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Studies on New Antiulcer Agents. I. Synthesis and Antisecretory Activity of Pyridazine Derivatives[1)]

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The pyridine ring of 2-phenyl-2-(2-pyridyl)thioacetamide (Ia), the lead compound for the present study, was replaced by a pyridazine ring in the hope of obtaining more potent and less toxic drugs with long-lasting action, and a series of 2-phenyl-2-(3-pyridazinyl)thioacetamide derivatives (II) was synthesized from halopyridazines (III) and phenylacetonitriles *via* the key intermediates, 2-phenyl-2-(3-pyridazinyl)acetonitrile derivatives (IV). The chemical structure of II appears to be in equilibrium between the pyridazine form and the pyridazinone-methide form on the basis of nuclear magnetic resonance (NMR) and ultraviolet (UV) spectral data. The antisecretory activity and acute toxicity of II were investigated and the structure-activity relationships are discussed. Among the compounds tested, 2-Phenyl-2-(3-pyridazinyl)thioacetamide (IIa) and 2-(6-methyl-3-pyridazinyl)-2-phenylthioacetamide (IIb) possessed long-lasting, potent activity when administered to rats at 20 mg/kg. The acute toxicities of IIa and IIb were about half to one-third of that of Ia in mice.

Keywords——2-phenyl-2-(3-pyridazinyl)thioacetamides; pyridazine ring; thioacetamide moiety; thiolysis; antisecretory activity; antiulcer; toxicity; structure-activity relationship

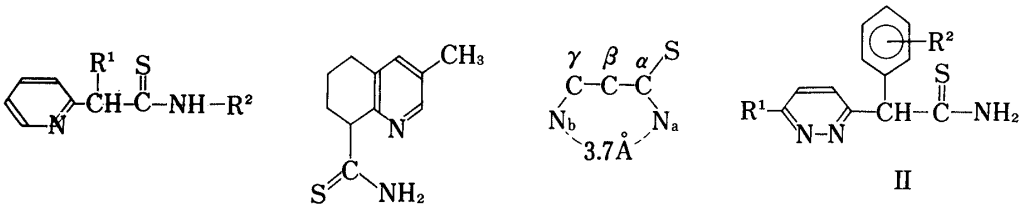
Introduction

The etiology of peptic ulceration is thought to be multifactorial, and various kinds of drugs are used in clinical therapy. For example, representative drugs include antacids and anticholinergic agents, which are applied to the treatment of patients with gastric ulcer in order to neutralize gastric acid or to inhibit its secretion, but their clinical usage is restricted by disadvantages such as short duration[2)] and side-effects.[3)] In recent years, studies on nonanticholinergic gastric antisecretory agents have given rise to many compounds with various modes of action that can be considered to be specific for a particular mediator, *i.e.*, antigastric agents or histamine H_2-receptor antagonists such as cimetidine.[4)]

Lee *et al.*[5)] initially focussed their attention on the C-terminal tetrapeptide of gastrin as a bioactive center and in 1967 they prepared 2-phenyl-2-(2-pyridyl)thioacetamide (SC-15396, Ia), which was proved to have a potent and long-lasting gastric antisecretory activity. Since then, pyridyl-2-thioacetamide (CMN-131, Ib),[6)] 2-methoxy-N-methyl-2-(2-pyridyl) thioacetamide (SKF-59377, Ic)[7)] and 3-methyl-5,6,7,8-tetrahydroquinolin-8-thiocarboxamide (Tiquinamide, Id)[8)] have been reported as analogs.

Subsequently, the structure-activity relationship of heterocyclic compounds with a thioamide group have been studied simultaneously by many investigators. After synthesis and pharmacological evaluation of many substances, the structural requisites for antisecretory activity in this series of compounds have been proposed;[9)] i) a thioamide group is essential, ii) one heterocycle including Cγ is necessary, iii) the distance between the two heteroatoms (Na and Nb) should preferably be about 3.7 Å, and so on (Chart 1).

