Pyridazinones. 2. Synthesis and Antisecretory and Antiulcer Activities of Thiourea and 2-Cyanoguanidine Derivatives

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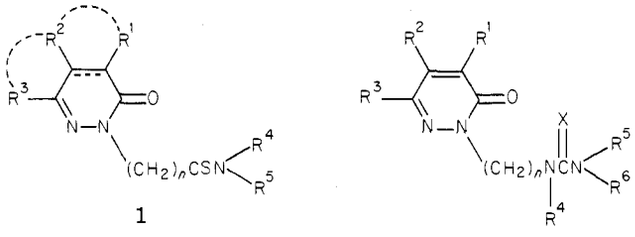
In an effort to develop new types of antiulcer agents, we synthesized a series of novel 2-[ω-(thioureido)alkyl]- and 2-[ω-(cyanoguanidino)alkyl]-3(2*H*)-pyridazinone derivatives. All target compounds were evaluated for gastric antisecretory activity in the pylorus-lygated rat by the method of Shay, and selected compounds were evaluated in the stress-induced ulcer test in rats. Structure–activity relationships were established. Two series of the compounds had significant activity in antisecretory and/or antiulcer tests. The molecular features essential for the activities are a thiourea group or a 2-cyanoguanidine group, a phenyl group in the C-6 position of the 3(2*H*)-pyridazinone ring, a four-carbon chain length between the 3(2*H*)-pyridazinone ring and the functional group, and a methyl group at the N-3 position of the functional group. Among them, the three thiourea derivatives (**24**, **26**, and **38**) and the six 2-cyanoguanidine derivatives (**61**, **62**, **65**, **75**, **85**, and **86**) had the most potent antisecretory and/or antiulcer activities. These compounds are not histamine H_2-receptor antagonists.

For development of new types of antiulcer agents without anticholinergic activity, a series of novel 3(2*H*)-pyridazinone derivatives have been synthesized and structural requirements for activity defined by molecular modification. We recently reported the synthesis of a series of 3(2*H*)-pyridazinone derivatives (**1**) having a 2-



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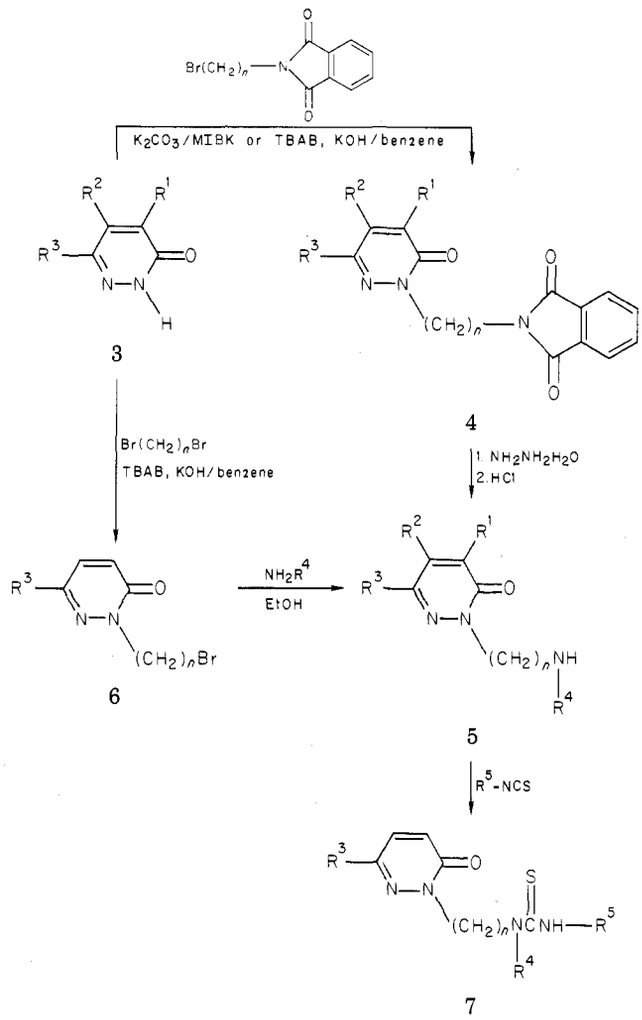
[ω-(thiocarbamoyl)alkyl] group, which were shown to possess marked gastric antisecretory and/or antiulcer activities in the rat.[1] It was shown that the molecular features essential for the activity are a thioamide group, a suitable number of carbon atoms in the methylene chains between the 3(2*H*)-pyridazinone ring and the thioamide group, and a phenyl ring in the C-6 position of the 3-(2*H*)-pyridazinone ring.

In this paper, we describe the synthesis and biological activity of 3(2*H*)-pyridazinone derivatives (**2**) having a thiourea or 2-cyanoguanidine group, in order to obtain a modification of the pharmaceutical profile of 3(2*H*)-pyridazinone derivatives. These two groups of compounds are similar in many of their physicochemical properties, such as acidity, hydrophobicity, and geometry.[2]

Chemistry. The 3(2*H*)-pyridazinone derivatives discussed in this paper have the 2-(ω-substituted-alkylene) part as a common structural unit and may be classified into the following two series according to the structure of their functional groups attached to the end of alkyl side chain: thiourea and 2-cyanoguanidine. Their synthetic routes are shown in Schemes I and II. The free amines **5** are the key intermediates to both thiourea and 2-cyanoguanidine derivatives, as shown in these schemes.

N-Alkylation of 3(2*H*)-pyridazinone (**3**) with *N*-(ω-bromoalkyl)phthalimides in the presence of K_2CO_3 in MIBK (methyl isobutyl ketone) gave 2-(ω-phthalimidoalkyl) derivatives (**4**), which was hydrolyzed with hydrazine hydrate to afford the free 2-(ω-aminoalkyl) derivatives (**5**) in good yield. Compounds **4** were also synthesized from **3** by a two-phase system with TBAB (tetra-*n*-butylammonium bromide) in benzene at room temperature.[3] When α,ω-dibromoalkanes were used as al-

Scheme I[a]



[a] $R^1 = R^2 = R^4 = H, CH_3$; $R^3 = CH_3$, Ar; R^5 = H, alkyl, Ar; n = 2–6.

(1) Yamada, T.; Nobuhara, Y.; Yamaguchi, A.; Ohki, M. *J. Med. Chem.* **1982**, *25*, 975.
(2) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D. Parsons, M. E.; Prain, H. D.; White, G. R. *J. Med. Chem.* **1977**, *20*, 901.
(3) Yamada, T.; Ohki, M. *Synthesis* **1981**, 631.

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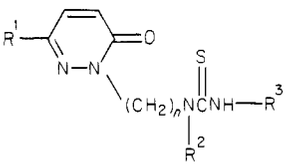
Table I. 2-[ω-(Thioureido)alkyl]-3(2*H*)-pyridazinones



no.	R^1	R^2	R^3	n	yield,[a] %	mp,[b] °C	crystn solvent[c]	formula[d]
10	CH_3	H	CH_3	2	68	125-126	EtOH + I	$C_9H_{14}N_4OS$
11	CH_3	H	CH_3	3	52	oil		$C_{10}H_{16}N_4OS$
12	CH_3	H	CH_3	4	54	oil		$C_{11}H_{18}N_4OS$
13	CH_3	H	CH_3	5	56	oil		$C_{12}H_{20}N_4OS$
14	CH_3	H	CH_3	6	51	oil		$C_{13}H_{22}N_4OS$
15	C_6H_5	H	CH_3	2	87	185-186	EtOH + I	$C_{14}H_{16}N_4OS$
16	C_6H_5	H	C_2H_5	2	92	183-185	EtOH	$C_{15}H_{18}N_4OS$
17	C_6H_5	H	c-C_6H_{11}	2	84	132-133	EtOH + I	$C_{19}H_{24}N_4OS$
18	C_6H_5	H	C_6H_5	2	90	141-142	EtOH + I	$C_{19}H_{18}N_4OS$
19	C_6H_5	H	CH_3	3	87	142-144	EtOH	$C_{15}H_{18}N_4OS$
20	C_6H_5	H	C_2H_5	3	85	120-121	EtOH	$C_{16}H_{20}N_4OS$
21	C_6H_5	H	c-C_6H_{11}	3	86	139-141	EtOH + I	$C_{20}H_{26}N_4OS$
22	C_6H_5	H	C_6H_5	3	91	188-189	EtOH	$C_{20}H_{20}N_4OS$
23	C_6H_5	H	H	4	34	65-68	EtOH	$C_{15}H_{18}N_4OS$
24	C_6H_5	H	CH_3	4	90	116-118	EtOH + I	$C_{16}H_{20}N_4OS$
25	C_6H_5	CH_3	CH_3	4	93	128-130	EtOH + ether	$C_{17}H_{22}N_4OS$
26	C_6H_5	H	C_2H_5	4	91	73-74	EtOH	$C_{17}H_{22}N_4OS$
27	C_6H_5	H	$CH_2CH{=}CH_2$	4	59	94-96	EtOH + I	$C_{18}H_{22}N_4OS$
28	C_6H_5	H	*i*-C_4H_9	4	37	oil		$C_{19}H_{26}N_4OS$
29	C_6H_5	H	*t*-C_4H_9	4	55	95-97	EtOH + I	$C_{19}H_{26}N_4OS$
30	C_6H_5	H	c-C_6H_{11}	4	53	oil		$C_{21}H_{28}N_4OS$
31	C_6H_5	H	$CH_2C_6H_5$	4	82	115-116	EtOH	$C_{22}H_{24}N_4OS$
32	C_6H_5	H	C_6H_5	4	96	156-157	EtOH	$C_{21}H_{22}N_4OS$
33	C_6H_5	H	C_6H_4(3-F)	4	86	153-155	EtOH	$C_{21}H_{21}FN_4OS$
34	C_6H_5	H	C_6H_4 (4-F)	4	76	171-174	EtOH	$C_{21}H_{21}FN_4OS$
35	C_6H_5	H	C_6H_4 (4-Cl)	4	68	153-154	EtOH + I	$C_{21}H_{21}ClN_4OS$
36	C_6H_5	H	C_6H_4 (4-SO_3Na)	4	46	256-260 dec	MeOH	$C_{21}H_{21}N_4O_4S_2Na$
37	C_6H_5	H	$C_{10}H_7$[e]	4	80	170-171	EtOH + $CHCl_3$	$C_{25}H_{24}N_4OS$
38	C_6H_5	H	CH_3	5	88	56-59	EtOH + I	$C_{17}H_{22}N_4OS$
39	C_6H_5	H	C_2H_5	5	93	105-106	EtOH	$C_{18}H_{24}N_4OS$
40	C_6H_5	H	CH_3	6	90	48-50	EtOH + I	$C_{18}H_{24}N_4OS$
41	C_6H_5	H	C_2H_5	6	77	76-78	EtOH + I	$C_{19}H_{26}N_4OS$

