and the solvent was evaporated. This was layered on a column of silica gel (100 g) and eluted with a solvent system of C_6H_6–EtOAc (10:1). After evaporation of the solvent, the first fraction gave crystals (480 mg), which were recrystallized from EtOAc–*n*-hexane to give colorless needles of **27**: mp 122–123 °C; ^{1}H NMR ($CDCl_3$) δ 8.70 (1 H, s), 8.10 (1 H, d, J = 2 Hz), 7.47–7.80 (2 H, m), 5.60 (2 H, s), 3.73 (3 H, s), 2.85 (2 H, q, J = 7 Hz), 1.33 (3 H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 173.7 (C-4), 166.1 (C-2′), 158.3 (C-2), 154.2 (C-9), 149.7 (C-11), 142.8 (C-6), 134.9 (C-7), 123.9 (C-5), 123.2 (C-10), 118.1 (C-8), 110.9 (C-3), 52.7 (C-3′), 49.9 (C-1′), 28.2 (C-12), 15.1 (C-13); mass spectrum m/e 314 (M), 227, 201, 200, 184. Anal. ($C_{15}H_{14}N_4O_4$) C, H, N. The second fraction gave crystals (330 mg), which were recrystallized from EtOAc to give colorless crystals of **28**: mp 159–160 °C; ^{1}H NMR ($CDCl_3$) δ 8.83 (1 H, s), 8.15 (1 H, d, J = 2 Hz), 7.37–7.70 (2 H, m), 5.57 (2 H, s), 3.80 (3 H, s), 2.82 (2 H, q, J = 7 Hz), 1.30 (3 H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 173.1 (C-4), 165.1 (C-2′), 159.0 (C-11), 156.4 (C-2), 153.9 (C-9), 142.0 (C-6), 133.9 (C-7), 124.2 (C-5), 123.9 (C-10), 117.7 (C-8), 112.9 (C-3), 53.1 (C-1′), 52.9 (C-3′), 28.1 (C-12), 15.2 (C-13); mass spectrum m/e 315 (M + 1), 314 (M), 286 (M – N_2), 243, 227, 201, 200, 184. Anal. ($C_{15}H_{14}N_4O_4$) C, H, N.

Biological Assay. Male Sprague-Dawley rats, 8 weeks old and weighing about 280 g, were used. Rat antiserum containing homocytotropic antibody was prepared according to the method of Mota.[11] In brief, the animals were sensitized by intramuscular injections of 1 mg of egg albumin in 1 mL of saline solution concomitantly with an intraperitoneal injection of 2×10^{10} of sterilized *Bordetella pertussis*. Serum collected from each animal 12 days after sensitization was pooled and frozen until use. The biological properties of the skin sensitizing antibody contained in these sera satisfy the requirements for a homocytotropic antibody; i.e., it fixes homologous skin tissue for a long time and is heat labile. The antisera showed passive cutaneous anaphylaxis (PCA, 72-h latent period) titers of 1:32 to 1:64. Homologous rat PCA response was elicited as follows. Four 0.05-mL aliquots of serum diluted fourfold with physiological saline solutions were injected intradermally into the shaved dorsal skin of the rat. After 72 h, the rat was challenged with an intravenous injection of 1 mL of saline solution containing 5 mg of egg albumin and 10 mg of Evans blue. Drugs to be tested or vehicles (saline or polyethylene glycol 400) were administered intravenously immediately before antigen challenge. In the case of oral administration, drugs suspended in 3% gum arabicum were administered 5 min before antigen challenge. Rats were sacrificed by bleeding 30 min later, and the area of the dye leakage was measured in square millimeters. The ID_{50} value, i.e., the dose required to cause 50% inhibition of the PCA reaction, was calculated from the relationship between logarithmic dose and area of dye leakage by the method of least squares. Fiducial limits of the ID_{50} values were calculated according to Fieller's theorem.[12]

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2-Mercaptoacetamidines as Gastric Antisecretory Agents

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A series of N-substituted 2-mercaptoacetamidines was synthesized and evaluated for gastric antisecretory activity in dogs stimulated with gastrin tetrapeptide. The most potent analogues showed 80–95% inhibition of acid secretion after an oral dose of 8 mg/kg. Thus, these compounds represent a new structural type having significant antisecretory activity. Disulfides had essentially the same antisecretory potency as the corresponding mercaptoacetamidines, indicating a metabolic interconversion. Alkylation of the mercapto group decreased potency. Higher carboxamidine homologues such as 2- and 3-mercaptopropionamidines had very low activity. Hydroxyacetamidines and mercaptoacetamides also had low potency. Side effects observed with this series of compounds included emesis, tachycardia, and gastric bleeding.

Pharmacological evaluation of the antiradiation agent *N*-(1-adamantylmethyl)-2-mercaptoacetamidine[2a,b] (**3**) revealed that it possesses gastric secretion inhibitory properties. Detailed examination of its gastric effects in dogs with secretion induced by gastrin tetrapeptide, histamine, and 2-deoxy-D-glucose confirmed antisecretory activity of significant degree, accompanied, however, by an emetic side effect. Since the compound is structurally unlike that of any antisecretory agent reported heretofore, a synthetic program was initiated to assess the antisecretory and antiulcer potential of mercaptoacetamidines and related structures. The objectives of this research were (a) to determine the extent of structural variation consistent with retention of significant antisecretory activity, (b) to identify the specific structures having maximal potency, and (c) to eliminate undesirable pharmacologic effects. Compounds chosen for preparation were designed to incorporate features permitting studies of the effect of size and lipophilicity of the amidine substituent, changes in the structure of the carboxamidine chain, amidine surrogates, and sulfhydryl group requirements.

Although compounds possessing sulfhydryl groups such as dithiothreitol and 2,3-dimercaptopropanol cause a protein-losing gastropathy,[3] the mercaptoacetamidine lead

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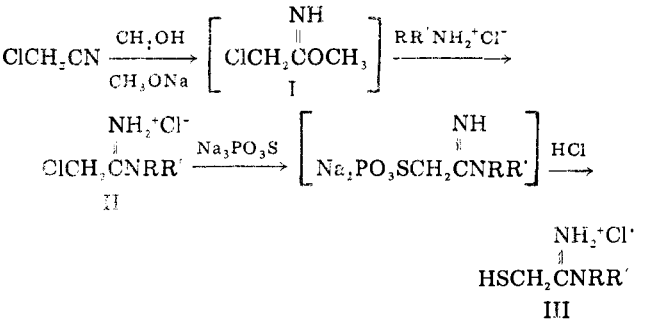
was deemed sufficiently different in structure, lipophilicity, and sulfhydryl acidity to warrant further exploration.

