Pyridazinones. 1. Synthesis and Antisecretory and Antiulcer Activities of Thio Amide Derivatives

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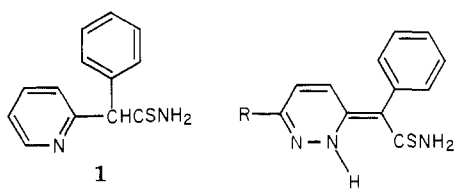
In an effort to develop new types of antiulcer agents, a series of novel 3(2*H*)-pyridazinone derivatives and related analogues was synthesized. Substituted 3(2*H*)-pyridazinones and their 4,5-dihydro analogues were alkylated by ω-haloalkyl cyanides at the N-2 position under phase-transfer catalytic reaction, and the nitrile group was converted to the thio amide group by treatment with hydrogen sulfide alone or with the appropriate primary or secondary amines. Various substituents were introduced on the nitrogen of thio amide, on the carbon in the side chain, and on the 3(2*H*)-pyridazinone ring. The synthesized compounds were evaluated for gastric antisecretory activity in the pylorus-ligated rat, and selected compounds were applied to experimental ulcer models, such as Shay's, aspirin-induced, and stress-induced ulcers in the rat. Structure–activity relationships are discussed. 3(2*H*)-Pyridazinones with a C-6 phenyl group and an N-2 alkyl side chain with a terminal thio amide group (**48**, **49**, **51**, and **52**) were the most potent among the compounds tested.

Since the discovery that 2-phenyl-2-(2-pyridyl)thioacetamide (1, SC-15396) is an effective gastric antisecretory



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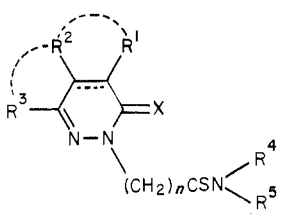

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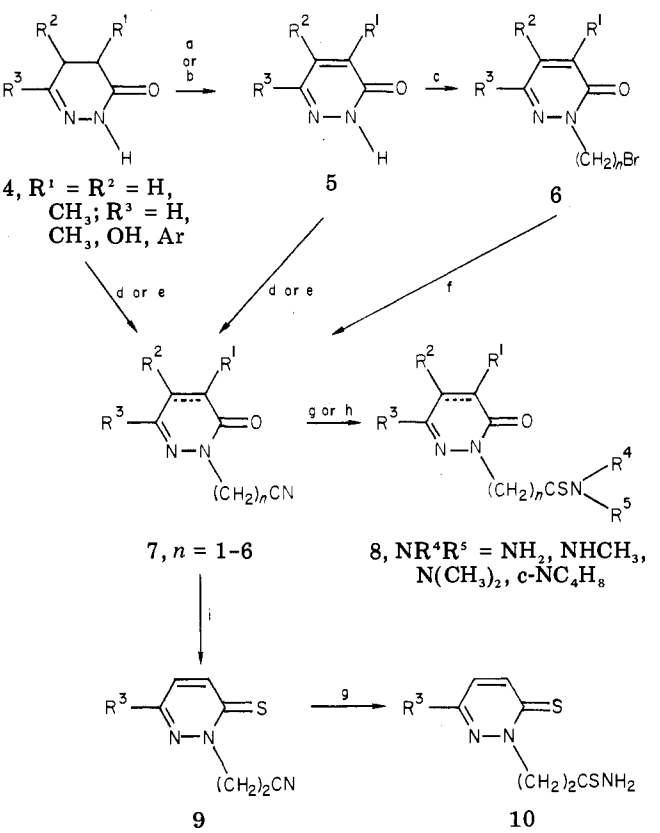
agent,[1] a large number of pyridine analogues with a thio amide moiety have been prepared and evaluated as nonanticholinergic antisecretory agents: 2-(2-pyridyl)thioacetamide (CMN-131),[2] 2-methoxy-*N*-methyl-2-(2-pyridyl)thioacetamide (SKF-59377),[3] and 3-methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide (tiquinamide).[4] All these compounds are consistent with a model of structural requisites for preventing peptic ulcers presented by Pascaud et al.[5] and Bustard and Martin[6] and derived by combining structural characteristics of several classes of effective compounds. In spite of intensive research, a clear structure–activity relationship has not been found.

In a recent report[7] from this laboratory, we reported a series of pyridazinone methide thio amides (**2**) having marked gastric antisecretory activity and noted that their structures were distinctly different from any of the above classes. These results prompted us to synthesize a new class of 3(2*H*)-pyridazinone derivatives and related analogues based on a concept different from the model proposed by Pascaud et al. and Bustard and Martin.

During the past decade, many 3(2*H*)-pyridazinone derivatives with various pharmacological activities, such as hypotensive,[8] antibacterial,[9] antifungal,[10] and antiinflammatory action,[11] have been reported, but derivatives pos-

Scheme I[a]



[a] a = Br_2/AcOH; b = SeO_2/EtOH-H_2O; c = $Br(CH_2)_nBr$, TBAB, KOH (route A); d = $Br(CH_2)_nCN$, TBAB, KOH (route B); e = $CHR^6{=}CR^7CN$ (R^6 = R^7 = H, CH_3), Triton B/EtOH (route C); f = KCN, TBAB; g = H_2S/Py-Et_3N; h = H_2S, R^4R^5NH/EtOH; i = P_2S_5/Py.

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(2) X. B. Pascaud, D. J. Errard, and M. M. Blouin, *Am. J. Dig. Dis.*, **19**, 503 (1974).
(3) W. Groves, L. Schlosser, F. Brennan, and P. Ridley, *Pharmacologist*, **15**, 238 (1973).
(4) D. E. Beattie, G. T. Dixon, D. A. Shriver, and B. J. Alps, *Arzneim.-Forsch. (Drug Res.)*, **29**(II), 1390 (1979).
(5) C. E. Malen, B. H. Danree, and X. B. L. Pascaud, *J. Med. Chem.*, **14**, 244 (1971).
(6) T. M. Bustard and Y. C. Martin, *J. Med. Chem.*, **15**, 1101 (1972).
(7) T. Yamada, Y. Nobuhara, H. Shimamura, K. Yoshihara, A. Yamaguchi, and M. Ohki, *Chem. Pharm. Bull.*, **29**, 3433 (1981).
(8) W. V. Curran and A. Ross, *J. Med. Chem.*, 17, 273 (1974).
(9) T. Novinson, R. K. Robins, and D. E. O'Brien, *J. Heterocycl. Chem.*, **10**, 835 (1973).
(10) I. B. Lundina, N. N. Frolova, I. Ya. Postovskii, A. V. Bedrin, and N. N. Vereshchagina, *Khim.-Farm. Zh.*, 6, 13 (1972).

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sessing gastric antisecretory and/or antiulcer activities have not been described.

Based on these considerations, it was decided to prepare compounds with the general structure **3** (the objective being novel, potent, and long-lasting antiulcer compounds without anticholinergic activity) and to define the structural requirements for activity by molecular modification.