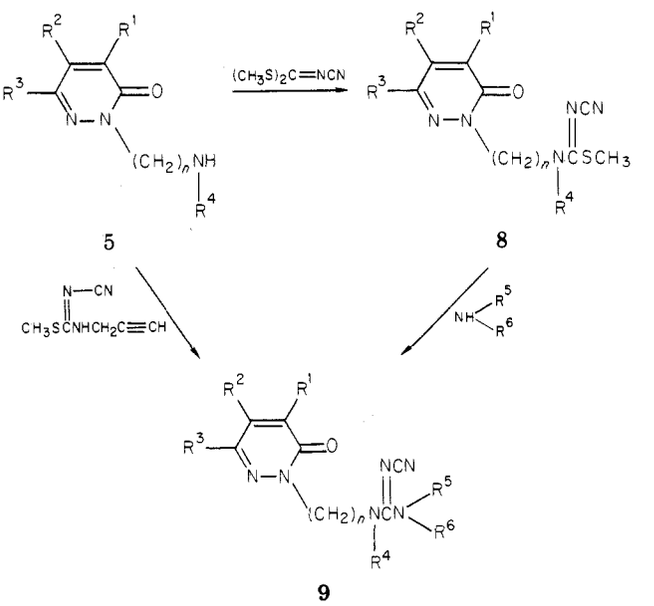
[a] The yield quoted was for the isolated purified product. [b] Oily compounds were directly recovered from the chromatographic column on silica gel (Wakogel C-200) with mix eluants (hexane–benzene–$CHCl_3$). [c] I = isopropyl ether. [d] All compounds were analyzed within ±0.4% of theory for C, H, and N. [e] 1-naphthyl.

kylating agents, only the ω-bromoalkylation product (**6**) was obtained by the two-phase system in good yield, in sharp contrast to the classical noncatalytic method (Na in EtOH[4] or NaH in DMF[5]) which usually gave rise to contamination with the bisalkylation product. Aminolyses of **6** were performed with NH_4OH in EtOH or 40% methylamine in MeOH at room temperature to afford only primary alkylamines or methylalkylamines (**5**).

The desired thiourea derivatives **7** were prepared by the reaction of **5** with the appropriate substituted isothiocyanates in good yield as shown in Table I.

The other desired 2-cyanoguanidine derivatives, **9**, were prepared by two synthetic routes from the key intermediates, **5**. The free amines **5** were converted with dimethyl cyanodithioimidocarbonate[6] to 3-cyano-2-methyl-1-isothioureas **8**, which gave the desired 2-cyano-3-substituted-1-guanidines **9** by the reaction with a suitable amine in an acceptable yield as shown in Table II. As for 3-propargyl derivatives **9**, 1-cyano-2-methyl-3-propargylisothiourea was prepared first from dimethyl cyanodithioimidocarbonate and propargylamine, because the nucleophilicity of propargylamine was too weak to react with the

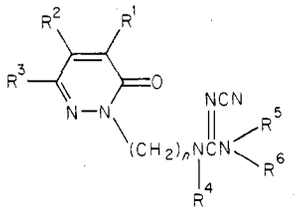
Scheme II[a]



[a] R^1 = R^2 = R^4 = H, CH_3; R^3 = CH_3, Ar; R^5, R^6 = H, alkyl, Ar, $CH_2C{=}CH$; n = 2-6.

(4) McMillan, F. H.; Kun, K. A.; McMillan, C. B.; Schwartz, B. S.; King, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 407.
(5) Holava, H. M.; Partyka, R. A. *J. Med. Chem.* **1971**, *14*, 262.
(6) Timmons, R. J.; Wittenbrook, L. S. *J. Org. Chem.* **1967**, *32*, 1566.