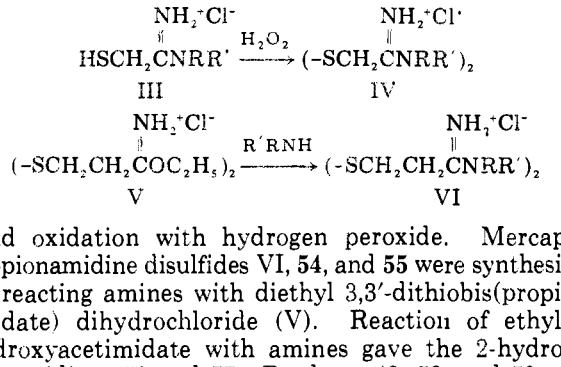
Chemistry. Several synthetic methods for the preparation of 2-mercaptoacetamidine derivatives have been reported, and these served as the basic preparative procedures for compounds required in the investigation. In the synthetic route generally used, methyl 2-chloroacetimidate (I) was prepared by the base-catalyzed reaction



of chloroacetonitrile with methanol[4,5] and allowed to react "in situ" with amine hydrochlorides to obtain the 2-chloroacetamidine hydrochlorides[5] II. Displacement of the halogen with phosphorothioate anion and subsequent acid hydrolysis produced the 2-mercaptoacetamidine hydrochlorides[6] III.

All the 2-mercaptoacetamidine hydrochlorides shown in Table I (compounds 1-42), including those previously reported by other investigators, were prepared via this pathway.

Compounds 43–59, shown in Table II, are analogues structurally related to the mercaptoacetamidines. The 2-mercaptoacetamides 44–46, 2-mercaptopropionamidine 47, and 4-mercaptobutyramidine 48 were prepared from their respective halo precursors by the same procedure used to prepare III from II. The 3-mercaptopropionamidine 49 was obtained by tributylphosphine cleavage of the corresponding disulfide[7] 55. Reaction of the 2-chloroacetamidine 15a with sodium methylmercaptide and sodium benzylmercaptide gave thioethers 50 and 51, respectively. Mercaptoacetamidine disulfides IV, 52, and 53 were formed from the appropriate mercaptans III by



mild oxidation with hydrogen peroxide. Mercaptopropionamidine disulfides VI, 54, and 55 were synthesized by reacting amines with diethyl 3,3′-dithiobis(propionimidate) dihydrochloride (V). Reaction of ethyl 2-hydroxyacetimidate with amines gave the 2-hydroxyacetamidines 56 and 57. Products 43, 58, and 59 were synthesized as reported in the literature.

The 2-chloroacetamidine intermediates for the products shown in Table I are listed in Table III and numbered correspondingly (1a-42a). The preparation of four previously unreported amine precursors to chloroacetamidines 7a, 14a, 17a, and 19a is described under Experimental Section. All were made by reduction of the corresponding carboxamides.

The proton dissociation constants, pK_a^1 for the reaction $-CH_2SH \rightleftharpoons -CH_2S^- + H^+$ and pK_a^2 for the reaction $-NHC(=NH)- + H^+ \rightleftharpoons -NHC(=NH_2^+)-$, were determined by potentiometric titration. Values for representative products are recorded in Table IV. A useful predictive correlation of these physical constants with antisecretory potency for the mercaptoacetamidines could not be established. Except for the aryl derivative 35, the pK_a^1 values for loss of the sulfhydryl proton of monosubstituted mercaptoacetamidines are all within the range of 6.50–6.80. The effects of the amidino group on the sulfhydryl moiety cause it to be considerably more acidic than an isolated sulfhydryl group of an alkyl mercaptan; e.g., the pK_a of ethyl mercaptan is 10.50.[8] As the length of the carbon chain separating the amidino and mercapto groups increased, the pK_a of the latter approached that of an isolated sulfhydryl, as shown by compound 48. The narrow pK_a^2 range of 10.70–11.00 for the gain of a proton by S-alkylated mercaptocarboxamidines is similar to the pK_a of the acetamidine 58 and demonstrates the lack of effect of the sulfhydryl group on the basicity of the amidino group.

Discussion

The original lead, compound 3, inhibits gastric secretion in the dog induced by a gastrin analogue, histamine, 2-deoxy-D-glucose, as shown in Table V. Volume and acid concentration were inhibited approximately equally, regardless of the stimulant. Corresponding data for metiamide,[9] *N*-methyl-*N*′-[2-[(5-methyl-1*H*-imidazol-4-yl)methylthio]ethyl]thiourea, obtained in the same dog colony with gastrin tetrapeptide stimulation are included in the table for comparison.

The antisecretory potency of the mercaptoacetamidines and related structures vs. gastrin tetrapeptide stimulations is expressed as inhibition of total acid output in Tables I and II. Although many of the new compounds are more active inhibitors of gastric secretion than the lead, 3, side effects such as emesis remained a major problem.

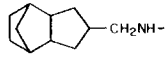
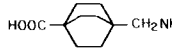
Polycyclic alkyl derivatives showed some promise of decreased side effects. A homologous group, 1 and 5–8, was prepared to evaluate the effectiveness of greater separation of the polycyclic alkyl and amidino groups. Side effects were decreased but not completely eliminated with compound 6, the most potent of the group. Lowered potency resulted from disubstitution on nitrogen, as shown by a comparison of 21 and 40. Aryl substitution on the amidine group also lowered potency. The disulfide derivatives 52 and 53 have essentially the same antisecretory activity as the corresponding mercapto analogues 21 and 3, indicating a possible metabolic interconversion of the former to the latter. Alkylation of the mercapto group as in the *S*-methyl (50) and *S*-benzyl (51) derivatives of 15 decreases antisecretory activity. Increasing the length of the carbon chain as in 48 and 49 results in a decreased potency relative to the corresponding mercaptoacetamidines 12 and 21. Branching at the mercapto carbon as in 47 also decreases potency. Acetamidines 58 and 59, hydroxyacetamidines 56 and 57, and mercaptoacetamides 44–46 showed a sharply reduced potency.

