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Synthesis and Gastric Antisecretory Activity of *N*-Cyano-*N'*-(phenyl-pyridinylmethyl)guanidine Derivatives[1)]

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N-Alkyl-*N'*-cyano-*N''*-(substituted phenyl-pyridinylmethyl)guanidine derivatives were synthesized and tested for inhibitory activity against gastric secretion in rats. Several of the compounds synthesized showed an inhibiting activity as potent as that of cimetidine against basal gastric secretion but showed less potent activity than cimetidine against histamine-stimulated gastric secretion. Some structure–activity relationships are discussed.

Keywords——cyanoguanidine; antisecretory activity; histamine H_1 antagonist; histamine H_2 antagonist

In the process of developing the H_2 histaminic antagonist, cimetidine (III), starting from burimamide (I) *via* metiamide (II), it has been shown that the cyanoguanidine group is bioisosteric with the thiourea group.[2)] It is noteworthy that kidney damage and agranulocytosis have not been seen as toxicological effects of cimetidine, although they were observed with metiamide in high-dose chronic toxicity tests.[2)] This suggested that these toxic effects of metiamide may be attributable to the presence of a thiourea group in the drug molecule. Thus, attempts have been made to replace the thiourea group with a cyanoguanidine group in several biologically active thiourea compounds.

Pyridinylalkylthiourea (IV) or *N*-cyano-*N'*-pyridinylalkylguanidine (V) derivatives were reported to have H_2 antihistaminic or gastric antisecretory activity.[3)] On the other hand, *N*, *N'*-dialkyl-*N''*-pyridinylguanidine (VI)[4)] and *N*-alkyl-*N'*-cyano-*N''*-pyridinylguanidine (VII) derivatives[5)] have been reported to have potent hypotensive activity. SC-15396 (VIII), known as Antigastrin, was reported to have gastric antisecretory activity.[6)] The phenyl-2-pyridinylmethyl group, the constituent group of VIII, is also the carrier moiety of the H_1 antihistaminic, pheniramine (IX).[7)]

We planned to synthesize new cyanoguanidine derivatives bearing the cyanoguanidine and phenyl-pyridinylmethyl groups in the same molecule and to explore their pharmacological activities. After we started this research, a patent on the synthesis of *N*-alkyl-*N'*-cyano-*N''*-heterocyclylguanidine derivatives,[8)] in particular of *N*-cyano-*N'*-methyl-*N''*-[β-(2-pyridinyl)phenethyl]guanidine (X-4), *N*-cyano-*N'*-methyl-*N''*-[α-(2-pyridinyl)benzyl]guanidine (X-11), and *N*-cyano-*N'*-methyl-*N''*-[α-(3-pyridinyl)benzyl]guanidine (X-30), was published. However, only a few such compounds were mentioned. It was reported that these compounds had gastric antisecretory activity but no pharmacological data were given.

We synthesized more than one hundred derivatives X and found several compounds with potent gastric antisecretory activity. In this paper we report the synthesis of compounds X and the results of pharmacological screening for inhibitory activity against gastric secretion in

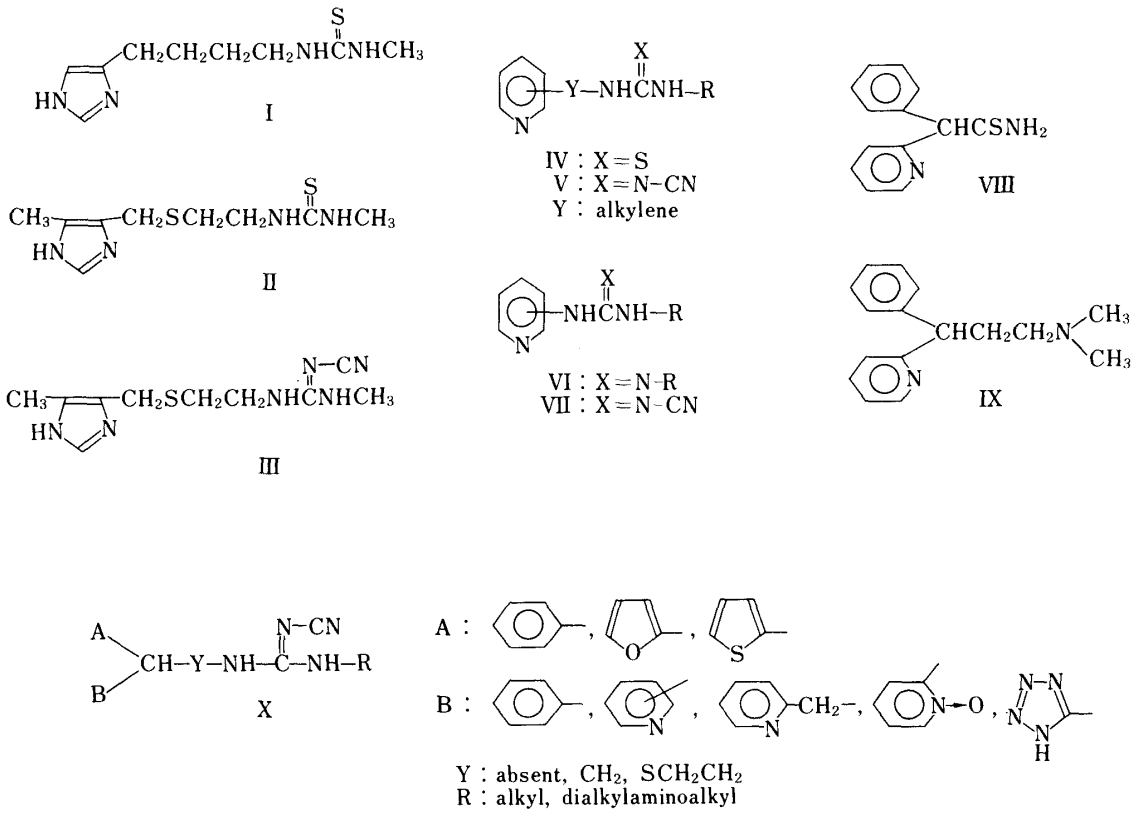


Fig. 1

rats. Some structure–activity relationships will also be discussed.

Chemistry

The *N*-alkyl-*N'*-cyano-*N''*-(phenyl-pyridinylalkyl)guanidine derivatives (X) were synthesized by the route shown in Chart 1. The intermediate 3-cyano-2-methyl-1-(phenyl-pyridinylalkyl)-isothiourea derivatives (XI) were reacted with a primary alkylamine to give compounds X. Phenyl-2-pyridinylmethanamine (XII-1) was synthesized from the corresponding phenyl pyridinyl ketone (XIV) *via* oxime formation and then reduction. 2-(Phenyl-2-pyridinylmethyl)thioethanamine (XII-2) was obtained by the condensation of phenyl-2-pyridinylmethyl chloride (XV) with thioethanolamine. Phenyl-2-pyridinylmethanamine N^{ar}-oxide (XII-3) was synthesized by the oxidation of ethoxycarbonyl-(phenyl-2-pyridinyl-methyl)amine (XVI) followed by hydrolysis.

As a result of the pharmacological tests, *N*-alkyl-*N'*-cyano-*N''*-(substituted phenyl-2-pyridinylmethyl)guanidines (X-40 to X-105) were chosen as the main targets for synthesis. The Y group is absent from their structure X. For R, one of the following may be selected: methyl, ethyl, propenyl, 3-(diethylamino)propyl and *N*-ethyl-2-pyrrolidinylmethyl groups.

The compounds X and XI synthesized are listed in Table I and Table II, respectively. All compounds were obtained as free bases.