Table II. 2-[ω-(2-Cyanoguanidino)alkyl]-3(2*H*)-pyridazinones



no.	R^1	R^2	R^3	n	R^4	R^5	R^6	yield,[a] %	mp,[b] °C	crystn solvent[c]	formula[d]
42	H	H	CH_3	3	H	H	CH_3	86	165–166	EtOH	$C_{11}H_{16}N_6O$
43	H	H	CH_3	3	H	H	C_2H_5	61	147–149	EtOH + ether	$C_{12}H_{18}N_6O$
44	H	H	CH_3	3	H	H	n-C_3H_7	93	146–148	EtOH + ether	$C_{13}H_{20}N_6O$
45	H	H	CH_3	4	H	H	CH_3	86	151–152	EtOH	$C_{12}H_{18}N_6O$
46	H	H	CH_3	4	H	H	C_2H_5	93	152–154	EtOH	$C_{13}H_{20}N_6O$
47	H	H	CH_3	5	H	H	CH_3	32	oil		$C_{13}H_{20}N_6O$
48	H	H	C_6H_5	2	H	H	H	84	234–236	EtOH	$C_{14}H_{14}N_6O$
49	H	H	C_6H_5	2	H	H	CH_3	89	228–229	EtOH + I	$C_{15}H_{16}N_6O$
50	H	H	C_6H_5	2	H	CH_3	CH_3	65	119–121	A + I	$C_{16}H_{18}N_6O$
51	H	H	C_6H_5	3	H	H	H	71	164–166	EtOH	$C_{15}H_{16}N_6O$
52	H	H	C_6H_5	3	H	H	CH_3	90	185–186	EtOH	$C_{16}H_{18}N_6O$
53	CH_3	H	C_6H_5	3	H	H	CH_3	73	193–195	EtOH + I	$C_{17}H_{20}N_6O$
54	H	CH_3	C_6H_5	3	H	H	CH_3	68	207–209	MeOH	$C_{17}H_{20}N_6O$
55	H	H	C_6H_5	3	H	H	C_2H_5	90	156–158	A + I	$C_{17}H_{20}N_6O$
56	CH_3	H	C_6H_5	3	H	H	C_2H_5	83	165–166	EtOH	$C_{18}H_{22}N_6O$
57	H	CH_3	C_6H_5	3	H	H	C_2H_5	72	192–194	EtOH	$C_{18}H_{22}N_6O$
58	H	H	C_6H_5	3	H	H	n-C_3H_7	94	136–137	A + I	$C_{18}H_{22}N_6O$
59	H	H	C_6H_5	3	H	H	$CH_2C{\equiv}CH$	54	180–182	A	$C_{18}H_{18}N_6O$
60	H	H	C_6H_5	3	H	CH_3	CH_3	66	123–125	A + I	$C_{17}H_{20}N_6O$
61	H	H	C_6H_5	4	H	H	H	82	145–147	EtOH	$C_{16}H_{18}N_6O$
62	H	H	C_6H_5	4	H	H	CH_3	85	184–185	EtOH + I	$C_{17}H_{20}N_6O$
63	CH_3	H	C_6H_5	4	H	H	CH_3	79	158–159	MeOH	$C_{18}H_{22}N_6O$
64	H	CH_3	C_6H_5	4	H	H	CH_3	66	168–170	EtOH	$C_{18}H_{22}N_6O$
65	H	H	C_6H_5	4	H	CH_3	CH_3	81	141–143	A + I	$C_{18}H_{22}N_6O$
66	H	H	C_6H_5	4	CH_3	H	CH_3	89	144–146	EtOH + ether	$C_{18}H_{22}N_6O$
67	H	H	C_6H_4(4-Cl)	4	H	H	CH_3	83	208–209	EtOH	$C_{17}H_{19}ClN_6O$
68	H	H	C_6H_4(4-CH_3)	4	H	H	CH_3	88	169–170	EtOH	$C_{18}H_{22}N_6O$
69	H	H	C_6H_4(4-OCH_3)	4	H	H	CH_3	74	163–165	EtOH	$C_{18}H_{22}N_6O_2$
70	H	H	$N(CH_3)_2$	4	H	H	CH_3	92	136–137	EtOH	$C_{13}H_{21}N_7O$
71	H	H	c-NC_4H_8	4	H	H	CH_3	68	162–164	EtOH	$C_{15}H_{23}N_7O$
72	H	H	c-$N(CH_2CH_2)_2O$	4	H	H	CH_3	94	199–201	EtOH	$C_{15}H_{23}N_7O_2$
73	H	H	c-$N(CH_2CH_2)_2NCH_3$	4	H	H	CH_3	95	169–170	EtOH	$C_{16}H_{26}N_8O$
74	H	H	NHC_6H_5	4	H	H	CH_3	91	142–143	EtOH	$C_{17}H_{21}N_7O$
75	H	H	C_6H_5	4	H	H	C_2H_5	65	163–165	A + I	$C_{18}H_{22}N_6O$
76	CH_3	H	C_6H_5	4	H	H	C_2H_5	82	128–130	A	$C_{19}H_{24}N_6O$
77	H	CH_3	C_6H_5	4	H	H	C_2H_5	77	165–167	EtOH	$C_{19}H_{24}N_6O$
78	H	H	C_6H_5	4	H	H	n-C_3H_7	94	120–122	A	$C_{19}H_{24}N_6O$
79	H	H	C_6H_5	4	H	H	$CH_2C{\equiv}CH$	58	138–139	A	$C_{19}H_{20}N_6O$
80	H	H	C_6H_5	4	H	H	C_2H_4-C_6H_5	29	140–141	EtOH	$C_{24}H_{26}N_6O$
81	H	H	C_6H_5	5	H	H	H	85	138–139	EtOH + I	$C_{17}H_{20}N_6O$
82	H	H	C_6H_5	5	H	H	CH_3	69	148–149	EtOH + ether	$C_{18}H_{22}N_6O$
83	CH_3	H	C_6H_5	5	H	H	CH_3	69	138–140	EtOH + H_2O	$C_{19}H_{24}N_6O$
84	H	CH_3	C_6H_5	5	H	H	CH_3	64	106–107	EtOH	$C_{19}H_{24}N_6O$
85	H	H	C_6H_5	5	H	CH_3	CH_3	61	105–107	A + I	$C_{19}H_{24}N_6O$
86	H	H	C_6H_5	5	H	H	C_2H_5	71	145–146	A	$C_{19}H_{24}N_6O$
87	H	H	C_6H_5	5	H	H	n-C_3H_7	74	124–126	A + ether	$C_{20}H_{26}N_6O$
88	H	H	C_6H_5	6	H	H	H	61	115–117	EtOH + I	$C_{18}H_{22}N_6O$
89	H	H	C_6H_5	6	HH	H	CH_3	81	73–35	EtOH + H_2O	$C_{19}H_{24}N_6O$
90]	H	H	C_6H_5	6	H	CH_3	CH_3	56	77–79	A + I	$C_{20}H_{26}N_6O$
91	H	H	C_6H_5	6	H	H	C_2H_5	72	76–78	EtOH + H_2O	$C_{20}H_{26}N_6O$

[a, b] See corresponding footnotes in Table I. [c] A = acetonitrile; I = isopropyl ether. [d] See corresponding footnote in Table I.

isothiourea **8**, and then 2-cyano-3-propargyl-1-guanidines (**59** and **79**) were prepared from the 1-cyano-2-methyl-3-propargylisothiourea and the free amines **5**.

Pharmacological Results and Discussion

All compounds synthesized in the present studies were tested for gastric antisecretory activity at a dose of 100 mg/kg in the pylorus-lygated rat by the method of Shay.[7] Of the compounds that showed about 50% or more inhibition in this first screening, dose range studies were performed, and ED_{50} values were determined. In addition, compounds that showed substantial antisecretory activity were selected and tested for inhibition of the generation of experimental ulcer induced by stress.[8] For comparison, the active references cimetidine and 2-[5-(*N*-methylthiocarbamoyl)pentyl]-6-phenyl-3(2*H*)-pyridazinone (MUL-

(7) Shay, H.; Sun, D. C. H.; Gruenstein, M. *Gastroenterology* **1954**, *26*, 906.

(8) Takagi, K., Okabe, S. *Jpn. J. Pharmacol.* **1968**, *18*, 9.

037), which was described in our previous paper,[1] were included in the biological determinations. The structure and physicochemical data of the compounds synthesized are shown in Tables I and II, and their pharmacological activities are shown in Table III.

As described in our previous paper,[1] a wide range of 3(2*H*)-pyridazinone derivatives with a thioamide side-chain bond to the nitrogen at the 2-position of the 3(2*H*)-pyridazinone ring had considerable antisecretory and/or antiulcer activities. The thioamide moiety was considered to be an essential requisite for the biological activity. As shown in Table III, 3(2*H*)-pyridazinone derivatives having a thiourea moiety or 2-cyanoguanidine moiety instead of the thioamide moiety also had biological activity. A close inspection of the results reveals some interesting facts with respect to structure–activity relationships.

In the series of thiourea derivatives, 6-phenyl-3(2*H*)-pyridazinone derivatives (**15**, **19**, **24**, **38**, and **40**) were generally more active than the 6-methyl derivatives (**10–14**), among which only **12** showed activity. 6-Phenyl substituent was found to be very preferable for antisecretory activity. The effects of carbon chain length linking the thiourea moiety with the 3(2*H*)-pyridazinone ring were examined in 3-methyl- (**15**, **19**, **24**, **38**, and **40**) and 3-ethyl-1-thioureas (**16**, **20**, **26**, **39**, and **41**). The relative potencies of these compounds were as follows (n): $4 > 5 > 3$. In the case of $n = 2$ and 6, the compounds were not active. This finding that the compounds having a four-carbon chain length were outstandingly more potent than their homologues can be corresponded to the results that the most potent thioamide derivatives have a five-carbon chain length. This correspondence may be easy to understand by an imaginary replacement of the α-methylene group (CH_2CSNHR) on the thioamide derivatives by an amine group (*NH*CSNHR) in the thiourea moiety.

The influence of substitution at the N-3 position of the thiourea moiety for activity has been surveyed in a series where $n = 4$. 3-Methyl (**24**) was the most potent. Introduction of a long-chain alkyl group at N-3 of the thiourea moiety decreased the activity according to the length (**24**, **26**, and **28–30**). Aryl-substituted derivatives (**32–37**) were less active than their alkyl derivatives (**24** and **26**), and the effect of several substituents on the aryl ring was not elucidated. Compounds **23**, **24**, **26**, and **38** had the most potent antisecretory activity among the thiourea derivatives (**7**). The introduction of a methyl substituent (e.g., **25**) at N-1 of the thiourea moiety extremely deminished the activity. This finding indicates that the presence of one proton at the N-1 position of the thiourea moiety is required for gastric antisecretory activity.

In the series of 2-cyanoguanidine derivatives (**9**), they generally showed slightly less activity than the thiourea derivatives (**7**), as shown in Table III. In a series of 6-methyl-3(2*H*)-pyridazinones having a ω-(2-cyanoguanidino)alkylene side chain, only **43** and **45** showed potent antisecretory activity, but its activity was weak. Modification of the substituent at the C-6 position of the 3(2*H*)-pyridazinone ring from phenyl to methyl (**42–47**) or various amines (**70–74**) led to a decrease in potency; this was also found in both series of thiourea (**7**) and thioamide derivatives. The effect of the substituent on the phenyl ring on biological activity was examined (**67–69**), but the biological advantage could not be elucidated as well as in the series of the corresponding thioamide derivatives. The effects of length of the carbon chain linking the 2-cyanoguanidine moiety with the 3(2*H*)-pyridazinone ring were examined in groups of 2-cyanoguanidines (**48**, **51**, **61**, **81**, and **88**), 2-cyano-3-methyl-1-guanidines (**49**, **52**, **62**, **82**, and **89**), and 2-cyano-3-ethyl-1-guanidines (**55**, **75**, **86**, and **91**). For the number of carbon atoms in methylene chains bound to 3(2*H*)-pyridazinone, the relative potencies of these compounds were generally summarized in the following order (n): $4 \geq 5 \geq 3 > 2$.

Compounds **54**, **64**, **77**, and **84**, with a 5-methyl substituent on the 3(2*H*)-pyridazinone ring, had an activity equal to or less than 4-methyl or the nonsubstituted counter part. N-Substituent effects of the N-3 position of the 2-cyanoguanidine moiety was examined in series where $n = 4$. Activity decreased according to carbon chain length (**62**, **75**, and **78**). It is clear that the potency depends upon the electron-donating effect of the substituent, since 3,3-dimethyl derivatives **50**, **60**, **65**, **85**, and **90**, respectively, had a stronger activity than 3-methyl derivatives **49**, **52**, **62**, **82**, and **89**. The introduction of a methyl substituent into the N-1 position of the 2-cyanoguanidine moiety, e.g., **66**, extremely decreased the activity, as well as in the thiourea **25**.