It therefore appears that maximal antisecretory activity resides in the mercaptoacetamidine nucleus, and changes in this part of the structure, except for oxidation to the corresponding disulfide, affect the potency adversely. Side effects, of which emesis, tachycardia, and gastric bleeding were the most common, were associated with activity, and total elimination of these undesirable characteristics was not achieved. Side effects were not quantitated and are not included in the tables of data.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer, and NMR

Table I. Gastric Antisecretory Screening in the Dog. 2-Mercaptoacetamidines, $RC(=NH)CH_2SH \cdot HCl$

compd	R	mp, °C	recrystn solvent	yield, %	formula[a]	dose: p	% inhib of total acid output[b] 4.0	8.0	16.0
1[d]	1-adamantyl-NH-	244-244.5 dec	EtOH-Et_2O	25	$C_{12}H_{20}N_2S \cdot HCl$			61	86
2[d]	2-adamantyl-NH-	206-210 dec	EtOH-Et_2O	69	$C_{12}H_{20}N_2S \cdot HCl$				85
3[e]	1-adamantyl-CH_2NH-	216-218 dec	H_2O-EtOH	70	$C_{13}H_{22}N_2S \cdot HCl$			47	74
4	2-adamantyl-CH_2NH-	185-186 dec	MeOH-Et_2O	85	$C_{13}H_{22}N_2S \cdot HCl$			67	
5	1-adamantyl-$(CH_2)_2NH$-	211-212.5 dec	EtOH-Et_2O	94	$C_{14}H_{24}N_2S \cdot HCl$		0	61	100
6[d]	1-adamantyl-$(CH_2)_3NH$-	234-235	*i*-PrOH-Et_2O	88	$C_{15}H_{26}N_2S \cdot HCl$		36	81	
7	1-adamantyl-$(CH_2)_4NH$-	181-183 dec	*i*-PrOH-Et_2O	87	$C_{16}H_{28}N_2S \cdot HCl$		0	67	
8	1-adamantyl-$(CH_2)_5NH$-	98-112 (hygroscopic)	*i*-PrOH-Et_2O	38	$C_{17}H_{30}N_2S \cdot HCl$			9	
9[f]	H_2N-	118.5-122	*i*-PrOH	62	$C_2H_6N_2S \cdot HCl$			89	
10	C_2H_5NH-	113.5-115.5	CH_3CN-EtOH	55	$C_4H_{10}N_2S \cdot HCl$		90[g]		
11	$(CH_3)_2CHNH$-	98-104	*i*-PrOH-Et_2O	83	$C_5H_{12}N_2S \cdot HCl$			58	
12	$(CH_3)_3CCH_2NH$-	140-142	CH_3CN	65	$C_7H_{16}N_2S \cdot HCl$		25	95	
13	c-$C_6H_{11}CH_2NH$-	70-72 dec	EtOH-Et_2O	24	$C_9H_{18}N_2S \cdot HCl$			86	
14	1-norbornyl-CH_2NH-	135 dec	*i*-PrOH-Et_2O	88	$C_{10}H_{18}N_2S \cdot HCl$		0	91	
15	*endo*-2-norbornyl-CH_2NH-	148-152	EtOH-Et_2O	57	$C_{10}H_{18}N_2S \cdot HCl$		28	83	
16	1-bicyclo[2.2.2]octyl-CH_2NH-	193.5-194.5 dec	EtOH-Et_2O	86	$C_{11}H_{20}N_2S \cdot HCl$[h]		48	87	
17	1-bicyclo[3.2.1]octyl-CH_2NH-	178 dec	*i*-PrOH-Et_2O	63	$C_{11}H_{20}N_2S \cdot HCl$[i]		0[j]	95	
18	1-bicyclo[3.3.1]nonyl-CH_2NH-	211-212.5 dec	EtOH-Et_2O	80	$C_{12}H_{22}N_2S \cdot HCl$			67	23
19		noncryst			$C_{13}H_{22}N_2S \cdot HCl$[k]			70	
20		amorphous	*i*-PrOH-Et_2O		$C_{12}H_{20}N_2O_2S \cdot HCl$[l]			0	
21[f]	$C_6H_5CH_2NH$-	116.5-118.5	*i*-PrOH-Et_2O	64	$C_9H_{12}N_2S \cdot HCl$		29	83	
22	4-$C_5H_4NCH_2NH$-	190-194 dec	MeOH-Et_2O	46	$C_8H_{11}N_3S \cdot 2HCl$			85	
23[f]	2-$C_5H_4NCH_2NH$-	198-200 dec	MeOH	60	$C_8H_{11}N_3S \cdot 2HCl$			82	
24	$C_6H_5CH{=}CHCH_2NH$-	noncryst		41	$C_{11}H_{14}N_2S \cdot HCl$[m]			53	
25	$(C_6H_5)_2CHCH_2NH$-	196-198 dec	EtOH-Et_2O	84	$C_{16}H_{18}N_2S \cdot HCl$			0	60
26	$(C_6H_5)_2CHNH$-	225-227 dec	EtOH-Et_2O	91	$C_{15}H_{16}N_2S \cdot HCl$				82
27	$(C_6H_5)(4\text{-}ClC_6H_4)CHNH$-	100-105 dec	EtOH-Et_2O	84	$C_{15}H_{15}ClN_2S \cdot HCl$				87
28	$C_6H_5CH_2(C_6H_5)CHNH$-	187	EtOH-Et_2O	76	$C_{16}H_{18}N_2S \cdot HCl$				84
29[f]	c-C_5H_9NH-	147-148.5	EtOH-Et_2O	46	$C_7H_{14}N_2S \cdot HCl$		63	100	
30[f]	c-$C_6H_{11}NH$-	168-171	EtOH-Et_2O	53	$C_8H_{16}N_2S \cdot HCl$		37	79	
31	*endo*-2-norbornyl-NH-	160-163 dec	*i*-PrOH-Et_2O	80	$C_9H_{16}N_2S \cdot HCl$			94	
32	2-indanyl-NH-	102 dec	EtOH-Et_2O	94	$C_{11}H_{14}N_2S \cdot HCl$				100
33	1-indanyl-NH-	163-166 dec	MeOH-Et_2O	86	$C_{11}H_{14}N_2S \cdot HCl$			20	85
34	9-fluorenyl-NH-	206-209 dec	*i*-PrOH-Et_2O	60	$C_{15}H_{14}N_2S \cdot HCl$				0
35	C_6H_5NH-	129-132	EtOH-Et_2O	80	$C_8H_{10}N_2S \cdot HCl$				0
36	3-ClC_6H_4NH-	126-128	EtOH-Et_2O	47	$C_8H_9ClN_2S \cdot HCl$				16[n]
37	1-naphthyl-NH-	226 dec	EtOH-Et_2O	45	$C_{12}H_{12}N_2S \cdot HCl$				64
38	5,6,7,8-tetrahydro-1-naphthyl-NH-	158 dec	*i*-PrOH-Et_2O	40	$C_{12}H_{16}N_2S \cdot HCl$				14
39	$(CH_3)_2N$-	157-159 dec	EtOH-Et_2O	57	$C_4H_{10}N_2S \cdot HCl$[o]		0	62	
40	$C_6H_5CH_2(CH_3)N$-	201.5-203	EtOH-Et_2O	32	$C_{10}H_{14}N_2S \cdot HCl$				0
41	morpholino-	143-145 dec	CH_3CN-*i*-PrOH	26	$C_6H_{12}N_2OS \cdot HCl$			2	23
42		173-175 dec	Me_2CO	70	$C_{10}H_{18}N_2S \cdot HCl$				92