The pyridine ring in some bioactive agents has sometimes been replaced by the pyridazine ring without loss of activity or increase in toxicity. As a typical example, the pyridine ring



Ia : R^1 : C_6H_5, R^2 : H (SC-15396)
Ib : R^1 : H, R^2 : H (CMN-131)
Ic : R^1 : OCH_3, R^2 : CH_3 (SKF-59377)

Id (tiquinamide)

model structure

R^1 : H, CH_3, C_6H_5 or SH
R^2 : H, Cl, Cl_2, CH_3 or OCH_3

Chart 1

in sulfapyridine was satisfactorily replaced by a pyridazine ring with a clear decrease in toxicity and with an increase of the effective duration, as seen in the development of sulfamethoxypyridazine by Druey.[10]

These results prompted us to synthesize a series of derivatives having a pyridazine ring instead of the pyridine ring of Ia in the hope of obtaining a less toxic drug with long-lasting efficacy. In this paper, we describe the synthesis of pyridazine derivatives with a thioamide group and their pharmacological activity.

Results and Discussion

Chemistry

All compounds reported in this paper were prepared by the synthetic procedures described in Chart 2. The key intermediate III was obtained in the usual manner[11] from hydroxypyridazines. The reaction of III with substituted or nonsubstituted phenylacetonitriles in the presence of sodium amide or sodium hydride in benzene or benzene–dimethylformamide gave the corresponding acetonitriles IV in 43—89% yields. The nitrile group in IV was converted into a thioamide moiety by treatment with hydrogen sulfide in pyridine-triethylamine at ordinary temperature in 46—92% yields.

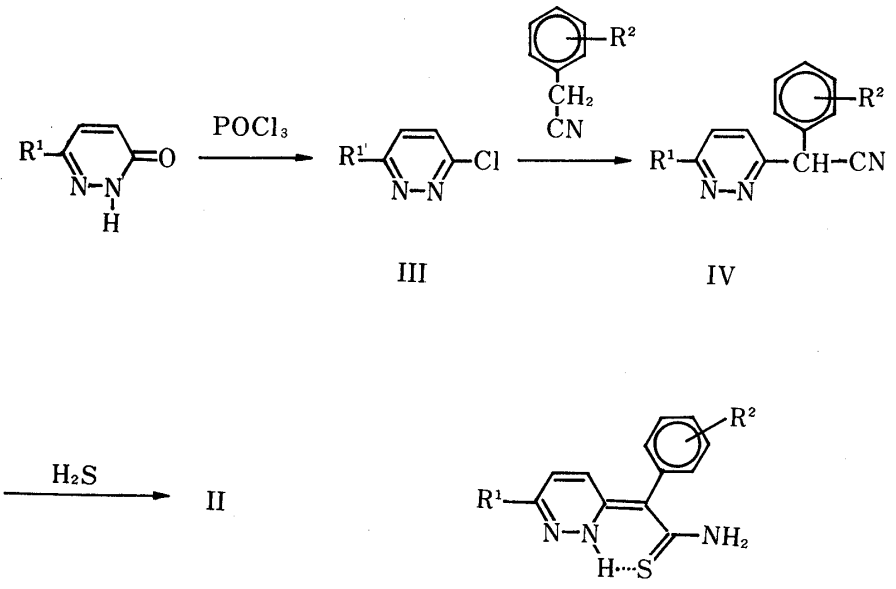
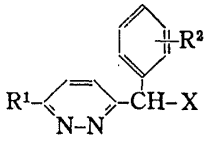


Chart 2

The structures of the compounds II and IV were confirmed by elemental analysis, infrared absorption (IR), nuclear magnetic resonance (NMR), and mass spectral data. Judging from the NMR spectral data, the methine proton in Ia was not exchanged even when Ia was treated with deuterium oxide in dimethylsulfoxide -d_6 (DMSO-d_6) under heating (50°C) for 30 min, but the methine proton in II was completely exchanged within 10 min at room temperature. This means that structure of the compounds II may be in equilibrium between two tautomers,

Table I. Pyridazine Derivatives (IV and II)