Compounds **50**, **60**, **62**, **63**, and **65** had the most potent antisecretory activity among the 2-cyanoguanidine derivatives (**9**).

It is worth noting that 2-cyanoguanidine derivatives (**9**) and thiourea derivatives (**7**) have the same essential requisites for potent activity: a phenyl group on C-6 of the 3(2*H*)-pyridazinone ring, a four-carbon chain length, and a methyl group on N-3 of the functional group.

Twenty-five compounds were selected to define the structural requirements for antiulcer activity on the basis of the gastric antisecretory activity described above. These compounds were subjected to stress-induced gastric lesions in the rat. When substantial activity (>50%) was observed at a dose of 100 mg/kg, full dose range studies were performed on the active compounds, and ED_{50} values were determined as shown in Table III.

Among the compounds tested, all the compounds having a phenyl ring at C-6 of the 3(2*H*)-pyridazinone ring had significantly potent antiulcer activity, while the compounds (**12** and **45**) having a methyl group at C-6 of the 3(2*H*)-pyridazinone ring were inactive. This suggests that phenyl substitution in the C-6 position of the 3(2*H*)-pyridazinone ring is desirable for enhanced stress-induced antiulcer activity.

Among eight compounds of thioureas derivatives (**15**, **19**, **24**, and **38**) and 2-cyanoguanidine derivatives (**52**, **62**, **82**, and **89**), compounds **24** and **62** had the most potent antiulcer activity. The effect of length of the carbon chain linking the 3(2*H*)-pyridazinone ring and the thiourea moiety or 2-cyanoguanidine moiety were such that the relative potencies of these compounds in both series were in the following order (n): $4 > 5 > 3 > 2$ or 6. This result suggested that the spatial distance between the 3(2*H*)-pyridazinone ring and the thiourea or 2-cyanoguanidine moiety must be very important to evoke activity.

Modification of compound **24** or **62** by the introduction of a proton (**61**), ethyl (**26** and **75**), dimethyl (**65**), allyl (**27**), or phenyl (**32**) group at N-3 of the functional moiety resulted in equal or less activity. In the cases of 2-cyanoguanidine derivatives with a longer carbon chain, however, 3,3-dimethyl-2-cyano-1-guanidine derivatives (**85** and **90**) were more active than their 3-methyl counterparts **82** and **89**.

In summary, the structural requirements for gastric antisecretory activity shown by the compounds having a thiourea or 2-cyanoguanidine group were very similar to those previously reported[1] for a series of 3(2*H*)-pyridazinones having a thioamide group. In addition, 6-phenyl-3(2*H*)-pyridazinones having a thiourea or 2-

cyanoguanidine group in the N-2 position of the side chain had a significant inhibitory effect on stress-induced gastric lesions in the rat. On the basis of the promising data obtained in these experiments, compounds **24**, **26**, **38**, **61**, **62**, **65**, **75**, **85**, and **86** seemed to merit further preclinical evaluation. In vitro experiments revealed that they had no anticholinergic activity[9] at 1×10^{-5} M, and no histamine H_2-receptor antagonistic activity[10] at 1×10^{-5} M. A more detailed pharmacological evaluation is required to assess the precise profile of the new compounds presented here. With compounds **24** (MUL-088) and **62** (MUN-114), we observed the most potent antisecretory and antiulcer activity among the individual series of thioureas and 2-cyanoguanidines.

The preliminary toxicological experiments (acute and short-term subchronic tests)[11] revealed that thiourea derivatives were more toxic than 2-cyanoguanidine derivatives. Furthermore, some of these selected compounds were subjected to a subchronic gastric ulcer model[12] and a chronic recurrence ulcer model,[13] both induced by acetic acid in rat. Among these compounds, compound **86** (MUN-118) was found to have significant preventive effects in both models. The details of the very interesting results of these experiments will be published elsewhere in the near future. A further pharmacological and toxicological investigation of these compounds is currently in progress in our laboratories to assess their precise profile as new candidates for antiulcer drugs.

Experimental Section

Chemistry. All melting points were obtained with a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi Type 215 spectrophotometer, and proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a JEOL JNM-PS-100 spectrometer and reported in parts per million (ppm, δ) relative to tetramethylsilane. Analyses were performed with a Hitachi 026 CHN analyzer; analyses indicated by elemental symbols were within 0.4% of the theoretical values. The following abbrevations are used: MIBK, methyl isobutyl ketone; TBAB, tetra-*n*-butylammonium bromide; IPE, isopropyl ether.

Starting Material (3). 6-Methyl-3(2*H*)-pyridazinone,[14] 6-phenyl-3(2*H*)-pyridazinone,[15] and their related derivatives were prepared by the cited procedure.[16]

6-Phenyl-2-(4-phthalimidobutyl)-3(2*H*)-pyridazinone (4, $R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 4$). To a mixture of 51.6 g (0.3 mol) of 6-phenyl-3(2*H*)-pyridazinone (**3**) in 500 mL of MIBK were added 85 g (0.3 mol) of *N*-(4-bromobutyl)phthalimide and 41.4 g (0.3 mol) of K_2CO_3. The mixture was heated at reflux temperature for 6 h. The reaction mixture was filtered after cooling and washed with 100 mL of MIBK. The filtrate was evaporated to dryness under reduced pressure, and the resulting residue was extracted with 500 mL of $CHCl_3$, washed with saturated $NaHCO_3$ (200 mL × 3) and 10% NaCl solution (200 mL × 3), and dried over Na_2SO_4. The dried solution was evaporated to give crude solid, which was recrystallized from EtOH and IPE to give 101 g (89.5%) of 4 ($R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 4$): mp 118–120 °C; IR (Nujol) 1760, 1700, 1650 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.8 [m, 4 H, $CH_2(CH_2)_2CH_2$], 3.70 [t, 2 H, J = 7 Hz, $CH_2N(CO)_2$], 4.24, (t, 2 H, J = 7 Hz, $CONCH_2$), 7.05 (d, 1 H, J = 10 Hz, C_4 H), 7.4–8.0 (m, 9 H, Ar H), 8.02 (d, 1 H, J = 10 Hz, C_5 H).

6-Phenyl-2-(2-phthalimidoethyl)-3(2*H*)-pyridazinone (4, $R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 2$). The title compound was prepared from 6-phenyl-3(2*H*)-pyridazinone (**3**) and *N*-(2-bromoethyl)phthalimide in 85% yield, as described for the preparation of 4 ($R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 4$): mp 183–185 °C; IR (Nujol) 1760, 1695, 1660 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 4.10 [t, 2 H, J = 7 Hz, $CH_2N(CO)_2$], 4.50 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.04 (d, 1 H, J = 10 Hz, C_4H), 7.4 (m, 3 H, Ar H), 7.7 (m, 2 H, Ar H), 7.86 (s, 4 H, Ar H), 8.00 (d, 1 H, J = 10 Hz, C_5 H).

6-Phenyl-2-(3-phthalimidopropyl)-3(2*H*)-pyridazinone (4, $R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 3$). The title compound was prepared from 6-phenyl-3(2*H*)-pyridazinone (**3**) and *N*-(3-bromopropyl)phthalimide in 74% yield, as described for the preparation of 4 ($R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 4$): mp 143–145 °C; IR (Nujol) 1760, 1700, 1660 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.28 (quintet, 2 H, J = 7 Hz, $CH_2CH_2CH_2$), 3.77 [t, 2 H, J = 7 Hz, $CH_2N(CO)_2$], 4.27 (t, 2 H, J = 7 Hz, $CONCH_2$), 6.96 (d, 1 H, J = 10 Hz, C_4H), 7.4 (m, 3 H, Ar H), 7.7 (m, 2 H, Ar H), 7.78 (s, 4 H, Ar H), 7.90 (d, 1 H, J = 10 Hz, C_5H).

6-Phenyl-2-(6-phthalimidohexyl)-3(2*H*)-pyridazinone (4, $R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 6$). The title compound was prepared from 6-phenyl-3(2*H*)-pyridazinone (**3**) and *N*-(6-bromohexyl)phthalimide in 80% yield, as described for the preparation of 4 ($R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 4$): mp 80–81 °C; IR (Nujol) 1770, 1720, 1660 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.4 [m, 2 H, $(CH_2)_2CH_2(CH_2)_2$], 1.8 (m, 4 H, $CH_2CH_2CH_2CH_2CH_2CH_2$), 3.40 [t, 2 H, J = 7 Hz, $CH_2N(CO)_2$], 4.17 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.04 (d, 1 H, J = 10 Hz, C_4H), 7.5 (m, 3 H, Ar H), 7.8 (m, 2 H, Ar H), 7.84 (s, 4 H, Ar H), 8.02 (d, 1 H, J = 10 Hz, C_5 H).