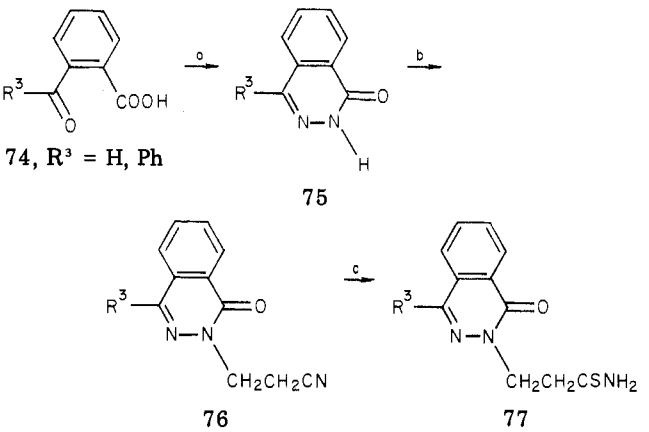
Chemistry. The general synthetic routes for the preparation of **3** are illustrated in Scheme I. 4,5-Dihydro-3(2*H*)-pyridazinones **4** were dehydrogenated by bromine in acetic acid[12] or selenium dioxide in ethanol–water[13] to give 3(2*H*)-pyridazinones **5** in about 80% yield. N-Alkylation of **5** with α,ω-dibromoalkanes or ω-bromoalkyl cyanides in the presence of a phase-transfer catalyst gave an acceptable yield[14] of 2-(ω-bromoalkyl)- or 2-(ω-cyanoalkyl)-3(2*H*)-pyridazinones (**6** or **7**). Alternative methods of N-alkylation using strong bases, such as sodium hydride,[15] or sodium metal[16] were limited to those compounds which had no sensitive group. The key intermediates **7** were also prepared from **6** in good yield by reaction with KCN in the same two-phase system. Hydrothiolysis of **7** by treatment with hydrogen sulfide in pyridine–triethylamine, gave the desired compounds **8** unsubstituted on the thio amide group. For the preparation of **8** with substituents on the nitrogen of the thio amide, hydrothiolysis was carried out in the presence of the N-substituted amines in ethanol.[17] The 4,5-dihydro analogues of **3** were also prepared in the same manner by ω-cyanoalkylation of **4**, followed by hydrothiolysis of **7** (4,5-dihydro). For two methylene units in the side chain, a Michael-type of alkylation of **4** or **5** with acrylonitrile, crotonitrile, or 2-methylacrylonitrile provided the desired compounds **7** (n = 2) more readily. This alkylation reaction was effectively catalyzed by Triton B (trimethylbenzylammonium hydroxide) in ethanol or by tetrabutylammonium bromide (TBAB) in a two-phase system.

The synthesis of 3(2*H*)-pyridazinethione with a thio amide group in the side chain is shown in Scheme I. When thio amide **12** derived from **7** (R^1, R^2, and R^3 = H, n = 2) by the method mentioned above was treated with phosphorus pentasulfide in an anticipation of obtaining 3-(2*H*)-pyridazinethione product **64**, the starting material **7** was unexpectedly recovered. Therefore, the nitriles **7** were treated first with phosphorus pentasulfide to obtain the key intermediate, 3(2*H*)-pyridazinethione **9**, which was then hydrothiolyzed with hydrogen sulfide to give **10**. A thionation of the 3(2*H*)-pyridazinone skeleton to 3(2*H*)-pyridazinethiones was confirmed by physicochemical analysis, such as ^{1}H NMR, IR, and elemental analysis. For example, the proton at the C-4 position of 3(2*H*)-pyridazinethione **9** (R^3 = H) was observed at δ 7.82, which was shifted to 0.9 ppm lower field than 3(2*H*)-pyridazinone **7** (R^3 = H); in addition, the chemical shift of the methylene protons in the side chain of **9** (R^3 = H) was also lower by 0.38 ppm than that of the parent **7**.

1(2*H*)-Phthalazinone derivatives **77**, the fused type of 3(2*H*)-pyridazinones, were also prepared by methods similar to those described above (Scheme II). Phthaldehydic acid (R^3 = H in **74**) or 2-benzoylbenzoic acid (R^3 = C_6H_5 in **74**) was allowed to condense with hydrazine sulfate in hot aqueous solution containing sodium acetate[18] to give 1(2*H*)-phthalazinones **75** in quantitative yield. A Michael addition of **75** with acrylonitrile took place in ethanol in the presence of Triton B to afford the corresponding nitriles **76**, which were hydrothiolized with hydrogen sulfide to yield the desired products **77**.

A novel tricyclic derivative **82** was prepared in good yield by the procedures shown in Scheme III, starting from 1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic acid (**80**).

Scheme II[a]



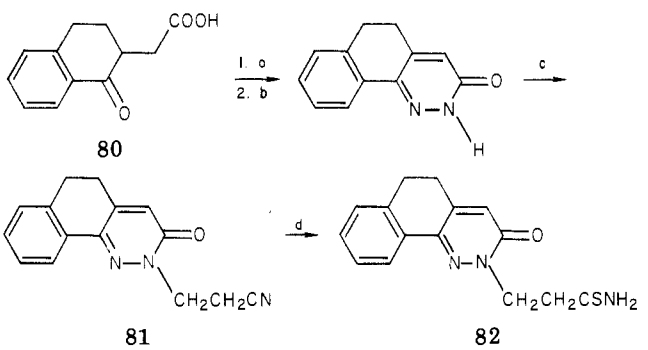
74, R^3 = H, Ph

75

76 77

[a] a = NH_2NH_2-H_2O; b = CH_2=CHCN; c = H_2S/Py-Et_3N.

Scheme III



80

81 82

[a] a = NH_2NH_2-H_2O; b = Br_2; c = CH_2=CHCN; d = H_2S/Py-Et_3N.

Biological 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-ligated rat according to Shay's method.[19] When substantial activity (>50% inhibition) was observed, full dose range studies were performed on the more active compounds, and an ED_{50} was determined. In addition, selected compounds which showed substantial antisecretory activity were tested for inhibition of the generation of experimental ulcers induced by Shay's procedure,[20] aspirin,[21] or stress.[22] For comparison, the active references SC-15396, cimetidine, and atropine sulfate were

(11) G. Nannini, G. Biasoli, E. Perrone, A. Forgione, A. Buttinoni, and M. Ferrari, *Eur. J. Med. Chem.*, 14, 53 (1979).
(12) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.*, 73, 1117 (1953).
(13) M. Kumagai, *Nippon Kagaku Zasshi*, 81, 489 (1960).
(14) T. Yamada and M. Ohki, *Synthesis*, 631 (1981).
(15) H. M. Holava and R. A. Partyka, *J. Med. Chem.*, 14, 262 (1971).
(16) F. H. McMillan, K. A. Kun, C. B. McMillan, B. S. Schwarts, and J. A. King, *J. Am. Chem. Soc.*, 78, 407 (1956).
(17) P. L. Benneville, J. S. Strong, and V. T. Elkind, *J. Org. Chem.*, 21, 772 (1956).
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(19) H. G. Shay, D. C. H. Sun, and M. Gruenstein, *Gastroenterology*, 26, 906 (1954).
(20) H. G. Shay, S. A. Komarow, S. S. Felds, D. Meranze, M. Gruenstein, and H. Siplet, *Gastroenterology*, 5, 43 (1945).
(21) S. Okabe, K. Takeuchi, K. Nakamura, and K. Takagi, *Jpn. J. Pharmacol.*, 24, 363 (1974).
(22) K. Takagi and S. Okabe, *Jpn. J. Pharmacol.*, 18, 9 (1968).

included in the biological determinations. The structures and physicochemical data for the compounds synthesized in the present research, as well as the gastric antisecretory activities, are shown in Tables I–IV. Table V presents the antiulcer activities of the selected compounds.

