Novel Pharmacological Activity of a Series of Substituted Pyridines

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A series of substituted pyridines was synthesized and found to inhibit gastric secretion without anticholinergic, ganglionic blocking, or adrenergic blocking activity. The structure–activity relationships are discussed. The most active compounds include: 4-phenoxypyridine, 3-phenoxypyridine, 2-phenylpyridine *N*-oxide, 2-(2-thienyl)-pyridine, 3-phenylpyridine, and 2,2′-bipyridine. 2,2′-Bipyridine was chosen for clinical trial.

For many years peptic ulcers have been treated through the use of antacids and anticholinergic agents. Antacids are often taken in doses that are inadequate to alter the pH of the gastric contents and, since they enhance stomach emptying, their duration of action is shortened by their rapid removal from the stomach.[1] In fact, the enhanced stomach-emptying may be a major factor in their symptomatic relief of gastric distress. The anticholinergics reduce gastric secretion by blocking the parasympathetic stimuli to the stomach. These drugs also block the parasympathetic stimuli to many other organs—*e.g.*, the eye, the heart, and the urinary bladder. Code[2] reviewed antisecretory agents in 1951 and Brodie recently reexamined this area.[3] A number of experimental agents and approaches to the peptic ulcer problem have been reviewed.[4-7]

A potentially useful clinical agent could be one which effectively reduces the volume and acidity of gastric secretion through mechanisms other than the blockade of the cholinergic system. Compounds devoid of anticholinergic activity, as demonstrated by their failure to antagonize the blood pressure effect of acetylcholine, were tested in a modified pylorus-ligated rat[8,9] technique. Results were expressed as the dose necessary to reduce gastric secretion to 50% (ED_{50}). Compounds with ED_{50}'s equal to or less than 10 mg/kg sc were also checked for anticholinergic activity in a rat chromodacryorrhea test[10] and for antagonism of the blood pressure effects of epinephrine and dimethylphenylpiperazinium iodide (DMPP) in an anesthetized dog preparation. The gastric antisecretory results are presented in Tables I and II.

Chemistry.—The compounds were prepared as described in the references in Tables I and II or by the methods described in the Experimental Section.

Structure–Activity Relationships.—For ease in discussion, the compounds can be separated into 2 types; the phenoxypyridines and the arylpyridines. Some relationships will be observed to be common to both groups.

Among the phenoxypyridines, a number of compounds with substituents in the 2′ position of 4-phenoxypyridine[11] (**5**) retained high activity. Substituents in the 3′ and 4′ positions severely depressed activity. In 3-phenoxypyridine[12] (**3**), even 2′ substitution lowered activity. 2-Phenoxypyridine[13] (**1**) was less active than the 3 or 4 analogs. The *N*-oxide derivatives of compounds with ED_{50}'s less than 10 mg/kg usually were less active, while in compounds with ED_{50}'s between 10 and 100 mg/kg the *N*-oxide was often more active. The improvement in the *N*-oxides, when seen, did not provide highly active compounds (ED_{50} < 10 mg/kg). Replacement of the phenoxy group by alkyloxy, cycloalkyloxy, phenylthio, and benzyl either lowered or destroyed activity.

The 4-arylpyridines were less active than either the 2 or 3 isomers. In 2-phenylpyridine[14] (**56**), 2′-chloro, 2′-nitro, and the *N*-oxide substituents enhanced activity. Other substituents such as 2′-methyl, 2′-amino, 2′-hydroxyl, or 3′ and 4′ substitution lowered or destroyed activity. The *N*-oxides of compounds with ED_{50}'s less than 5 mg/kg were usually less active with some exceptions. The change from 2-phenylpyridine (**56**) (ED_{50} = 10) to 2-phenylpyridine *N*-oxide[15] (**57**) (ED_{50} = 2.2) was the most dramatic observed. Activity was retained in some Me, Ph disubstituted pyridines and in some bridged arylpyridines, as an indenopyridine. The Ph could be replaced by another pyridine or a thiophene resulting in compounds with enhanced activity. All of the isomeric bipyridines tested possessed high activity except the 4,4′ isomer. All the compounds with ED_{50}'s less than 10 mg were tested and found inactive in the agonist–antagonist tests in the anesthetized dog preparation.