Pharmacological Tests

Method

1. Test for Inhibitory Activity against Basal Gastric Secretion (Pylorus-Ligated Rats) ——Male Sprague-Dawley strain rats were used after being fasted for 24 h. The pylorus

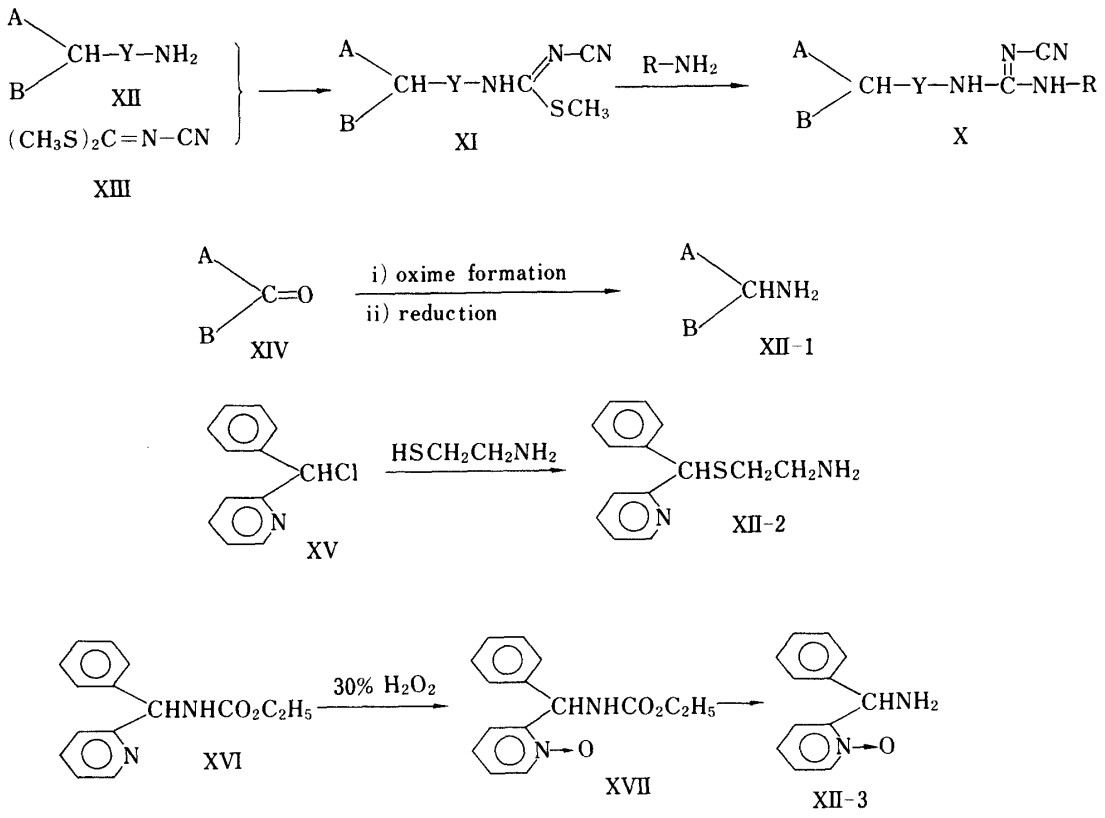


Chart 1

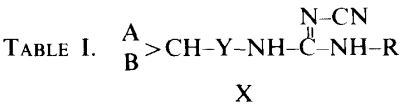
was ligated according to the procedure described by Shay[9] and the compound being tested was administered into the duodenum. Each compound was given as a 5% suspension in gum arabicum. After 4 h the animals were sacrificed with ether and gastric juice was collected. The volume of the juice was measured and its acidity was titrated with 1/50 N sodium hydroxide solution using Toepfer reagent. The free acid concentration was measured, and the free acid output was calculated. Cimetidine and propantheline bromide were used as the reference drugs. Six animals were used for each compound.

2. Test for Inhibitory Activity against Gastric Secretion Stimulated by Histamine—Male Sprague-Dawley strain rats, 7 to 8 weeks old, were used after being fasted for 24 h. The pylorus was ligated according to Shay's procedure[9] and 20 mg/kg histamine dihydrochloride (Sigma) was administered subcutaneously. The compound under test was administered into the duodenum at the same time. After 2 h the rats were sacrificed and the gastric juice was collected, its volume measured, and its free acid concentration found by titration.

Results

The results of pharmacological tests are shown in Table III. The 105 compounds synthesized were tested for inhibitory activity against the basal gastric secretion. The test for inhibitory activity against histamine-stimulated gastric secretion was conducted on 49 selected compounds. The compounds which showed strong activity against basal secretion and representative compounds from each of the homologues with different chemical structures were selected for testing.

Many of the compounds tested showed inhibitory activity against basal gastric secretion,

TABLE I. 

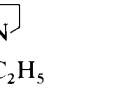
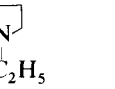
Compd. No.	A	B	Y	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
								C	H	N
X-1	Ph[a]	2-Py[b]	$S(CH_2)_2$	CH_3	157—158	61.5	$C_{17}H_{19}N_5S$	62.74 (62.76)	5.88 (5.62)	21.52 (21.34)
X-2	Ph	2-Py	$S(CH_2)_2$	C_2H_5	137—138	55.0	$C_{18}H_{21}N_5S$	63.69 (63.77)	6.24 (6.07)	20.63 (20.68)
X-3	Ph	2-Py	$S(CH_2)_2$	$CH_2CH=CH_2$	118—120	58.0	$C_{19}H_{21}N_5S$	64.93 (64.79)	6.02 (5.82)	19.93 (19.63)
X-4	Ph	2-Py	CH_2	CH_3	158—159[d]	66.7	$C_{16}H_{17}N_5S$	68.79 (68.62)	6.13 (6.30)	25.07 (24.56)
X-5	Ph	2-Py	CH_2	$(CH_2)_3N(C_2H_5)_2$	104—105	41.0	$C_{22}H_{30}N_6$	69.81 (69.75)	7.99 (7.90)	22.20 (22.08)
X-6	Ph	2-Py	CH_2		136—138	40.8	$C_{22}H_{28}N_6$	70.18 (70.38)	7.50 (7.63)	22.32 (22.46)
X-7	Ph	CH_2–(2-Py)	NE[c]	CH_3	193—194	71.6	$C_{16}H_{17}N_5$	68.79 (68.61)	6.13 (6.11)	25.07 (25.05)
X-8	Ph	CH_2–(2-Py)	NE	$CH_2CH=CH_2$	148—150	56.8	$C_{18}H_{19}N_5$	70.79 (71.24)	6.27 (6.09)	22.93 (22.93)
X-9	Ph	Ph	NE	CH_3	147—150	78.5	$C_{16}H_{16}N_4$	72.70 (73.01)	6.10 (6.05)	21.20 (21.60)
X-10	Ph	Ph	NE	$CH_2CH=CH_2$	149—150	78.8	$C_{18}H_{18}N_4$	74.45 (74.78)	6.25 (6.11)	19.30 (19.20)
X-11	Ph	2-Py	NE	CH_3	156—157[e]	79.2	$C_{15}H_{15}N_5$	67.89 (67.66)	5.71 (5.69)	26.40 (26.54)
X-12	Ph	2-Py	NE	C_2H_5	187—189	85.6	$C_{16}H_{17}N_5$	68.78 (68.51)	6.15 (6.17)	25.07 (25.13)
X-13	Ph	2-Py	NE	*n*-C_3H_7	134—135	79.6	$C_{17}H_{19}N_5$	69.59 (69.58)	6.54 (6.46)	23.87 (23.63)
X-14	Ph	2-Py	NE	*n*-C_4H_9	107—109	81.4	$C_{18}H_{21}N_5$	70.32 (69.99)	6.90 (6.99)	22.78 (22.18)
X-15	Ph	2-Py	NE	*n*-C_6H_{11}	108—109	54.7	$C_{20}H_{25}N_5$	71.59 (71.52)	7.53 (7.59)	20.88 (20.76)
X-16	Ph	2-Py	NE	CH_2CH_2OH	144—145	73.4	$C_{16}H_{17}N_5O$	65.06 (64.86)	5.81 (5.75)	23.72 (23.35)
X-17	Ph	2-Py	NE	$CH_2CH=CH_2$	136—137	64.9	$C_{17}H_{17}N_5$	70.07 (69.88)	5.89 (5.88)	24.04 (23.61)
X-18	Ph	2-Py	NE	CH_2–Ph	177—178	83.1	$C_{21}H_{19}N_5$	73.86 (73.75)	5.62 (5.72)	20.52 (20.36)
X-19	Ph	2-Py	NE	3,4-$(CH_3O)_2$–CH_2–Ph	128—129	73.6	$C_{24}H_{25}N_5O_2$	69.37 (69.07)	6.08 (6.15)	16.86 (16.22)
X-20	Ph	2-Py	NE	$(CH_2)_2N(CH_3)_2$	142—144	58.7	$C_{18}H_{22}N_6$	67.04 (67.09)	6.89 (6.97)	26.07 (25.96)
X-21	Ph	2-Py	NE	$(CH_2)_2N(C_2H_5)_2$	151—152	82.5	$C_{20}H_{26}N_6$	68.53 (68.76)	7.49 (7.56)	23.98 (23.97)
X-22	Ph	2-Py	NE	$(CH_2)_3N(CH_3)_2$	143	86.0	$C_{19}H_{24}N_6$	67.81 (67.86)	7.20 (7.47)	24.98 (24.11)
X-23	Ph	2-Py	NE	$(CH_2)_3N(C_2H_5)_2$	84—85	58.0	$C_{21}H_{28}N_6$	69.18 (69.21)	7.76 (7.81)	23.06 (22.89)
X-24	Ph	2-Py	NE	CH_2 	136—137	67.5	$C_{21}H_{26}N_6$	69.58 (70.15)	7.23 (7.44)	23.19 (23.17)