As shown in Table I, a wide range of 3(2*H*)-pyridazinones with a thio amide side chain bound to the nitrogen at the 2-position had fairly strong antisecretory activity. A close inspection of the results reveals some interesting facts with respect to structure–activity relationships.

The thio amide moiety, considered to be an essential requisite for the gastric antisecretory or antiulcer activity of these compounds,[1,2,3,7] was found to be required in the present study too. When the thio amide group in **20** or **30** was converted to other related moieties, such as the amide (**21**, **31**, or **32**), the acid (**33**), the ester (**34**), and the nitrile (**22** or **35**), the antisecretory activity was extremely diminished in all these cases.

For the various gastric antisecretory and/or antiulcer thio amides, few studies have surveyed the influence of thio amide nitrogen substituents on biological activity. Secondary thio amides **13**, **17**, **18**, **36**, **37**, and **52** have greater or equal activity, which is unexpected considering the features which have been noted before.[1-3] Some tertiary thio amides (**14**, **39**, and **53**) also retained respectable levels of activity, although slightly reduced compared to the corresponding primary thio amides. On the other hand, it is worth noting that introduction of a methanol residue on the nitrogen resulted in a complete loss of the activity (**30** vs. **38**). The reason why a terminal hydroxy group in **38** abolished the effectiveness of **30** and **36** may be because of a change in the electronic environment around the thio amide group, altering the interaction with the active site in vivo.

Biological action and activity reflect aspects of the fundamental physicochemical properties of the bioactive compounds.[23] Accordingly, the effects of length and branching of the carbon chain linking the thio amide group with the 3(2*H*)-pyridazinone ring were examined. In a group of 6-methyl-3(2*H*)-pyridazinones having a ω-(thiocarbamoyl)alkylene side chain, the compound with a two-carbon chain (**20**) was outstandingly more potent than its homologues (**19** and **25–28**), but the relative potencies of the 6-phenyl counterparts (**29**, **30**, **49–51**, and **54**) were in the following order (n) $5 \gg 3 > 2 \geq 4 = 6$. Compound **51** had the most potent antisecretory activity among the compounds tested. In the series of 4,5-dihydro-6-phenyl-3(2*H*)-pyridazinones (**60** and **65–68**), biological activity was not extremely affected by the length of the side chain (Table II).

The effect of the introduction of a methyl branching on the side-chain carbons was also examined. In the case of 3(2*H*)-pyridazinones **12** and **13**, the introduction of methyl branches, as seen in **15** and **16** as well as **17** and **18**, slightly enhanced their biological potency; however, in 6-substituted (methyl or phenyl) compounds, the introduction of a branch into the alkylene side chain decreased the antisecretory activities, with the exception of **48** which showed increased activity.

It was already mentioned above that 3(2*H*)-pyridazinones having the alkylene chain in proper relationship to the terminal thio amide had fairly strong biological activities. Furthermore, the present results indicated that various structural changes in the 3(2*H*)-pyridazinone ring might induce various changes in their biological activities. When C-6 methyl and C-6 phenyl were compared, the latter was generally more active than the former as long as the length of the side chain was larger than three carbons (**25** vs. **49**, **26** vs. **50**, **27** vs. **51**, and **28** vs. **54**). This was especially true in the case of **49** and **51**; namely, the C-6 phenyl group was found to be very preferable for antisecretory activity. Furthermore, the effect of several substituents on the phenyl ring on biological activity was examined. Methyl (**41**), methoxy (**42**), and chloro (**43** and **44**) substituents on the phenyl ring did not give the products any biological advantage.

Except for **66** and **68**, replacement of the 3(2*H*)-pyridazinone ring by 4,5-dihydro-3(2*H*)-pyridazinone ring decreased of the biological activity.

Only a small number of 4- and/or 5-substituted 3-(2*H*)-pyridazinones were prepared, but the result of their biological evaluation was interesting. Thus, among 6-phenyl-3(2*H*)-pyridazinones, a 5-methyl substituent decreased the activity of the nonsubstituted counterpart (**30** and **45**), while the 4-methyl-substituted compound **46** had an activity equal to or greater than **30**. This may be correlated with the fact that the novel tricyclic compound **82** was completely inactive. Steric interference with the coplanarity of the 6-phenyl group to the 3(2*H*)-pyridazinone ring may be the reason that biological activity was lowered seriously. In other examples, 4-chloro and 5-alicyclic amino compounds were ineffective. These findings indicate that substitution at the 5-position in the 3(2*H*)-pyridazinone ring is unfavorable.

The possibility of replacing the 3(2*H*)-pyridazinone ring by other heterocycles was examined, and the results are presented in Table IV. The fused compounds, **78** and **79** were more potent than the corresponding nonfused 3-(2*H*)-pyridazinones **12** and **30**, respectively.

The ten compounds (**18**, **20**, **30**, **36**, **46**, **48**, **49**, **51**, **52**, and **68**) selected on the basis of gastric antisecretory activities mentioned above were subjected to antiulcer evaluation, and the ED_{50} values are shown in Table V. All tested compounds had marked antiulcer activity at least in one experimental model, and several of them were tolerably effective in all three different types of ulcer models. From Table V it is apparent that 6-phenyl-3(2*H*)-pyridazinones with a side chain three or five carbons in length (**49** and **51**) were the most active. The degree of antiulcer activity of these selected compounds was nearly parallel to their gastric antisecretory activity.

It is generally accepted that gastric lesions in a Shay rat are induced by the accumulated gastric juice in the gastric lumen.[24] When the selected ten compounds were given at 100 mg/kg, no ulcerous lesions developed, and a significant inhibitory effect was found even at 30 mg/kg for **48**, **51**, and **52**. It has been proposed that aspirin induces gastric ulcers by disrupting the gastric mucosal barrier, resulting in the back diffusion of acid.[25] Compound **51** had a significant inhibitory effect on the aspirin-induced gastric lesion. Several compounds (**49**, **51**, and **52**) had a significant inhibitory effect on the stress-induced gastric lesions in the rat. It has been reported that in the rat an augmented gastric motility was caused under stress, and this was thought to be one of the mechanisms by which the gastric lesion developed.[26] In our preliminary work, compounds **49**, **51**, and **52**, given orally at 30 mg/kg, had

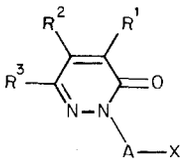
(23) E. J. Ariëns, "Drug Design", Vol. 1, Academic Press, New York, 1971.

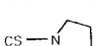
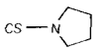
(24) Y. Ishii, *Jpn. J. Pharmacol.*, **19**, 125 (1969).

(25) H. W. Davenport, H. A. Warner, and C. F. Code, *Gastroenterology*, **47**, 142 (1964).

(26) K. Takagi, Y. Kasuya, and K. Watanabe, *Chem. Pharm. Bull.*, **12**, 465 (1964).