[a] All compounds had analyses within 0.4% for C, H, and N, except as noted otherwise. [b] Average of values obtained in up to five dogs with secretion induced by gastrin tetrapeptide. [c] Base weight of compound. [d] Ref 2b. [e] Ref 2a. [f] Ref 6. [g] 27% inhibition at 2 mg/kg. [h] N: calcd, 11.26; found, 10.84. [i] C: calcd, 53.09; found, 53.60. [j] 44% inhibition at 6 mg/kg. [k] C: calcd, 56.80; found, 57.62; Cl: calcd, 12.90; found, 13.00. [l] N: calcd, 9.57; found, 10.08. [m] Calcd includes 11% EtOH shown by NMR; C: calcd, 54.18; found, 53.08. [n] 61% inhibition at 32 mg/kg. [o] N: calcd, 18.12; found, 17.62.

Table II. Gastric Antisecretory Screening in the Dog. Compounds Related to 2-Mercaptoacetamidines

compd	structure	mp, °C	recrystn solvent	yield, %	formula[a]	% inhib of total acid output,[b] dose in mg/kg[c] 4.0	8.0	16.0
43[d]	2-(2-imidazolinyl)-CH_2SH				$C_4H_8N_2S\cdot HCl$	[e]	[f]	
44[g]	$C_6H_5CH_2NHC(=O)CH_2SH$				$C_9H_{11}NOS$		0	
45[h]	c-$C_6H_{11}NHC(=O)CH_2SH$				$C_8H_{15}NOS$		0	[f]
46[i]	1-adamantyl-$NHC(=O)CH_2SH$	106.5-108.5	$C_6H_{11}CH_3$	86	$C_{12}H_{19}NOS$			58
47[j]	$(CH_3)_3CCH_2NHC(=NH)CH(CH_3)SH$	212.5-214 dec	EtOH-Et_2O	20	$C_8H_{18}N_2S\cdot HCl$		0	28
48[j]	$(CH_3)_3CCH_2NHC(=NH)(CH_2)_3SH$	143-145	CH_3CN-Et_2O	12	$C_9H_{20}N_2S\cdot HCl$		11	
49	$C_6H_5CH_2NHC(=NH)(CH_2)_2SH$	noncryst			$C_{10}H_{14}N_2S\cdot HCl\cdot 0.25(C_4H_9)_3PO$[k]			18[l]
50	*endo*-2-norbornyl-$CH_2NHC(=NH)CH_2SCH_3$	61-62.5	hexane	58	$C_{11}H_{20}N_2S$		35	
51	*endo*-2-norbornyl-$CH_2NHC(=NH)CH_2SCH_2C_6H_5$	77-80	hexane	49	$C_{17}H_{24}N_2S$			19
52[d]	$[C_6H_5CH_2NHC(=NH)CH_2S-]_2$				$C_{18}H_{22}N_4S_2\cdot 2HCl$	84		
53[m]	[1-adamantyl-$CH_2NHC(=NH)CH_2S-]_2$				$C_{26}H_{42}N_4S_2\cdot 2HCl$		62	80
54	$[(CH_3)_3CCH_2NHC(=NH)CH_2CH_2S-]_2$	noncryst			$C_{16}H_{34}N_4S_2\cdot 2HCl$[n]		21	75
55	$[C_6H_5CH_2NHC(=NH)CH_2CH_2S-]_2$	noncryst			$C_{20}H_{26}N_4S_2\cdot 2HCl$[o]			42
56	$(CH_3)_3CCH_2NHC(=NH)CH_2OH$	164-166	*i*-PrOH-Et_2O	78	$C_7H_{16}N_2O\cdot HCl$		22	61
57	$C_6H_5CH_2NHC(=NH)CH_2OH$	151-153	*i*-PrOH-Et_2O	79	$C_9H_{12}N_2O\cdot HCl$			0
58[p]	$C_6H_5CH_2NHC(=NH)CH_3$				$C_9H_{12}N_2\cdot HCl$[q]			19
59[p]	c-$C_6H_{11}NHC(=NH)CH_3$				$C_8H_{16}N_2$[q]			0

[a] See corresponding footnote in Table I. [b] See corresponding footnote in Table I. [c] See corresponding footnote in Table I. [d] Ref 6. [e] 100% inhibition at 2 mg/kg. [f] Mortality in one animal; test abandoned. [g] H. Nishimura and H. Takamatsu, *Yakugaku Zasshi*, 84, 944 (1964); *Chem. Abstr.*, 62, 2750f (1965). [h] German Patent 1 253 869 (1967); *Chem. Abstr.*, 68, 24510w (1968). [i] Precursor *N*-(1-adamantyl)chloroacetamide reported in Netherlands Patent 6 509 927 (1966); *Chem. Abstr.*, 64, 19450e (1966). [j] Halo precursor described under Experimental Section. [k] NMR spectra and analyses indicate the presence of 0.25 mol of tributylphosphine oxide, the reaction byproduct. Test levels were adjusted accordingly. C: calcd, 54.74; found, 56.25. [l] 42% inhibition at 32 mg/kg. [m] Ref 2b. [n] C: calcd, 45.80; found, 46.85. [o] C: calcd, 52.28; found, 54.25. [p] L. Baiocchi and G. Palazzo, *Ann. Chim.* (*Rome*), 58, 608 (1968). [q] Not analyzed.

spectra were obtained with a Varian A-60 spectrometer. NMR spectra were obtained for all intermediates and final products and are consistent with the assigned structures. Elemental analyses as indicated by the symbols of the elements were within ±0.4% of the calculated value, unless stated otherwise. For products listed in Tables I, II, or III, yields, recrystallization solvents, physical constants, and analyses are recorded in the tabular form rather than in this section.

