Antiulcer Agents. 1. Gastric Antisecretory and Cytoprotective Properties of Substituted Imidazo[1,2-*a*]pyridines

James J. Kaminski,* James A. Bristol, Chester Puchalski, Raymond G. Lovey, Arthur J. Elliott, Henry Guzik, Daniel M. Solomon, David J. Conn, Martin S. Domalski, Shing-Chun Wong, Elijah H. Gold, James F. Long, P. J. S. Chiu, Merl Steinberg, and Andrew T. McPhail†

Pharmaceutical Research Division, Schering-Plough Corporation, Bloomfield, New Jersey 07003. *Received August 16, 1984*

A novel class of antiulcer agents, the substituted imidazo[1,2-*a*]pyridines, is described. The present compounds are not histamine (H_2) receptor antagonists nor are they prostaglandin analogues, yet they exhibit both gastric antisecretory and cytoprotective properties. The mechanism of gastric antisecretory activity may involve inhibition of the H^+/K^+-ATPase enzyme. Structure–activity studies led to the identification of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, SCH 28080 (**27**), which was selected for further development and clinical evaluation.

Peptic ulcer has been generally thought to result from an imbalance between the aggressive forces of acid and pepsin and the defensive forces of resistance.[1] Consequently, antiulcer therapy has been directed toward these two factors. The histamine (H_2) receptor antagonists, anticholinergics, and antacids are known to lower acid secretion. However, only about 30% of ulcer patients have been identified as being hypersecretory. This observation implies that weakened mucosal resistance must play a significant role in the pathogenesis of ulcers in the remainder of the patient population.

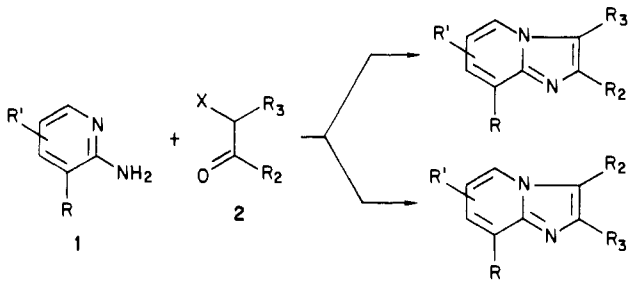
The ulcer-healing effects of carbenoxolone[2] and sucralfate[3] are not related to the acid inhibition and have been attributed to their ability to strengthen the defensive mechanisms. This latter property was defined by Robert et al.[4] as cytoprotection. Robert first demonstrated in rats that the prostaglandins have gastrointestinal cytoprotective activity, in addition to antisecretory activity, and that these two activities were separable.

Despite intensive research in recent years, the exact mechanism(s) of cytoprotection remains unknown.[5] However, a prevalent hypothesis is that the gastric cytoprotectants stimulate release of gastric mucous or increase the thickness of the mucous that provides a protective barrier between the gastric mucosa and acid.[6,7] Although an established cytoprotective mechanism(s) remains elusive, several clinical studies have demonstrated the efficacy of PGE_2 and analogues in treating gastric and duodenal ulcers.[8-11] The therapeutic effect of prostaglandins can be attributed to their cytoprotective activity alone or concomitant with their antisecretory activity. Whether or not the efficacy of the prostaglandins is based on such a dual action, an antiulcer agent exhibiting both activities should afford the most effective control of peptic ulcer disease in the majority of ulcer patients.

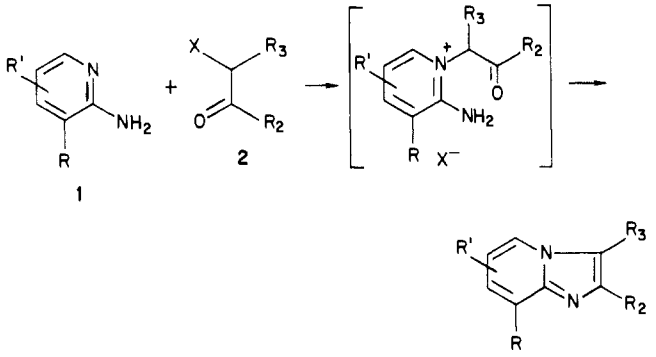
As part of our efforts to identify novel antiulcer agents, we are reporting a series of substituted imidazo[1,2-*a*]-pyridines that represent a new class of antiulcer agents. The present compounds are not competitive histamine (H_2) receptor antagonists, yet are potent inhibitors of gastric acid secretion in the pylorous-ligated rat and in the histamine-stimulated dog. Additionally, while not prostaglandin analogues, these compounds also inhibit gastric lesions in rats induced by the administration of acidic nonsteroidal antiinflammatory drugs, ethanol, and other noxious agents.[7,12,13]

Development of this serendipitously discovered series of compounds led to the selection for clinical evaluation of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo-[1,2-*a*]pyridine, SCH 28080 (**27**), as a potential antiulcer drug exhibiting both gastric antisecretory and cytoprotective properties.[14,15]

Scheme I. General Synthesis of Substituted Imidazo[1,2-*a*]pyridines



Scheme II. Proposed Mechanism to Substituted Imidazo[1,2-*a*]pyridines



†Department of Chemistry, Duke University, Durham, North Carolina 27706.

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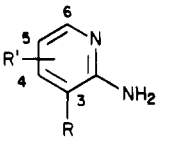
Table I. Substituted 2-Aminopyridines 1

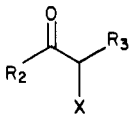


1

compd	R	R'	mp, °C	yield, %	formula	anal.	ref
1a	OH	H					a
1b	$PhCH_2O$	H					30
1c	2-$FPhCH_2O$	H					30
1d	4-$ClPhCH_2O$	H					30
1e	3,4-$Cl_2C_6H_3CH_2O$	H					30
1f	3-CF_3PhCH_2O	H					30
1g	4-$CH_3SO_2PhCH_2O$	H	187–189[b]	61	$C_{13}H_{14}N_2O_3S$	C, H, N, S	Ex[c]
1h	4-*t*-$BuPhCH_2O$	H					30
1i	$PhCH_2CH_2O$	H					30
1j	$PhCH_2CH_2CH_2O$	H					30
1k	$PhCHCH_3$	H					30
1l	2-$PyCH_2O$	H					30
1m	3-$PyCH_2O$	H	107–109[b]	56	$C_{11}H_{11}N_3O$	C, H, N	Ex[c]
1n	4-$PyCH_2O$	H	173–176[d]	67	$C_{11}H_{11}N_3O$	C, H, N	Ex[c]
1o	2-thienyl-CH_2O	H					30
1p	$PhCH_2CH_2$	H	106–108	33	$C_{13}H_{14}N_2$	C, H, N	Ex[c]
1q	H	4-$PhCH_2CH_2$	138–139[e]	73	$C_{13}H_{14}N_2$	C, H, N	Ex[c]
1r	H	5-$PhCH_2CH_2$	107–108	20	$C_{13}H_{14}N_2$	C, H, N	Ex[c]
1s	H	6-$PhCH_2CH_2$	55–57[e]	65	$C_{13}H_{14}N_2$	C, H, N	Ex[c]
1t	$PhCH_2NH$	H	126–129	36	$C_{12}H_{13}N_3$	C, H, N	Ex[c]
1u	CHO	H					32

[a] Available from the Aldrich Chemical Co. [b] From methanol. [c] Ex = experimental procedure described. [d] From acetonitrile. [e] From ethyl acetate–hexanes.