Table I. 3(2*H*)-Pyridazinones



no.	R^1	R^2	R^3	A	X	yield,[a] %	route[b]	mp or bp (mmHg), °C	crystn solvent[c]	formula[d]	antisecretory act. (id)[e] % inhibn at 100 mg/kg	antisecretory act. (id)[e] ED_{50}, mg/kg
11	H	H	OH	$(CH_2)_2$	$CSNH_2$	67	C	163–164	EtOH	$C_7H_9N_3O_2S$	−13.4 (NS)[f]	
12	H	H	H	$(CH_2)_2$	$CSNH_2$	93	C	145–147	EtOH-IPE	$C_7H_9N_3OS$	28.8	>100
13	H	H	H	$(CH_2)_2$	$CSNHCH_3$	43	C	142–144	$CHCl_3$-IPE	$C_8H_{11}N_3OS$	35.7	>100
14	H	H	H	$(CH_2)_2$		17	C	127–129	EtOH-IPE	$C_{11}H_{15}N_3OS$	29.7	>100
15	H	H	H	$CH(CH_3)CH_2$	$CSNH_2$	62	C	140–143	EtOH-IPE	$C_8H_{11}N_3OS$	38.8	>100
16	H	H	H	$CH_2CH(CH_3)$	$CSNH_2$	97	C	149–152	EtOH	$C_8H_{11}N_3OS$	40.3	>100
17	H	H	H	$CH(CH_3)CH_2$	$CSNHCH_3$	27	C	155–157	$CHCl_3$-IPE	$C_9H_{13}N_3OS$	42.7	>100
18	H	H	H	$CH_2CH(CH_3)$	$CSNHCH_3$	43	C	172–175	EtOH-IPE	$C_9H_{13}N_3OS$	50.2	100[g]
19	H	H	CH_3	CH_2	$CSNH_2$	74	B	209–212	EtOH-IPE	$C_7H_9N_3OS$	31.5	>100
20	H	H	CH_3	$(CH_2)_2$	$CSNH_2$	88	C	156–158	EtOH	$C_8H_{11}N_3OS$	73.9	43.2 (22.7–82.1)
21	H	H	CH_3	$(CH_2)_2$	$CONH_2$	84	C	148–150	EtOH	$C_8H_{11}N_3O_2$	−2.9 (NS)	
22	H	H	CH_3	$(CH_2)_2$	CN	88	C	96–97	EtOH	$C_8H_9N_3O$	−0.2 (NS)	
23	H	H	CH_3	$CH(CH_3)CH_2$	$CSNH_2$	56	C	101–104	EtOH	$C_9H_{13}N_3OS$	32.5	>100
24	H	H	CH_3	$CH_2CH(CH_3)$	$CSNH_2$	63	C	106–107	EtOH	$C_9H_{13}N_3OS$	30.2	>100
25	H	H	CH_3	$(CH_2)_3$	$CSNH_2$	68	B	86–87	EtOH	$C_9H_{13}N_3OS$	36.3	>100
26	H	H	CH_3	$(CH_2)_4$	$CSNH_2$	77	B	113–115	EtOH	$C_{10}H_{15}N_3OS$	29.5	>100
27	H	H	CH_3	$(CH_2)_5$	$CSNH_2$	65	B	69–72	EtOH	$C_{11}H_{17}N_3OS$	36.6	>100
28	H	H	CH_3	$(CH_2)_6$	$CSNH_2$	26	B	121–122	EtOH	$C_{12}H_{19}N_3OS$	29.5	>100
29	H	H	C_6H_5	CH_2	$CSNH_2$	78	B	245–245.5	EtOH	$C_{12}H_{11}N_3OS$	5.5 (NS)	
30	H	H	C_6H_5	$(CH_2)_2$	$CSNH_2$	83	C	173–175	EtOH-IPE	$C_{13}H_{13}N_3OS$	53.7	87.3 (45.5–157.1)
31	H	H	C_6H_5	$(CH_2)_2$	$CONH_2$	53	C	177–179	EtOH-IPE	$C_{13}H_{13}N_3O_2$	−2.8 (NS)	
32	H	H	C_6H_5	$(CH_2)_2$	$CONHCH_3$	92	C	165–167	EtOH-H_2O	$C_{15}H_{17}N_3O_2$	3.5 (NS)	
33	H	H	C_6H_5	$(CH_2)_2$	COOH	67	C	142–144	$CHCl_3$	$C_{13}H_{12}N_2O_3$	26.1 (NS)	
34	H	H	C_6H_5	$(CH_2)_2$	$COOC_2H_5$	86	C	199–202/0.9		$C_{15}H_{16}N_2O_3$	6.3 (NS)	
35	H	H	C_6H_5	$(CH_2)_2$	CN	77	C	103–104	EtOH-IPE	$C_{13}H_{11}N_3O$	10.1 (NS)	
36	H	H	C_6H_5	$(CH_2)_2$	$CSNHCH_3$	52	C	149–150	$CHCl_3$-IPE	$C_{14}H_{15}N_3OS$	68.2	58.5 (30.8–111.2)
37	H	H	C_6H_5	$(CH_2)_2$	$CSNHC_2H_5$	41	C	140–145	EtOH-IPE	$C_{15}H_{17}N_3OS$	50.3	100[g]
38	H	H	C_6H_5	$(CH_2)_2$	$CSNHCH_2OH$	94	C	120–121	EtOH-H_2O	$C_{14}H_{15}N_3O_2S$	5.1 (NS)	
39	H	H	C_6H_5	$(CH_2)_2$	$CSN(CH_3)_2$	53	C	132–134	EtOH	$C_{15}H_{17}N_3OS$	46.0	
40	H	H	C_6H_5	$(CH_2)_2$		28	C	110–113	EtOH	$C_{17}H_{19}N_3OS$	38.2	>100
41	H	H	$C_6H_4(4\text{-}CH_3)$	$(CH_2)_2$	$CSNH_2$	57	C	208–210	EtOH	$C_{14}H_{15}N_3OS$	18.2 (NS)	
42	H	H	$C_6H_4(4\text{-}CH_3O)$	$(CH_2)_2$	$CSNH_2$	58	C	203–205	EtOH	$C_{14}H_{15}N_3O_2S$	20.7	>100
43	H	H	$C_6H_4(4\text{-}Cl)$	$(CH_2)_2$	$CSNH_2$	33	C	183–185	EtOH	$C_{12}H_{12}ClN_3OS$	42.5	>100
44	H	H	$C_6H_3(3,4\text{-}Cl_2)$	$(CH_2)_2$	$CSNH_2$	59	C	203–205	EtOH	$C_{13}H_{11}Cl_2N_3OS$	55.8	78.1 (45.9–132.8)
45	H	CH_3	C_6H_5	$(CH_2)_2$	$CSNH_2$	48	C	105–106	EtOH	$C_{14}H_{15}N_3OS$	32.0	>100
46	CH_3	H	C_6H_5	$(CH_2)_2$	$CSNH_2$	79	C	132–134	EtOH	$C_{14}H_{15}N_3OS$	60.2	66.7 (44.5–100.1)
47	H	H	C_6H_5	$CH(CH_3)CH_2$	$CSNH_2$	65	C	248–250	EtOH	$C_{14}H_{15}N_3OS$	15.5 (NS)	
48	H	H	C_6H_5	$CH_2CH(CH_3)$	$CSNH_2$	75	C	172–174	$CHCl_3$	$C_{14}H_{15}N_3OS$	86.4	28.1 (18.5–42.7)
49	H	H	C_6H_5	$(CH_2)_3$	$CSNH_2$	47	A	129–130	EtOH-IPE	$C_{14}H_{15}N_3OS$	75.6	31.9 (19.7–51.7)