TABLE I. (continued)

Compd. No.	A	B	Y	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
X-25	Ph	2-Py–oxide	NE	CH_3	178—181	84.9	$C_{15}H_{15}N_5O$	64.09 (63.80)	5.34 (5.08)	24.91 (24.77)
X-26	Ph	2-Py–oxide	NE	C_2H_5	97—98	58.6	$C_{16}H_{17}N_5O$	65.08 (64.92)	5.76 (5.60)	23.73 (23.49)
X-27	Ph	2-Py–oxide	NE	$CH_2CH=CH_2$	167—168	67.9	$C_{17}H_{17}N_5O$	66.45 (66.80)	5.54 (5.38)	22.80 (22.76)
X-28	Ph	2-Py–oxide	NE	$(CH_2)_3N(C_2H_5)_2$	128—129	70.6	$C_{21}H_{28}N_6O$	66.32 (66.35)	7.37 (7.44)	22.11 (22.01)
X-29	Ph	2-Py–oxide	NE	CH_2 	185—187	34.9	$C_{21}H_{26}N_6O$	66.64 (66.31)	6.92 (6.93)	22.21 (21.91)
X-30	Ph	3-Py	NE	CH_3	201—203[f]	76.5	$C_{15}H_{15}N_5$	67.89 (67.93)	5.71 (5.68)	26.40 (26.62)
X-31	Ph	3-Py	NE	C_2H_5	177—179	70.6	$C_{16}H_{17}N_5$	68.78 (68.91)	6.15 (6.11)	25.07 (24.95)
X-32	Ph	3-Py	NE	$CH_2CH=CH_2$	145—147	87.1	$C_{17}H_{17}N_5$	70.07 (69.84)	5.89 (5.82)	24.04 (23.81)
X-33	Ph	4-Py	NE	CH_3	189—190	65.6	$C_{15}H_{15}N_5$	67.89 (67.98)	5.70 (5.82)	26.40 (25.98)
X-34	Ph	4-Py	NE	C_2H_5	180—182	78.6	$C_{16}H_{17}N_5$	68.78 (69.06)	6.15 (6.13)	25.07 (25.10)
X-35	Ph	4-Py	NE	$CH_2CH=CH_2$	149—150	49.1	$C_{17}H_{17}N_5$	70.07 (70.33)	5.89 (5.87)	24.04 (24.04)
X-36	Ph	5-Tetrazolyl	NE	CH_3	189—191	83.0	$C_{11}H_{12}N_8$	51.55 (51.59)	4.72 (4.51)	43.73 (43.69)
X-37	Ph	5-Tetrazolyl	NE	C_2H_5	171—173.5	57.9	$C_{12}H_{14}N_8$	53.32 (53.35)	5.22 (5.07)	41.46 (41.10)
X-38	cyclo-C_6H_{11}	2-Py	NE	CH_3	195—197	76.1	$C_{15}H_{21}N_5$	66.38 (66.23)	7.80 (7.90)	25.81 (25.74)
X-39	cyclo-C_6H_{11}	2-Py	NE	C_2H_5	153—155	78.5	$C_{16}H_{23}N_5$	67.33 (67.48)	8.12 (8.18)	24.54 (24.56)
X-40	cyclo-C_6H_{11}	2-Py	NE	$CH_2CH=CH_2$	100—102	53.6	$C_{17}H_{23}N_5$	68.65 (68.89)	7.79 (8.07)	23.55 (23.72)
X-41	2-Furanyl	2-Py	NE	CH_3	141—143	72.8	$C_{13}H_{12}N_5O$	61.40 (61.49)	4.75 (5.03)	27.54 (27.76)
X-42	2-Furanyl	2-Py	NE	C_2H_5	131—133	72.6	$C_{14}H_{15}N_5O$	62.43 (62.74)	5.61 (5.66)	26.00 (25.35)
X-43	2-Furanyl	2-Py	NE	$CH_2CH=CH_2$	129—130	87.0	$C_{15}H_{15}N_5O$	64.03 (64.30)	5.37 (5.66)	24.90 (25.35)
X-44	2-Thienyl	2-Py	NE	CH_3	137—139	66.0	$C_{13}H_{13}N_5S$	57.53 (57.87)	4.82 (4.85)	25.81 (25.77)
X-45	2-Thienyl	2-Py	NE	C_2H_5	161—163	64.9	$C_{14}H_{15}N_5S$	58.91 (58.95)	5.29 (5.16)	24.54 (24.26)
X-46	2-Thienyl	2-Py	NE	$CH_2CH=CH_2$	123—125	73.9	$C_{15}H_{15}N_5S$	60.57 (60.90)	5.08 (4.97)	23.55 (23.24)
X-47	2-$\dot{C}H_3$–Ph	2-Py	NE	CH_3	187—189	85.0	$C_{16}H_{17}N_5$	68.78 (68.83)	6.13 (6.01)	25.07 (25.26)
X-48	2-CH_3–Ph	2-Py	NE	C_2H_5	132—133	81.0	$C_{17}H_{19}N_5$	69.59 (69.98)	6.52 (6.52)	23.87) (23.76)
X-49	2-CH_3–Ph	2-Py	NE	$CH_2CH=CH_2$	147—149	79.5	$C_{18}H_{19}N_5$	70.79 (71.21)	6.27 (6.16)	22.93 (22.96)
X-50	2-CH_3–Ph	2-Py	NE	$(CH_2)_3N(C_2H_5)_2$	115—117	86.0	$C_{22}H_{30}N_6$	69.80 (70.12)	7.99 (8.09)	22.20 (22.30)

TABLE I. (continued)