Table II. α-Halo Carbonyl Intermediates 2



2

compd	R_2	R_3	X	bp, °C (mmHg)	ref
2a	H	H	Br		a, b
2b	CH_3	H	Cl		b
2c	CH_3CH_2	H	Br		b
2d	$(CH_3)_2CH$	H	Br	80–85 (50)	37
2e	CH_3	CH_3	Br		c
2f	CH_3CH_2	CH_3	Br	d	38
2g	CH_3	CH_3CH_2	Br	50–54 (12)	39
2h	$CH_2CH_2CH_2$		Cl		b
2i	$CH_2CH_2CH_2CH_2$		Cl		b
2j	CH_3	$COCH_3$	Cl		b
2k	CH_3	CO_2Et	Cl		b
2l	CH_3	CH_2CO_2Et	Br	98–103 (6)	40
2m	CF_3	CO_2Et	Br	80–90 (30)	41
2n	CH_3	CH_2CN	Cl	83–93 (0.3)	Ex[e]

[a] Used as the diethyl acetal. [b] Available from the Aldrich Chemical Co. [c] Available from Eastman Kodak Co. [d] Isolated product used without further purification. [e] Ex = experimental procedure described.

Chemistry. The most convenient and general method for the preparation of substituted imidazo[1,2-*a*]pyridines is the condensation of substituted 2-aminopyridines with α-halo carbonyl intermediates.[16] Two isomeric imidazo[1,2-*a*]pyridine products are possible when unsymmetrical carbonyl compounds are used and the structure of the product is determined by which nitrogen atom in the pyridine initiates the reaction[17] (Scheme I).

The reaction is generally believed to proceed via the initial displacement of the halogen atom by the pyridine ring nitrogen atom followed by facile closure of the intermediate (Scheme II). This mechanism appears reasonable since the intermediate pyridinium salt is resonance stabilized; more recent time-dependent proton magnetic resonance studies,[18] as well as STO-3G ab initio calculations,[19] support the initial displacement by the pyridine ring nitrogen atom.

The substituted imidazo[1,2-*a*]pyridines (Table III) were prepared from the substituted 2-aminopyridines 1 (Table I) and the α-halo carbonyl intermediates 2 (Table II),

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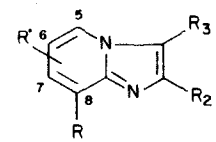
Table III. Substituted Imidazo[1,2-*a*]pyridines



compd	R_2	R_3	R	R′	method of synthesis	mp, °C	recrystn[a] solvent	yield, %	formula	anal.
3	CH_3	H	OH	H	A	211–223	CH_2Cl_2–CH_3OH	20	$C_8H_8N_2O$	C, H, N
4	H	H	$PhCH_2O$	H	B	102–105	$PhCH_2$	46	$C_{14}H_{12}N_2O$	C, H, N
5	CH_3	H	$PhCH_2O$	H	A	93–95	(*i*-Pr)$_2$O	48	$C_{15}H_{14}N_2O$	C, H, N
6	CH_3CH_2	H	$PhCH_2O$	H	A	97–99	EtOAc	90	$C_{16}H_{16}N_2O$	C, H, N
7	$(CH_3)_2CH$	H	$PhCH_2O$	H	A	82–84	EtOAc–hexanes	52	$C_{17}H_{18}N_2O$	C, H, N
8	CH_3	H	2-$FPhCH_2O$	H	A	98	EtOAc–hexanes	39	$C_{15}H_{13}FN_2O$	C, H, N
9	CH_3	H	4-$ClPhCH_2O$	H	A	149–151	CH_3CN	73	$C_{15}H_{13}ClN_2O$	C, H, N
10	CH_3	H	3,4-$Cl_2C_6H_3$-CH_2O	H	A	117–118	EtOAc–hexanes	75	$C_{15}H_{12}Cl_2N_2O$	C, H, N
11	CH_3	H	3-CF_3PhCH_2O	H	A	79–80	(*i*-Pr)$_2$O	37	$C_{16}H_{13}F_3N_2O$	C, H, N
12	CH_3	H	4-*t*-BuPh-CH_2O	H	A	110–112	EtOAc–hexanes	60	$C_{19}H_{22}N_2O$	C, H, N
13	CH_3	H	$PhCH_2CH_2O$	H	A	114–119		15	$C_{16}H_{15}N_2O$	C, H, N
14	CH_3	H	2-$PyCH_2O$	H	A	210–213	*i*-PrOH	64	$C_{14}H_{13}N_2O_3 \cdot 2HCl \cdot {}^1/_2H_2O$	C, H, N, Cl
15	CH_3	H	2-thienyl-CH_2O	H	A	124–126	EtOAc–EtOH	40	$C_{13}H_{12}N_2O_3$	C, H, N
16	CH_3	H	$PhCH_2CH_2$	H	A	175–177	EtOH–Et_2O	59	$C_{16}H_{16}N_2HCl$	C, H, N
17	CH_3	H	H	7-$PhCH_2CH_2$	A	92–102	EtOH–Et_2O	41	$C_{16}H_{16}N_2 \cdot HCl \cdot {}^1/_4H_2O$	C, H, N
18	CH_3	H	H	6-$PhCH_2CH_2$	A	104–105	EtOAc	59	$C_{16}H_{16}N_2$	C, H, N
19	CH_3	H	H	5-$PhCH_2CH_2$	A	86–88	hexanes	53	$C_{16}H_{16}N_2$	C, H, N
20	CH_3	H	4-$FPhCH_2O$	H	C	136–137	EtOAc–hexanes	70	$C_{15}H_{13}FN_2O$	C, H, N
21	CH_3	H	4-CF_3PhCH_2O	H	C	143–144	EtOAc–hexanes	66	$C_{16}H_{13}F_3N_2O$	C, H, N
22	CH_3	H	4-$CNPhCH_2O$	H	C	130–170	(*i*-Pr)$_2$O	72	$C_{16}H_{13}N_3O$	C, H, N
23	CH_3	H	4-CH_3OPh-CH_2O	H	C	178–180	EtOAc	27	$C_{16}H_{16}N_2O_2$	C, H, N
24	CH_3	H	2,4,6-$(CH_3)_3$-$C_6H_2CH_2O$	H	C	160	EtOAc–hexanes	59	$C_{18}H_{20}N_2O$	C, H, N
25	CH_3	$CH_2N(CH_3)_2$	$PhCH_2O$	H	D	210–211	CH_3CN–CH_3OH	77	$C_{18}H_{21}N_3O \cdot 2HCl$	C, H, N, Cl
26	CH_3	$CH_2N^+(CH_3)_3I^-$	$PhCH_2O$	H	E	158–163		75	$C_{19}H_{24}IN_3O$	C, H, N, I
27	CH_3	CH_2CN	$PhCH_2O$	H	D, E, F, or G	163–166	CH_3CN	70	$C_{17}H_{15}N_3O$	C, H, N
28	H	CH_2CN	$PhCH_2O$	H	D, E, F	163–165	*i*-PrOH	52	$C_{16}H_{13}N_3O$	C, H, N
29	CH_3CH_2	CH_2CN	$PhCH_2O$	H	D, E, F	154–156	*i*-PrOH	45	$C_{18}H_{17}N_3O$	C, H, N
30	$(CH_3)_2CH$	CH_2CN	$PhCH_2O$	H	D, E, F	136–140	EtOAc–hexanes	64	$C_{19}H_{19}N_3O$	C, H, N
31	CH_3	CH_2CN	2-$FPhCH_2O$	H	D, E, F	172–173	EtOAc–hexanes	62	$C_{17}H_{14}FN_3O$	C, H, N
32	CH_3	CH_2CN	4-$ClPhCH_2O$	H	D, E, F	185–186	CH_3CN	38	$C_{17}H_{14}ClN_3O$	C, H, N
33	CH_3	CH_2CN	3,4-$Cl_2C_6H_3$-CH_2O	H	D, E, F	229–231	$CHCl_3$–CH_3CN	57	$C_{17}H_{13}ClN_3O$	C, H, N
34	CH_3	CH_2CN	3-CF_3PhCH_2O	H	D, E, F	177–179	EtOAc–hexanes	36	$C_{18}H_{14}F_3N_3O$	C, H, N
35	CH_3	CH_2CN	4-*t*-BuPh-CH_2O	H	D, E, F	163–164	EtOAc–hexanes	21	$C_{21}H_{23}N_3O$	C, H, N
36	CH_3	CH_2CN	$PhCH_2CH_2O$	H	D, E, F	125–126	EtOAc–hexanes	38	$C_{16}H_{17}N_3O$	C, H, N
37	CH_3	CH_2CN	2-$PyCH_2O$	H	D, E, F	121–124	CH_3CN	46	$C_{16}H_{14}N_4O$	C, H, N
38	CH_3	CH_2CN	3-$PyCH_2O$	H	G	160–163	CH_3CN	54	$C_{16}H_{14}N_4O \cdot {}^1/_4H_2O$	C, H, N
39	CH_3	CH_2CN	4-$PyCH_2O$	H	G	140–143	CH_3CN	48	$C_{16}H_{14}N_4O \cdot {}^1/_4H_2O$	C, H, N
40	CH_3	CH_2CN	2-thienyl-CH_2O	H	D, E. F	155–157	EtOAc	43	$C_{15}H_{13}N_3OS$	C, H, N, S
41	CH_3	CH_2CN	$PhCH_2CH_2$	H	G	249–251 dec	CH_3CN	47	$C_{18}H_{17}N_3 \cdot HCl \cdot {}^1/_2H_2O$	C, H, N, Cl
42	CH_3	CH_2CN	H	7-$PhCH_2CH_2$	D, E, F	118	EtOAc–hexanes	11	$C_{18}H_{17}N_3 \cdot {}^1/_2H_2O$	C, H, N
43	CH_3	CH_2CN	H	6-$PhCH_2CH_2$	D, E, F	139–141	(*i*-Pr)$_2$O–CH_2Cl_2	23	$C_{18}H_{17}N_3$	C, H, N