50	H	C_6H_5	$(CH_2)_4$	$CSNH_2$	50	A	154–156	EtOH–IPE	$C_{15}H_{17}N_3OS$	33.8	>100
51	H	C_6H_5	$(CH_2)_5$	$CSNH_2$	67	A	102–103	EtOH–IPE	$C_{16}H_{19}N_3OS$	91.4	23.3 (14.6–37.3)
52	H	C_6H_5	$(CH_2)_5$	$CSNHCH_3$	48	A	73–75	EtOH–IPE	$C_{17}H_{21}N_3OS$	92.3	25.2 (16.8–37.8)
53	H	C_6H_5	$(CH_2)_5$	$CSN(CH_3)_2$	57	A	60–63	EtOH–IPE	$C_{18}H_{23}N_3OS$	58.2	100[g]
54	H	C_6H_5	$(CH_2)_6$	$CSNH_2$	56	A	72–73	EtOH–IPE	$C_{17}H_{21}N_3OS$	33.9	>100
55	H	C_6H_5	$2\text{-}C_4H_3S$[h]	$CSNH_2$	40	C	160–163	EtOH	$C_{11}H_{11}N_3OS_2$	50.2	100[g]
56	H	C_6H_5	$2\text{-}C_{10}H_6(6\text{-}CH_3O)$[i]	$CSNH_2$	36	C	151–153	EtOH	$C_{18}H_{17}N_3O_2S$	48.9	100[g]

[a] The yield quoted was for isolated purified product. [b] Refers to route shown in Scheme I. [c] IPE = isopropyl ether. [d] All compounds were analyzed within ±0.4% of theory for C, H, and N, except 54 (N: calcd, 13.32; found, 13.92). [e] Statistically significant activity ($p < 0.05$) was determined in the 7-h pylorus-lygated rat using the technique of Shay. For comparison purposes: SC-15396, 86.3% inhibition at 100 mg/kg and ED_{50} = 18.2 (13.5–24.6) mg/kg; cimetidine, 27.9% inhibition at 100 mg/kg; atropine sulfate, ED_{50} = 3.1 (2.6–3.7) mg/kg. [f] NS = not statistically significant. [g] Graphically calculated. [h] 2-Thienyl. [i] 6-Methoxynaphth-2-yl.

no effect on charcoal transport in the intestine. In vitro experiments revealed that they had no anticholinergic activity at 1×10^{-4} M. It may be concluded from these findings that the inhibitory effect of these compounds on the stress-induced gastric lesion was neither due to suppression of the augmented gastric motility nor due to anticholinergic action. These compounds were also shown not to have histamine H_2-receptor antagonistic activity at 1×10^{-4} M.

In summary, synthetic variations in a series of 3(2*H*)-pyridazinones with a thio amide moiety led to compounds displaying gastric antisecretory and antiulcer activity. This novel type of compound may open the way to new candidates for antiulcer drugs.

Experimental Section

Chemistry. All melting points were obtained using a Yanagimoto micro melting 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 as parts per million (ppm, δ) relative to tetramethylsilane.

Starting Materials (5). 3(2*H*)-Pyridazinone,[27] 6-methyl-3-(2*H*)-pyridazinone,[13] and 6-phenyl-3(2*H*)-pyridazinone[12] and its related derivatives were prepared by the cited procedure.

Synthetic Route A. Using Phase-Transfer Catalysis. 2-(5-Cyanopentyl)-6-phenyl-3(2*H*)-pyridazinone (7, $R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 5$). To a solution of 10.3 g (0.06 mol) of **5** ($R^1 = R^2 = H$; $R^3 = C_6H_5$) in 300 mL of benzene were added 41.4 g (0.18 mol) of 1,5-dibromopentane, 3.4 g (0.06 mol) of KOH, and 3.9 g (0.012 mol) of tetra-*n*-butylammonium bromide (TBAB). The mixture was stirred at room temperature for 8 h. The organic layer was washed with 5% NaOH solution, 10% HCl solution and then H_2O, and dried over Na_2SO_4. The solvent and 1,5-dibromopentane were removed under reduced pressure. Distillation of the residue gave 13.3 g (69%) of **6** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 5$) as a colorless oil: bp 191–195 °C (1.5 mm Hg); IR (film) 1665 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.6–2.0 [m, 6 H, $CH_2(CH_2)_3CH_2$], 3.36 (t, 2 H, J = 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), 7.4 (m, 3 H, Ar H), 7.56 (d, 1 H, J = 10 Hz, C_5H), 7.7 (m, 2 H, Ar H).

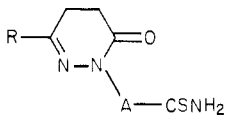
To a solution of 9.6 g (0.03 mol) of **6** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 5$) in 200 mL of benzene were added 2.1 g (0.033 mol) of KCN and 2.0 g (0.006 mol) of TBAB. The mixture was stirred at 50–60 °C for 10 h. The organic layer was washed with H_2O and dried over Na_2SO_4. After evaporation of the dried solution, distillation of the residue afforded 6.5 g (81%) of light yellow oil of **7** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 5$): bp 200–207 °C (0.7 mmHg); IR (film) 2240 (C≡N), 1670 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.6–1.9 [m, 6 H, $CH_2(CH_2)_3CH_2$], 2.24 (t, 2 H, J = 7 Hz, CH_2CN), 4.24 (t, 2 H, J = 7 Hz, $CONCH_2$), 6.98 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.68 (d, 1 H, J = 10 Hz, C_5 H), 7.7 (m, 2 H, Ar H).

Synthetic Route B. Using Phase-Transfer Catalysis. 2-(3-Cyanopropyl)-6-phenyl-3(2*H*)-pyridazinone (7, $R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 3$). To a solution of 4.7 g (0.027 mol) of **5** ($R^1 = R^2 = H$; $R^3 = C_6H_5$) in 150 mL of benzene were added 4.2 g (0.027 mol) of 4-bromobutyl cyanide, 1.5 g (0.027 mol) of KOH, and 1.7 g (0.0054 mol) of TBAB. The mixture was stirred at room temperature for 6 h. The organic layer was washed with 5% NaOH solution, 10% HCl solution, and then H_2O and dried over Na_2SO_4, and the dried solution was evaporated in vacuo to give the crude product, which was distilled to give 5.6 g (88%) of **7** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; $n = 3$): bp 185–190 °C (0.3 mmHg); IR (film) 2245 (C≡N), 1660 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.28 (quintet, 2 H, J = 7 Hz, $CH_2CH_2CH_2$), 2.48 (t, 2 H, J = 7 Hz, CH_2CN), 4.38 (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), 7.76 (d, 1 H, J = 10 Hz, C_5 H), 7.8 (m, 2 H, Ar H).

Synthetic Route C. Michael's Reaction Using Triton B. 2-(2-Cyanoethyl)-6-phenyl-3(2*H*)-pyridazinone (35). To a solution of 30 g (0.18 mol) of **5** ($R^1 = R^2 = H$; $R^3 = C_6H_5$) in 300

(27) R. Evans and F. Weislogle, *J. Am. Chem. Soc.*, 67, 60 (1945).