The most active compounds include 4-phenoxypyridine[11] (**5**), 3-phenoxypyridine[12] (**3**), 2-phenylpyridine *N*-oxide[15] (**57**), 2-(2-thienyl)pyridine[16] (**81**), 3-phenylpyridine[17] (**58**), 2,2′-bipyridine[18] (**85**), and several of its isomers. 2,2′-Bipyridine (**85**) was chosen for clinical trial. Bass and coworkers have published the gastric antisecretory and other pharmacologic studies on this drug in 1966.[19]

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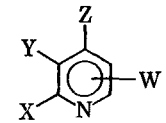
TABLE I



Compd	X	Y	Z	W[a]	ED_{50},[b] mg/kg sc (free base)	Ref source or exp method[c]	Mp or bp (mm), °C	Yield, %	Recrystn solvent[rr]	Empirical[ss] formula
1	C_6H_5O	H	H		11.5	P				$C_{11}H_9NO$
2	C_6H_5O	H	H	O	15.0	*d*, D	90–92	32	I	$C_{11}H_9NO_2$
3	H	C_6H_5O	H		4.5	*d*, *e*	147–149 (12)	68		$C_{11}H_9NO$
4	H	C_6H_5O	H	O	6.0	D	80–82	84	J	$C_{11}H_9NO_2$
5	H	H	C_6H_5O		5.0	*f*, A	46–48	77	K	$C_{11}H_9NO$
6	H	H	C_6H_5O	O	12.0	*g*, E	130–131	57	J	$C_{11}H_9NO_2$
7	H	2-$CH_3C_6H_4O$	H		96.0	C	147–148 (12)	62		$C_{12}H_{11}NO$
8	H	2-$CH_3C_6H_4O$	H	O	57.5	D	64–66	56	J	$C_{12}H_{11}NO_2$
9	H	H	2-$CH_3C_6H_4O$		9.7	*f*, A	97–98 (0.8)	13		$C_{12}H_{11}NO$
10	H	H	2-$CH_3C_6H_4O$	O	13.0	E	130–132	53	I	$C_{12}H_{11}NO_2$
11	H	H	3-$CH_3C_6H_4O$		84.0	*f*, A	84–85 (0.1)	79		$C_{12}H_{11}NO$
12	H	H	3-$CH_3C_6H_4O$	O	80.0	E	91–92	45	J	$C_{12}H_{11}NO_2$
13	H	H	4-$CH_3C_6H_4O$		105.0	*f*, A	84–85 (0.25)	79		$C_{12}H_{11}NO$
14	H	H	4-$CH_3C_6H_4O$	O	81.0	E	145–147.5	58	J	$C_{12}H_{11}NO_2$
15	H	H	4-$C_2H_5C_6H_4O$		20.0	A	140–142 (10)	84		$C_{13}H_{13}NO$
16	H	H	4-$C_3H_7C_6H_4O$		21.0	A	78–79 (0.08)	50		$C_{14}H_{15}NO$
17	H	H	4-*i*-$C_3H_7C_6H_4O$		0/100	A	104–105 (0.1)	73		$C_{14}H_{15}NO$
18	H	2-$CH_3OC_6H_4O$	H		27.0	C	53–55	14	L	$C_{12}H_{11}NO_2$
19	H	2-$CH_3OC_6H_4O$	H	O	18.5	D	117–119	62	I	$C_{12}H_{11}NO_3$
20	H	H	2-$CH_3OC_6H_4O$		9.5	A	84–85 (0.1)	72		$C_{12}H_{11}NO_2$
21	H	H	2-$C_2H_5OC_6H_4O$		51.0	A	99–100 (0.1)	87		$C_{13}H_{13}NO_2$
22	H	H	2-$C_4H_9OC_6H_4O$		0/50	A	150–152 (1.5)	42		$C_{15}H_{17}NO_2$
23	H	H	4-$CH_3OC_6H_4O$	O	130	E	154–156	74	M	$C_{12}H_{11}NO_3$
24	H	H	2-BrC_6H_4O		8.9	A	64–66	75	L	$C_{11}H_8BrNO$
25	H	H	2-BrC_6H_4O	O	19.0	D	116–118	17	J	$C_{11}H_8BrNO_2$
26	H	H	2-ClC_6H_4O		6.0	*h*, A	53–54	53	L	$C_{11}H_8ClNO$
27	H	H	2-FC_6H_4O		4.5	*i*, A	70–71 (0.1)	70		$C_{11}H_8FNO$
28	H	H	3-FC_6H_4O		0/25	*i*, A	130–131 (10)	76		$C_{11}H_8FNO$
29	H	H	4-FC_6H_4O		0/25	*i*, A	130–131 (10)	52		$C_{11}H_8FNO$
30	H	H	2-$CF_3C_6H_4O$		44	A	129–131 (10)	73		$C_{12}H_8F_3NO$
31	H	H	3-$CF_3C_6H_4O$		0/100	A	126–127 (10)	76		$C_{12}H_8F_3NO$
32	H	H	2,4-$Cl_2C_6H_3O$		50	*j*, A	100–101 (0.1)	71		$C_{11}H_7Cl_2NO$
33	H	H	2,4-$Cl_2C_6H_3O$	O	0/25	D	91–92	24	J	$C_{11}H_7Cl_2NO_2$
34	C_4H_9	H	C_6H_5O		145	F	100–101 (0.1)	44		$C_{15}H_{17}NO$
35	C_6H_5	H	C_6H_5O		0/100	F	128–130 (0.06)	39		$C_{17}H_{13}NO$
36	C_6H_5	H	C_6H_5O	O	0/25	D	132–134	67	J	$C_{17}H_{13}NO_2$
37	H	H	2-HOC_6H_4O		0/25	*h*, A	175–177	66	N	$C_{11}H_9NO_2$
38	H	H	2-$HCOC_6H_4O$		145	A	115–117 (0.15)	60		$C_{12}H_9NO_2$
39	H	H	2-$NH_2C_6H_4O$		0/25	*h*	98–100	53	I	$C_{11}H_{10}N_2O$
40	H	H	2-$NO_2C_6H_4O$		0/25	*h*	79–81	60	O	$C_{11}H_8N_2O_3$
41	H	H	2,6-$(CH_3)_2C_6H_3O$		0/100	A	54–56	71.5	K	$C_{13}H_{13}NO$