Compd. No.	A	B	Y	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
X-51	2-CH_3–Ph	2-Py	NE	CH_2–N(–C_2H_5)–	171—172	55.5	$C_{22}H_{28}N_6$	70.17 (70.58)	7.49 7.56	22.32 22.54)
X-52	3-CH_3–Ph	2-Py	NE	CH_3	172—174	76.0	$C_{16}H_{17}N_5$	68.78 (69.09)	6.13 6.14	25.07 25.07)
X-53	3-CH_3–Ph	2-Py	NE	C_2H_5	145—147	83.1	$C_{17}H_{19}N_5$	69.59 (69.46)	6.52 6.63	23.87 23.68)
X-54	3-CH_3–Ph	2-Py	NE	$CH_2CH=CH_2$	112—114	75.5	$C_{18}H_{19}N_5$	70.79 (70.78)	6.27 6.38	22.93 22.81)
X-55	3-CH_3–Ph	2-Py	NE	CH_2–N(–C_2H_5)–	100—102	47.4	$C_{22}H_{28}N_6$	70.19 (70.38)	7.49 7.67	22.32 22.43)
X-56	4-CH_3–Ph	2-Py	NE	CH_3	171—172	95.9	$C_{16}H_{17}N_5$	68.78 (68.97)	6.13 6.30	25.07 24.95)
X-57	4-CH_3–Ph	2-Py	NE	C_2H_5	153—154	87.5	$C_{17}H_{19}N_5$	69.59 (69.81)	6.52 6.50	23.87 23.85)
X-58	4-CH_3–Ph	2-Py	NE	$CH_2CH=CH_2$	144—145	88.0	$C_{18}H_{19}N_5$	70.79 (70.83)	6.27 6.44	22.93 22.83)
X-59	4-CH_3–Ph	2-Py	NE	$(CH_2)_3N(C_2H_5)_2$	84—85	67.7	$C_{22}H_{30}N_6$	69.80 (69.78)	7.99 8.06	22.20 22.09)
X-60	4-CH_3–Ph	2-Py	NE	CH_2–N(–C_2H_5)–	113—115	87.4	$C_{22}H_{28}N_6$	70.17 (69.94)	7.49 7.54	22.32 22.29)
X-61	2-Cl–Ph	2-Py	NE	CH_3	210—211	89.3	$C_{15}H_{14}ClN_5$	60.10 (60.15)	4.67 4.56	23.40 23.34)
X-62	2-Cl–Ph	2-Py	NE	C_2H_5	176—177	84.9	$C_{16}H_{16}ClN_5$	61.24 (61.28)	5.10 4.89	22.33 22.43)
X-63	2-Cl–Ph	2-Py	NE	$CH_2CH=CH_2$	144—145	81.7	$C_{17}H_{16}ClN_5$	62.27 (62.54)	4.92 4.72	21.51 21.74)
X-64	2-Cl–Ph	2-Py	NE	$(CH_2)_3N(C_2H_5)_2$	103—104	90.1	$C_{21}H_{27}ClN_6$	63.24 (63.16)	6.77 6.88	21.08 21.01)
X-65	2-Cl–Ph	2-Py	NE	CH_2–N(–C_2H_5)–	169—172.5	70.3	$C_{21}H_{25}ClN_6$	63.56 (63.56)	6.30 6.20	21.18 21.24)
X-66	3-Cl–Ph	2-Py	NE	CH_3	194—195	84.2	$C_{15}H_{14}ClN_5$	60.10 (60.05)	4.67 4.60	23.40 23.40)
X-67	3-Cl–Ph	2-Py	NE	C_2H_5	153—155	92.9	$C_{16}H_{16}ClN_5$	61.24 (61.11)	5.10 5.14	22.33 22.25)
X-68	3-Cl–Ph	2-Py	NE	$CH_2CH=CH_2$	136—137	87.5	$C_{17}H_{16}ClN_5$	62.27 (61.90)	4.92 4.80	21.51 20.87)
X-69	3-Cl–Ph	2-Py	NE	$(CH_2)_3N(C_2H_5)_2$	80—84	69.8	$C_{21}H_{27}ClN_6$	63.24 (63.30)	6.77 6.79	21.08 21.22)
X-70	4-Cl–Ph	2-Py	NE	CH_3	180—181	96.2	$C_{15}H_{14}ClN_5$	60.10 (59.85)	4.67 4.67	23.40 23.40)
X-71	4-Cl–Ph	2-Py	NE	C_2H_5	159—160	98.6	$C_{16}H_{16}ClN_5$	61.24 (61.04)	5.10 5.16	22.33 21.98)
X-72	4-Cl–Ph	2-Py	NE	$CH_2CH=CH_2$	177	87.5	$C_{17}H_{16}ClN_5$	62.27 (62.43)	4.92 4.84	21.51 21.36)
X-73	4-Cl–Ph	2-Py	NE	CH_2–N(–C_2H_5)–	157—161	66.1	$C_{21}H_{25}ClN_6$	63.56 (63.66)	6.30 6.54	21.18 20.98)
X-74	3,4-Cl_2–Ph	2-Py	NE	CH_3	217—218	81.5	$C_{15}H_{13}Cl_2N_5$	53.89 (54.04)	3.89 4.13	20.96 20.32)
X-75	3,4-Cl_2–Ph	2-Py	NE	C_2H_5	137—139	88.1	$C_{16}H_{15}Cl_2N_5$	55.17 (55.09)	4.31 4.30	20.11 19.91)

TABLE I. (continued)

Compd. No.	A	B	Y	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
X-76	3,4-Cl_2-Ph	2-Py	NE	$CH_2CH=CH_2$	142—144	70.7	$C_{17}H_{15}Cl_2N_5$	56.67	4.17	19.47
								(56.57	4.12	19.35)
X-77	2-CH_3O-Ph	2-Py	NE	CH_3	173—174	78.2	$C_{16}H_{17}N_5O$	65.06	5.80	23.72
								(65.36	5.81	23.70)
X-78	2-CH_3O-Ph	2-Py	NE	C_2H_5	121—122	64.6	$C_{17}H_{19}N_5O$	66.00	6.19	22.64
								(66.17	6.34	22.63)
X-79	2-CH_3O-Ph	2-Py	NE	$CH_2CH=CH_2$	118—119	72.0	$C_{18}H_{19}N_5O$	67.27	5.96	21.79
								(67.21	6.02	21.74)
X-80	2-CH_3O-Ph	2-Py	NE	$(CH_2)_3N(C_2H_5)_2$	73—75	41.2	$C_{22}H_{30}N_6O$	66.97	7.67	21.30
								(66.91	7.84	21.22)
X-81	2-CH_3O-Ph	2-Py	NE	CH_2[N-C_2H_5]	136—138	54.1	$C_{22}H_{28}N_6O$	67.32	7.19	21.41
								(67.56	7.43	21.20)
X-82	3-CH_3O-Ph	2-Py	NE	CH_3	149—150	71.9	$C_{16}H_{17}N_5O$	65.06	5.80	23.72
								(65.27	5.79	23.91)
X-83	3-CH_3O-Ph	2-Py	NE	C_2H_5	115—116	74.7	$C_{17}H_{19}N_5O$	66.00	6.19	22.64
								(66.22	6.17	22.87)
X-84	3-CH_3O-Ph	2-Py	NE	$CH_2CH=CH_2$	99—100	60.3	$C_{18}H_{19}N_5O$	67.27	5.96	21.79
								(67.72	5.85	21.94)
X-85	4-CH_3O-Ph	2-Py	NE	CH_3	187—188	74.0	$C_{16}H_{17}N_5O$	65.06	5.80	23.72
								(65.59	6.03	23.48)
X-86	4-CH_3O-Ph	2-Py	NE	C_2H_5	144—145	84.9	$C_{17}H_{19}N_5O$	66.00	6.19	22.64
								(66.05	6.12	22.52)
X-87	4-CH_3O-Ph	2-Py	NE	$CH_2CH=CH_2$	139—140	70.0	$C_{18}H_{19}N_5O$	67.27	5.96	21.79
								(67.22	5.67	21.83)
X-88	4-CH_3O-Ph	2-Py	NE	$(CH_2)_3N(C_2H_5)_2$	74—75	58.6	$C_{22}H_{30}N_6O$	66.97	7.67	21.30
								(67.22	7.68	21.35)
X-89	4-CH_3O-Ph	2-Py	NE	CH_2[N-C_2H_5]	134—135	46.2	$C_{22}H_{28}N_6O$	67.32	7.19	21.41
								(67.61	7.15	21.42)
X-90	3,4-$(CH_3O)_2$-Ph	2-Py	NE	CH_3	161—162	86.3	$C_{17}H_{19}N_5O_2$	62.75	5.89	21.53
								(62.44	5.52	21.51)
X-91	3,4-$(CH_3O)_2$-Ph	2-Py	NE	C_2H_5	154—155	80.7	$C_{18}H_{21}N_5O_2$	63.70	6.24	20.64
								(63.79	6.20	20.58)
X-92	3,4-$(CH_3O)_2$-Ph	2-Py	NE	$CH_2CH=CH_2$	102—103	64.3	$C_{19}H_{21}N_5O_2$	64.94	6.02	19.93
								(65.22	6.12	19.92)
X-93	2-(iso-C_3H_7O)-Ph	2-Py	NE	CH_3	148—149	69.5	$C_{18}H_{21}N_5O$	66.85	6.55	21.66
								(67.25	6.52	21.88)
X-94	2-(iso-C_3H_7O)-Ph	2-Py	NE	C_2H_5	141—142	72.6	$C_{19}H_{23}N_5O$	67.63	6.87	20.76
								(67.55	6.75	20.39)
X-95	2-(iso-C_3H_7O)-Ph	2-Py	NE	$CH_2CH=CH_2$	120—121	62.4	$C_{20}H_{23}N_5O$	68.74	6.63	20.04
								(68.59	6.56	20.00)
X-96	4-CH_3S-Ph	2-Py	NE	CH_3	206—207	65.4	$C_{16}H_{17}N_5S$	61.72	5.50	22.50
								(62.01	5.39	22.52)
X-97	4-CH_3S-Ph	2-Py	NE	C_2H_5	132—133	66.6	$C_{17}H_{19}N_5S$	62.75	5.89	21.53
								(62.55	5.66	21.38)
X-98	4-CH_3S-Ph	2-Py	NE	$CH_2CH=CH_2$	111—112	68.1	$C_{18}H_{19}N_5S$	64.08	5.68	20.76
								(64.28	5.59	20.66)
X-99	4-CH_3SO_2-Ph	2-Py	NE	CH_3	152—153	67.2	$C_{16}H_{17}N_5O_2S$	55.97	4.99	20.40
								(55.76	4.74	20.27)
X-100	4-CH_3SO_2-Ph	2-Py	NE	C_2H_5	109—110	62.5	$C_{17}H_{19}N_5O_2S$	57.13	5.36	19.60
								(57.18	5.65	19.68)
X-101	4-CH_3SO_2-Ph	2-Py	NE	$CH_2CH=CH_2$	124—125	64.4	$C_{18}H_{19}N_5O_2S$	58.53	5.19	18.96
								(58.75	5.08	18.97)