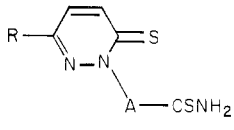
Table II. 4,5-Dihydro-3(2*H*)-pyridazinones



no.	R	A	yield,[a] %	mp,[j] °C	route[b]	crystn solvent[c]	formula[d]	antisecretory act. (id)[e] % inhibn at 100 mg/kg	antisecretory act. (id)[e] ED_{50}, mg/kg
57	CH_3	$(CH_2)_2$	75	143-145	C	EtOH-ether	$C_8H_{13}N_3OS$	34.8	>100
58	CH_3	$CH(CH_3)CH_2$	26	166-167	C	EtOH	$C_9H_{15}N_3OS$	17.4 (NS)[f]	
59	CH_3	$CH_2CH(CH_3)$	37	oil	C		$C_9H_{15}N_3OS$	15.6 (NS)	
60	C_6H_5	$(CH_2)_2$	77	193-195	C	EtOH-IPE	$C_{13}H_{15}N_3OS$	38.2	>100
61	C_6H_4(4-Cl)	$(CH_2)_2$	73	155-157	C	EtOH-IPE	$C_{13}H_{14}ClN_3OS$	43.1	>100
62	C_6H_3(3,4-Cl_2)	$(CH_2)_2$	81	203-205	C	EtOH	$C_{13}H_{13}Cl_2N_3OS$	47.2	>100
63	C_6H_5	$CH(CH_3)CH_2$	49	183-186	C	EtOH	$C_{14}H_{17}N_3OS$	9.2 (NS)	
64	C_6H_5	$CH_2CH(CH_3)$	53	154-156	C	CH_3CN	$C_{14}H_{17}N_3OS$	28.2 (NS)	
65	C_6H_5	$(CH_2)_3$	49	136-137	B	CH_3CN-IPE	$C_{14}H_{17}N_3OS$	50.3	100[g]
66	C_6H_5	$(CH_2)_4$	38	oil	B		$C_{15}H_{19}N_3OS$	50.2	100[g]
67	C_6H_5	$(CH_2)_5$	65	oil	A		$C_{16}H_{21}N_3OS$	48.5	100[g]
68	C_6H_5	$(CH_2)_6$	48	oil	A		$C_{17}H_{23}N_3OS$	68.3	58.8 (45.2-76.4)
69	2-C_4H_3S[h]	$(CH_2)_2$	64	135-137	C	EtOH-IPE	$C_{11}H_{13}N_3OS_2$	58.5	77.3 (53.3-112.1)

[a-h] See corresponding footnotes in Table I. [j] Oily compounds were directly recovered from the chromatographic column on silica gel (Wakogel C-200) with mix eluants (hexane-benzene-$CHCl_3$).

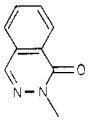
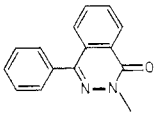
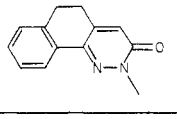
Table III. 3(2*H*)-Pyridazinethiones



no.	R	A	yield,[a] %	mp, °C	crystn solvent[c]	formula[d]	antisecretory act. (id)[e] % inhibn at 100 mg/kg	antisecretory act. (id)[e] ED_{50}, mg/kg
70	H	$(CH_2)_2$	62	163-164	$CHCl_3$	$C_7H_9N_3S_2$	50.0	100[g]
71	H	$CH_2CH(CH_3)$	51	108-109	$CHCl_3$	$C_8H_{11}N_3S_2$	-1.0 (NS)[f]	
72	CH_3	$(CH_2)_2$	56	123-126	$CHCl_3$	$C_8H_{11}N_3S_2$	48.5	100[g]
73	C_6H_5	$(CH_2)_2$	78	168-172	$CHCl_3$	$C_{13}H_{13}N_3S_2$	62.3	73.4 (48.9-110.1)

[a,c-g] See corresponding footnotes in Table I.

Table IV. Miscellaneous Compounds

no.	Het-$(CH_2)_2CSNH_2$ Het	yield,[a] %	mp, °C	crystn solvent[c]	formula[d]	antisecretory act. (id)[e] % inhibn at 100 mg/kg	antisecretory act. (id)[e] ED_{50}, mg/kg
78		86	159-161	EtOH-IPE	$C_{11}H_{11}N_3OS$	58.3	90.1 (59.3-136.9)
79		89	194-195	$CHCl_3$-IPE	$C_{17}H_{15}N_3OS$	73.3	66.5 (40.8-108.4)
82		63	191-193	EtOH-IPE	$C_{15}H_{15}N_3OS$	1.6 (NS)[f]	

[a,c-f] See corresponding footnotes in Table I.

mL of EtOH were added 11.5 g (0.22 mol) of acrylonitrile and 2 mL of Triton B. The mixture was heated at reflux temperature for 8 h. The reaction mixture was cooled, EtOH was removed under reduced pressure, and the residue was dissolved in $CHCl_3$. The organic layer was washed with H_2O and dried over Na_2SO_4. The dried solution was evaporated in vacuo to give crude solid, which was recrystallized from EtOH–isopropyl ether to give 30.1 g (76%) of **35**: mp 103–104 °C; IR (nujol) 2240 (C≡N), 1650 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (t, 2 H, J = 7 Hz, CH_2CN), 4.52 (t, 2 H, J = 7 Hz, $CONCH_2$), 6.98 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.62 (d, 1 H, J = 10 Hz, C_5 H), 7.7 (m, 2 H, Ar H).

2-(2-Carboxyethyl)-6-phenyl-3(2*H*)-pyridazinone (33). The reaction sequences were run in the same manner as for **35** on 2.6 g (0.015 mol) of **5** (R^1 = R^2 = H; R^3 = C_6H_5) and 3 g (0.03 mol) of ethyl acrylate to give 3.5 g (86%) of **34**, bp 199–202 °C (0.9 mmHg). Compound **34** was saponified to the carboxylic acid **33**.

2-(2-Cyano-1-methylethyl)-4,5-dihydro-6-phenyl-3(2*H*)-

Table V. Antiulcer Activities of 3(2*H*)-Pyridazinones

compd	ED_{50}, mg/kg		
	Shay's ulcer[a] (id)	aspirin ulcer[b] (id)	stress ulcer[c] (po)
18	40.0 (24.1-66.4)	68.5 (41.3-113.7)	>50
20	51.3 (42.0-62.6)	>100	>50
30	23.2 (16.7-32.2)	53.5 (38.5-74.4)	34.5 (17.6-57.3)
36	50.1 (39.1-64.1)	66.3 (33.8-129.9)	28.3 (14.3-56.0)
46	32.0 (16.3-62.7)	73.1 (36.9-144.7)	>50
48	18.2 (8.5-39.1)	35.0 (16.3-75.3)	36.1 (21.7-59.9)
49	15.5 (7.2-33.2)	38.0 (22.9-63.1)	10.5 (8.2-12.8)
51	9.2 (4.6-18.2)	18.2 (9.2-36.0)	10.2 (7.7-13.6)
52	15.0 (9.0-24.9)	45.5 (21.2-97.8)	18.3 (9.2-36.2)
68	24.8 (12.7-48.6)	72.3 (33.6-155.4)	23.0 (12.1-43.7)
SC-15396	20.0 (10.1-39.6)	18.5 (11.1-30.7)	50.3 (27.9-90.5)
cimetidine	>100	38.5 (31.6-46.9)	43.2 (25.4-73.4)
atropine sulfate	1.1 (0.5-2.4)	4.5 (3.7-5.4)	0.9 (0.6-1.35)

[a-c] See Experimental Section.

pyridazinone (7, $R^1 = R^2 = H$; $R^3 = C_6H_5$). The reaction sequences were run in the same manner as for **35** on 5.2 g (0.03 mol) of **4** ($R^1 = R^2 = H$; $R^3 = C_6H_5$) and 4.0 g (0.06 mol) of crotonitrile to give 4.7 g (65%) of the title compound: bp 192–195 °C (2.0 mmHg); IR (Nujol) 2240 (C≡N), 1670 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.30 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.60 (m, 2 H, C_4H_2), 2.86 (d, 2 H, J = 7 Hz, CH_2CN), 2.98 (m, 2 H, C_5H_2), 5.10 (sextet, 1 H, J = 7 Hz, $CONCH_2$), 7.5 (m, 3 H, Ar H), 7.8 (m, 2 H, Ar H).