Compd. No.	R^1	R^2	X	mp (°C)	Yield[a] (%)	Formula	Analysis, (%) Calcd. (Found) C	N	H
IVa	H	H	CN	136—137	65	$C_{12}H_9N_3$	73.83 (74.05	4.65 4.65	21.53 21.53)
IVb	CH_3	H	CN	121—122	70	$C_{13}H_{11}N_3$	74.21 (74.62	5.09 5.30	19.97 20.08)
IVc	C_6H_5	H	CN	201—203	89	$C_{18}H_{13}N_3$	79.68 (79.48	4.83 4.83	15.47 15.30)
IVd	Cl	H	CN	131—133	54	$C_{12}H_8ClN_3$	62.76 (62.49	3.51 3.63	18.30 18.24)
IVe	H	4-Cl	CN	115—117	80	$C_{12}H_8ClN_3$	62.76 (62.79	3.51 3.68	18.30 18.12)
IVf	H	4-CH_3	CN	127—129	73	$C_{13}H_{11}N_3$	74.62 (74.58	5.30 5.52	20.08 20.00)
IVg	H	4-CH_3O	CN	147—149	40	$C_{13}H_{11}N_3O$	69.32 (69.22	4.92 4.78	18.66 18.86)
IVh	H	3,4-Cl_2	CN	115—117	48	$C_{12}H_7Cl_2N_3$	54.57 (54.52	2.65 2.83	15.92 15.69)
IVi	CH_3	4-Cl	CN	111—113	73	$C_{13}H_{10}ClN_3$	64.10 (64.22	4.11 4.21	17.24 17.03)
IVj	CH_3	4-CH_3	CN	103—105	43	$C_{14}H_{13}N_3$	75.31 (75.49	5.87 5.92	18.82 18.62)
IIa	H	H	CS–NH_2	173—174	92	$C_{12}H_{11}N_3S$	62.86 (62.67	4.84 4.82	18.33 18.53)
IIb	CH_3	H	CS–NH_2	135—136	79	$C_{13}H_{13}N_3S$	64.17 (64.21	5.39 5.37	17.27 17.41)
IIc	C_6H_5	H	CS–NH_2	201—203	68	$C_{18}H_{15}N_3S$	70.79 (70.89	4.95 4.74	13.76 14.01)
IId	SH[b]	H	CS–NH_2	192—195	65	$C_{12}H_{11}N_3S_2$	55.15 (55.03	4.24 4.36	16.08 16.14)
IIe	H	4-Cl	CS–NH_2	171—173	66	$C_{12}H_{10}ClN_3S$	54.65 (65.65	3.82 3.71	15.93 15.63)
IIf	H	4-CH_3	CS–NH_2	127—129	46	$C_{13}H_{13}N_3S$	64.17 (64.18	5.39 5.62	17.27 17.07)
IIg	H	4-CH_3O	CS–NH_2	147—149	55	$C_{13}H_{13}N_3OS$	60.21 (60.02	5.05 5.12	16.20 16.09)
IIh	H	3,4-Cl_2	CS–NH_2	173—175	47	$C_{12}H_9Cl_2N_3S$	48.37 (48.21	3.04 3.11	14.10 13.81)
IIi	CH_3	4-Cl	CS–NH_2	68—70	74	$C_{13}H_{12}ClN_3S$	56.21 (56.10	4.35 4.48	15.13 15.18)
IIj	CH_3	4-CH_3	CS–NH_2	91—93	49	$C_{14}H_{15}N_3S$	65.34 (65.08	5.88 6.09	16.33 16.43)

a) Yields of nitrile derivatives (IV) were calculated on the basis of III and those of thioamide derivatives(II) were calculated on the basis of IV.
b) Thiation product of the 6-chloropyridazine ring.

the pyridazine form and the pyridazinone–methide form, as shown in Chart 2. The ultraviolet absorption maximum at 315 nm observed in Fig. 1 indicates the presence of a more extended conjugate system in II than in Ia, which is consistent with the lability of the methine proton in II mentioned above. The chemical differences between Ia and II might be reflected in their biological actions *in vivo*.