42	H	H	2,6-$(CH_3O)_2C_6H_3O$		64	A	88–89.5	72	K	$C_{13}H_{13}NO_3$
43	H	H	2,6-$(i\text{-}C_3H_7)_2C_6H_3O$		0/50	A	71–74	47	K	$C_{17}H_{21}NO$
44	H	H	2-$C_6H_5C_6H_4O$		0/25	A	89–91	53	K	$C_{17}H_{13}NO$
45	H	H	1-$C_{10}H_7O$		0/25	A	89–91	68	K	$C_{15}H_{11}NO$
46	H	H	2-$C_{10}H_7O$		0/25	A	64–66	72.5	K	$C_{15}H_{11}NO$
47	H	H	CH_3O		0/100	*e*, F	79–79.5 (14)	55		C_6H_7NO
48	H	H	C_2H_5O		0/50	*g*, F	78–79 (8)	45		C_7H_9NO
49	H	H	C_4H_9O		46	*e*, A	106–107 (8)	75		$C_9H_{13}NO$
50	H	H	$C_6H_{11}O$		36	*f*, B	109–110 (1)	61		$C_{11}H_{15}NO$
51	H	H	C_6H_5S		28	*h*, A	99–100 (0.08)	75		$C_{11}H_9NS$
52	H	H	C_6H_5S	O	22	*k*	137–139	73	M	$C_{11}H_9NOS$
53	H	H	$C_6H_5SO_2$	O	0/12.5	*k*	139–140	83	I	$C_{11}H_9NO_3S$
54	H	H	$C_6H_5CH_2$		0/25	P				$C_{12}H_{11}N$
55	H	H	$C_6H_5CH_2$	O	63	*l*, D	106–107	80	J	$C_{12}H_{11}NO$
56	C_6H_5	H	H		9.5	*m*, *n*	137–138 ($HClO_4$)	50	R	$C_{11}H_9N \cdot HClO_4$
57	C_6H_5	H	H	O	2.3	*o*, D	158–159	75	J	$C_{11}H_9NO$
58	H	C_6H_5	H		2.0	*p*, *q*	82–84 (0.4)	10 (39)		$C_{11}H_9N$
59	H	C_6H_5	H	O	4.4	*l*, D	115–117	52	J	$C_{11}H_9NO$
60	H	H	C_6H_5		15.0	*m*, *r*	76–77	36	Q	$C_{11}H_9N$
61	H	H	C_6H_5	O	37.0	*s*, D	154–155	45	J	$C_{11}H_9NO$
62	2-ClC_6H_4	H	H		2.5	G	176–178 (HCl)	35	R	$C_{11}H_8ClN \cdot HCl$
63	2-ClC_6H_4	H	H	O	3.0	D	150–151	66	J	$C_{11}H_8ClNO$
64	2-$CH_3C_6H_4$	H	H		27.0	*t*	163–165 ($HClO_4$)	60	N	$C_{12}H_{11}N \cdot HClO_4$
65	2-$CH_3C_6H_4$	H	H	O	6.9	D	118–119	50	J	$C_{12}H_{11}NO$
66	3-$CH_3C_6H_4$	H	H		0/25	*u*	99–101 ($HClO_4$)	58	N	$C_{12}H_{11}N \cdot HClO_4$