44	CH_3	CH_2CN	H	5-$PhCH_2CH_2$	D, E, F	118–119	EtOAc–hexanes	20	$C_{16}H_{17}N_3$	C, H, N
45	CH_3	CH_2CN	4-$FPhCH_2O$	H	D, E, F	200–201	EtOAc–hexanes	66	$C_{17}H_{14}FN_3O$	C, H, N
46	CH_3	CH_2CN	4-CF_3PhCH_2O	H	D, E, F	180–191	EtOAc–hexanes	53	$C_{18}H_{14}F_3N_3O$	C, H, N
47	CH_3	CH_2CN	4-$CNPhCH_2O$	H	D, E, F	185–187	CH_3CN	30	$C_{18}H_{14}N_4O \cdot {}^1/_4H_2O$	C, H, N
48	CH_3	Ch_2CN	4-CH_3Ph-CH_2O	H	D, E, F	159–160	EtOAc–hexanes	39	$C_{1H17}N_3O_2$	C, H, N
49	CH_3	CH_2CN	2,4,6-$(CH_3)_3$-$C_6H_2CH_2O$	H	D, E, F	244–247 dec	CH_3CN	65	$C_{20}H_{21}N_3O$	C, H, N
50	CH_3	CH_2CN	OH	H	H	216–228 dec	CH_3OH–EtOAc	100	$C_{10}H_9N_3O$	C, H, N
51	CH_3	CH_2CN	3-thienyl-CH_2O	H	I	159–161	EtOAc–hexanes	65	$C_{15}H_{13}N_3OS \cdot {}^1/_4H_2O$	C, H, N
52	CH_3	CH_2CN	3-furanyl-CH_2O	H	I	150–151.5	EtOAc–EtOH	40	$C_{16}H_{13}N_3O_2 \cdot {}^3/_4H_2O$	C, H, N
53	CH_3	CH_2CN	α-napthyl-CH_2O	H	I	238–239	CH_3OH–EtOAc	40	$C_{21}H_{17}N_3O$	C, H, N
54	CH_3	CH_2CN	4-CH_3SO_2-$PhCH_2O$	H	G	206–208	CH_3CN	55	$C_{18}H_{17}N_3O_3S \cdot {}^1/_2H_2O$	C, H, N, S
55	CH_3	CH_2CN	$PhCH_2CH_2CH_2O$	H	G	143–145	Et_2O–$(i\text{-}Pr)_2O$	17	$C_{19}H_{19}N_3O$	C, H, N
56	CH_3	CH_2CN	$PhCHCH_3$	H	G	132–134	$PhCH_3$	20	$C_{18}H_{17}N_3O$	C, H, N
57	CH_3	CH_2CN	$PhCH_2NH$	H	G	56–75	EtOAc–hexanes	62	$C_{17}H_{16}N_4$	C, H, N
58	CH_3	CH_2CN	$PhCH_2NCH_3$	H	Ex[b]	99–101	$(i\text{-}Pr)_2O$	4	$C_{18}H_{18}N_4$	
59	CH_3	H	OC(=S)N-$(CH_3)_2$	H	Ex[b]	154–155	$PhCH_3$	26	$C_{11}H_{13}N_3O_5$	C, H, N
60	CH_3	H	SC(=O)N-$(CH_3)_2$	H	Ex[b]	172–174	CH_3CN	55	$C_{11}H_{13}N_3OS$	C, H, N
61	CH_3	H	$PhCH_2S$	H	Ex[b]	154–156	CH_3CN	47	$C_{15}H_{14}N_2S$	C, H, N
62	CH_3	CH_2CN	$PhCH_2S$	H	D, E, F	146–147	EtOAc–hexanes	25	$C_{17}H_{15}N_3S$	C, H, N
63	CH_3	CH_2CN	$PhCH_2SO$	H	Ex[b]	183–185	CH_3CN	35	$C_{17}H_{15}N_3OS$	C, H, N
64	CH_3	CH_2CN	$PhCH_2SO_2$	H	Ex[b]	200–201	EtOAc–hexanes	24	$C_{17}H_{15}N_3O_2S$	C, H, N
65	CH_3	CH_2CN	PhO	H	Ex[b]	137–138	EtOAc–hexanes	6	$C_{16}H_{13}N_3O$	C, H, N
66	CH_3	CH_3	CHO	H	A	151–153	EtOAc	30	$C_{10}H_{16}N_2O$	C, H, N
67	CH_3	CH_3	CH_2OH	H	Ex[b]	155–158	*i*-PrOH	85	$C_{10}H_{12}N_2O$	C, H, N
68	CH_3	CH_3	CH_2OPh	H	Ex[b]	108–109	EtOAc	58	$C_{16}H_{16}N_2O$	C, H, N
69	CH_3	CH_3	CH_2SPh	H	Ex[b]	78–79.5	EtOAc–hexanes	48	$C_{16}H_{16}N_2S$	C, H, N, S
70	CH_3	CH_3	CH_2SOPh	H	Ex[b]	144–146	EtOAc–hexanes	53	$C_{16}H_{16}N_2OS$	C, H, N, S
71	CH_3	CO_2Et	$PhCH_2O$	H	A	112–113.5	CH_3CN	28	$C_{16}H_{18}N_2O_3 \cdot {}^1/_4H_2O$	C, H, N
72	CH_3	CO_2H	$PhCH_2O$	H	Ex[b]	204–205 dec	DMF	87	$C_{16}H_{14}N_2O_3$	C, H, N
73	CH_3	$CONH_2$	$PhCH_2O$	H	Ex[b]	225–227	CH_3CN	30	$C_{15}H_{15}N_3O_2$	C, H, N
74	CH_3	$COCH_3$	$PhCH_2O$	H	A	160–162	CH_3OH	44	$C_{17}H_{16}N_2O_2$	C, H, N
75	CH_3	CN	$PhCH_2O$	H	Ex[b]	170–171	CH_3OH	69	$C_{16}H_{13}N_3O$	C, H, N
76	CH_3	CH_2CH_2CN	$PhCH_2O$	H	Ex[b]	130–131	EtOAc	37	$C_{18}H_{17}N_3O$	C, H, N
77	CH_3	$CH(CH_3)CN$	$PhCH_2O$	H	Ex[b]	188–189	*i*-PrOH	10	$C_{18}H_{17}N_3O \cdot HCl$	C, H, N, Cl
78	CH_3	$C(CH_3)_2CN$	$PhCH_2O$	H	Ex[b]	102–104	$(i\text{-}Pr)_2O$	6	$C_{19}H_{19}N_3O$	C, H, N
79	CH_3	CH_2NC	$PhCH_2O$	H	Ex[b]	156–163	CH_3CN	85	$C_{17}H_{15}N_3O$	C, H, N
80	CH_3	CH_2OH	$PhCH_2O$	H	Ex[b]	132–134	CH_3CN	65	$C_{16}H_{16}N_2O_2$	C, H, N
81	CH_3	CH_2OCH_3	$PhCH_2O$	H	Ex[b]	106–108.5	$(i\text{-}Pr)_2O$	31	$C_{17}H_{16}N_2O_2 \cdot {}^1/_2HCl$	C, H, N
82	CH_3	$CH_2OCH_2CH_3$	$PhCH_2O$	H	Ex[b]	94–96	*i*-PrOH	7	$C_{18}H_{20}N_2O_2 \cdot {}^1/_2H_2O$	C, H, N
83	CH_3	CH_2SCH_3	$PhCH_2O$	H	Ex[b]	88–90	$(i\text{-}Pr)_2O$	40	$C_{17}H_{18}N_2O_2S \cdot {}^1/_2H_2O$	C, H, N
84	CH_3	$CH_2SCH_2CH_3$	$PhCH_2O$	H	Ex[b]	76–78	$(i\text{-}Pr)_2O$	50	$C_{18}H_{20}N_2O_3S$	C, H, N, S
85	CH_3	CH_2SOCH_3	$PhCH_2O$	H	Ex[b]	125–126	EtOAc–hexanes	90	$C_{17}H_{18}N_2O_2S \cdot {}^1/_1H_2O$	C, H, N
86	CH_3	$CH_2SO_2CH_3$	$PhCH_2O$	H	Ex[b]	165–166	EtOAc–hexanes	58	$C_{17}H_{18}N_2O_3S$	C, H, N
87	CH_3	Cl	$PhCH_2O$	H	Ex[b]	195–197	CH_3OH–EtOAc	52	$C_{15}H_{13}ClN_3OHCl \cdot {}^1/_2H_2O$	C, H, N
88	CH_3	Br	$PhCH_2O$	H	Ex[b]	106–107	1-chlorobutane–hexanes	20	$C_{15}H_{13}BrN_2O$	C, H, N
89	CH_3	CH_2CO_2Et	$PhCH_2O$	H	A	78–80	$(i\text{-}Pr)_2O$	70	$C_{19}H_{20}N_2O_3$	C, H, N
90	CH_3	CH_2CO_2H	$PhCH_2O$	H	Ex[b]	122–126	H_2O	34	$C_{17}C_{16}N_2O_3$	C, H, N
91	CH_3	CH_2CONH_2	$PhCH_2O$	H	Ex[b]	219–221	CH_3OH	36	$Cl_7H_{17}N_3O_2$	C, H, N
92	CH_3	$CH_2CONHCH_3$	$PhCH_2O$	H	Ex[b]	167–169	CH_3CN	30	$C_{18}H_{19}N_3O_2$	C, H, N
93	CH_3	$CH_2CON(CH_3)_2$	$PhCH_2O$	H	Ex[b]	165–167	CH_3OH–H_2O	22	$C_{19}H_{21}N_3O_2$	C, H, N
94	CH_3	CH_2CSNH_2	$PhCH_2O$	H	Ex[b]	190–192 dec	DMF–H_2O	50	$C_{17}H_{17}N_3O_2$	C, H, N