TABLE II. IR and NMR Spectral Data for Pyridazine Derivatives (IV and II)

Comp. No.	IR ν_{max}^{Nujol} cm^{-1}	NMR(in DMSO-d_6) δ
IVa	2260(CN)	5.68 (1H, s, CH), 7.4 (7H, m, Ar–H), 9.2 (1H, m, C_6–H)
IVb	2250(CN)	2.72 (3H, s, CH_3), 5.64 (1H, s, CH), 7.4 (7H, m, Ar–H)
IVc	2250(CN)	6.22 (1H, s, CH), 7.5 (8H, m, Ar–H), 7.78 (1H, d, J=8 Hz, C_4–H), 8.2 (2H, m, Ar–H), 8.28 (1H, d, J=8 Hz, C_6–H)
IVd	2250(CN)	5.65 (1H, s, CH), 7.40 (5H, m, Ar–H), 7.50 (2H, s, C_4–H and C_5–H)
IVe	2250(CN)	6.77 (1H, s, CH), 8.10 (4H, s, Ar–H), 8.4 (2H, m, C_4–H and C_5–H), 10.0 (1H, m, C_6–H)
IVf	2250(CN)	2.45 (3H, s, CH_3), 6.57 (1H, s, CH), 7.76 (2H, d, J=9 Hz, Ar–H), 7.92 (2H, d, J=9 Hz, Ar–H), 8.28 (2H, m, C_4–H and C_5–H), 9.9 (1H, m, C_6–H)
IVg	2250(CN)	3.80 (3H, s, OCH_3), 6.19 (1H, s, CH), 7.10 (2H, d, J=9 Hz, Ar–H), 7.56 (2H, d, J=9 Hz, Ar–H), 7.9 (2H, m, C_4–H and C_5–H), 9.4 (1H, m, C_6–H)
IVh	2245(CN)	6.37 (1H, s, CH), 7.9 (5H, m, Ar–H), 9.4 (1H, m, C_6–H)
IVi	2440(CN)	2.82 (3H, s, C_6–CH_3), 6.28 (1H, s, CH), 7.58 (4H, s, Ar–H), 7.70 (2H, s, Ar–H)
IVj	2240(CN)	2.30 (3H, s, CH_3), 2.68 (3H, s, C_6–CH_3), 5.52 (1H, s, CH), 7.02 (2H, d, J=8 Hz, Ar–H), 7.20 (2H, d, J=8 Hz, Ar–H), 7.22 (1H, d, J=8 Hz, C_4 or C_5–H), 7.28 (1H, d, J=8 Hz, C_4 or C_5–H)
IIa	3260, 3120(NH)	5.85 (1H, s, CH), 7.5 (7H, m, Ar–H), 9.14 (1H, m, C_6–H), 9.88 (2H, d, J=20 Hz, $CSNH_2$)
IIb	3280, 3140(NH)	2.58 (3H, s, CH_3), 5.82 (1H, s, CH), 7.5 (7H, m, Ar–H), 9.90 (2H, d, J=20 Hz, $CSNH_2$)
IIc	3280, 3150(NH)	5.88 (1H, s, CH), 7.5 (5H, m, Ar–H), 8.10 (2H, m, Ar–H), 9.84 (2H, d, J=20Hz, $CSNH_2$)
IId	3300(NH)	5.39 (1H, s, CH), 7.10 (1H, d, J=9 Hz, C_4–H), 7.4 (5H, m, Ar–H), 7.52 (1H, d, J=9 Hz, C_5–H), 9.80 (2H, d, J=32 Hz, $CSNH_2$), 14.7 (1H, s, SH)
IIe	3280, 3200(NH)	5.85 (1H, s, CH), 7.42 (4H, s, Ar–H), 7.58 (2H, m, C_4–H and C_5–H), 9.08 (1H, m, C_6–H), 9.72 (2H, d, J=20 Hz, $CSNH_2$)
IIf	3260, 3100(NH)	2.20 (3H, s, CH_3), 6.00 (1H, s, CH), 7.14 (2H, d, J=9 Hz, Ar–H), 7.30 (2H, d, J=9 Hz, Ar–H), 7.6 (2H, m, C_4–H and C_5–H), 9.10 (1H, m, C_6–H), 9.75 (2H, d, J=20 Hz, $CSNH_2$)
IIg	3260, 3180(NH)	3.80 (3H, s, OCH_3), 5.83 (1H, s, CH), 6.96 (2H, d, J=8 Hz, Ar–H), 7.42 (2H, d, J=8 Hz, Ar–H), 7.6 (2H, m, C_4–H and C_5–H), 9.08 (1H, m, C_6–H), 9.68 (2H, d, J=20 Hz, $CSNH_2$)
IIh	3220, 3180(NH)	5.76 (1H, s, CH), 7.6 (5H, m, Ar–H), 9.04 (1H, m, C_6–H), 9.80 (2H, d, J=24 Hz, $CSNH_2$)
IIi	3280, 3150(NH)	2.70 (3H, s, C_6–CH_3), 5.98 (1H, s, CH_3), 7.6 (6H, m, Ar–H), 9.9 (2H, d, J=20 Hz, $CSNH_2$)
IIj	3260, 3160(NH)	2.35 (3H, s, CH_3), 2.60 (3H, s, C_6–CH_3), 5.55 (1H, s, CH), 7.05 (2H, d, J=8 Hz, Ar–H), 7.26 (2H, d, J=8 Hz, Ar–H), 7.24 (1H, d, J=9 Hz, C_4 or C_5–H), 7.32 (1H, d, J=9 Hz, C_4 or C_5–H), 9.7 (2H, d, J=20 Hz, $CSNH_2$)