67	3-$CH_3C_6H_4$	H	H	O	0/25	D	134–135	43	J	$C_{12}H_{11}NO$
68	4-$CH_3C_6H_4$	H	H		0/25	*o*	173–175 ($HClO_4$)	64	N	$C_{12}H_{11}N \cdot HClO_4$
69	4-$CH_3C_6H_4$	H	H	O	0/25	D	145–146	50	J	$C_{12}H_{11}NO$
70	2-$NO_2C_6H_4$	H	H		3.1	*v*, *w*	58–59	15	J	$C_{11}H_8N_2O_2$
71	2-$NO_2C_6H_4$	H	H	O	16.0	*x*, D	160–161	90	J	$C_{11}H_8N_2O_3$
72	C_6H_5	CH_3	H		0/25	*y*, *z*	137–138 ($HClO_4$)	76	N	$C_{12}H_{11}N \cdot HClO_4$
73	C_6H_5	CH_3	H	O	13.5	D	167–168	80	J	$C_{12}H_{11}NO$
74	C_6H_5	H	CH_3		27	*aa*, *bb*	50–51	45	T	$C_{12}H_{11}N$
75	CH_3	C_6H_5	H		3.5	*z*, *cc*	135–137 ($HClO_4$)	93	R	$C_{12}H_{11}N \cdot HClO_4$
76	CH_3	C_6H_5	H	O	4.1	*z*, D	75–76	80	J	$C_{12}H_{11}NO$
77	2-$H_2NC_6H_4$	H	H		35.0	*w*	145–150 (0.3)	90		$C_{11}H_{10}N_2$
78	2-$H_2NC_6H_4$	H	H	O	0/25	*x*	185–186	90	U	$C_{11}H_{10}N_2O$
79	2-HOC_6H_4	H	H		0/100	*dd*	159–161	60	R	$C_{11}H_9NO$
80	2-$CH_3OC_6H_4$	H	H		25.0	*ee*	105–106 (0.5)	30		$C_{12}H_{11}NO$
81	2-C_4H_3S	H	H		4.2	*ff*, H	61–63	23	K	C_9H_7NS
82	C_6H_5	CO_2H	H		0/25	*gg*, *hh*	168–169	45	V	$C_{12}H_9NO_2$
83	C_6H_5	H	H	6-NH_2	25.4	*ii*	70–71	71	W	$C_{11}H_{10}N_2$
84	C_6H_5	H	H	6-CH_3CONH	0/12.5	*jj*	164–165	71	J	$C_{13}H_{12}N_2O$
85	2-C_5H_4N	H	H		2.4	P				$C_{10}H_8N_2$
86	2-C_5H_4N	H	H	O	5.1	*kk*	57–59	35	N	$C_{10}H_8N_2O$
87	2-$C_5H_4N\rightarrow O$	H	H	O	54.0	*ll*	310–311 dec	95	U	$C_{10}H_8N_2O_2$
88	3-C_5H_4N	H	H		1.6	*mm*, *nn*	163–165 (16)	50		$C_{10}H_8N_2$
89	H	3-C_5H_4N	H		4.5	*mm*, *oo*	66–68 167–168 (20)	40		$C_{10}H_8N_2$