Table III (Continued)

compd	R_2	R_3	R	R′	method of synthesis	mp, °C	recrystn[a] solvent	yield, %	formula	anal.
95	CH_3	$CH_2CSNHCH_3$	$PhCH_2O$	H	Ex[b]	215–217	CH_3CN	38	$C_{19}H_{21}N_3OS$	C, H, N, S
96	CH_3	$CH_2CSN(CH_3)_2$	$PhCH_2O$	H	Ex[b]	199–201 dec	CH_3CN	38	$C_{19}H_{21}N_3OS$	C, H, N, S
97	CH_3	$CH_2C(NH)NH_2$	$PhCH_2O$	H	Ex[b]	191–193 dec	CH_3CN	8	$C_{17}H_{18}N_4O$·HCl	C, H, N, Cl
98	CH_3		$PhCH_2O$	H	Ex[b]	157–160	CH_3CN	50	$C_{19}H_{20}N_4O$	C, H, N
99	CH_3	$CH_2O_2CCH_3$	$PhCH_2O$	H	Ex[b]	133–136	CH_2Cl_2–Et_2O	80	$C_{18}H_{18}N_2O_3$	C, H, N
100	CH_3	$CH_2O_2CC_4H_9$-*n*	$PhCH_2O$	H	Ex[b]	108–109	CH_2Cl_2–Et_2O	88	$C_{21}H_{24}N_2O_3$	C, H, N
101	CH_3	$CH_2O_2CC_4H_9$-*t*	$PhCH_2O$	H	Ex[b]	145–147	(*i*-Pr)$_2O$	31	$C_{21}H_{24}N_2O_3$	C, H, N
102	CH_3	CH_2O_2C-3-Py	$PhCH_2O$	H	Ex[b]	139–140	CH_2Cl_2–Et_2O	94	$C_{22}H_{19}N_3O_3$	C, H, N
103	CH_3	$CH_2O_2CN(CH_3)_2$	$PhCH_2O$	H	Ex[b]	123–125	EtOAc	44	$C_{19}H_{21}N_3O_3$	C, H, N
104	CH_3	CH_3	$PhCH_2O$	H	A	203–205	CH_3CN	62	$C_{16}H_{16}N_2O$·HBr	C, H, N
105	CH_3	CH_2CH_3	$PhCH_2O$	H	A	87–89	(*i*-Pr)$_2O$	54	$C_{17}H_{18}N_2O$	C, H, N
106	CH_3CH_2	CH_3	$PhCH_2O$	H	A	61–63	EtOAc	40	$C_{17}H_{18}N_2O$	C, H, N
107		$CH_2CH_2CH_3$	$PhCH_2O$	H	A	170–172	CH_3CN	6	$C_{17}H_{16}N_2O$	C, H, N
108		$CH_2CH_2CH_2CH_3$	$PhCH_2O$	H	A	135–137	EtOAc	31	$C_{18}H_{18}N_2O$	C, H, N
109	CF_3	CO_2Et	$PhCH_2O$	H	A	88–91	CH_3CN	74	$C_{18}H_{15}F_3N_2O_3$	C, H, N
110	CF_3	CH_2OH	$PhCH_2O$	H	Ex[b]	164–170	CH_3CN	76	$C_{16}H_{13}F_3N_2O_2$	C, H, N
111	CF_3	CH_2CN	$PhCH_2O$	H	Ex[b]	176–179	EtOAc–hexanes	8	$C_{17}H_{12}F_3N_3O$	C, H, N

[a] Isolated and used without further purification, unless noted otherwise. [b] Ex = experimental procedure described.

following the general methods and specific experimental procedures described.

Method A. Condensation of the appropriately substituted 2-aminopyridine 1 with the appropriate α-halo carbonyl intermediate 2 gave the corresponding substituted imidazo[1,2-*a*]pyridines **3**, **5–19**, **66**, **71**, **74**, **89**, and **104–109**.

Method B. 8-(Phenylmethoxy)imidazo[1,2-*a*]pyridine (**4**) was prepared by condensing 2-amino-3-(phenylmethoxy)pyridine (**1b**) with 2-bromoacetaldehyde diethyl acetal (**2a**).[20]

Method C. Alkylation of 8-hydroxy-2-methylimidazo[1,2-*a*]pyridine (**3**) with the appropriately substituted phenylmethyl halide gave the corresponding substituted imidazo[1,2-*a*]pyridines **20–24**.