Biological Evaluation

The gastric antisecretory activity was evaluated in 7 h pylorus-ligated rats according to Shay.[12] Most of the compounds tested possessed potent and long-lasting antisecretory activity as shown in Table III.

It was found that the effectiveness of substitutents on the pyridazine ring decreased in the following order: unsubstituted=6-methyl->6-phenyl≫6-mercapto. The 6-mercapto analog IId was practically inactive, and the precursors, the nitriles IV, had no activity. The presence of substituents on the phenyl ring did not improve the biological activity; the unsubstituted derivatives (IIa and IIb) had more potent activity than the substituted ones (IIe, IIf, and IIg). The compounds IIa, IIb, IIi, and IIj were as potent as Ia.

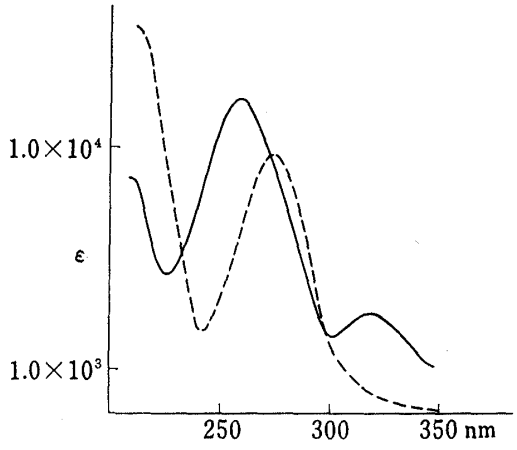


Fig. 1. UV Spectra of IIa (—) and Ia (---)

The acute toxicity is given as LD_{50} values in Table III. The toxicities of the active compounds were about half to one-third of that of Ia, and the introduction of a methyl group on the pyridazine ring tended to decrease the toxicity (IIa *vs* IIb, IIe *vs* IIi, and IIf *vs* IIj).

Okabe *et al.* have already reported[13] the results of extensive studies on the effects of IIa and IIb on gastric secretion and various experimental ulcers in rats, indicating that they had marked antiulcer properties as well as potent antisecretory activities. On the other hand, our preliminary experiments revealed that the compounds had no anticholinergic or histamine H_2-receptor antagonistic activity (unpublished data). Further pharmacological and toxicological experiments are in progress in our laboratories, and the results will be reported elsewhere.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were measured with a Hitachi TYPA-215 spectrophotometer and NMR spectra were recorded with a JEOL JNM-PS-100 spectrometer (100 MHz) using tetramethylsilane as an internal standard. In the representation of NMR data, the following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra (MS) were measured with a JEOL JMS-01SG mass spectrometer. UV spectra were determined in MeOH on a Hitachi 124 spectrophotometer.