6-Phenyl-2-(5-phthalimidopentyl)-3(2*H*)-pyridazinone (4, $R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 5$). A mixture of 17.2 g (0.1 mol) of 6-phenyl-3(2*H*)-pyridazinone (**3**), 34 g (0.1 mol) of *N*-(5-bromopentyl)phthalimide, 5.6 g (0.1 mol) of KOH, and 3.8 g (0.01 mol) of TBAB in benzene (500 mL) was stirred at room temperature for 8 h. The organic layer was separated, washed with aqueous 5% NaOH solution (200 mL × 2) and aqueous 10% HCl solution (200 mL × 2), and was dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was recrystallized from EtOH and IPE to give 34 g (88%) of 4 ($R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 5$): mp 175–176 °C; IR (Nujol) 1760, 1700, 1655 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.4 (m, 2 H, $C_2H_4CH_2C_2H_4$), 1.8 (m, 4 H, $CH_2CH_2CH_2CH_2CH_2$), 3.62 [t, 2 H, J = 7 Hz, $CH_2N(CO)_2$], 4.17 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.06 (d, 1 H, J = 10 Hz, C_4H), 7.4–8.0 (m, 9 H, Ar H), 8.02 (d, 1 H, J = 10 Hz, C_5 H).

2-(4-Bromobutyl)-6-phenyl-3(2*H*)-pyridazinone (6, $R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 4$). A mixture of 17.2 g (0.1 mol) of 6-phenyl-3(2*H*)-pyridazinone (**3**), 65 g (0.3 mol) of 1,4-dibromobutane, 5.6 g (0.1 mol) of KOH, and 3.8 g (0.01 mol) of TBAB in benzene (500 mL) was stirred at room temperature for 6 h. The organic layer was separated, washed with aqueous 5% NaOH solution (200 mL × 2) and aqueous 10% HCl solution (200 mL × 2), and was dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was distilled to recover excess 1,4-dibromobutane. The residue was distilled to give 22 g (72%) of **6** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 4$): bp 210–215 °C (mmHg); mp 42–43 °C; IR (Nujol) 1650 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.95 (m, 4 H, $CH_2C_2H_4CH_2$), 3.58 (t, 2 H, J = 7 Hz, CH_2Br), 4.20 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.06 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.02 (d, 1 H, J = 10 Hz, C_5 H).

2-(5-Bromopentyl)-6-phenyl-3(2*H*)-pyridazinone (6, $R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 5$). A mixture of 20 g (0.12 mol) of 6-phenyl-3(2*H*)-pyridazinone (**3**), 82.8 g (0.36 mol) of 1,5-dibromopentane, 6.7 g (0.12 mol) of KOH, and 3.8 g (0.01 mol) of TBAB in benzene (500 mL) was stirred at room temperature for 8 h. The reaction mixture was allowed to react as described for the preparation of **6** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 4$): bp 191–195 °C (1.5 mmHg); IR (Nujol) 1650 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.6–2.0 (m, 6 H, $CH_2C_3H_6CH_2$), 3.36 (t, 2 H, J =

(9) Bass, P.; Butler, D. E.; Patterson, M. A.; Purdon R. A. *Arch. Int. Pharmacodyn. Ther.* **1967**, *169*, 131.
(10) Black, J. W.; Duncan, W. A. M.; Ganellin, C. J.; Parsons, E. M. *Nature (London)* **1972**, *236*, 385.
(11) Ohki, M., Morishita Pharmaceutical Co., Ltd., unpublished results.
(12) Takagi, K.; Okabe, S.; Saziki, R. *Jpn. J. Pharmacol.* **1969**, *19*, 418.
(13) Okabe, S.; Pfeiffer, J. *Am. J. Dig. Dis.* **1972**, *17*, 619.
(14) Kumagai, M. *Nippon Kagaku Zasshi* **1960**, *81*, 489.
(15) Steck, E. A.; Brundage, R. P.; Fletcher, L. T. *J. Am. Chem. Soc.* **1953**, *75*, 1117.
(16) Castle, R. N. *Chem. Heterocycl. Compd.* **1973**, *28*, 23.

Table III. Antisecretory and Antiulcer Activities of 3(2*H*)-Pyridazinones

	antisecretory act.[a]		
no.	% inhibn at 100 mg/kg	ED_{50}, mg/kg	antiulcer act.:[b] ED_{50}, mg/kg
10	6.0 (NS)[c]		
11	-8.2 (NS)		
12	44.5	>100	NS
13	3.2 (NS)		
14	-12.5 (NS)		
15	23.3		>100
16	8.1 (NS)		
17	12.3 (NS)		
18	-3.4 (NS)		
19	38.9	>100	58.0 (49.2-68.4)
20	39.0	>100	88.2 (73.3-105.6)
21	23.6 (NS)		
22	12.1 (NS)		
23	72.0	36.3 (30.0-43.9)	
24	87.1	28.9 (22.2-34.7)	17.3 (14.4-20.8)
25	17.5 (NS)		
26	67.7	37.2 (28.6-48.4)	19.8 (15.2-25.7)
27	27.1	>100	78.6 (60.5-102.2)
28	35.8	>100	
29	33.6	>100	
30	18.1 (NS)		
31	5.4 (NS)		
32	38.4	>100	>100
33	30.4	>100	
34	45.6	>100	
35	43.2	>100	
36	25.1 (NS)		
37	42.3	>100	
38	68.9	35.3 (27.2-45.9)	42.1 (35.1-50.5)
39	66.4	51.8 (37.0-72.5)	
40	22.2 (NS)		
41	-5.6 (NS)		
42	6.8 (NS)		
43	34.5	>100	
44	17.5 (NS)		
45	23.5	>100	NS
46	13.5 (NS)		
47	14.9 (NS)		
48	18.5 (NS)		
49	-3.5 (NS)		
50	63.9	62.8 (44.9-87.9)	>100
51	33.3	>100	
52	40.5	>100	78.1 (52.1-117.2)
53	42.8	>100	
54	17.2 (NS)		
55	62.9	78.3 (60.2-101.8)	88.5 (73.8-106.2)
56	23.5 (NS)		
57	0.2 (NS)		
58	52.9	100[d]	
59	-11.8 (NS)		
60	72.2	53.0 (44.2-63.6)	93.1 (71.6-121.0)
61	61.2	77.2 (59.4-100.4)	59.3 (39.5-57.8)
62	79.0	32.4 (27.0-38.9)	38.5 (25.7-57.8)
63	68.6	60.8 (38.0-97.3)	
64	46.4	>100	
65	80.7	30.3 (23.3-39.4)	52.9 (40.7-68.3)
66	27.0	>100	
67	51.0	100[d]	
68	45.7	>100	
69	48.5	>100	
70	26.3	>100	
71	-1.0 (NS)		
72	-10.2 (NS)		
73	7.9 (NS)		
74	24.4	>100	
75	58.8	92.0 (61.3-138.0)	60.7 (46.7-78.9)
76	42.5	>100	
77	38.8	>100	
78	26.3	>100	
79	-12.9 (NS)		
80	0.3 (NS)		
81	31.0	>100	
82	47.6	100[d]	76.2 (50.8-114.3)
83	33.8	>100	
84	28.5	>100	
85	63.9	81.5 (54.3-122.3)	53.1 (35.4-79.6)

Table III (*Continued*)

no.	antisecretory act.[a] % inhibn at 100 mg/kg	antisecretory act.[a] ED_{50}, mg/kg	antiulcer act.:[b] ED_{50}, mg/kg
86	48.2	100[d]	60.3 (39.5–91.7)
87	27.5	>100	
88	20.5 (NS)		
89	31.7	>100	>100
90	58.4	93.1 (62.1–139.7)	92.5 (60.9–140.6)
91	29.1	>100	>100
cimetidine	80.6	60.3 (50.3–72.4)	43.2 (25.4–73.4)
MUL-037	90.3	23.8 (17.6–32.2)	18.3 (9.2–36.2)

[a] Statistically significant activity ($p < 0.05$) was determined in the 4-h pylorus-ligated rat by the technique of Shay. [b] Stress ulcer (see Experimental Section). [c] NS = not statistically significant. [d] Graphically calculated.

7 Hz, CH_2Br), 4.22 (t, 2 H, J = 7 Hz, $CONCH_2$), 6.90 (d, 1 H, J = 10 Hz, C_4 H), 7.35 (m, 3 H, Ar H), 7.6 (m, 2 H, Ar H), 8.03 (d, 1 H, J = 10 Hz, C_5 H).