Methods D–F. Application of the Mannich reaction to the 3-unsubstituted imidazo[1,2-*a*]pyridines, formation of the trimethylammonium quaternary salts, and subsequent cyanide displacement gave the corresponding 3-cyanomethyl-substituted imidazo[1,2-*a*]pyridines **27–37**, **40**, **42–49**, and **62**.

Method G. Condensation of the appropriately substituted 2-aminopyridine 1 with 3-chloro-4-oxopentanenitrile (**2n**) gave the corresponding 3-cyanomethyl-substituted imidazo[1,2-*a*]pyridines **38**, **39**, **41**, and **54–57**. 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**) has also been prepared by using this method by the condensation of **1b** and **2n**.

Method H. 3-(Cyanomethyl)-8-hydroxy-2-methylimidazo[1,2-*a*]pyridine (**50**) was prepared by debenzylation of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**).

Method I. Alkylation of 3-(cyanomethyl)-8-hydroxy-2-methylimidazo[1,2-*A*]pyridine (**50**) with the appropriate arylalkyl halide gave the corresponding substituted imidazo[1,2-*a*]pyridines **51–53**.

Following the specific experimental procedures described below, the remaining substituted imidazo[1,2-*a*]pyridines **58–61**, **63–65**, **67–70**, **72**, **73**, **75–88**, **90–103**, **110**, and **111** were prepared (Table III).

In order to establish unequivocally the direction of condensation of substituted 2-aminopyridines with unsymmetrical α-halo carbonyl compounds, the representative product **27**, obtained from the reaction of **1b** with **2n**, was subjected to a single-crystal X-ray analysis. The structure was determined by direct methods,[21] and least-squares refinement of atomic parameters converged to R[22] = 0.051 over 1923 reflections. A view of the solid-state conformation is provided in Figure 1. Bond lengths and angles[23] are in accord with expected values. The directly bonded substituent atoms and the oxymethylene carbon atom (Δ = 0.120 Å) lie close to the least-squares plane through the essentially planar imidazo[1,2-*a*]pyridine ring system[23] (root mean square displacement = 0.005 Å); the phenyl ring is almost orthogonal to this plane (C_1'–C_7'–O_8'–O_8 = 177.1 (2)° and C_2'–C_1'–C_7'–O_8' = −92.7°).

Since the identical product **27** was derived by the reaction of **1b** with **2b**, followed by application of the Mannich reaction–quaternization–cyanide displacement sequence (methods D–F), the structure of the original ring-closed intermediate as the 2-methyl-3-unsubstituted

(20) Hand, E. S.; Paudler, W. S. *J. Org. Chem.* **1978**, *43*, 2900.
(21) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declerq, J. P. "MULTAN76, A System of Computer Programmes for the Automatic Solutions of Crystal Structures"; Universities of York and Louvain, 1976.
(22) $R = \sum||F_o| - |F_c||/\sum|F_o|$.
(23) Supplementary material: see paragraph at the end of the paper.

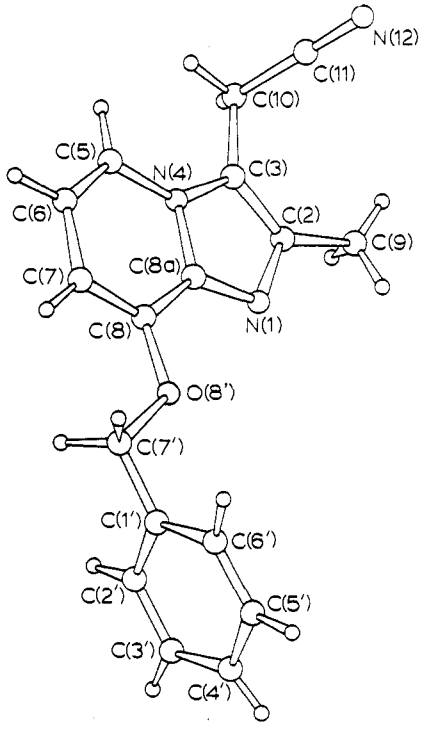


Figure 1. Structure and solid-state conformation of **27**; small circles denote hydrogen atoms.

derivative **5** was thereby also unequivocally established, as were the structures of all the other compounds subsequently derived from **5**.

The indicated regiospecificity of the closure has been shown to prevail even when this direction of closure results in a product with substantial steric interaction between ring substituents.[24] Thus, the imidazopyridine-forming reactions between the substituted aminopyridines **1** and the remaining unsymmetrical α-halo carbonyl compounds (Table II) were presumed to follow the same course suggested by the literature cited earlier and supported by our own findings with α-halo ketones **2b** and **2n**.

Biological Test Methods. The compounds were evaluated for gastric antisecretory activity in two animal models (Table IV). The pylorus-ligated rat[25] was used as the primary screen to assess antisecretory activity and to identify potentially toxic compounds. In this test, the compounds were administered at a 40 mg/kg dose intraperitoneally (ip) at the time of ligation, and the reduction in acid output was measured after 4 h.

The secondary model was the inhibition of histamine-stimulated gastric acid secretion in adult mongrel dogs[26] with surgically prepared Heidenhain pouches. Compounds were first administered intravenously (iv), 0.1–5 mg/kg, and reduction in acid output, relative to the non-drug-treated control value, in the same animal was measured. Selected compounds were also tested against histamine in the Heidenhain pouch dog after oral (po) administration, 2–8 mg/kg.

The compounds were tested for gastric cytoprotective activity in the rat (Table IV). In this test, the compound was administered orally (po), 1–30 mg/kg, 30 min before oral administration of absolute ethanol. The effect of the compound against ethanol-induced lesions was determined after 1 h.

Results and Discussion

The gastric antisecretory and cytoprotective activities determined for the substituted imidazo[1,2-*a*]pyridines in the rat and dog models are described in Table IV.

Most of the compounds tested exhibited significant antisecretory activity in the pylorus-ligated rat model. However, there appears to be no significant correlation between the activity in this model and the antisecretory activity determined in the histamine-stimulated dog. The nonspecific nature of the pylorus-ligated rat model is probably responsible for the number of "false positives" identified. Agents with diverse pharmacologic activity are known to inhibit acid secretion in the pylorus-ligated rat, e.g., anticholinergic, α- and β-adrenergic, and antihistaminic agents.[27] No meaningful structure–activity relationships can be derived from the pylorus-ligated rat antisecretory data.

Inhibition of histamine-stimulated acid secretion in the dog is a more specific model that correlates well with antisecretory activity observed in man.[28] Many of the substituted imidazo[1,2-*a*]pyridines tested exhibited a significant level of antisecretory activity upon intravenous administration in the dog.

The following compounds were the most active substituted imidazo[1,2-*a*]pyridines when tested intravenously: 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**), 3-(cyanomethyl)-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]pyridine (**41**), 3-(cyanomethyl)-2-methyl-8-(3-thienylmethoxy)imidazo[1,2-*a*]pyridine (**51**), 3-(cyanomethyl)-2-methyl-8-[(phenylmethyl)amino]imidazo[1,2-*a*]pyridine (**57**), 3-(hydroxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**79**), 3-(isocyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**80**), and 2,3-dimethyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**104**).

However, only 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**), 3-(cyanomethyl)-2-methyl-8-(3-thienylmethoxy)imidazo[1,2-*a*]pyridine (**51**), and 3-(cyanomethyl)-2-methyl-8-[(phenylmethyl)amino]-imidazo[1,2-*a*]pyridine (**57**) exhibited significant levels of antisecretory activity after oral administration in the dog. The oral antisecretory ED_{50}'s determined in the dog for **27**, **51**, and **57** were 4.4, 2.7, and 6.7 mg/kg, respectively.