Synthesis of 2-Chloroacetamidine Hydrochlorides. General Method. Most of the amine hydrochlorides used in this synthesis were prepared by published procedures or were obtained from commercial sources as indicated in Table III. Syntheses of previously undescribed amine hydrochlorides are documented later in this section.

Chloroacetonitrile (0.10 mol) was added to a cold solution of MeONa (0.01 mol) in 50 mL of dry MeOH, and the solution was stirred at ambient temperature for 0.5 to 1 h. Then the amine hydrochloride (0.11 mol) was added, and stirring was continued at ambient temperature for 1 to 3 h. Secondary and sterically hindered amines required a reaction period of up to 16 h. Product was obtained by filtering the cold mixture to remove precipitated salt, followed by concentration of the filtrate in vacuo. The oily residue usually crystallized upon trituration with Me_2CO.

Synthesis of Mercaptocarboxamidine Hydrochlorides and Mercaptoacetamides. General Method. The chlorocarboxamidine hydrochloride or chlorocarboxamide (0.025 mol) was added to a solution of trisodium phosphorothioate[10] (0.025 mol) in 35 mL of H_2O at room temperature under N_2. The solution was stirred at ambient temperature until the $AgNO_3$ test[11] for phosphorothioate anion was negative (usually 2-10 min). Then 6 N HCl (25 mL) was added, and the solution was heated for 10 min on a steam bath and concentrated in vacuo. The residue was treated with *i*-PrOH (25 mL), filtered, and diluted with excess Et_2O to precipitate the product as the HCl salt.

***N*-Benzyl-3-mercaptopropionamidine Hydrochloride (49).** 3,3′-Dithiobis(*N*-benzylpropionamidine) dihydrochloride (**55**) (4.3 g, 0.00925 mol) was stirred under N_2 with tributylphosphine (5.66 g, 0.028 mol) in 90 mL of MeOH containing 3 mL of H_2O for 48 h. The mixture was concentrated below 40 °C, the residue was suspended in 50 mL of H_2O, and 50 mL of CCl_4 was added dropwise with cooling and stirring. The aqueous layer was repeatedly extracted with CCl_4 and then lyophilized to obtain a gummy residue of 4 g. The gum was dissolved in *i*-PrOH, filtered from insoluble matter, and reprecipitated with Et_2O. The reprecipitation was repeated several times. The product was dried at 55 °C under high vacuum. NMR confirmed the structure but indicated about a 0.25 mol contamination with tributylphosphine oxide.

***N*-(*endo*-2-Norbornylmethyl)-2-methylthioacetamidine (50).** The reaction was carried out under N_2 atmosphere. A solution of MeSNa was prepared by bubbling MeSH into 50 mL of EtOH containing MeONa (0.54 g, 0.01 mol). This solution was added to 50 mL of EtOH containing *N*-(*endo*-2-norbornylmethyl)-2-chloroacetamidine hydrochloride (**15a**) (2.37 g, 0.01 mol) and MeONa (0.54 g, 0.01 mol). The mixture was stirred at ambient temperature for 1.5 h, filtered, and concentrated in vacuo. Trituration of the residue with hexane gave compound **50**.

***N*-(*endo*-2-Norbornylmethyl)-2-benzylthioacetamidine (51).** Compound **51** was prepared by the procedure for the synthesis of compound **50** by replacing the methyl mercaptan with an equivalent amount of benzyl mercaptan.

3,3′-Dithiobis(*N*-benzylpropionamidine) Dihydrochloride (55). Diethyl 3,3′-dithiobis(propionimidate) dihydrochloride[12] (16.9 g, 0.05 mol) was suspended in 100 mL of absolute EtOH, and benzylamine (10.7 g, 0.1 mol) in 25 mL of EtOH was added over 10 min with cooling to keep the temperature below 35 °C. After stirring for 24 h at room temperature, the mixture was concentrated under vacuum at 25 °C. On trituration with Et_2O, the residue solidified to an amorphous hygroscopic mass. A 3-g portion of the crude product was dissolved in 9 mL of EtOH and filtered from insoluble matter; addition of Et_2O precipitated the salt. The precipitation was repeated, and the sample was dried at room temperature for 48 h over P_2O_5 under vacuum. NMR indicated solvation.

3,3′-Dithiobis[*N*-(2,2-dimethylpropyl)propionamidine] dihydrochloride (54) was prepared in the same manner as **55** by replacing the benzylamine with an equimolar amount of 2,2-dimethylpropylamine.

***N*-(2,2-Dimethylpropyl)-2-hydroxyacetamidine Hydrochloride (56).** Ethyl 2-hydroxyacetimidate hydrochloride[13] (9.5 g, 0.068 mol) was suspended in 50 mL of absolute EtOH and cooled to 5 °C. 2,2-Dimethylpropylamine (5.65 g, 0.065 mol) was added

Table III. 2-Chloroacetamidines, $RC(=NH)CH_2Cl \cdot HCl$[a]