TABLE I. (continued)

Compd. No.	A	B	Y	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
X-102	3-CF_3-Ph	2-Py	NE	CH_3	175—177	63.0	$C_{16}H_{14}F_3N_5$	57.65 (57.54	4.23 4.25	21.01 21.00)
X-103	3-CF_3-Ph	2-Py	NE	C_2H_5	158—159	70.7	$C_{17}H_{16}F_3N_5$	58.78 (58.58	4.64 4.64	20.16 20.20)
X-104	3-CF_3-Ph	2-Py	NE	$CH_2CH=CH_2$	115—116	64.3	$C_{18}H_{16}F_3N_5$	60.16 (60.07	4.49 4.50	19.49 19.53)
X-105	3-CF_3-Ph	2-Py	NE	CH_2 	137—138	60.6	$C_{22}H_{25}F_3N_6$	61.38 (61.36	5.84 5.87	19.52 19.60)

a) Ph: phenyl. b) Py: pyridinyl. *c*) NE: non-existent.
d) Ref.[8] mp 153—155 C. *e*) Ref.[8] mp 152—154 C.
f) Ref.[8] mp 196—198 C.

TABLE II. 

XI

Compd. No.	A	B	Y	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
XI-1	Ph[a]	2-Py[b]	$S(CH_2)_2$	130—131	66.7	$C_{17}H_{18}N_4S_2$	59.62 (59.77	5.30 5.28	16.36 16.30)
XI-2	Ph	2-Py	CH_2	130—131[d]	80.8	$C_{16}H_{16}N_4S$	64.84 (64.74	5.44 5.33	18.90 18.82)
XI-3	Ph	CH_2-(2-Py)	NE[c]	140—141	54.0	$C_{16}H_{16}N_4S$	64.84 (65.09	5.44 5.46	18.90 19.04)
XI-4	Ph	Ph	NE	150—152	46.3	$C_{16}H_{15}N_3S$	68.29 (68.30	5.38 5.52	14.94 14.87)
XI-5	Ph	2-Py	NE	133—134[e]	74.5	$C_{15}H_{14}N_4S$	63.79 (63.65	5.01 4.98	19.84 19.97)
XI-6	Ph	2-Py-oxide	NE	182—183	65.5	$C_{15}H_{14}N_4OS$	60.40 (60.73	4.70 4.58	18.79 18.82)
XI-7	Ph	3-Py	NE	131—133[f]	89.5	$C_{15}H_{14}N_4S$	63.79 (64.28	4.99 4.91	19.84 19.79)
XI-8	Ph	4-Py	NE	143—145	73.4	$C_{15}H_{14}N_4S$	63.79 (63.58	4.99 4.92	19.84 19.81)
XI-9	Ph	5-Tetrazolyl	NE	190—191	31.8	$C_{11}H_{11}N_7S$	48.35 (48.45	4.03 3.85	35.90 36.10)
XI-10	cyclo-C_6H_{11}	2-Py	NE	140—143	73.3	$C_{15}H_{20}N_4S$	62.46 (62.82	6.98 6.99	19.43 19.20)
XI-11	2-Furanyl	2-Py	NE	116—118	70.0	$C_{13}H_{12}N_4OS$	57.33 (57.50	4.44 4.18	20.57 20.54)
XI-12	2-Thienyl	2-Py	NE	104—106	56.0	$C_{13}H_{12}N_4S_2$	54.13 (54.43	4.19 4.18	19.43 19.72)

Table II. (continued)

Compd. No.	A	B	Y	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
XI-13	2-CH_3-Ph	2-Py	NE	162—164	66.4	$C_{16}H_{16}N_4S$	64.83 (65.03	5.44 5.31	18.90 18.79)
XI-14	3-CH_3-Ph	2-Py	NE	166—168	63.5	$C_{16}H_{16}N_4S$	64.83 (64.87	5.44 5.26	18.90 19.01)
XI-15	4-CH_3-Ph	2-Py	NE	148—149	76.7	$C_{16}H_{16}N_4S$	64.83 (65.05	5.44 5.36	18.90 18.91)
XI-16	2-Cl-Ph	2-Py	NE	119—120	71.7	$C_{15}H_{13}ClN_4S$	56.87 (56.60	4.10 4.09	17.69 17.05)
XI-17	3-Cl-Ph	2-Py	NE	205—206	80.1	$C_{15}H_{13}ClN_4S$	56.87 (56.65	4.10 3.94	17.69 17.45)
XI-18	4-Cl-Ph	2-Py	NE	121—122	85.5	$C_{15}H_{13}ClN_4S$	56.87 (56.79	4.10 4.06	17.69 17.50)
XI-19	3,4-Cl_2-Ph	2-Py	NE	118—119	55.3	$C_{15}H_{12}Cl_2N_4S$	51.28 (51.09	3.42 3.29	15.95 15.62)
XI-20	2-CH_3O-Ph	2-Py	NE	126—127	64.5	$C_{16}H_{16}N_4OS$	61.53 (61.43	5.16 4.98	17.94 17.47)
XI-21	3-CH_3O-Ph	2-Py	NE	162—163	84.0	$C_{16}H_{16}N_4OS$	61.53 (61.90	5.16 5.03	17.94 17.79)
XI-22	4-CH_3O-Ph	2-Py	NE	151—152	70.0	$C_{16}H_{16}N_4OS$	61.53 (61.60	5.16 5.05	17.94 18.08)
XI-23	3,4-$(CH_3O)_2$-Ph	2-Py	NE	155—156	88.0	$C_{17}H_{18}N_4O_2S$	59.64 (59.76	5.30 5.24	16.37 16.77)
XI-24	2-(iso-C_3H_7O)-Ph	2-Py	NE	138—139	87.5	$C_{18}H_{20}N_4OS$	63.51 (63.54	5.92 5.84	16.46 15.96)
XI-25	4-CH_3S-Ph	2-Py	NE	103—104	68.8	$C_{16}H_{16}N_4S$	58.54 (58.71	4.91 4.69	17.07 17.41)
XI-26	4-CH_3SO_2-Ph	2-Py	NE	139—140	71.1	$C_{16}H_{16}N_4O_2S$	53.33 (53.14	4.48 4.19	15.55 15.43)
XI-27	3-CF_3-Ph	2-Py	NE	163—164	68.9	$C_{16}H_{13}F_3N_4S$	54.86 (54.88	3.74 3.76	16.00 16.12)

a) Ph: phenyl. *b*) Py: pyridinyl. *c*) NE: non-existent.
d) Ref.[8] mp 130—132 C. *e*) Ref.[8] mp 128—130 C.
f) Ref.[8] reported as a syrup.