The cytoprotective activity of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**), 3-(cyanomethyl)-2-methyl-8-(3-thienylmethoxy)imidazo-[1,2-*a*]pyridine (**51**), and 3-(cyanomethyl)-2-methyl-8-[(phenylmethyl)amino]imidazo[1,2-*a*]pyridine (**57**) was also determined in the rat against ethanol-induced lesions. The cytoprotective activities for **27**, **51**, and **57** were found to be comparable; the oral cytoprotective ED_{50}'s determined in the rat for **27**, **51**, and **57** were 3.0, 2.0, and 2.0 mg/kg, respectively.

Structure–Activity Relationships. The histamine-stimulated dog data described in Table IV suggested the following structure–activity relationships.

R_2 Substituent. The presence of an alkyl group at the 2-position of the imidazo[1,2-*a*]pyridine ring system appeared to be necessary to maintain oral antisecretory potency. The 2-methyl-substituted analogue **27** and the 2-ethyl-substituted analogue **29** exhibited comparable oral antisecretory activity in the dog, while the oral antise-

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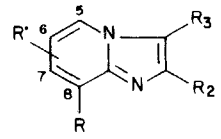
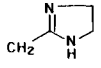
(28) Brimblecombe, R. W.; Duncan, W. A. M.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Leslie, G. B.; Parsons, M. E. *J. Pharmacol. Exp. Ther.* **1978**, *74*, 339.

Table IV. Gastric Antisecretory and Cytoprotective Activities of Substituted Imidazo[1,2-*a*]pyridines



						antisecretory act.: % inhib of acid secretion histamine-stimulated dog									
						iv dose, mg/kg					oral dose, mg/kg				
compd	R_2	R_3	R	R′	pylorus-ligated rat, 40 mg/kg, ip	5	2	1	0.1	ED_{50}^{iv}, mg/kg	8	4	2	ED_{50}^{po}, mg/kg	ED_{50}^{po}, mg/kg
5	CH_3	H	$PhCH_2O$	H	62	70	61				0				4.0
25	CH_3	$CH_2N(CH_3)_2$	$PhCH_2O$	H	*a*										
26	CH_3	$CH_2N(CH_3)_3I^-$	$PhCH_2O$	H											
27	CH_3	CH_2CN	$PhCH_2O$	H	98	99	95	88	49	0.09 (0.01–1.19)[a]	77	42	20	4.4 (2.1–14.0)[a,b]	3.0
28	H	CH_2CN	$PhCH_2O$	H	99		96	52			46		6		1.0
29	CH_3CH_2	CH_2CN	$PhCH_2O$	H	91		95		16		93	54			4.0
30	$(CH_3)_2CH$	CH_2CN	$PhCH_2O$	H	72	96					39	36			5.0
31	CH_3	CH_2CN	$2\text{-}FPhCH_2O$	H	96	97					65	34			6.0
32	CH_3	CH_2CN	$4\text{-}ClPhCH_2O$	H	90	95	58		29		70	56	30		6.6
33	CH_3	CH_2CN	$3,4\text{-}Cl_2C_6H_3CH_2O$	H	42		89				23	16			6.0
34	CH_3	CH_2CN	$3\text{-}CF_3PhCH_2O$	H	61	30					38				6.5
35	CH_3	CH_2CN	$4\text{-}t\text{-}BuPhCH_2O$	H	47	52					47	37			
36	CH_3	CH_2CN	$PhCH_2CH_2O$	H	70	95					89	47	0		6.0
37	CH_3	CH_2CN	$2\text{-}PyCH_2O$	H	56	29									2.4
38	CH_3	CH_2CN	$3\text{-}PyCH_2O$	H	46	8									7.4
39	CH_3	CH_2CN	$4\text{-}PyCH_2O$	H	51	36									2.6
40	CH_3	CH_2CN	2-thienyl-CH_2O	H	96	99		90	26		75	17			7.0
41	CH_3	CH_2CN	$PhCH_2CH_2$	H	99	96	92		74		83	3			7.0
42	CH_3	CH_2CN	H	$7\text{-}PhCH_2CH_2$	11		26								3.0
43	CH_3	CH_2CN	H	$6\text{-}PhCH_2CH_2$	8	0									2.7
44	CH_3	CH_2CN	H	$5\text{-}PhCH_2CH_2$	20			71			9				7.2
45	CH_3	CH_2CN	$4\text{-}FPhCH_2O$	H	99	95					87	35			5.0
46	CH_3	CH_2CN	$4\text{-}CF_3PhCH_2O$	H	26	59	44				25	27			3.0
47	CH_3	CH_2CN	$4\text{-}CNPhCH_2O$	H	69	71					33	0			8.0
48	CH_3	CH_2CN	$4\text{-}CH_3OPhCH_2O$	H	25		43				7	13			
49	CH_3	CH_2CN	$2,4,6\text{-}(CH_3)_3C_6H_2CH_2O$	H	49	86	22				40	0			
50	CH_3	CH_2CN	OH	H	0	0									inactive
51	CH_3	CH_2CN	3-thienyl-CH_2O	H	91	97			70		88	77	40	2.7[c]	2.0
52	CH_3	CH_2CN	3-furanyl-CH_2O	H	99	60					42				1.4
53	CH_3	CH_2CN	α-naphthyl-CH_2O	H	0	78					15				9.8
54	CH_3	CH_2CN	$4\text{-}CH_3SO_2PhCH_2O$	H	2										
55	CH_3	CH_2CN	$PhCH_2CH_2CH_2O$	H	64	80					8				4.3
56	CH_3	CH_2CN	$PhCHCH_3$	H	96	97	78				45	6			3.7
57	CH_3	CH_2CN	$PhCH_2NH$	H	98	98	96		85		75	35	oi	6.7[d]	2.0
58	CH_3	CH_2CN	$PhCH_2NCH_3$	H	94		46					23			
62	CH_3	CH_2CN	$PhCH_2S$	H	22	89					2				7.0
63	CH_3	CH_2CN	$PhCH_2SO$	H	37	26									5.0
64	CH_3	CH_2CN	$PhCH_2SO_2$	H	9	6									16.0
65	CH_3	CH_2CN	PhO	H	24	0									3.4
68	CH_3	CH_3	CH_2OPh	H	48		44				21				6.0
69	CH_3	CH_3	CH_2SPh	H	29			31							6.4
70	CH_3	CH_3	CH_2SOPh	H	42		0								
71	CH_3	CO_2Et	$PhCH_2O$	H	22	0									