compd	mp, °C	recrystn solvent	yield, %	formula[b]	RH[c] source
1a	257-258 dec	EtOH-*i*-Pr_2O		$C_{12}H_{19}ClN_2 \cdot HCl$[d]	A
2a	248-249.5 dec	*i*-PrOH-Et_2O	90	$C_{12}H_{19}ClN_2 \cdot HCl$[e]	A
3a[f]					
4a	218-220	MeOH-Et_2O	77	$C_{13}H_{21}ClN_2 \cdot HCl$[g]	B[h]
5a	255-256 dec	EtOH-*i*-PrOH	76	$C_{14}H_{23}ClN_2 \cdot HCl$	B[i]
6a	219-220	*i*-PrOH-Et_2O	76	$C_{15}H_{25}ClN_2 \cdot HCl$	B[j]
7a	196-197.5	*i*-PrOH-Et_2O	62	$C_{16}H_{27}ClN_2 \cdot HCl$	C
8a	161-163	*i*-PrOH-Et_2O	94	$C_{17}H_{29}ClN_2 \cdot HCl$[k]	B[l]
9a[m]					
10a[n]					
11a	164-166	*i*-PrOH-Et_2O	53	$C_5H_{11}ClN_2 \cdot HCl$	A
12a	165-166.5	EtOH-Et_2O	74	$C_7H_{15}ClN_2 \cdot HCl$	A
13a	145-146.5	*i*-PrOH-*i*-Pr_2O	77	$C_9H_{17}ClN_2 \cdot HCl$	A
14a	178-180	*i*-PrOH-Et_2O	77	$C_{10}H_{17}ClN_2 \cdot HCl$[d]	C
15a	171-173.5	*i*-PrOH-*i*-Pr_2O	55	$C_{10}H_{17}ClN_2 \cdot HCl$	A
16a	249.5-251 dec	EtOH-Et_2O	77	$C_{11}H_{19}ClN_2 \cdot HCl$	B[o]
17a	227 dec	*i*-PrOH-Et_2O	92	$C_{11}H_{19}ClN_2 \cdot HCl$[d]	C
18a	252-255 dec	MeOH-Et_2O	81	$C_{12}H_{21}ClN_2 \cdot HCl$	B[p]
19a	162-164	*i*-PrOH-*i*-Pr_2O	74	$C_{13}H_{21}ClN_2 \cdot HCl$	C
20a	noncryst			$C_{12}H_{19}ClN_2O \cdot HCl$[d]	B[q]
21a[n]					
22a	202-205 dec	MeOH-Et_2O	80	$C_8H_{10}ClN_3 \cdot 2HCl$[r]	A
23a[s]					
24a	noncryst		85	$C_{11}H_{13}ClN_2 \cdot HCl$[d]	B[t]
25a	187-190	EtOH-Et_2O	60	$C_{16}H_{17}ClN_2 \cdot HCl$[u]	A
26a	236-237 dec	*i*-PrOH	74	$C_{15}H_{15}ClN_2 \cdot HCl$	A
27a	191-193	CH_3CN	33	$C_{15}H_{14}Cl_2N_2 \cdot HCl$[d]	A
28a	198-200	CH_3CN	52	$C_{16}H_{17}ClN_2 \cdot HCl$[d]	A
29a[v]					
30a[v]					
31a[f]					
32a	noncryst		56	$C_{11}H_{13}ClN_2 \cdot HCl$[d]	A
33a	172.5-175	MeOH-Et_2O	82	$C_{11}H_{13}ClN_2 \cdot HCl$	A
34a	222-225	EtOH-Et_2O	71	$C_{15}H_{13}ClN_2 \cdot HCl$[d]	A
35a	160-163	EtOH-Et_2O	34	$C_8H_9ClN_2 \cdot HCl$[w]	A
36a	153 dec	Me_2CO	14	$C_8H_8Cl_2N_2 \cdot HCl$[d]	A
37a	150-153	Me_2CO-Et_2O	16	$C_{12}H_{11}ClN_2 \cdot HCl$[d]	A
38a	noncryst		20	$C_{12}H_{15}ClN_2 \cdot HCl$[d]	A
39a[n]					
40a	158.5-160.5	CH_3CN	45	$C_{10}H_{13}ClN_2 \cdot HCl$	A
41a	162-165	*i*-PrOH	72	$C_6H_{11}ClN_2O \cdot HCl$	A
42a	236-238 dec	EtOH	39	$C_{10}H_{17}ClN_2 \cdot HCl$	A

[a] Compounds are numbered to correspond with the mercapto products in Table I. The R structure is shown in that table. [b] All new compounds had analyses within 0.4% for C, H, and N, except as noted otherwise. [c] A, commercial source; B, known, prepared by previously reported method; C, new, described under Experimental Section. [d] Not analyzed, NMR spectra consistent with structure assigned. [e] H: calcd, 7.66; found, 8.14. [f] Ref 2a. [g] C: calcd, 56.32; found, 55.25. [h] I. S. Yankovskaya, I. Mayeika, D. Kruskops, and J. Polis, *Zh. Obshch. Khim.*, 43, 490 (1973); *Chem. Abstr.*, 79, 31049h (1973). [i] V. L. Narayanan and J. Bernstein, German Patent 2 136 702 (1972); *Chem. Abstr.*, 76, 112796q (1972). [j] J. K. Chakrabarti, M. J. Foulis, T. M. Hotten, S. S. Szinai, and A. Todd, *J. Med. Chem.*, 17, 602 (1974). [k] C: calcd, 61.25; found, 60.70. [l] W. Hoek, H. Wynberg, and J. Strating, *Recl. Trav. Chim. Pays-Bas*, 85, 1054 (1966); *Chem. Abstr.*, 66, 28600g (1967). [m] Ref 5. [n] L. Bauer and T. L. Welsh, *J. Org. Chem.*, 27, 4382 (1962). [o] J. G. Whitney, W. A. Gregory, J. C. Kauer, J. R. Roland, J. A. Snyder, R. E. Benson, and C. E. Hermann, *J. Med. Chem.*, 13, 254 (1970). [p] British Patent 1 104 058; *Chem. Abstr.*, 69, 51739e (1968). [q] L. J. Loeffler, S. F. Britcher, and W. Baumgarten, *J. Med. Chem.*, 13, 926 (1970). [r] N: calcd, 16.38; found, 15.77. [s] A. P. Parulkar and L. Bauer, *J. Heterocycl. Chem.*, 3, 472 (1966). [t] Japanese Patent, 28 351 (1965); *Chem. Abstr.*, 64, 17480h (1966). [u] C: calcd, 62.14; found, 61.69. [v] Ref 6. [w] C: calcd, 46.85; found, 45.83.

Table IV. pK_a^1 and pK_a^2 of Selected Mercaptoacetamidines and Related Structures

compd	pK_a^1[a]	pK_a^2[b]	compd	pK_a^1[a]	pK_a^2[b]
9	6.78	11.00	39	6.30	11.00
11	6.70	10.80	41	6.30	11.00
12	6.50	10.75	43	6.60	10.70
15	6.65	10.75	47	6.70	11.00
21	6.50	10.85	48	9.50	10.90
29	6.80	11.00	51		11.00[c]
30	6.70	10.80	58		10.60
35	6.40	10.38			

[a] Proton lost. [b] Proton gained. [c] Determined in 20% EtOH-H_2O.

with stirring over 5 min while the temperature rose to 25 °C. After stirring at 25 °C for 3 h, the reaction mixture was filtered from insoluble matter. Addition of 500 mL of Et_2O precipitated crude **56**, wt 9.2 g.