Table I (*Continued*)

Compd	X	Y	Z	W[a]	ED_{50},[b] mg/kg sc (free base)	Ref source of exp method[c]	Mp or bp (mm), °C	Yield, %	Recrystn solvent[rr]	Empirical[ss] formula
90	H	H	4-C_5H_4N		15.0	P				$C_{10}H_8N_2$
91	2-$C_5H_4NCH{=}CH$	H	H		8.0	P				$C_{12}H_{10}N_2$
92	2-(3-$CH_3C_5H_3N$)	CH_3	H		17.5	*pp*	280–281 dec (2HBr)	54	R	$C_{12}H_{12}N_2 \cdot 2HBr$
93	2-(4-$CH_3C_5H_3N$)	H	CH_3		17.5	*pp*	170–172	15	K	$C_{12}H_{12}N_2$
94	2-(5-$CH_3C_5H_3N$)	H	H	5-CH_3	0/12.5	*pp*	114.5–116	0.5	K	$C_{12}H_{12}N_2$
95	2-(6-$CH_3C_5H_3N$)	H	H	6-CH_3	26.0	*qq*	87.5–89.5	20	K	$C_{12}H_{12}N_2$
96	2-(4-$C_6H_5C_5H_3N$)	H	C_6H_5		0/25	P				$C_{22}H_{16}N_2$
97	C_6H_5	C_6H_5	H		0/25	*z*	211–213 (HCl)	94	R	$C_{17}H_{13}N \cdot HCl$
98	H	C_6H_5	H	5-C_6H_5	0/25	P				$C_{17}H_{13}N$
99	2-C_5H_4N	H	H	6-(2-C_5H_4N)	lethal/0.1	P				$C_{15}H_{11}N_3$
100	H	H	Cl	O	0/50	P				C_5H_4ClNO
101	H	H	NO_2	O	8.2	P				$C_5H_4N_2O_3$