72	CH_3	CO_2H	$PhCH_2O$	H	0	4							inactive
73	CH_3	$CONH_2$	$PhCH_2O$	H	42	2							
74	CH_3	$COCH_3$	$PhCH_2O$	H	57	9							
75	CH_3	CN	$PhCH_2O$	H	25	4							inactive
76	CH_3	CH_2CH_2CN	$PhCH_2O$	H	40	20							1.5
77	CH_3	$CH(CH_3)CN$	$PhCH_2O$	H	74		4				1		2.9
78	CH_3	$C(CH_3)_2CN$	$PhCH_2O$	H	57	0							12.3
79	CH_3	CH_2NC	$PhCH_2O$	H	96		94		37		94	8	2.2
80	CH_3	CH_2OH	$PhCH_2O$	H	99	80	80	57			43	20	16.0
81	CH_3	CH_2OCH_3	$PhCH_2O$	H	99	29					37		
82	CH_3	$CH_2OCH_2CH_3$	$PhCH_2O$	H	84	35					0		
83	CH_3	CH_2SCH_3	$PhCH_2O$	H	29	8							
84	CH_3	$CH_2SCH_2CH_3$	$PhCH_2O$	H	36	0							
85	CH_3	CH_2SOCH_3	$PhCH_2O$	H	0	18							
86	CH_3	$CH_2SO_2CH_3$	$PhCH_2O$	H	61	0							
87	CH_3	Cl	$PhCH_2O$	H	93	37					43		
88	CH_3	Br	$PhCH_2O$	H	26	63					0		
89	CH_3	$CH_2CO_2CH_3$	$PhCH_2O$	H	23	16							
90	CH_3	CH_2CO_2H	$PhCH_2O$	H	12	24							inactive
91	CH_3	CH_2CONH_2	$PhCH_2O$	H	28	46						0	27.0
92	CH_3	$CH_2CONHCH_3$	$PhCH_2O$	H	24	14							
93	CH_3	$CH_2CON(CH_3)_2$	$PhCH_2O$	H	37			16					
94	CH_3	CH_2CSNH_2	$PhCH_2O$	H	67	62	21				60	34	7.0
95	CH_3	$CH_2CSNHCH_3$	$PhCH_2O$	H	7	0							
96	CH_3	$CH_2CSN(CH_3)_2$	$PhCH_2O$	H	21	0							
97	CH_3	$CH_2C(NH)NH_2$	$PhCH_2O$	H	79	0							
98	CH_3		$PhCH_2O$	H	69								
99	CH_3	$CH_2O_2CCH_3$	$PhCH_2O$	H	88	87	54				24		5.5
100	CH_3	$CH_2O_2CC_4H_9$-*n*	$PhCH_2O$	H	45	96					13		
101	CH_3	$CH_2O_2CC_4H_9$-*t*	$PhCH_2O$	H	48		43				12		8.0
102	CH_3	CH_2O_2C-3-Py	$PhCH_2O$	H	87	88					0		
103	CH_3	$CH_2O_2CN(CH_3)_2$	$PhCH_2O$	H	75	23					49		
104	CH_3	CH_3	$PhCH_2O$	H	99			90			26	0	10.0
105	CH_3	CH_2CH_3	$PhCH_2O$	H	*e*		37						2.0
106	CH_3CH_2	CH_3	$PhCH_2O$	H	79		78				27		9.8
107		$CH_2CH_2CH_2$	$PhCH_2O$	H	26	0							
108		$CH_2CH_2CH_2CH_2$	$PhCH_2O$	H			24				28		
111	CF_3	CH_2CN	$PhCH_2O$	H	0	0							inactive

[a] Confidence limits, $p = 0.05$. [b] Relative potency = 1.0. [c] Relative potency (95% fiducial limits) = 0.6 (0.4–7.7). [d] Relative potency (95% fiducial limits) = 1.5 (0.1–2.1). [e] Lethalities observed in the pharmacologic evaluation of the test drug.

cretory activity of the 2-hydrogen-substituted analogue **28** was lower.

Introduction of a branched 2-alkyl substituent, the 2-isopropyl-substituted analogue **30**, resulted in a reduction of oral antisecretory activity relative to either **27** or **29**.

Interestingly, the 2-trifluoromethyl-substituted analogue **111** exhibited neither antisecretory nor cytoprotective activity.

R_8 Substituent. Substituted Phenyl. Introduction of an *o*-fluoro substituent, a *p*-chloro substituent, or a *p*-fluoro substituent into the 8-phenylmethoxy group of **27** resulted in analogues **31**, **32**, and **45**, respectively. The oral antisecretory activity of **31**, **32**, and **45** in the dog were comparable to the activity of the unsubstituted phenylmethoxy analogue **27**.

Introduction of other electron-withdrawing and electron-donating substituents into the 8-phenylmethoxy group of **27** led to less active analogues (Table IV).

Aromatic Replacement. Isosteric replacement of the 8-phenylmethoxy group in **27** with the 3-thienylmethoxy substituent resulted in analogue **51**. The oral antisecretory activity in the dog and cytoprotective activity in the rat of **51** were comparable to **27**. Interestingly, replacement of the 3-thienylmethoxy group in **51** with the isomeric 2-thienylmethoxy substituent resulted in analogue **40**, which exhibited reduced antisecretory and cytoprotective activity relative to either **51** or **27**.

Replacement of the 8-phenylmethoxy substituent in **27** with other heteroaromatic or aromatic systems led to analogues **37–39**, **52**, and **53**. These substituted imidazo[1,2-*a*]pyridines also exhibited reduced antisecretory activity relative to **27**.

Heteroatom Substitution. Substitution of the oxygen atom in the 8-phenylmethoxy substituent of **27** with a nitrogen atom resulted in the 8-(phenylmethyl)amino analogue **57**. The oral antisecretory activity in the dog and the oral cytoprotective activity in the rat of **57** were comparable to those of **27**. On the other hand, substitution of the oxygen atom in the 8-phenylmethoxy substituent of **27** with a sulfur atom led to analogue **62** that exhibited oral cytoprotective activity but only intravenous antisecretory activity. Oxidation of the sulfur atom in **62** resulted in the sulfinyl analogue **63** and the sulfonyl analogue **64**; both of the sulfur-oxidized analogues were devoid of any significant antisecretory activity.

Homologation. The 8-phenylmethoxy substituent in **27** was homologated by increasing (analogues **36** and **55**) and decreasing (analogue **65**) the number of methylene groups between the oxygen atom and the phenyl ring. In all cases, the analogues **36**, **55**, and **65** exhibited reduced antisecretory activity relative to that of **27**.

The effect of introducing branching into the 8-phenylmethoxy substituent was tested by examining the 8-(1-phenylethoxy) derivative **56** and found to result in reduced antisecretory activity as compared to that of **27**.

The effect of reversing the oxygen and methylene moieties of the 8-substituent was evaluated by comparing 2,3-dimethylated analogues **104** (8-phenylmethoxy) and **68** (8-phenoxymethyl). Although the oral antisecretory activity of **68** was comparable to that of **104**, its intravenous antisecretory activity was lower.

Replacement of the oxygen atom in **68** with sulfur and oxidation of the sulfur atom led to analogues **69** and **70**, respectively. Both compounds exhibited diminished antisecretory activity compared to that of **68**.

Heteroatom Replacement. Replacement of the oxygen atom in the 8-phenylmethoxy substituent of **27** with a methylene group resulted in the 8-(2-phenylethyl) analogue **41**. While the intravenous antisecretory activity of **41** in the dog was comparable to that of **27**, the oral antisecretory activity of **41** was much reduced.

Interestingly, the 7-(2-phenylethyl) (**42**), the 6-(2-phenylethyl) (**43**), and the 5-(2-phenylethyl) (**44**) isomers all exhibited oral cytoprotective activity in the rat comparable to that of **41**. However, only the 5-(2-phenylethyl) isomer **44** exhibited significant antisecretory activity in the dog and this could be elicited only by intravenous administration.

R_3 Substituent. The gastric antisecretory and cytoprotective properties of a significant number of substituted imidazo[1,2-*a*]pyridines containing different functional groups at the 3-position were examined (Table IV).

It became apparent after introduction of a considerable number of 3-substituents with widely varying physical and chemical properties that the cyanomethyl group was almost uniquely effective in imparting the desired levels of oral antisecretory activity combined with cytoprotective action. In view of the unconventional nature of the cyanomethyl function and a consequent dearth of information on its medicinally relevant properties, we naturally gave consideration to the design of surrogate substituents selected on the basis of their chemical (e.g., inductive effect, heteroatom content) and physical (e.g., partition coefficient) parameters. However, no thoroughly satisfactory bioequivalent of the cyanomethyl moiety could be identified. The discussion that follows focuses on key 3-substituted analogues from the more extensive list in Table IV and briefly summarizes the essential results of the effort to identify the optimal 3-substituent.

2,3-Dimethyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**104**) exhibited intravenous antisecretory activity in the dog comparable to that of **27**. However, the oral antisecretory activity of **104** was less than that of **27**. Further structural modification of **104** resulted in analogues **105–108**, which exhibited less antisecretory activity than **104** and in one case, analogue **105**, introduced undesirable side effects.

3-(Hydroxymethyl)-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (**80**), like analogue **104**, exhibited intravenous antisecretory activity in the dog comparable to that of **27**. However, the antisecretory activity of **80** was substantially reduced upon oral administration. Examination of latentiated (prodrug) forms of **80**, analogues **99–103**, did not reveal significant oral antisecretory activity.