2-(2-Cyanoethyl)-5,6-dihydro-3(2*H*)-benzo[*h*]cinnolinone (81). This compound was prepared from 5,6-dihydro-3(2*H*)-benzo[*h*]cinnolinone (4 g, 0.02 mol) using acrylonitrile (1.2 g, 0.023 mol) and Triton B (0.3 mL) in EtOH (50 mL) as described for **35**. Recrystallization from EtOH–isopropyl ether gave 2.5 g (49%) of **81**: mp 178–180 °C; IR (Nujol) 2245 (C≡N), 1650 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88 (s, 4 H, 2 CH_2), 2.95 (t, 2 H, J = 7 Hz, CH_2CN), 4.48 (t, 2 H, J = 7 Hz, $CONCH_2$), 6.76 (s, 1 H, C_4 H), 7.3 (m, 3 H, Ar H), 8.1 (m, 1 H, Ar H).

6-Phenyl-2-[2-(thiocarbamoyl)ethyl]-3(2*H*)-pyridazinone (30). To a solution of 4.5 g (0.02 mol) of **35** in 50 mL of dry pyridine, maintained at <5 °C, was added 30 mL of Et_3N. After standing for 2 h, dry H_2S was passed through the solution in a steady stream at 0 °C for 15 min. The sealed mixture was then stirred at room temperature for 2 days. The reaction mixture was concentrated under vacuum to give dark yellow residue, which was dissolved in $CHCl_3$. The organic layer was washed with H_2O and dried over Na_2SO_4. The dried solution was evaporated in vacuo to give crude solid, which was recrystallized from EtOH–isopropyl ether (1:3) to give 4.3 g of **30**: IR (KBr) 3250 (NH), 1665 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.02 (t, 2 H, J = 7 Hz, CH_2CS), 4.50 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.02 (d, 1 H, J = 10 Hz, C_4 H), 7.4 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.00 (d, 1 H, J = 10 Hz, C_5 H), 9.48 (d, 2 H, J = 14 Hz, $CSNH_2$).

2-[2-Methyl-2-(thiocarbamoyl)ethyl]-6-phenyl-3(2*H*)-pyridazinone (48). The title compound was prepared from **7** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; n = 2), as described for the preparation of **30**: IR (Nujol) 3300, 3190 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.18 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.57 (sextet, 1 H, J = 7 Hz, $CHCH_3$), 4.40 (d, 2 H, J = 7 Hz, $CONCH_2$), 7.12 (d, 1 H, J = 10 Hz, C_4 H), 7.6 (m, 3 H, Ar H), 8.0 (m, 2 H, Ar H), 8.12 (d, 1 H, J = 10 Hz, C_5 H), 9.52 (br d, 2 H, J = 12 Hz, $CSNH_2$).

6-Phenyl-2-[3-(thiocarbamoyl)propyl]-3(2*H*)-pyridazinone (49). The title compound was prepared from **7** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; n = 3) as described for the preparation of **30**: IR (Nujol) 3355, 3190 (NH), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.22 (quintet, 2 H, J = 7 Hz, $CH_2CH_2CH_2$), 2.55 (t, 2 H, J = 7 Hz, CH_2CS), 4.23 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.10 (d, 1 H, J = 10 Hz, C_4 H), 7.6 (m, 3 H, Ar H), 8.0 (m, 2 H, Ar H), 8.12 (d, 1 H, J = 10 Hz, C_5 H), 9.42 (br d, 2 H, J = 16 Hz, $CSNH_2$).

6-Phenyl-2-[5-(thiocarbamoyl)pentyl]-3(2*H*)-pyridazinone (51). The title compound was prepared from **7** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; n = 5) as described for the preparation of **30**: IR (Nujol) 3260, 3090 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.4 [m, 2 H, $(CH_2)_2CH_2(CH_2)_2$], 1.8 (m, 4 H, $CH_2CH_2CH_2CH_2CH_2$), 2.58 (t, 2 H, J = 7 Hz, CH_2CS), 4.22 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.10 (d, 1 H, J = 10 Hz, C_4 H), 7.6 (m, 3 H, Ar H), 8.0 (m, 2 H, Ar H), 8.04 (d, 1 H, J = 10 Hz, C_5 H), 9.2 (br, 2 H, $CSNH_2$).

4,5-Dihydro-6-phenyl-2-[6-(thiocarbamoyl)hexyl]-3(2*H*)-pyridazinone (68). The title compound was prepared from **7** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; n = 6) as described for the preparation of **30**. After workup, the residue was chromatographed on silica gel, and the product was eluted with hexane, with a hexane–benzene mixture, and then with a benzene–$CHCl_3$ mixture to give a slightly yellow oil: IR (film) 3300 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.6 [m, 8 H, $CH_2(CH_2)_4CH_2$], 2.5 (m, 4 H, CH_2CS and C_4 H_2), 3.96 (t, 2 H, J = 9 Hz, C_5 H_2), 3.82 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.5 (m, 3 H, Ar H), 7.8 (m, 2 H, Ar H), 9.1 (br, 2 H, $CSNH_2$).

4-Phenyl-2-[2-(thiocarbamoyl)ethyl]-2(1*H*)-phthalazinone (79). The title compound was prepared from **76** ($R^3 = C_6H_5$), as described for the preparation of **30**. IR (Nujol) 3320, 3180 (NH), 1630 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.09 (t, 2 H, J = 7 Hz, CH_2CS), 4.62 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.66 (s, 5 H, Ar H), 7.8, 8.0, and 8.4 (m, 4 H, Ar H), 9.4 (br, 2 H, $CSNH_2$).

5,6-Dihydro-2-[2-(thiocarbamoyl)ethyl]-3(2*H*)-benzo[*h*]-cinnolinone (82). The title compound was prepared from **81**, as described for the preparation of **30**: IR (Nujol) 3350, 3280 (NH), 1640 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.94 (s, 4 H, C_5 H_2 and C_6 H_2), 2.98 (t, 2 H, J = 7 Hz, CH_2CS), 4.44 (t, 2 H, J = 7 Hz, $CONCH_2$), 6.77 (s, 1 H, C_4 H), 7.2 (m, 3 H, Ar H), 7.9 (m, 1 H, Ar H), 9.34 (br d, 2 H, J = 14 Hz, $CSNH_2$).

2-[2-(*N*-Methylthiocarbamoyl)ethyl]-3(2*H*)-pyridazinone (13). Compound **7** ($R^1 = R^2 = R^3 = H$; n = 2; 3 g, 0.02 mol) was dissolved in 30 mL of 30% $MeNH_2$–MeOH solution and stirred at room temperature for 17 h. The mixture was allowed to react as described for the preparation of **30**: IR (Nujol) 3280 (NH), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.98 (d, 3 H, J = 5 Hz, $NHCH_3$), 3.02 (t, 2 H, J = 7 Hz, CH_2CS), 4.42 (t, 2 H, J = 7 Hz, $CONCH_2$), 6.95 (dd, 1 H, J = 2 and 10 Hz, C_4 H), 7.44 (dd, 1 H, J = 4 and 10 Hz, C_5 H), 7.92 (dd, 1 H, J = 2 and 4 Hz, C_6 H), 10.2 (br, 1 H, CSNH).