[a] A fourth substituent on the pyridine, O represents the *N*-oxide. [b] 0/dose mg/kg sc indicates a test dose without effect upon gastric secretion. [c] The original reference is indicated by the first small letter, a second lower case letter represent the reference by which the compounds were prepared. The capital letters refer to the methods mentioned in the Experimental Section. P stands for a purchased sample. [d] M. Hamana and M. Yamazaki, *Yakugaku Zasshi*, **81**, 612 (1961); *Chem. Abstr.*, **55**, 24742*h* (1961). [e] R. R. Renshaw and R. C. Conn, *J. Amer. Chem. Soc.*, **59**, 297 (1937). [f] E. Koenigs and H. Greiner, *Ber.*, **64**, 1049 (1931); German Patent No. 554,702 (1930). [g] E. Ochiai and M. Katada, *Yakugaku Zasshi*, **63**, 265 (1943); *Chem. Abstr.*, **45**, 9541*i* (1951). [h] D. Jerchel, H. Fischer, and K. Thomas, *Ber.*, **89**, 2921 (1956). [i] Patent, Netherlands Application 6,409,825 March 1, 1965, to Parke, Davis and Company; *Chem. Abstr.*, **63**, 11517*d* (1965). [j] Patent, Netherlands Application 6,501,589 Aug 11, 1965, to CIBA Ltd.; *Chem. Abstr.*, **64**, 5050*e* (1966). [k] E. Hayashi, H. Yamanaka, and C. Iyima, *Yakugaku Zasshi*, **80**, 1145 (1960); *Chem. Abstr.*, **55**, 546*d* (1961). [l] A. R. Hands and A. R. Katritzky, *J. Chem. Soc.*, 1754 (1958). [m] R. Mohlau and R. Berger, *Ber.*, **26**, 1994 (1893). [n] J. C. W. Evans and C. F. H. Allen in "Organic Synthesis," Collected Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 517. [o] H. Gilman and J. T. Edward, *Can. J. Chem.*, **31**, 457 (1953). [p] Z. Skraup and A. Cobenzl, *Monatsh. Chem.*, **4**, 456 (1883). [q] H. Rapoport, M. Look, and G. J. Kelly, *J. Amer. Chem. Soc.*, **74**, 6293 (1952). [r] C. J. Schmidle and R. C. Mansfield, *ibid.*, **78**, 1702 (1956). [s] A. Risaliti, *Ricerca Sci.*, **26**, 2782 (1956); *Chem. Abstr.*, **51**, 12084*g* (1957). [t] I. Murakoski, *Yakugaku Zasshi*, **77**, 490 (1957). [u] J. S. Meek, R. T. Merrow, and S. J. Cristol, *J. Amer. Chem. Soc.*, **74**, 2667 (1952). [v] R. Forsyth and F. L. Pyman, *J. Chem. Soc.*, 2912 (1926). [w] J. W. Haworth, I. M. Heilbron, and D. H. Hey, *ibid.*, 349 (1940). [x] R. A. Abramovitch and K. A. H. Adams, *Can. J. Chem.*, **39**, 2516 (1961). [y] R. A. Abramovitch, G. C. Seng, and A. D. Notation, *ibid.*, **38**, 761 (1960). [z] R. F. Parcell and F. P. Hauck, Jr., *J. Org. Chem.*, **28**, 3468 (1963). [aa] G. J. Janz and W. J. H. McCullock, *J. Amer. Chem. Soc.*, **77**, 3143 (1955). [bb] C. Osuch and R. Levine, *ibid.*, **78**, 1723 (1956). [cc] Takeo Ishiguro, Japanese Patent 6382 (1960). [dd] T. A. Geissman, M. J. Schlatter, I. D. Webb, and J. D. Roberts, *J. Org. Chem.*, **11**, 741 (1946). [ee] J. W. Haworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 358 (1940). [ff] H. Wynberg, T. J. van Bergen, and R. M. Kellogg, *J. Org. Chem.*, **34**, 3175 (1969). [gg] T. Ishiguro, Y. Morita, and K. Ikuskima, *Yakugaku Zasshi*, **78**, 220 (1958). [hh] R. A. Abramovitch, G. C. Seng, and A. D. Notation, *Tetrahedron Lett.* 1 (1959). [ii] F. H. Case and T. J. Kasper, *J. Amer. Chem. Soc.*, **78**, 5842 (1956). [jj] By treatment of **83** with acetic anhydride. [kk] I. Murase, *Nippon Kogaku Zasshi*, **77**, 682 (1956). [ll] J. Kaginiwa, *Yakugaku Zasshi*, **75**, 731 (1955). [mm] C. R. Smith, *J. Amer. Chem. Soc.*, **46**, 414 (1924). [nn] R. L. Frank and J. V. Crawford, *Bull. Soc. Chim. Fr.*, 419 (1958). [oo] M. Busch, W. Weber, C. Darboven, W. Renner, H. J. Hahn, G. Mathauser, F. Strätz, K. Zitzmann, and H. Engelhardt, *J. Prakt. Chem.*, **146**, 1 (1936); *Chem. Abstr.*, **30**, 7563 (1936). [pp] F. H. Case, *J. Amer. Chem. Soc.*, **68**, 2574 (1946). [qq] F. H. Burstall, *J. Chem. Soc.*, 1662 (1938). [rr] I, benzene; J, benzene–petr ether; K, anhyd Et_2O; L, cyclohexane; M, MeCN; N, EtOH; O, EtOH–H_2O; Q, MeOH–H_2O; R, *i*-PrOH–Et_2O; T, petr ether; U, MeOH; V, H_2O; W, Et_2O–petr ether. [ss] All nonpurchased samples were analyzed for C and H, and the results were within ±0.4% of the theoretical values.