X-23 (dosage: 100 mg/kg), X-24 (100 mg/kg), X-48, X-53, X-54, X-67, X-75, X-77, X-78, X-79 (all 50 mg/kg), in particular, showing more than 75% inhibition. The activities of most of these compounds were almost equal to that of cimetidine, and X-48, X-77 and X-78 were a little more potent than either cimetidine (50 mg/kg, 85.8%) or propantheline bromide (30 mg/kg, 89.3%).

Several compounds showed inhibitory activity against gastric secretion stimulated by histamine, but less potently than against basal secretion. X-24 (100 mg/kg), X-48, X-69, X-70, X-77, X-78 and X-79 all showed more than 40% inhibition of acid output. Cimetidine

TABLE III. Activities against Gastric Secretion in Rats

Compd. No.	Dose (mg/kg)	Inhibition of basal secretion (%)			Inhibition of histamine-stimulated secretion (%)		
		Vol.	H^+ conc.	H^+ output	Vol.	H^+ conc.	H^+ output
X-1	50	28.7	−0.2	30.0	ND[a]	ND	ND
X-2	50	−4.8	8.4	2.7	ND	ND	ND
X-3	50	1.7	21.7	23.7	ND	ND	ND
X-4	50	−11.6	−6.2	28.2	−5.8	4.1	−0.8
X-5	50	−5.8	−17.0	−14.1	−3.2	7.5	5.8
X-6	50	19.7	15.1	26.0	15.0	9.8	22.6
X-7	50	4.0	−2.5	−3.4	ND	ND	ND
X-8	50	11.6	−2.8	−13.1	ND	ND	ND
X-9	50	24.4	−2.7	19.1	ND	ND	ND
X-10	50	27.1	4.2	32.3	ND	ND	ND
X-11	100	36.8	54.4[c]	69.3[b]	30.8[b]	11.6	39.7[b]
X-12	100	10.5	7.4	25.9	ND	ND	ND
X-13	100	−21.1	−1.6	−6.9	ND	ND	ND
X-14	100	−36.8	−13.0	−46.1	ND	ND	ND
X-15	100	−21.1	−3.4	−26.7	ND	ND	ND
X-16	100	−15.8	23.1	−4.6	ND	ND	ND
X-17	100	−26.3	11.5	46.8	−13.4	15.5	3.3
X-18	100	−15.8	12.3	−1.4	ND	ND	ND
X-19	100	−21.2	1.0	−18.7	ND	ND	ND
X-20	100	15.8	28.5	35.5	ND	ND	ND
X-21	100	5.3	6.3	14.2	ND	ND	ND
X-22	100	7.7	−12.6	0	ND	ND	ND
X-23	100	52.9[b]	51.9[b]	81.0[b]	7.3	10.5	19.0
X-24	100	68.4[b]	64.8[b]	86.0[c]	47.7[c]	27.3	64.6[c]
X-25	50	18.2	9.9	26.0	ND	ND	ND
X-26	50	33.7	29.7	50.5	19.3	19.5	35.5
X-27	50	35.8[b]	9.0	40.9[b]	10.0	3.5	13.3
X-28	50	−6.1	−4.2	−21.2	ND	ND	ND
X-29	50	−16.5	−10.9	−38.5	ND	ND	ND
X-30	50	29.3	14.5	36.5	16.9	1.7	18.1
X-31	50	19.0	14.5	28.8	23.5	4.3	26.3
X-32	50	39.7[b]	31.3[b]	59.5[b]	8.0	−2.0	5.9
X-33	50	15.8	−12.2	9.0	ND	ND	ND
X-34	50	34.0	−7.2	30.4	10.9	3.4	13.0
X-35	50	−12.2	12.7	5.5	ND	ND	ND
X-36	50	33.3[b]	21.5	46.7[b]	11.2	8.7	19.8
X-37	50	12.7	9.2	23.4	ND	ND	ND
X-38	50	−32.5	2.8	−29.9	ND	ND	ND
X-39	50	14.3	5.8	21.3	ND	ND	ND
X-40	50	−33.3	23.0[b]	−9.3	−35.5	2.6	−29.0
X-41	50	23.0	11.5	29.7	ND	ND	ND
X-42	50	22.2	20.4[b]	40.0	7.0	6.2	17.0
X-43	50	−40.5	4.4	−46.8	ND	ND	ND
X-44	50	29.0	−12.7	21.0	ND	ND	ND
X-45	50	−29.8	3.6	−23.7	ND	ND	ND
X-46	50	18.9	12.4	24.8	ND	ND	ND
X-47	50	46.7[b]	15.7	51.6[b]	22.9	8.7	30.7
X-48	50	77.8[d]	80.6[d]	93.5[d]	41.3[b]	5.0	45.4[b]
X-49	50	−28.8	−6.3	−51.0	ND	ND	ND
X-50	50	40.1	13.3	43.8	ND	ND	ND
X-51	50	14.2	−6.3	4.5	ND	ND	ND
X-52	50	47.0[b]	9.4	52.2[b]	20.7	18.9	34.5

Table III. (continued)

Compd. No.	Dose (mg/kg)	Inhibition of basal secretion (%)			Inhibition of histamine-stimulated secretion (%)		
		Vol.	H^+ conc.	H^+ output	Vol.	H^+ conc.	H^+ output
X-53	50	75.3[d]	31.3[b]	79.5[d]	23.9	4.7	26.7
X-54	50	66.3[c]	45.0[b]	79.0[c]	28.6[b]	13.8	38.4[b]
X-55	50	7.1	4.9	9.0	ND	ND	ND
X-56	50	24.6	12.8	29.5	−0.9	11.0	5.9
X-57	50	42.7[b]	21.0	54.5[b]	19.2	6.5	23.0
X-58	50	26.7	8.5	29.4	−6.6	3.4	6.0
X-59	50	17.5	5.5	20.3	ND	ND	ND
X-60	50	26.7	20.1	41.5	ND	ND	ND
X-61	50	−21.3	−29.5	−48.2	−5.2	10.0	3.1
X-62	50	52.9[b]	47.0	71.1[c]	24.0	9.5	32.4
X-63	50	−47.1	−25.6	−69.8	−14.3	0.6	−11.6
X-64	50	24.1	5.6	26.0	ND	ND	ND
X-65	50	65.2	−36.8	−127.2	13.0	14.0	23.4
X-66	50	51.6[d]	21.5	62.3[d]	16.2	9.9	26.0
X-67	50	55.5[c]	50.5[c]	79.2[d]	5.8	16.1	19.5
X-68	50	1.9	−18.2	−18.5	14.9	16.2	29.4
X-69	50	48.1[c]	35.7	64.5[c]	31.8[b]	13.9	42.9[c]
X-70	50	−14.1	−9.5	−27.4	29.2	43.1[b]	58.0[b]
X-71	50	−12.9	−18	−42.3	22.7	10.3	32.0
X-72	50	−20.6	−27.0	−46.0	−14.9	−2.5	−15.0
X-73	50	1.9	8.9	10.6	27.9	19.5	42.6
X-74	50	30.7	7.1	35.5	ND	ND	ND
X-75	50	65.0[d]	34.5[b]	78.0[d]	19.7	11.1	28.8[b]
X-76	50	23.0	7.1	26.7	8.4	0.3	8.7
X-77	50	85.0[d]	57.0[c]	91.6[d]	43.2[b]	13.9[b]	41.2[b]
X-78	50	86.7[d]	72.4[d]	96.7[d]	41.3[c]	3.3	41.1[c]
X-79	50	78.3[d]	43.0[c]	87.8[d]	44.1[c]	8.9	48.6[c]
X-80	50	24.5	5.2	18.2	ND	ND	ND
X-81	50	12.3	6.1	4.5	ND	ND	ND
X-82	50	23.8	20.0	39.5	ND	ND	ND
X-83	50	11.1	28.4	33.9	0	2.5	4.4
X-84	50	−29.4	9.5	−14.4	ND	ND	ND
X-85	50	22.0	13.7	27.5	−8.5	−1.8	−8.7
X-86	50	42.7[b]	20.5	63.3[b]	6.1	2.8	7.5
X-87	50	4.6	−0.3	4.8	4.7	5.0	8.7
X-88	50	12.8	−8.7	0	ND	ND	ND
X-89	50	18.7	7.5	23.6	19.2	2.5	20.2
X-90	50	−32.0	9.8	−21.4	ND	ND	ND
X-91	50	10.3	21.2[b]	30.1	ND	ND	ND
X-92	50	−25.4	0.9	−47.1	ND	ND	ND
X-93	50	20.6	20.0	39.5	20.6	17.4[b]	35.5[b]
X-94	50	−46.0	0.3	−59.3	ND	ND	ND
X-95	50	0.8	17.2	23.8	ND	ND	ND
X-96	50	41.2[b]	27.6[b]	57.7[b]	−8.3	−1.0	−7.9
X-97	50	−16.0	8.4	−1.8	ND	ND	ND
X-98	50	−3.3	−1.4	−5.4	ND	ND	ND
X-99	50	18.2	3.3	15.3	ND	ND	ND
X-100	50	14.3	5.8	17.2	ND	ND	ND
X-101	50	−0.8	12.5	2.8	ND	ND	ND
X-102	50	12.3	8.3	15.3	ND	ND	ND
X-103	50	28.3	1.3	24.7	ND	ND	ND
X-104	50	5.1	10.0	8.3	ND	ND	ND