2-[2-(*N*-Methylthiocarbamoyl)ethyl]-6-phenyl-3(2*H*)-pyridazinone (36). The title compound was prepared from **7** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; n = 2) and 30% $MeNH_2$–MeOH solution as described for the preparation of **30**: IR (Nujol) 3220 (NH), 1640 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.96 (d, 3 H, J = 4 Hz, $NHCH_3$), 3.06 (t, 2 H, J = 7 Hz, CH_2CS), 4.51 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.02 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 8.00 (d, 1 H, J = 10 Hz, C_5 H), 10.0 (br, 1 H, CSNH).

2-[2-(*N*,*N*-Dimethylthiocarbamoyl)ethyl]-6-phenyl-3-(2*H*)-pyridazinone (39). The title compound was prepared from **7** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; n = 2) and Me_2NH gas in EtOH as described for the preparation of **30**: IR (Nujol) 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.22 (t, 2 H, J = 7 Hz, CH_2CS), 3.36 (s, 3 H, N-CH_3 or S-CH_3), 3.40 (s, 3 H, N-CH_3 or S-CH_3), 4.52 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.01 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 7.98 (d, 1 H, J = 10 Hz, C_5 H).

2-[5-(*N*-Methylthiocarbamoyl)pentyl]-6-phenyl-3(2*H*)-pyridazinone (52). The title compound was prepared from **7** ($R^1 = R^2 = H$; $R^3 = C_6H_5$; n = 5) and 30% $MeNH_2$–MeOH

solution as described for the preparation of **30**: IR (Nujol) 3320, 3240 (NH), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.4–1.8 [m, 6 H, $CH_2(CH_2)_3CH_2$], 2.75 (t, 2 H, J = 7 Hz, CH_2CS), 2.94 (d, 3 H, J = 5 Hz, $NHCH_3$), 4.43 (t, 2 H, J = 7 Hz, $CONCH_2$), 7.00 (d, 1 H, J = 10 Hz, C_4 H), 7.5 (m, 3 H, Ar H), 7.9 (m, 2 H, Ar H), 7.99 (d, 1 H, J = 10 Hz, C_5 H), 9.3 (br, 1 H, $NHCH_3$).

2-[2-[*N*-(Hydroxymethyl)thiocarbamoyl]ethyl]-6-phenyl-3(2*H*)-pyridazinone (38). Formalin (40%, 10 mL) was added to a solution of 2.6 g (0.01 mol) of **30** in 100 mL of EtOH–H_2O (3:7), and the mixture was heated at reflux temperature for 15 min. The reaction mixture was cooled and then evaporated under reduced pressure to give crude solid, which was recrystallized from EtOH–H_2O to give 2.7 g of **38**: IR (Nujol) 3200 (NH), 1645 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.08 (t, 2 H, J = 7 Hz, CH_2CS), 4.52 (t, 2 H, J = 7 Hz, $CONCH_2$), 4.96 (m, 2 H, $NHCH_2OH$), 6.06 (t, 1 H, J = 7 Hz, CH_2OH), 7.03 (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), 10.6 (br, 1 H, CSNH).

2-(2-Cyanoethyl)-3(2*H*)-pyridazinethione (9, R^3 = H). Phosphorus pentasulfide (4.4 g, 0.02 mol) was added to a solution of 3 g (0.02 mol) of **7** ($R^1 = R^2 = R^3$ = H; n = 2) in dry pyridine and heated at 110–120 °C for 15 min. The reaction mixture was evaporated to give dark orange oil. The oil was dissolved in 50 mL of 10% NaOH solution, extracted with 50 mL of $CHCl_3$, and then extracted with 50 mL of concentrated HCl solution from the $CHCl_3$ phase. After neutralization with $NaHCO_3$ solution, the mixture was extracted with 100 mL of $CHCl_3$, washed with H_2O, and dried over Na_2SO_4. The dried solution was evaporated to give a yellow solid cake, which was recrystallized from EtOH to give 1.5 g (47%) of **9** (R^3 = H): mp 63–64 °C; IR (Nujol) 2250 (C≡N), 1080 (C=S) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.22 (t, 2 H, J = 7 Hz, CH_2CN), 4.81 (t, 2 H, J = 7 Hz, $CSNCH_2$), 7.30 (dd, 1 H, J = 4 and 10 Hz, C_5 H), 7.82 (dd, 1 H, J = 2 and 10 Hz, C_4 H), 8.42 (dd, 1 H, J = 2 and 4 Hz, C_6 H).

2-(2-Cyanoethyl)-6-phenyl-3(2*H*)-pyridazinethione (9, R^3 = C_6H_5). The title compound was prepared from **30**, as described for the preparation of **9** (R^3 = H): 72% yield; mp 127–128 °C; IR (Nujol) 1085 (C=S) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.28 (t, 2 H, J = 7 Hz, CH_2CN), 4.88 (t, 2 H, J = 7 Hz, $CSNCH_2$), 7.8 (m, 3 H, Ar H), 7.93 (s, 2 H, C_4 H and C_5 H), 7.9 (m, 2 H, Ar H).

Pharmacology. Gastric Antisecretory Activity. Gastric antisecretory activity was evaluated using the technique of Shay.[19] 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 performed, 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. Seven 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 percentage 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} was calculated.

Antiulcer Activity. Shay's Ulcer. Male Wistar rats, weighing 220–240 g, were fasted for 48 h and thereafter the animals were allotted to groups of six each. Immediately after the pylorus was ligated according to the method described by Shay et al.,[20] the test compounds were administered intraduodenally. Eighteen hours after administration, the rat was sacrificed and the stomach was removed. The stomach was slightly inflated by an injection of 1% formalin solution and immersed in the same solution for 10 min to fixing of the gastric wall. Subsequently, the stomach was incised along the greater curvature, and the area of the gastric lesions in the forestomach was measured under a dissecting microscope. The ulcer index (mm^2) was given by the summation of the area of the lesions.

Aspirin Ulcer. The technique used was essentially the same as that described elsewhere.[21] Male Donryu rats, weighing 200–220 g, were deprived of food for 24 h. Ten animals per group were used. After fasting, the pylorus was ligated, and the test compounds were administered intraduodenally. Ten minutes later, aspirin, suspended in 1% carboxymethylcellulose solution, was given orally in a dose of 100 mg/kg. Seven hours after aspirin administration, 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.

Stress Ulcer. Ten male Wistar rats, weighing 200–220 g, per group were used. After oral administration of test compounds, animals were immobilized in the stress cage and immersed in a water bath according to the method described by Takagi et al.[22] Seven hours later, the stomach was removed and the ulcer index (mm) was obtained by the same procedure as mentioned above. The ED_{50} for antiulcer activity was calculated by the method of Litchfield and Wilcoxon.[28]

Anticholinergic Activity. The anticholinergic activity was determined using the guinea pig isolated ileum preparation suspended in Tyrode 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 (3×10^{-7} to 1×10^{-4} M) or atropine (3×10^{-8} to 3×10^{-6} M).

Histamine H_2-Receptor Antagonistic Activity. The histamine H_2-receptor antagonistic activity was determined using 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 (3×10^{-7} to 1×10^{-4} M) or cimetidine (3×10^{-6} to 3×10^{-5} M).

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