2-(4-Aminobutyl)-6-phenyl-3(2*H*)-pyridazinone (5, R^1 = R^2 = R^4 = H; R^3 = C_6H_5; n = 4). To a solution of 75 g (0.2 mol) of 6-phenyl-2-(4-phthalimidobutyl)-3(2*H*)-pyridazinone (4, R^1 = R^2 = H; R^3 = C_6H_5; n = 4) in 500 mL of EtOH at 50 °C was added 12 g (0.24 mol) of 100% hydrazine hydrate, and the mixture was refluxed for 4 h. After the mixture was cooled, the pH of the mixture was adjusted to 4.0 with aqueous 10% HCl solution, and the reaction mixture was allowed to reflux for 2 h. After the mixture was cooled, the precipitate (phthalhydrazide) was filtered, and the filtrate was evaporated under reduced pressure to give crude solid, which was removed by filtration. The pH of the filtrate was adjusted to 9.0 with aqueous 30% NaOH solution to give a dark orange oil. The oily product was extracted with three 200-mL portions of $CHCl_3$. The organic layers were washed with three 200-mL portions of saturated $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to give 46 g (95%) of **5** (R^1 = R^2 = H; R^3 = C_6H_5; n = 4): IR (Film) 3360, 3300 (NH), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.5–1.8 (m, 4 H, $CH_2C_2H_4CH_2$), 1.77 (s, 2 H, NH_2), 2.66 (t, 2 H, J = 7 Hz, CH_2NH_2), 4.20 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.06 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.02 (d, 1 H, J = 10 Hz, C_5 H).

This free amine was used without further purification, and its HCl salt (mp 206–207 °C) was prepared in the usual manner.

2-(2-Aminoethyl)-6-phenyl-3(2*H*)-pyridazinone (5, R^1 = R^2 = R^4 = H; R^3 = C_6H_5; n = 2). The title compound was prepared from 6-phenyl-2-(2-phthalimidoethyl)-3(2*H*)-pyridazinone (4) by hydrazinolysis with 100% hydrazine hydrate in 83% yield as described for the preparation of **5** (R^1 = R^2 = H; R^3 = C_6H_5; n = 4): mp 75–77 °C; IR (Nujol) 3340, 3300 (NH), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.55 (s, 2 H, NH_2), 3.20 (t, 2 H, J = 7 Hz, CH_2NH_2), 4.32 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.03 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.70 (d, 1 H, J = 10 Hz, C_5 H), 7.8 (m, 2 H, Ar H).

This free amine was converted to the HCl salt (mp 196–197 °C) by the usual procedure.

2-(3-Aminopropyl)-6-phenyl-3(2*H*)-pyridazinone (5, R^1 = R^2 = R^4 = H; R^3 = C_6H_5; n = 3). The title compound was prepared from 6-phenyl-2-(3-phthalimidopropyl)-3(2*H*)-pyridazinone (4) by hydrazinolysis with 100% hydrazine hydrate in 79% yield as described for the preparation of **5** (R^1 = R^2 = H; R^3 = C_6H_5; n = 4): mp 53–55 °C; IR (Nujol) 3360, 3280 (NH), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.89 (quintet, 2 H, J = 7 Hz, $CH_2CH_2CH_2$), 2.26 (s, 2 H, NH_2), 2.64 (t, 2 H, J = 7 Hz, CH_2NH_2), 4.25 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.07 (d, 1 H, J = 10 Hz, C_4 H), 7.48 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.06 (d, 1 H, J = 10 Hz, C_5 H).

This free amine was converted to the HCl salt (mp 250–251 °C) in the usual procedure.

2-(5-Aminopentyl)-6-phenyl-3(2*H*)-pyridazinone (5, R^1 = R^2 = R^4 = H; R^3 = C_6H_5; n = 5). The title compound was prepared from 6-phenyl-2-(5-phthalimidopentyl)-3(2*H*)-pyridazinone (4) by hydrazinolysis with 100% hydrazine hydrate in 87% yield as described for the preparation of **5** (R^1 = R^2 = H; R^3 = C_6H_5; n = 4): IR (Nujol) 3360, 3300 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.4–1.8 (m, 6 H, $CH_2C_3H_6CH_2$), 1.80 (s, 2 H, NH_2), 2.60 (t, 2 H, J = 7 Hz, CH_2NH_2), 4.19 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.10 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.95 (m, 2 H, Ar H), 8.08 (d, 1 H, J = 10 Hz, C_5 H).

This free amine was converted to the HCl salt (mp 196–198 °C) in the usual procedure.

This compound was also prepared via **6**. To a solution of 6.4 g (0.02 mol) of 2-(5-bromopentyl)-6-phenyl-3(2*H*)-pyridazinone (**6**) in 100 mL of EtOH was added 75 g (0.6 mol) of 28% ammonium hydroxide. The mixture was warmed at 40 °C for 24 h. The reaction mixture was evaporated to give dark orange oil. The oil was dissolved in 100 mL of $CHCl_3$, and extracted with three 100-mL portions of 5% aqueous HCl solution. After alkalization (pH 11) of the aqueous solution with 30% aqueous NaOH, the mixture was extracted with three 100-mL portions of benzene, and the extract was washed with H_2O and dried over Na_2SO_4. The dried solution was evaporated to give 3.4 g (66%) of the title compound.

2-(6-Aminohexyl)-6-phenyl-3(2*H*)-pyridazinone (5, R^1 = R^2 = R^4 = H; R^3 = C_6H_5; n = 6). The title compound was prepared from 6-phenyl-2-(6-phthalimidohexyl)-3(2*H*)-pyridazinone (4) by hydrazinolysis with 100% hydrazine hydrate in 93% yield as described for the preparation of **5** (R^1 = R^2 = H; R^3 = C_6H_5; n = 4): IR (film) 3360, 3290 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.4–1.8 (m, 8 H, $CH_2C_4H_8CH_2$), 2.36 (s, 2 H, NH_2), 2.56 (t, 2 H, J = 7 Hz, CH_2NH_2), 4.17 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.10 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.06 (d, 1 H, J = 10 Hz, C_5 H).

This free amine was converted to the HCl salt (mp 75–78 °C) in the usual procedure.

2-[4-(Methylamino)butyl]-6-phenyl-3(2*H*)-pyridazinone (5, R^1 = R^2 = H; R^3 = C_6H_5; R^4 = CH_3; n = 4). To a solution of 15.4 g (0.05 mol) of 2-(4-bromobutyl)-6-phenyl-3(2*H*)-pyridazinone (**6**) was added 200 mL of 40% $MeNH_2$–MeOH solution. The mixture was warmed at 50 °C for 20 h. The reaction mixture was evaporated to give a dark orange oil. The oil was dissolved in 150 mL of 5% aqueous HCl solution (pH 2) and extracted with 50 mL of benzene and then 50 mL of $CHCl_3$. After alkalinization of the aqueous phase (pH 10) with 30% aqueous NaOH solution, the mixture was extracted with three 100-mL portions of benzene, washed with H_2O, and dried over Na_2SO_4. The dried solution was evaporated to give 8.7 g (68%) of the title compound as a brown oil: IR (Film) 3300 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.52 (quintet, 2 H, CH_2CH_2NH), 1.86 (quintet, 2 H, $CONCH_2CH_2$), 2.28 (s, 3 H, $NHCH_3$), 2.54 (t, 2 H, J = 7 Hz, CH_2NH), 4.18 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.05 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.01 (d, 1 H, J = 10 Hz, C_5 H).

6-Phenyl-2-[4-(thioureido)butyl]-3(2*H*)-pyridazinone (23). To a mixture of 4.8 g (0.02 mol) of 2-(4-aminobutyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) and 30 mL of ice-cold water was added 8 mL of 5 N HCl solution with stirring. The mixture was heated at 70–80 °C, and 2.4 g (0.022 mol) of KSCN (potassium thiocyanate) was added portionwise. After 5 h of continued heating, the reaction mixture was extracted with 200 mL of $CHCl_3$, washed with H_2O, and dried over Na_2SO_4. The dried solution was evaporated to give crude solid, which was recrystallized from EtOH to give 2.1 g (34%) of **23**: IR (Nujol) 3310 (NH), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.3–2.0 (m, 4 H, $CH_2C_2H_4CH_2$), 2.68 (quartet, 2 H, J = 7 Hz, CH_2NH), 2.7–3.1 (br, 3 H, NH + NH_2), 4.14 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.02 (d, 1 H, J = 10 Hz, C_4 H), 7.46 (m, 3 H, Ar H), 7.90 (m, 2 H, Ar H), 8.00 (d, 1 H, J = 10 Hz, C_5 H).

2-[4-(3-Methylthioureido)butyl]-6-phenyl-3(2*H*)-pyridazinone (24, MUL-088). To a solution of 18 g (0.074 mol) of 2-(4-aminobutyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) in 200 mL of $CHCl_3$ was added 6.1 g (0.085 mol) of methyl isothiocyanate. The mixture was refluxed at 80 °C for 2 h and then evaporated to dryness under reduced pressure. The residue was extracted with 300 mL of $CHCl_3$, washed with water, and dried over Na_2SO_4. The dried solution was evaporated to give crude solid, which was recrystallized from EtOH and IPE to give 21 g (90%) of **24**: IR (Nujol) 3320, 3230 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.5–2.1 (m, 4 H, $CH_2C_2H_4CH_2$), 2.92 (d, 3 H, J = 5 Hz, $NHCH_3$), 3.52 (quintet, J = 7 Hz, CH_2CH_2NH), 4.23 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.08 (d, 1 H, J = 10 Hz, C_4 H), 7.3 (br, 2 H, NHCSNH), 7.4 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.08 (d, 1 H, J = 10 Hz, C_5 H).