***N*-Benzyl-2-hydroxyacetamidine hydrochloride (57)** was prepared analogously to **56** by replacing the 2,2-dimethylpropylamine with an equivalent amount of benzylamine.

Bicyclo[3.2.1]octane-1-carboxamide. Bicyclo[3.2.1]octane-1-carboxylic acid[14] (15.5 g, 0.1 mol) was refluxed with 40 mL of $SOCl_2$ in 50 mL of CCl_4 for 6 h. The mixture was then concentrated under vacuum and the residue was dissolved in 15 mL of Et_2O. Concentrated NH_4OH (125 mL) was added dropwise with vigorous stirring at 0 °C. After 2 h, the product, 15.8 g (mp 186-188 °C), was filtered and recrystallized from CH_3CN to obtain the amide of mp 187-189 °C. Anal. ($C_9H_{15}NO$) C, H, N.

The following carboxamides were synthesized by the procedure described for the preparation of bicyclo[3.2.1]octane-1-carboxamide. These carboxamides were reduced to the corresponding amines without further purification.

4-(1-Adamantyl)butyramide. From 4-(1-adamantyl)butyric acid[15] (20.0 g, 0.09 mol) was obtained 17.1 g of crude amide, mp 95-100 °C. Several recrystallizations from cyclohexane established

Table V. Effect of Compound 3 and Metiamide on Gastric Secretion in the Dog

compd	gastric stimulant	dose,[a] mg/kg po	% inhibition[b] vol	titratable acid	total acid output
3	gastrin tetrapeptide	8	7 ± 7	0 ± 0	8 ± 8
	gastrin tetrapeptide	16	74 ± 17	91 ± 5	83 ± 15
	histamine	32	36 ± 18	40 ± 18	55 ± 21
	2-deoxy-D-glucose	8	31 ± 13	18 ± 8	42 ± 12
	2-deoxy-D-glucose	16	79 ± 6	85 ± 15	97 ± 3
metiamide	gastrin tetrapeptide	16	65 ± 6	5 ± 5	64 ± 5
	gastrin tetrapeptide	32	83 ± 6	70 ± 14	90 ± 5

[a] Base weight. [b] Average values for compound 3 in three dogs and metiamide in four dogs.

the mp of 106–108.5 °C (yield 47%). The structure was confirmed by NMR.

Tricyclo[5.2.1.0^{2,6}]decane-4-carboxamide. This amide was obtained in 40% yield from tricyclo[5.2.1.0^{2,6}]decane-4-carboxylic acid. After recrystallization from isopropyl ether it had a mp of 120–126 °C. NMR confirmed the structure.

1-Bicyclo[3.2.1]octanemethylamine Hydrochloride. The reduction was conducted under N_2 atmosphere. Red-al[®] [70% sodium bis(2-methoxyethoxy)aluminum hydride in benzene] (86.5 g, 0.3 mol) was dissolved in 300 mL of dry C_6H_6 and bicyclo[3.2.1]octane-1-carboxamide (18.4 g, 0.12 mol) was added in portions over 20 min. The stirred reaction mixture was kept below 50 °C. On completion of the addition, the mixture was refluxed for 2 h and then cooled to 5 °C while 200 mL of 5 N NaOH was slowly added. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine and dried ($MgSO_4$). Addition of excess 6 N ethanolic HCl precipitated the product hydrochloride, 16.4 g (77%), mp 322–324 °C dec. Recrystallization from *i*-PrOH brought the melting point to 325–327 °C dec. Anal. ($C_9H_{17}N$·HCl) H, N; C: calcd, 61.52; found, 62.02.

The following amines were prepared by reduction of the corresponding carboxamides as illustrated in the preparation of 1-bicyclo[3.2.1]octanemethylamine hydrochloride.

4-(1-Adamantyl)butylamine Hydrochloride. Reduction of 4-(1-adamantyl)butyramide (14.5 g, 0.066 mol) to the amine and conversion to the HCl salt produced 9.5 g of white solid, which was recrystallized from EtOH-Et_2O: mp 268–271 °C dec; yield 49%. Anal. ($C_{14}H_{29}N$·HCl) C, H, N.

Tricyclo[5.2.1.0^{2,6}]decane-4-methylamine Hydrochloride. Tricyclo[5.2.1.0^{2,6}]decane-4-methylamine hydrochloride was obtained in 44% yield by reduction of the corresponding carboxamide and recrystallized from *i*-PrOH-*i*-Pr_2O, mp 275–278 °C dec. Anal. ($C_{11}H_{19}N$·HCl) H, N; C: calcd, 65.49; found, 65.06.

1-Norbornanemethylamine Hydrochloride. Norbornane-1-carboxamide[16] (13.99 g, 0.1 mol) was reduced to obtain 11.1 g (69%) of the amine hydrochloride. Recrystallization from *i*-PrOH-Et_2O brought the mp to 330 °C dec. Anal. ($C_8H_{15}N$·HCl) H, N; C: calcd, 59.43; found, 60.47.

4-Bromo-*N*-(2,2-dimethylpropyl)butyramidine Hydrochloride. 2,2-Dimethylpropylamine (4.36 g, 0.05 mol) was added to a stirred solution of ethyl 4-bromobutyrimidate hydrochloride[17] (11.5 g, 0.05 mol) in 100 mL of EtOH at 5 °C. Stirring was continued at ambient temperature for 1.75 h. The solution was concentrated in vacuo at room temperature and, on dilution of the residue with Me_2CO, 5.2 g of white solid was obtained, mp 152–156 °C. Recrystallization from CH_3CN raised the mp to 156–157 °C. The yield was 39%. Anal. ($C_9H_{19}BrN_2$·HCl) H, N; C: calcd, 39.79; found, 40.78.

2-Chloro-*N*-(2,2-dimethylpropyl)propionamidine Hydrochloride. Sodium methoxide (0.27 g, 0.005 mol) was added to a cold solution of 2-chloropropionitrile (4.48 g, 0.05 mol) in 50 mL of MeOH and stirred at ambient temperature for 1.5 h. Then a solution of 2,2-dimethylpropylamine (4.35 g, 0.05 mol) in 20 mL of MeOH containing 8.3 mL of ethanolic HCl (6 N) was added, and stirring was continued for 3 h. The mixture was concentrated in vacuo, and the solid residue was washed with cold Me_2CO and Et_2O. The white solid, 9.1 g, mp 238–242 °C, was recrystallized from EtOH-Et_2O to give pure material, mp 240–242 °C, yield 82%. Anal. ($C_8H_{17}ClN_2$·HCl) C, H, N.