Table III. (continued)

Compd. No.	Dose (mg/kg)	Inhibition of basal secretion (%)			Inhibition of histamine-stimulated secretion (%)		
		Vol.	H^+ conc.	H^+ output	Vol.	H^+ conc.	H^+ output
X-105	50	33.0	−3.7	25.6	ND	ND	ND
Cimetidine	50	64.0[d]	60.4[d]	85.8[d]	61.6[d]	50.4[c]	79.1[d]
Propantheline bromide	30	78.7[d]	57.7[b]	89.3[d]	47.4[b]	10.0	53.4[b]

a) ND: Not determined.
b) $p<0.05$. c) $p<0.01$. d) $p<0.001$.

(50 mg/kg) and propantheline bromide (30 mg/kg) caused 79.1 and 53.4% inhibition, respectively.

Discussion

1. Comparison between Inhibition of Basal Gastric Secretion and That of Histamine-Stimulated Gastric Secretion

Several of the derivatives X of cyanoguanidine (mostly 50 mg/kg; some, 100 mg/kg) showed potent inhibitory activity against basal secretion. They had almost the same degree of activity as cimetidine and propantheline bromide (30 mg/kg). The compounds X showed less potent inhibition of histamine-stimulated gastric secretion than of the basal gastric secretion. Cimetidine showed almost equal activity against basal and histamine-stimulated secretion, whereas propantheline bromide showed less potent activity against the latter than against the former. In other tests, conducted *in vitro*, compounds X did not show either antagonistic activity on H_2 histaminergic receptors in an isolated guinea-pig atrium preparation or anticholinergic activity in an isolated guinea-pig ileum preparation.[10] On the other hand, compounds X were found to have potent agonistic activity on adrenergic α_2-adrenoreceptors.[11] Whether or not the gastric antisecretory activity of the structure X involves stimulation of α_2-adrenoreceptors remains to be studied.

2. Structure–Activity Relationships

1) Chain Length of Y in Compounds X——The compounds showed antisecretory activity when the cyanoguanidine group was attached directly to the phenyl-pyridinylmethyl group, so that Y was not present in the structure X. When Y was a methylene or thioethyl group, X did not show any antisecretory activity. This suggested that the distance between the nitrogen atom of the pyridine nucleus and that of guanidine was important, and if the distance became too great, the antisecretory activity would disappear.

2) B Ring——When the A ring was a phenyl group, the compounds with a 2-pyridinyl group as the B ring exhibited the greatest antisecretory activity. The compounds carrying a 3-pyridinyl group or a 2-pyridinyl N^{ar}-oxide group as the B ring had some activity, but those in which a 4-pyridinyl, 2-pyridinylmethyl, phenyl, cyclohexyl, or 5-tetrazolyl group formed the B group did not show any antisecretory activity. This suggested that the presence of 2-pyridinyl or 3-pyridinyl group was necessary for such activity.

3) Substituent Groups on Benzene Ring A——When the 2-pyridinyl group was present as the B ring, substitution at the *ortho* position of benzene ring A strengthened the antisecretory activity. Some *meta*-substituted compounds also exhibited this activity, but *para*-substituted compounds other than 4-methylthio compounds did not show any activity. The differences in antisecretory activity of the different substituent groups—chloro, methyl,

and methoxy groups—were not great. On the other hand, isopropyl substitution on the *ortho* position of benzene ring A caused a considerable diminution of the activity. *ortho* substituents may therefore strengthen the antisecretory activity, but their size should be limited.

4) R Substituents on N′ of Guanidine——The compounds with a methyl or ethyl group on the N′ nitrogen atom of guanidine showed high antisecretory activity and those with an allyl group showed some activity. 3-(Dimethylamino)propyl and 1-ethyl-2-pyrrolidinylmethyl groups also showed some activity, but larger alkyl groups and aralkyl groups did not have any activity.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 215 spectrophotometer and proton nuclear magnetic (^{1}H-NMR) spectra were taken with a Hitachi R-24 (60 MHz) spectrophotometer with tetramethylsilane as an internal standard (δ ppm). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra (MS) were measured with a JEOL JMS-01SG mass spectrometer.

Substituted Phenyl-pyridinylmethanamines (XII-1)——The oxime of the appropriate phenyl pyridinyl ketone (XIV) was reduced by using zinc in acetic acid or ammonium hydroxide aqueous solution.[12] The newly synthesized XII-1 compounds were as follows. 2-Furyl-2-pyridinylmethanamine, bp 125—133 °C (0.7 mmHg). IR ν_{max}^{neat} cm^{-1}: 3375, 3300 (NH_2), 800, 750, 740 (furan). MS *m/e*: 174 (M^+). 2-Ethoxyphenyl-2-pyridinylmethanamine, bp 162—168 °C (2.3 mmHg). IR ν_{max}^{neat} cm^{-1}: 3340, 3290 (NH_2), 1235 (C–O). MS *m/e*: 228 (M^+). 2-Isopropoxyphenyl-2-pyridinylmethanamine, bp 162.5—171 °C (2.6 mmHg). IR ν_{max}^{neat} cm^{-1}: 3360, 3200 (NH_2), 1240 (C–O). MS *m/e*: 242 (M^+). 4-Methylthiophenyl-2-pyridinylmethanamine, bp 188—198 °C (1.7 mmHg). IR ν_{max}^{neat} cm^{-1}: 3360, 3290 (NH_2), 1430 (S–CH_3). MS *m/e*: 230 (M^+). 4-Methylsulfonylphenyl-2-pyridinylmethanamine, a viscous oil (decomposed on heating). IR ν_{max}^{neat} cm^{-1}: 3370, 3320 (NH_2), 1305, 1155 (SO_2). MS *m/e*: 262 (M^+). Phenyl-(5-tetrazolyl)methanamine acetate, mp 218—220 °C (dec.). IR ν_{max}^{neat} cm^{-1}: 3400, 2600—3000 (NH_3^+). MS *m/e*: 175 (M^+).