2-[2-(3-Methylthioureido)ethyl]-6-phenyl-3(2*H*)-pyridazinone (15). The title compound was prepared from 2-(2-aminoethyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) and methyl isothiocyanate, as described for the preparation of **24**: IR (Nujol) 3240 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.84 (d, 3 H, J = 5 Hz, $NHCH_3$), 3.97 (quartet, 2 H, J = 7 Hz, CH_2CH_2NH), 4.40 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.10 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.6 (br, 2 H, NHCSNH), 8.07 (d, 1 H, J = 10 Hz, C_5 H), 8.30 (m, 2 H, Ar H).

2-[3-(3-Methylthioureido)propyl]-6-phenyl-3(2*H*)-pyridazinone (19). The title compound was prepared from 2-(3-aminopropyl)-3(2*H*)-pyridazinone (**5**) and methyl isothiocyanate, as described for the preparation of **24**: IR (Nujol) 3340, 3225 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.06 (quintet, 2 H, J = 7 Hz, $CH_2CH_2CH_2$), 2.86 (d, 3 H, J = 5 Hz, $NHCH_3$), 3.70 (t, 2 H, J = 7 Hz, CH_2NH), 4.23 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.11 (d, 1 H, J = 10 Hz, C_4 H), 7.6 (m, 3 H, Ar H), 7.6 (br, 2 H, NHCSNH), 8.03 (m, 2 H, Ar H), 8.09 (d, 1 H, J = 10 Hz, C_5 H).

2-[5-(3-Methylthioureido)pentyl]-6-phenyl-3(2*H*)-pyridazinone (38). The title compound was prepared from 2-(5-aminopentyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) and methyl isothiocyanate, as described for the preparation of **24**: IR (Nujol) 3310, 3240 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.2–2.0 (m, 6 H, $CH_2C_3H_6CH_2$), 2.86 (d, 3 H, J = 5 Hz, $NHCH_3$), 3.40 (t, 2 H, J = 7 Hz, CH_2NH), 4.18 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.06 (d, 1 H, J = 10 Hz, C_4 H), 7.4 (br, 2 H, NHCSNH), 7.4–8.0 (m, 5 H, Ar H), 8.06 (d, 1 H, J = 10 Hz, C_5 H).

2-[6-(3-Methylthioureido)hexyl]-6-phenyl-3(2*H*)-pyridazinone (40). The title compound was prepared from 2-(6-aminohexyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) and methyl isothiocyanate, as described for the preparation of **24**: IR (Nujol) 3300 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.2–2.0 (m, 8 H, $CH_2C_4H_8CH_2$), 2.90 (d, 3 H, J = 5 Hz, $NHCH_3$), 3.43 (t, 2 H, J = 7 Hz, CH_2NH), 4.18 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.08 (d, 1 H, J = 10 Hz, C_4 H), 7.4 (br, 2 H, NHCSNH), 7.4–8.0 (m, 5 H, Ar H), 8.07 (d, 1 H, J = 10 Hz, C_5 H).

6-Phenyl-2-[4-(3-phenylthioureido)butyl]-3(2*H*)-pyridazinone (32). To a solution of 10 g (0.041 mol) of 2-(4-aminobutyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) in 100 mL of $CHCl_3$ was added 6.8 g (0.05 mol) of phenyl isothiocyanate. The mixture was worked up by the same method as for **24** to give 14.8 g (96%): IR (Nujol) 3240 (NH), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.4–2.1 (m, 4 H, $CH_2C_2H_4CH_2$), 3.6 (quintet, 2 H, J = 7 Hz, CH_2NH), 4.22 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.04 (d, 1 H, J = 10 Hz, C_4 H), 7.1–7.6 (m, 5 H, Ar H), 7.90 (m, 2 H, Ar H), 7.8 (br, 1 H, NH), 8.01 (d, 1 H, J = 10 Hz, C_5 H), 9.44 (br, 1 H, NH).

2-[2-(3-Cyano-2-methyl-1-isothioureido)ethyl]-6-phenyl-3(2*H*)-pyridazinone (8, $R^1 = R^2 = R^4 = H$; $R^3 = C_6H_5$; n = 2). To a solution of 21.5 g (0.1 mol) of 2-(2-aminoethyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) in 70 mL of EtOH in an ice–water bath at 0–5 °C was added dropwise a solution of 14.6 g (0.1 mol) of dimethyl cyanodithioimidocarbonate in 30 mL of EtOH for 30 min. The mixture was stirred vigorously for 2 h at the temperature and then for 3 h at room temperature. The reaction mixture becomes practically solid, and the stirrer may have to be stopped. At the end of the reaction time, the precipitate was filtered and washed with 30 mL of cooled EtOH and 20 mL of IPE. Recrystallization of this product from EtOH and IPE afforded 25.7 g (82%) of a slight yellow powder: mp 155–156 °C; IR (Nujol) 3300 (NH), 2160 (C≡N), 1655 (C=O); ^1H NMR (Me_2SO-d_6) δ 2.42 (s, 3 H, SCH_3), 3.70 (t, 2 H, J = 7 Hz, CH_2NH), 4.30 (t, 2 H, J = 7 Hz, $CONCH_2$), 6.98 (d, 1 H, J = 10 Hz, C_4 H), 7.4 (m, 3 H, Ar H), 7.8 (m, 2 H, Ar H), 7.95 (d, 1 H, J = 10 Hz, C_5 H), 8.0–8.6 (br, 1 H, NH).

2-[3-(3-Cyano-2-methyl-1-isothioureido)propyl]-6-phenyl-3(2*H*)-pyridazinone (8, $R^1 = R^2 = R^4 = H$; $R^3 = C_6H_5$; n = 3). The title compound was prepared from 2-(3-aminopropyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) and dimethyl cyanodithioimidocarbonate in 82% yield, as described for the preparation of **8** (n = 2): mp 159–160 °C; IR (Nujol) 3200 (NH), 2185 (C≡N), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.10 (quintet, 2 H, J = 7 Hz, $CH_2CH_2CH_2$), 2.62 (s, 3 H, SCH_3), 3.42 (t, 2 H, J = 7 Hz, CH_2NH), 4.22 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.08 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.06 (d, 1 H, J = 10 Hz, C_5 H), 8.3 (br, 1 H, NH).

2-[4-(3-Cyano-2-methyl-1-isothioureido)butyl]-6-phenyl-3(2*H*)-pyridazinone (8, $R^1 = R^2 = R^4 = H$; $R^3 = C_6H_5$; n = 4). The title compound was prepared from 2-(4-aminobutyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) and dimethyl cyanodithioimidocarbonate in 87% yield, as described for the preparation of **8** (n = 2): mp 171–172 °C; IR (Nujol) 3280 (NH), 2170 (C≡N), 1670 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.7 (m, 4 H, $CH_2C_2H_4CH_2$), 2.58 (s, 3 H, SCH_3), 3.38 (t, 2 H, J = 7 Hz, CH_2NH), 4.19 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.06 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.06 (d, 1 H, J = 10 Hz, C_5 H), 8.3 (br, 1 H, NH).

2-[5-(3-Cyano-2-methyl-1-isothioureido)pentyl]-6-phenyl-3(2*H*)-pyridazinone ($R^1 = R^2 = R^4 = H$; $R^3 = C_6H_5$; n = 5). The title compound was prepared from 2-(5-aminopentyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) and dimethyl cyanodithioimidocarbonate in 76% yield, as described for the preparation of **8** (n = 2): mp 103–105 °C; IR (Nujol) 3280 (NH), 2180 (C≡N), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.3–1.8 (m, 6 H, $CH_2C_3H_6CH_2$), 2.60 (s, 3 H, SCH_3), 3.34 (t, 2 H, J = 7 Hz, CH_2NH), 4.17 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.08 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.06 (d, 1 H, J = 10 Hz, C_5 H), 8.5 (br, 1 H, NH).

2-[6-(3-Cyano-2-methyl-1-isothioureido)hexyl]-6-phenyl-3(2*H*)-pyridazinone (8, $R^1 = R^2 = R^4 = H$; $R^3 = C_6H_5$; n = 6). The title compound was prepared from 2-(6-aminohexyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) and dimethyl cyanodithioimidocarbonate in 72% yield, as described for the preparation of **8** (n = 2): mp 117–118 °C; IR (Nujol) 3270 (NH), 2160 (C≡N), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.2–1.8 (m, 8 H, $CH_2C_4H_8CH_2$), 2.56 (s, 3 H, SCH_3), 3.26 (t, 2 H, J = 7 Hz, CH_2NH), 4.12 (t, 2 H, J = 7 Hz, $CONCH_2$), 6.84 (d, 1 H, J = 10 Hz, C_4 H), 7.4–7.9 (m, 5 H, Ar H), 7.96 (d, 1 H, J = 10 Hz, C_5 H), 8.3 (br, 1 H, NH).

