium cyanide, 143-33-9; cyanamide, 420-04-2; 2-(thiomethyl)pyridine, 2044-73-7; acrylonitrile, 107-13-1; chloroacetonitrile, 107-14-2; formic acid hydrazide, 624-84-0; sodium 3-mercaptopropionitrile, 77132-03-7; 5-methyl-4-(chloromethyl)imidazole hydrochloride, 51605-33-5; furfuryl mercaptan, 98-02-2; dimethylamine hydrochloride, 506-59-2; 3-mercaptopropionitrile, 1001-58-7; 5-[(dimethylamino)-methyl]-2-thiophenemethanol, 69340-23-4; 3-[(dimethylamino)-methyl]phenol, 60760-04-5; 4-bromobutyronitrile, 5332-06-9; *S*-[(2-amino-4-thiazoyl)methyl]isothiourea dihydrochloride, 20167-22-0; 3-chloropropionitrile, 542-76-7; benzoyl isothiocyanate, 532-55-8; methyl isothiocyanate, 556-61-6; diazomethane, 334-88-3; 5-chlorovaleryl chloride, 1575-61-7; 1,6-dichloro-2-hexanone, 62343-98-0; amidinothiourea, 2114-02-5; ethyl acetimidate, 1000-84-6; 1,1-dimethylthiosemicarbazide, 2289-53-4; 4-(chloromethyl)imidazole hydrochloride, 38585-61-4; 5-ethyl-4-(chloromethyl)imidazole hydrochloride, 74337-20-5; 5-(trifluoromethyl)-4-(chloromethyl)imidazole hydrochloride, 89378-98-3; 5-[(diaminomethylene)amino]-4-(chloromethyl)-1,2,4-oxadiazole hydrochloride, 89378-99-4; piperidine hydrochloride, 6091-44-7; morpholine hydrochloride, 10024-89-2; dichloroacetone, 534-07-6; thiourea, 62-56-6; 3-(1-pyrrolidinylmethyl)phenol, 69383-70-6; 3-(piperidinomethyl)phenol, 73279-04-6.

The 3,4-Catechol Derivative of Propranolol, a Minor Dihydroxylated Metabolite

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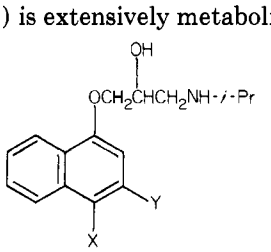
The *O,O*-dibenzyl ether of the 3,4-catechol derivative of propranolol (11) was prepared to determine whether the catechol is a product of metabolic hydroxylation. 4-(Allyloxy)-1,2-naphthoquinone (5) was reduced with sodium dithionite and alkylated with benzyl chloride to produce ether 7. Osmium tetroxide oxidation of 7 afforded glycol 8. Subsequent monotosylation, oxirane formation with KOH, and opening with isopropylamine afforded benzyl ether 11. Although hydrogenolysis was successful, catechol 3 was rapidly oxidized to the corresponding *o*-quinone (12). Reduction of 12 with sodium bisulfite afforded 3, which was derivatized with *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) to serve as a standard for the metabolic experiments. Gas chromatography–mass spectrometry of the Me_3Si ethers of the products of metabolism of pseudoracemic propranolol (made up of equal molar (2*R*)-propranolol-d_0/(2*S*)-propranolol-3′,3′-d_2) in the presence of the rat liver 9000*g* supernatant fraction showed four dihydroxylated metabolites, of which catechol 3 was in smallest amount, approximately 9% of the sum of dihydroxylated metabolites. Each of the four dihydroxylated propranolols arises stereoselectively from the 2*R* enantiomer of propranolol (by 1.15- to 2-fold), as determined by parent ion intensities at m/z 507 vs. 509. Quinone 12 was a nonselective competitive β-adrenoceptor antagonist, being about 16-fold less potent than propranolol in both β_1 and β_2 assays.

Propranolol (1) is extensively metabolized in man and



1, X = Y = H (propranolol)
2, X = OH Y = H (4-hydroxypropranolol)
3, X = Y = OH (3,4-dihydroxypropranolol)

other species by several metabolic pathways, including oxidative N-dealkylation, aromatic hydroxylation, and glucuronidation.[1-7] In man, 4-hydroxypropranolol (2) is the major identified product of aromatic hydroxylation, and in rats, regioisomeric products of 2-, 4-, 5-, and 7-hydroxylation have been reported.[3-5,8] These isomeric monohydroxylated propranolols have significant β-adrenergic antagonist activity.[9] Since propranolol is structurally related to the adrenergic transmitters epinephrine and norepinephrine, interest has also focussed on the 3,4-catechol derivative of propranolol (3). In addition, catechol derivatives of other (aryloxy)propanolamines have had significant activity as β-adrenergic agonists and/or antagonists,[10-13] and formation of catechols from phenols

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