3-Chloro-6-substitutedpyridazines (III)——3-Chloropyridazine,[14a] 3-chloro-6-methylpyridazine,[14b] 3-chloro-6-phenylpyridazine,[14c] and 3,6-dichloropyridazine[14d] were prepared by the cited procedures.

Synthesis of 2-Phenyl-2-(3-pyridazinyl)acetonitrile (IVa); Typical Procedure——Pulverized sodium amide (1.6 g) was added to a stirred solution of 6 g of 3-chloropyridazine and 5.2 g of phenylacetonitrile in 100 ml of benzene under ice-water cooling. The mixture was stirred for 6 h at room temperature, and then refluxed for 4 h. After cooling, the mixture was neutralized with 10% hydrochloride solution and extracted with benzene. The benzene layer was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a red-orange oil, which was crystallized from a mixture of ethanol and isopropylether to obtain 6.7 g of colorless needles, 65% yield, mp 136—137°C. MS *m/e*: 195. UV λ_{max}^{MeOH} (ε): 250 (1.2×10^3), 316 (0.8×10^3). Analysis, IR, and NMR data of IVa are summarized in Tables I and II together with IVb—j.

Synthesis of 2-Phenyl-2-(3-pyridazinyl)thioacetamide (IIa); Typical Procedure——Triethylamine (50 ml) was added to a solution of 30 g of IVa in 200 ml of pyridine, and the mixture was stirred at room temperature for 30 min. Hydrogen sulfide was passed into the mixture in a steady stream at 0°C for 20 min. The container was then sealed and the mixture was allowed to stand at room temperature for 2 days. The reaction mixture was concentrated under a vacuum. The residue was extracted with 500 ml of chloroform and the extract was washed with water, dried over anhydrous sodium sulfate, treated with Norit, filtered, and concentrated. The residue was recrystallized from ethanol to give 32 g of colorless needles, 92% yield, mp 173—174°C, MS *m/e*: 229, UV λ_{max}^{MeOH} (ε): 254 (2.3×10^4), 315 (2.3×10^3). Analysis, IR, and NMR data for IIa are summarized in Tables I and II together with those for IIb—j.

Gastric Antisecretory Activity——Six male rats (Wistar) weighing 150—180 g were used per compound. After 24 h fasting, animals were subjected to ligature of the pylorus under ether anesthesia, and the test compounds were administered directly into the duodenum as a dispersion in aqueous 1% CMC solution. The control group was given vehicle alone. After 7 h, the stomach was extirpated under ether anesthesia to collect the accumulated gastric juice therein. The inhibiting effect of the compounds on the gastric secretion was calculated by means of the following formula: $\text{Inhibition}(\%)=100\times(A+B/A)$, where A(ml) is the volume of gastric juice in the control group and B (ml) is that in the treated group. The results are shown in Table III.

Table III. Gastric Antisecretory Activity and Toxicity of Pyridazine Derivatives (II and IV)

Comp. No.	Gastric antisecretory activity[a]	Toxicity[b] LD_{50} (mg/kg)
IIa	##	980
IIb	##	1700
IIc	+	1280
IId	±	
IIe	##	875
IIf	##	920
IIg	+	
IIh	##	1260
IIi	##	1355
IIj	##	1550
IVa	±	
IVb	±	
IVc	±	
Ia	##	570[c]

a) Activity was assessed according to the following criteria: ±, marginal or insignificant inhibition; +, 20—40% inhibition; ##, 40—60% inhibition; ##, 60—80% inhibition at 20 mg/kg.
b) Acute toxicity was tested by oral administration to male mice.
c) Ref. 9.

Acute Toxicity——The test compounds were administered orally to ddY male mice, which were allowed free access to food and tap water. At 72 h after treatment, mortality ratios were obtained and LD_{50} values were calculated according to Litchfield and Wilcoxon.[15]

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References and Notes

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