2-[4-(2-Cyano-3-methyl-1-guanidino)butyl]-6-phenyl-3-(2*H*)-pyridazinone (62, MUN-114). A mixture of 68.2 g (0.2 mol) of 2-[4-(3-cyano-2-methyl-1-isothioureido)butyl]-6-phenyl-3(2*H*)-pyridazinone (**8**) and 400 mL of 30% $MeNH_2$–MeOH solution was heated at 50–60 °C for 8 h. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in 500 mL of $CHCl_3$. The organic layer was washed with aqueous 10% HCl solution and water and dried over Na_2SO_4. The dried solution was evaporated to give crude solid, which was chromatographed (SiO_2–$CHCl_3$). The product was recrystallized from EtOH and IPE to give 55.4 g (85%) as a colorless crystal: IR (Nujol) 3330, 3300 (NH), 2160 (C≡N), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.6–1.9 (m, 4 H, $CH_2C_2H_4CH_2$), 2.74 (s, 3 H, $NHCH_3$), 3.22 (t, 2 H, J = 7 Hz, CH_2NH), 4.20 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.0 (br, 2 H, NHCNH), 7.08 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.05 (d, 1 H, J = 10 Hz, C_5 H).

2-[5-(2-Cyano-3-ethyl-1-guanidino)pentyl]-6-phenyl-3-(2*H*)-pyridazinone (86, MUN-118). The title compound was prepared from 2-[5-(3-cyano-2-methyl-1-isothioureido)pentyl]-6-phenyl-3(2*H*)-pyridazinone (**8**) and 70% $EtNH_2$–H_2O solution in EtOH, as described for the preparation of **62**: IR (Nujol) 3350, 3220 (NH), 2160 (C≡N), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.08 (t, 3 H, J = 7 Hz, $NHCH_2CH_3$), 1.4–2.0 (m, 6 H, $CH_2C_3H_6CH_2$), 3.18 (quartet, 2 H, J = 7 Hz, $NHCH_2CH_3$), 3.20 (t, 2 H, J = 7 Hz, CH_2NH), 4.20 (t, 2 H, J = 7 Hz, $CONCH_2$), 6.8 (br, 2 H, NHCNH), 7.06 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.05 (d, 1 H, d, J = 10 Hz, C_5 H).

2-[4-(2-Cyano-3-propargyl-1-guanidino)butyl]-6-phenyl-3(2*H*)-pyridazinone (79). To a solution of 4.9 g (0.02 mol) of 2-(4-aminobutyl)-6-phenyl-3(2*H*)-pyridazinone (**5**) in 50 mL of acetonitrile was added 3.1 g (0.02 mol) of 1-cyano-2-methyl-3-propargylisothiourea. The mixture was refluxed at 80 °C for 24 h. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in 100 mL of $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ solution and water and dried over Na_2SO_4. The dried solution was evaporated to give crude solid, which was recrystallized from acetonitrile to give 4.0 g (58%): IR (Nujol) 3280 (NH), 2150 (C≡N), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.4-2.0 (m, 4 H, $CH_2C_2H_4CH_2$), 3.0-3.3 (m, 3 H, CH_2NH and C≡C*H*), 3.92 (s, 2 H, $NHCH_2C{\equiv}CH$), 4.15 (t, 2 H, J = 7 Hz, CH_2NH), 6.98 (d, 1 H, J = 10 Hz, C_4 H), 7.1 (br, 1 H, NH), 7.3 (br, 1 H, NH), 7.5 (m, 3 H, Ar H), 7.8 (m, 2 H, Ar H), 7.94 (d, 1 H, J = 10 Hz, C_5 H).

Pharmacology. Gastric Antisecretory Activity. Gastric antisecretory activity was evaluated by the technique of Shay.[7] Male Wistar rats, weighing 150-200 g, were fasted for 24 h prior to the test in cages with wire-mesh floor to prevent coprophagy, but they were allowed water ad libitum. After fasting, the rats were divided into groups of six animals each. One group served as the control. A small midline incision was made, and the pylorus was ligated under ether anesthesia. The test compounds, dissolved or suspended in 1% carboxymethylcellulose solution, or the vehicle was administered intraduodenally to each group. Four hours after closing the abdomen, the stomach was extirpated under ether anesthesia, and the volume of accumulated gastric juice therein was measured. The gastric juice was titrated against 0.1 N NaOH to determine the concentration of free acid (at pH 3.0), and hourly outputs of free acid were calculated for each rat. In the first experiment, the test compounds were administered at a dose level of 100 mg/kg, and the results were represented as percent inhibition against control. In the next step, the selected test compounds from the first experiment were administered at several dose levels, and the ED_{50} values were calculated.[17]

Antiulcer Activity Induced by Stress. Ten male Wistar rats, weighing 200-220 g, per group were used. After oral administration of test compound, animals were immobilized in the stress cage and immersed in a water bath according to the method described by Takagi et al.[8] Seven hours later, the stomach was extirpated, and the length of lesions in the glandular portion was measured. The ulcer index (mm) was obtained by the summation of the length of the lesions. The ED_{50} values for antiulcer activity was calculated by the method of Litchfield and Wilcoxon.[17]

Anticholinergic Activity. Anticholinergic activity was determined by the guinea pig isolated ileum preparation suspended in Tyrode's solution aerated with 95% O_2/5% CO_2 at 30 °C. Cumulative dose-response curves for acetylcholine-induced contraction were determined in the absence or in the presence of test compounds (1×10^{-7} to 1×10^{-5} M) or atropine (3×10^{-7} to 1×10^{-4} M).

Histamine H_2-Receptor Antagonistic Activity. The histamine H_2-receptor antagonistic activity was determined by the guinea pig isolated right atrium preparation suspended in Krebs solution aerated with 95% O_2/5% CO_2 at 32 °C. Cumulative dose-response curves for histamine-induced positive chronotropic action were determined in the absence or in the presence of test compounds (1×10^{-7} to 1×10^{-5} M) or cimetidine (3×10^{-6} to 3×10^{-5} M).

(17) Lichfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.

Antihypertensive Agents: Angiotensin Converting Enzyme Inhibitors. 1-[3-(Acylthio)-3-aroylpropionyl]-L-prolines

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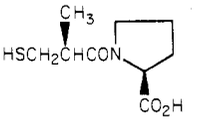
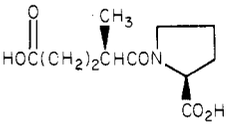
A series of 1-[3-(acylthio)-3-aroylpropionyl]-L-proline derivatives was synthesized. A number of these compounds are potent angiotensin converting enzyme (ACE) inhibitors that lowered blood pressure in aorta-coarcted renal hypertensive rats. The most active derivatives are 1-[3(*R*)-(acetylthio)-3-substituted-benzoyl)-2(*S*)-methylpropionyl]-L-prolines with an in vivo activity equivalent to SQ 14,225 (captopril). Structure-activity relationships are discussed. Changes in the configuration of the α-methyl group and the *S*-acetyl group affect the ACE activity. Coupling of 3-(substituted-benzoyl)-2-methylpropionic acids to L-proline via enol lactones is described.

Since the discovery of the renin-angiotensin system, there have been continued efforts to determine the role of the renin-angiotensin system in the regulation of blood pressure. One of the principal physiological functions of angiotensin converting enzyme (ACE) is to catalyze the removal of the terminal dipeptide from the decapeptide angiotensin I to give the octapeptide angiotensin II.[1-3] Angiotensin II is a potent peptide that causes vasoconstriction of blood vessels and is involved in regulation of blood pressure. ACE is also involved in the inactivation of bradykinin, a nonapeptide present in blood plasma, by successively removing two dipeptides. Bradykinin is a potent vasodilator and might be involved in the control of blood pressure.

Early work centered on competitive peptide antagonists of angiotensin II and peptide inhibitors of angiotensin converting enzyme. The peptide ACE inhibitor isolated from venom of *Bothrope jararaca* (SQ 20,881, teprotide)[4] was shown to lower blood pressure in humans and demonstrated that ACE inhibitors could effectively lower blood pressure.[5] In 1977 Ondetti reported[6] on a new class of ACE inhibitors (**1** and **2**) that contain only one amino acid and are orally active antihypertensive agents. One of these derivatives, **1** (SQ 14,225, captopril), is an effective antihypertensive drug.[7]



1



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(1) Skeggs, L. T.; Marsh, W. H.; Kahn, J. R.; Shumway, N. P. *J. Exp. Med.* **1954**, *99*, 275-282.
(2) Skeggs, L. T.; Kahn, J. R.; Shumway, N. P. *J. Exp. Med.* **1956**, *103*, 295-300.
(3) Skeggs, L. T.; Kahn, J. R.; Shumway, N. P. *J. Exp. Med.* **1956**, *103*, 301-307.
(4) Ondetti, M. A. *Biochemistry*, **1971**, *19*, 4033-4039.
(5) Ondetti, M. A.; Cushman, D. W. *Annu. Rep. Med. Chem.* **1978**, *13*, 82.
(6) Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science* **1977**, *196*, 441-443.
(7) Bravo, E. L.; Tarazi, R. C. *Hypertension* **1979**, *1*, 39-46.

0022-2623/83/1826-0381$01.50/0