TABLE II

	Compd	ED_{50},[a] mg/kg sc (free base)	Reference source or experimental method[b]	Mp, °C	Empirical formula
102	Quinoline *N*-oxide	13	P		C_9H_7NO
103	8-Hydroxyquinoline	0/100	P		C_9H_7NO
104	8-Hydroxyquinoline *N*-oxide	22	P		$C_9H_7NO_2$
105	2-Phenylquinoline	0/25	*c*	83–85	$C_{15}H_{11}N$
106	2-Phenylquinoline *N*-oxide	14.5	*d*	142–144	$C_{15}H_{11}NO$
107	2-(2-Quinolinyl)quinoline	0/25	P		$C_{18}H_{12}N_2$
108	1,10-Phenanthroline	5.1	P		$C_{12}H_8N_2$
109	2,9-Dimethyl-1,10-phenanthroline	13.8	P		$C_{14}H_{12}N_2$
110	5-Phenyl-1,10-phenanthroline	0/25	P		$C_{18}H_{12}N_2$
111	5*H*-Indeno[1,2-*b*]pyridine	2.5	*e*	263–264 (HCl)	$C_{12}H_9N \cdot HCl$
112	5*H*-Indeno[1,2-*b*]pyridine *N*-oxide	7.0	*f*	163–164	$C_{12}H_9NO$
113	5*H*-Indeno[1,2-*b*]pyridin-5-one	6.3	*g*	139.5–140	$C_{12}H_7NO$

[a] Footnote *b*, Table I. [b] P stands for a purchased sample. [c] F. W. Birgstrom and S. H. McAllister, *J. Amer. Chem. Soc.*, **52**, 2845 (1930). [d] M. Colonna and A. Risalti, *Boll. Sci. Fac. Chim. Ind. Bologna*, **9**, 82 (1951); *Chem. Abstr.*, **46**, 7102*e* (1952). [e] J. N. Chatterjea and K. Prasad, *J. Indian Chem. Soc.*, **32**, 371 (1955). [f] See Table I, footnote *y*. [g] See Table I, footnote *z*.

Experimental Section[20]

Gastric Antisecretory Testing.—The detailed method has been published.[9] Briefly, antisecretory properties were studied in pylorus-ligated Carworth farm rats, 130–150 g. The test drugs and carrier controls were coded and assigned to the rats in a random block design (6 animals/group). They were administered sc immediately after pyloric ligation. Four hr later, secretions were collected and the vols were recorded. ED_{50}'s were detd by testing the effect of each compound on gastric secretory vol at log interval doses. The results were plotted on semilogarithmic paper and the value that produced a 50% reduction of secretion was read from the graph. An ED_{50} of less than 10 mg/kg was confirmed and the average value was reported.

Compds were tested for antagonism of the blood pressure effects of ACh (15 μg/kg), epinephrine (2 μg/kg), and DMPP (15 μg/kg) in an anesthetized dog prepn. The compd was administered every 20 min in increasing log intervals (log 2) starting with 0.5 mg/kg to an accumulative dose of 64 mg/kg. Each injection of compd was followed in 5-min intervals by agonists. Both agonists and antagonists were administered iv. Water-insoluble compds were dissolved in 50% propylene glycol.

In the rat chromodacryorrhea test,[10] the compds were administered ip to each of 5 rats per group 0.5 hr before methacholine (10 mg/kg) was injected ip. All drugs were tested at dose levels that were 5 times the gastric antisecretory ED_{50}. Saline and atropine sulfate (3 mg/kg) were run as carrier and standard controls, respectively. Chromodacryorrhea was detd 10 min after methacholine administration. The dosing procedure was randomized and evaluation of chromodacryorrhea performed without knowledge of specific drug administered. The presence of chromodacryorrhea in at least 4 of the 5 animals was considered as evidence of the absence of anticholinergic properties.