Determination of pK_a. The "apparent" pK_a values were obtained by a method in which the pK_a is considered to be equal to the pH at the half neutralization point. (An apparent pK_a does not include corrections for ionic strength. For dilute solutions, these corrections are usually less than 0.1 pK unit.[18])

The sample (0.05 mol) was either dissolved in H_2O for a direct titration with 0.5 N NaOH or in 30 mL of H_2O containing NaOH (0.15 mol) for a back-titration with 0.5 N HCl using a glass-calomel electrode system on an expanded pH scale. The pH at the half neutralization point was taken from the neutralization curve. Benzamidine under these conditions has a pK_a value in water of 11.5 and 11.2 in 50% EtOH. The corresponding reported values are 11.6[19] and 11.2,[20] respectively.

Biological Test Methods. Nonanesthetized female beagles weighing 5–9 kg with a chronic gastric fistula were administered test compounds directly into the stomach via the gastric cannula (identified herein as oral administration). The compounds were administered in 50 mL of a 1% methylcellulose solution 1 h prior to stimulation of gastric secretion. Control animals received vehicle alone. Secretion was stimulated with gastrin tetrapeptide (64 μg/kg sc from a 30% Me_2SO solution containing 640 μg/mL), histamine (64 μg base wt/kg sc from a solution of histamine diphosphate, 640 μg base wt/mL, in physiological saline), or 2-deoxy-D-glucose (200 mg/kg sc dissolved in physiological saline). Gastric output was collected for 2 h after stimulation. Total volume was measured, and the acid concentration (titratable acid) was determined on an aliquot by titration to pH 7 with 0.01 N NaOH using a glass-calomel electrode. Total acid output was calculated as the product of volume and concentration. The results are expressed as percent inhibition of volume, titratable acid and total acid output relative to the controls for the lead (3), and percent inhibition of total acid output for screening.

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Inhibition of Gastric Acid Secretion by 1,8-Naphthyridin-2(1*H*)-ones

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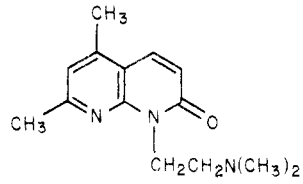
A number of 1-[(dialkylamino)alkyl]-1,8-naphthyridin-2(1*H*)-ones were prepared and evaluated in vivo for inhibition of gastric acid secretion evoked by gastrin tetrapeptide and also in vitro for antagonism of the rat uterine histamine H_2 receptor. The effect on activity of structural variation in the dialkylaminoalkyl group and the position and nature of naphthyridine ring substituents was examined. In this series, structural requirements for in vitro activity were found to be quite different from those required for maximal in vivo potency, and a positive correlation between histamine H_2-receptor antagonism and inhibition of gastrin tetrapeptide induced secretion could not be established. In addition, none of the compounds inhibited histamine-stimulated gastric secretion. 1-[2-(Dimethylamino)-ethyl]-1,8-naphthyridin-2(1*H*)-one and its 5- and 6-methyl analogues were the most potent in vivo inhibitors of gastrin tetrapeptide induced acid secretion, causing a 55–60% decrease in acid concentration at an oral dose of 20 mg/kg. However, they were only weakly active in vitro. On the other hand, 7-alkyl analogues, such as those with a 7-ethyl, 7-isopropyl, or 7-isobutyl substituent, had low in vivo potency but were excellent inhibitors, equivalent to metiamide, in the H_2-receptor assay.

Competitive antagonism of histamine H_2 receptors as a means of inhibiting gastric acid secretion has been established as an acceptable ulcer treatment.[1] The clinically effective antagonists metiamide (*N*-methyl-*N'*-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]ethyl]thiourea) and cimetidine (*N*-cyano-*N'*-methyl-*N''*-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]ethyl]guanidine) represent structural modifications of the physiological agonist histamine in which the imidazole nucleus was retained and major changes were made in the aminoethyl side chain.[2] In our approach to the inhibition of gastric acid secretion, the development of new structural types for H_2-receptor antagonism has been a major objective. As a working hypothesis, binding-site similarities were assumed for H_1- and H_2-histamine receptors, so that structural elements responsible for H_1-receptor antagonism could also be expected to interact with an H_2 receptor. Specifically, the presence on H_2 receptors of reactive sites for an alkylaminoalkyl group, a structure common to many antihistamine drugs, was postulated as a basis for an initial investigation.

Recent reports of the effects of dialkylaminoalkyl compounds on H_2 receptors or their dependent actions support the validity of these assumptions. Tripelennamine (*N*,*N*-dimethyl-*N'*-(phenylmethyl)-*N'*-2-pyridinyl-1,2-ethanediamine), an H_1 antagonist, has been shown to inhibit histamine-evoked gastric acid secretion in the dog stomach with an ED_{50} approximately tenfold that of metiamide,[3] while dimaprit (*S*-[3-(dimethylamino)-propyl]isothiourea) is a specific agonist for the H_2 receptor.[4a] Mepyramine (*N*-[(4-methoxyphenyl)methyl]-*N'*,*N'*-dimethyl-*N*-2-pyridinyl-1,2-ethanediamine) has been shown to inhibit both histamine- and dimaprit-induced activation of hippocampal adenylate cyclase,[4b] an H_2-receptor mediated response.

A variety of unique compounds having dialkylaminoalkyl substituents were tested in vitro in rat uterine tissue for antagonism of the H_2-receptor mediated response to histamine. Among the structures evaluated, an ethylenediamine analogue, 1-[2-(dimethylamino)ethyl]-5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one hydrochloride (**8**),



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was reasonably active and also inhibited gastric acid secretion in the dog. These findings prompted the synthesis of a number of analogues for evaluation in vitro as inhibitors of the histamine H_2 receptor and in vivo for inhibition of gastrin tetrapeptide evoked gastric secretion.

Chemistry. The majority of the compounds listed in Tables I and II were synthesized directly from the appropriate 1,8-naphthyridin-2(1*H*)-one by forming the alkali metal salt with sodium ethoxide in EtOH (method 1) or NaH in DMF (method 2), which was then allowed to react with a dialkylaminoalkyl halide. Two compounds containing a primary amino group in the side chain, **17** and the intermediate required for the preparation of **26**, were generated from the corresponding phthalimides. The monomethylamino derivative **18** was prepared by de-

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