2-(Phenyl-2-pyridinylmethylthio)ethanamine (XII-2)——2-Thioethanamine hydrochloride (9.4 g) was added to a solution of 3.8 g of sodium in 150 ml of EtOH. An EtOH solution (50 ml) of 15.2 g of phenyl-2-pyridinylmethyl chloride (XV) was added to the above solution and the mixture was refluxed for 2.5 h. The reaction mixture was concentrated *in vacuo*. Sodium carbonate solution was added to the residue and benzene extraction was performed. The benzene layer was washed, dried, concentrated *in vacuo*, and distilled. Yellowish oil, bp 175—196 °C (2.9—3 mmHg), 17.6 g (69%). IR ν_{max}^{neat} cm^{-1}: 3350, 3055 (NH_2), 1430 (SCH_2). MS *m/e*: 220 (M^+).

Phenyl-2-pyridinylmethanamine N^{ar}-Oxide (XII-3)——Ethyl chloroformate (2.9 g) was dropped into 20 ml of a pyridine solution of 5 g of phenyl-2-pyridinylmethanamine at 5 °C. After 1 h, water was added to the reaction mixture and the whole was extracted with ether to give 6 g of crude oily XVI. This was dissolved in 20 ml AcOH and 8 ml of 30% hydrogen peroxide was added. The reaction mixture was kept at 40 °C for 4 h, then water was added, and a solid mass separated. XVII, mp 244—245 °C, prismatic crystals, 5.6 g. *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.95; H, 5.93; N, 10.29. IR ν_{max}^{Nujol} cm^{-1}: 1718 (C=O), 1625 (N→O). ^{1}H-NMR ($CDCl_3$) δ: 2.19 (3H, t, J=7 Hz, CH_3), 4.15 (2H, q, J=7 Hz, CH_2), 6.45 (br s, 1H, CH). MS *m/e*: 272 (M^+). XVIII (5 g) was refluxed in conc. HCl solution for 20 h. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized from isopropyl alcohol (IPA). XII-3, mp 182—183 °C, 2 g. *Anal.* Calcd for $C_{12}H_{12}N_2O \cdot HCl \cdot 1/4H_2O$: C, 59.75; H, 5.49; N, 11.62. Found: C, 59.92; H, 5.49; N, 11.59. IR ν_{max}^{Nujol} cm^{-1}: 3400, 2500—3000 (NH_3^+), 1218 (N→O). MS *m/e*: 200 (M^+).

Bis(methylthio)methylenecyanamide (XIII)[13,14]——The synthetic procedure for XIII was improved to a one-pot reaction. First, 9.3 g of cyanamide, 16.7 g of carbon disulfide, and 25 ml of MeOH were mixed and then a solution of 22.4 g of potassium hydroxide in 100 ml of MeOH was added dropwise to the suspension at −2—0 °C. The mixture was kept for 3 h at this temperature, and then 50.4 g of dimethyl sulfate was added dropwise. The reaction mixture was left to stand overnight at room temperature. The precipitate was separated and recrystallized from IPA–isopropyl ether (IPE). XIII, yellowish needles, mp 52—53 °C, 16.2 g (53.5%).

3-Cyano-2-methyl-1-(phenyl-pyridinylalkyl)isothiourea (XI)——General Procedure: XII and the 1.1 eq of XIII were stirred in EtOH at room temperature. Precipitated XI was filtered off and recrystallized. Refer to Table II.

A Typical Example: Methyl *N*-cyano-*N′*-(phenyl-2-pyridinylmethyl)carbamimidothioate (XI-5), mp 133—134 °C. IR ν_{max}^{Nujol} cm^{-1}: 3375 (NH), 2175 (CN), 1380 (SCH_3). ^{1}H-NMR ($CDCl_3$–D_2O) δ: 2.50 (3H, s, CH_3), 5.83 (1H, s, CH), 6.95—7.40 (8H, m, aromatic), 8.30 (1H, m, C_2–H of pyridine). MS *m/e*: 282 (M^+).

***N*-Alkyl-*N′*-cyano-*N″*-(phenyl-2-pyridinylalkyl)guanidine (X)**——General Procedure: XI and 1.2 eq of primary alkylamine were mixed and stirred in EtOH at room temperature. If the reaction proceeded too slowly, the reaction mixture was warmed. After concentration of the mixture *in vacuo*, water was added to the residue. Compound X precipitated, and was filtered off and recrystallized. Refer to Table I.

Typical Examples: *N*-Methyl-*N′*-cyano-*N″*-(phenyl-2-pyridinylmethyl)guanidine (X-11): mp 156—157 °C. IR

ν_{max}^{Nujol} cm^{-1}: 3375, 3300 (NH), 2170 (CN). ^{1}H-NMR ($CDCl_3$–D_2O) δ: 2.80 (3H, s, CH_3), 5.81 (1H, s, CH), 6.90—7.60 (8H, m, aromatic), 8.25—8.35 (1H, m, C_6–H of pyridine). MS *m/e*: 265 (M^+).

N-Ethyl-*N'*-cyano-*N''*-(phenyl-2-pyridinylmethyl)guanidine (X-12): mp 187—189 °C. IR ν_{max}^{Nujol} cm^{-1}: 3345, 3230 (NH), 2175 (CN). ^{1}H-NMR ($CDCl_3$–D_2O) δ: 1.20 (3H, t, J=7 Hz, CH_3), 3.29 (2H, q, J=7 Hz, CH_2), 5.90 (1H, s, CH), 7.0—7.90 (8H, m, aromatic), 8.40—8.60 (1H, m, C_6–H of pyridine). MS *m/e*: 279 (M^+).

N-Allyl-*N'*-cyano-*N''*-(phenyl-2-pyridinylmethyl)guanidine (X-17): mp 136—137 °C. IR ν_{max}^{Nujol} cm^{-1}: 3345, 3225 (NH), 2170 (CN). ^{1}H-NMR ($CDCl_3$–D_2O) δ: 3.74 (2H, d, J=5 Hz, CH_2), 4.95 (1H, d, J=4 Hz, $C\underline{H}_2$=$CHCH_2$), 5.15 (1H, d, J=4 Hz, $C\underline{H}_2$=$CHCH_2$), 5.30—5.70 (1H, m, CH_2=$C\underline{H}CH_2$), 5.74 (1H, s, CH), 6.90—7.60 (8H, m, aromatic), 8.25—8.45 (1H, m, C_6–H of pyridine). MS *m/e*: 291 (M^+).

N-(3-Diethylaminopropyl)-*N'*-cyano-*N''*-(phenyl-2-pyridinylmethyl)guanidine (X-23): mp 84—85 °C. IR ν_{max}^{Nujol} cm^{-1}: 3345, 3230 (NH), 2170 (CN). ^{1}H-NMR ($CDCl_3$–D_2O) δ: 0.95 (6H, t, J=7 Hz, CH_3 × 2), 1.4—1.8 (2H, m, $NCH_2C\underline{H}_2CH_2N$), 2.1—2.6 (6H, m, $C\underline{H}_2N(C\underline{H}_2CH_3)_2$, 3.23 (2H, t, J=6 Hz, $NC\underline{H}_2CH_2CH_2NEt_2$), 5.77 (1H, s, CH), 6.80—7.50 (8H, m, aromatic), 8.20—8.40 (1H, m, C_6–H of pyridine). MS *m/e*: 350 (M^+).

N-[(1-Ethyl-2-pyrrolidinyl)methyl]-*N'*-cyano-*N''*-(phenyl-2-pyridinylmethyl)guanidine (X-24): mp 136—137 °C. IR ν_{max}^{Nujol} cm^{-1}: 3345, 3325 (NH), 2170 (CN). ^{1}H-NMR ($CDCl_3$–D_2O): 0.88 (3H, t, J=7 Hz, CH_3), 1.60 (4H, br s, C_3, C_4–H of pyrrolidine), 1.80—3.0 (5H, m, C_2–H, C_5–H of pyrrolidine, and N–$C\underline{H}_2CH_3$), 3.18 (2H, d, J=4 Hz, $NC\underline{H}_2$-2-pyrrolidine), 5.80 (1H, d, J=4 Hz, CH), 6.80—7.58 (8H, m, aromatic), 8.20—8.40 (1H, m, C_6–H of pyridine). MS *m/e*: 348 (M^+).

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References and Notes

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