4-Phenoxypyridines were prepd by the method of Jerchel, *et al.*[21] (method A), or that of Koenigs and Greiner[11] (method B). **3-Phenoxypyridines** were prepd by the procedure used by Renshaw and Conn[12] (method C). **Pyridine *N*-oxides** were obtained by oxidn as described by Ochiai and Sai[22] (method D), with the exception of some 4-substituted phenoxypyridines prepd by the method of Ochiai and Katada[23] (method E). **Arylpyridines** were prepd as described in the footnote references of Table I.

Method F. 2-Phenyl-4-phenoxypyridine (36).—A soln of PhLi was prepd from Li chips, 4 g (0.57 g-atom), and PhBr, 40 g (0.254 mole) in Et_2O, and a soln of 4-phenoxypyridine,[11] 43 g (0.25 mole) in 200 ml of Et_2O, was added dropwise with stirring.[24] After the mildly exothermic reaction had subsided, 6 ml of H_2O (0.33 mole) was added and the mixt was stirred until the excess Li had reacted. A soln of $PhNO_2$, 80 g (0.65 mole), in xylene, was added, followed by 0.2 g of com 5% Pd/C. The Et_2O was distd with the addn of xylene until the reaction temp reached 135° and the mixt was refluxed overnight under a Dean–Stark H_2O trap.[25] The mixt was cooled and the product was extd into dil HCl. The aq acid exts were made strongly basic (NaOH), extd (Et_2O), dried ($MgSO_4$), concd, and distd to yield 25 g, 39%, bp 128–130° (0.06 mm). *Anal.* ($C_{17}H_{13}NO$) C, H.

2-*n*-Butyl-4-phenoxypyridine (34).—This was prepd in the same manner using com BuLi.

Method G. 2-(*o*-Chlorophenyl)pyridine (62).—2-(*o*-Aminophenyl)pyridine,[26] 8.4 g (0.05 mole), was diazotized in cold dil HCl and treated with a freshly prepd soln of Cu_2Cl_2 in HCl. The mixt was allowed to warm to 25° and then heated to 60°, made strongly basic (NaOH) and extd (Et_2O). The exts were dried ($MgSO_4$), filtd, and evapd. The residue was converted to the hydrochloride and recrystd from *i*-PrOH–Et_2O to yield 4 g, 35%, mp 176–178°. *Anal.* ($C_{11}H_8ClN \cdot HCl$) C, H.

Method H. 2-(2-Thienyl)pyridine (81).[18]—3,4,5,6-Tetrahydro-2-(2-thienyl)pyridine (114) was prepd using the method Salathiel, *et al.*,[27] used to prep the Ph analog. The yield was 35%, bp 140–142° (12 mm).

3,4,5,6-Tetrahydro-2-(2-thienyl)pyridine (114), 30 g (0.182 mole), was mixed with 11.6 g (0.37 mole) of S and heated slowly until gas was evolved (*ca.* 160°). After the gas evoln subsided, the mixt was heated to 280° and allowed to cool.[28] The product was distd to yield 20 g, bp 138–140° (16 mm). Recrystn (Et_2O) yielded 10.1 g, 34%, mp 61–63°. *Anal.* (C_9H_7NS) C, H.

(20) Melting points (uncorrected) were taken in open capillary tubes in a Thomas-Hoover mp app. Ir spectra were detd on a Beckman IR7 instrument. The compds were tested only when the spectra, bp, or mp were consistent with those reported in the literature. The yields are based on pure isolated materials. C and H microanalyses were performed on all compds prepd and such anal. checked within 0.4%. We are indebted to Mr. C. E. Childs and associates for microanalyses, Dr. J. M. Vandenbelt and associates for spectral data, Mr. W. Pearlman for catalytic hydrogenations, and Misses R. A. Purdon and M. A. Patterson for performing the many pylorus-ligated rat prepns.

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