The 3-isocyanomethyl analogue **79** exhibited intravenous antisecretory activity comparable to that of **27**. However, the oral antisecretory activity of **79** in the dog was significantly lower than that of **27**. Introduction of an α-methyl (**77**) or α,α-dimethyl (**78**) group into the 3-cyanomethyl function reduced antisecretory and cytoprotective activity. Homologation of the 3-cyanomethyl group led to analogues **75** and **76**. Decreasing (analogue **75**) or increasing (analogue **76**) the number of methylene groups between the cyano function and the imidazo[1,2-*a*]pyridine ring system resulted in less active analogues relative to **27**.

None of the 3-substituted imidazo[1,2-*a*]pyridine derivatives examined (Table IV) exhibited the oral antisecretory activity in the dog of the 3-cyanomethyl-substituted analogues: 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**), 3-(cyanomethyl)-2-methyl-8-(3-thienylmethoxy)imidazo[1,2-*a*]pyridine (**51**), and 3-(cyanomethyl)-2-methyl-8-[(phenylmethyl)amino]-imidazo[1,2-*a*]pyridine (**57**).

Although most of the substituted imidazo[1,2-*a*]-pyridines tested exhibited cytoprotective activity in the rat against ethanol-induced lesions, no clear structure–

activity relationship was evident (Table IV). However, it did appear that the cytoprotective activity of the analogue and its antisecretory activity, regardless of the route of administration, were not interdependent.

Mechanism of Action. In view of the unique (for a nonprostaglandin) profile of combined antisecretory and cytoprotective properties exhibited by this series of compounds, some comment on mechanism of action would seem to be warranted. As discussed in the introduction to this paper, the mechanism(s) of cytoprotective action in general remain indeterminate. Antisecretory mechanisms are better understood, but with respect to this series of imidazopyridines, no definitive mechanism of gastric antisecretory action has been elucidated. However, some suggestive experimental evidence has been accumulated for our focal compound **27**: in the isolated guinea pig gastric mucosa, **27** abolished the acid secretory responses to both histamine and methacholine, as well as to dibutyryl cyclic AMP. Known H_2 antagonists and anticholinergic agents are incapable of inhibiting the effect of all three types of prosecretory challenges; only omeprazole and its congeners, which are potent inhibitors of H^+/K^+-ATPase,[29] share the antisecretory profile exhibited by **27**. Thus, the antisecretory effect of **27** would appear to involve a direct action on the parietal cells distal to the primary events mediating the cholinergic and H_2 histaminergic secretory mechanisms; this action may be the inhibition of the enzyme H^+/K^+-ATPase.[7]

In conclusion, the gastric antisecretory and cytoprotective properties of a new class of antiulcer agents, the substituted imidazo[1,2-*a*]pyridines, has been described. Structure–activity studies in this series led to the identification of three compounds, **27**, **51**, and **57**, that exhibited novel and potentially promising antiulcer profiles. Of these analogues, 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, SCH 28080 (**27**), was selected for further development and clinical evaluation. Compound **27** is representative of a novel class of antiulcer agents that are neither competitive histamine (H_2) receptor antagonists nor prostaglandin analogues, yet exhibit both gastric antisecretory and cytoprotective properties.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were recorded with a Varian CFT-20 spectrometer, IR spectra were recorded with a Perkin-Elmer 221 spectrophotometer, and mass spectra were determined with a Varian MAT CH5. Microanalyses were performed by the Physical-Analytical Service Department of the Schering-Plough Corp.

Chemistry. Preparation of Substituted 2-Aminopyridines 1. With use of the procedure described by Bristol et al.,[30] phase-transfer alkylation of 2-amino-3-hydroxypyridine with 4-(methylsulfonyl)benzyl bromide,[31] 3-picolyl chloride hydrochloride, and 4-picolyl chloride hydrochloride gave 2-amino-3-[[4-(methylsulfonyl)phenyl]methoxy]pyridine (**1g**), 2-amino-3-(3-pyridylmethoxy)pyridine (**1m**), and 2-amino-3-(4-pyridylmethoxy)pyridine (**1n**), respectively (Table I).

2-Amino-3-(2-phenylethyl)pyridine (1p) and 2-Amino-5-(2-phenylethyl)pyridine (1r). 3-(2-Phenylethenyl)pyridine[33] (142 g, 0.78 mol) was suspended in 1.2 L of ethanol (95%). To this suspension was added 5 g of palladium on carbon (5%), and the mixture was shaken until 1 mol/equiv of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate washed with ethanol (95%). The solvent was removed under reduced pressure to give 3-(2-phenylethyl)pyridine,[34] 140 g (0.77 mol), 99%, bp 136–138 °C (2 mm), mp 32–33 °C, which was used without further purification.

Sodium amide was prepared from sodium (16 g, 0.69 mol) and 250 mL liquid ammonia in the presence of ferric nitrate nonahydrate (0.16 g). *N,N*-Dimethylaniline (100 mL) was added and the mixture stirred without cooling. An additional 77 mL of *N,N*-dimethylaniline was added and the mixture was warmed to ambient temperature. 3-(2-Phenylethyl)pyridine (86 g, 0.46 mol) was added dropwise and the mixture heated to 160–165 °C for 5 h. Upon cooling, 5% sodium hydroxide (75 mL), water (300 mL), and hexanes (150 mL) were added. The mixture was stirred for 0.25 h and filtered to give a yellow solid, 40 g. Fractional crystallizations from isopropyl ether and ethyl acetate gave 29.7 g (0.15 mol) (33%) of 2-amino-3-(2-phenylethyl)pyridine (**1p**) [mp 106–108 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (q, 1 H), 7.15 (m, 6 H), 6.6 (q, 1 H), 4.3 (2 H), 2.6–3.0 (m, 4 H); anal. ($C_{13}H_{14}N_2$) C, H, N] and 17.8 g (0.09 mol) (20%) of 2-amino-5-(2-phenylethyl)pyridine (**1r**) [mp 107–108 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 1 H), 7.15 (m, 6 H), 6.38 (d, 1 H), 4.3 (2 H), 2.83 (s, 4 H); anal. ($C_{13}H_{14}N_2$) C, H, N].

With use of the procedure described above, treatment of 4-(2-phenylethyl)pyridine[35] and 2-(2-phenylethyl)pyridine[35] with sodium amide at 170 and 145 °C, respectively, gave 2-amino-4-(2-phenylethyl)pyridine (**1q**) and 2-amino-6-(2-phenylethyl)-pyridine (**1s**) (Table I).

2-Amino-3-[(phenylmethyl)amino]pyridine (1t). A mixture of 2,3-diaminopyridine (21.8 g, 0.2 mol), benzaldehyde (21.2 g, 0.2 mol), and 3A molecular sieves (3 g) in 250 mL of absolute ethanol was stirred at room temperature for 72 h. Sodium borohydride (3.0 g, 0.08 mol) was added and the mixture stirred an additional 1 h. The solvent was removed under reduced pressure and the residue obtained was partitioned between water (300 mL) and chloroform (700 mL). The chloroform layer was separated and dried (Na_2SO_4). Following filtration, the chloroform was removed under reduced pressure to give a brown oil. Chromatography on silica gel eluting with chloroform/ethyl acetate (1/1 by volume) gave a brown solid. Triturating of this solid in hot 1-chlorobutane (100 mL) gave 13.9 g (0.07 mol) (36%) of 2-amino-3-[(phenylmethyl)amino]pyridine (**1t**): mp 126–129 °C; mass spectrum (70 eV), *m/e* (relative intensity) 199 (99). Anal. ($C_{12}H_{13}N_3$) C, H, N.

Preparation of α-Halo Carbonyl Intermediates 2. 3-Chloro-4-oxopentanenitrile (2n). Into a single-neck round-bottom flask (3 L) were placed 100 g (1.0 mol) of 4-oxopentanenitrile[36] and 1 L of anhydrous ether. The magnetically stirred solution was cooled to 0–5 °C, one drop of ethereal hydrogen chloride was added, and sulfuryl chloride (97%) (185 mL) was added at once. The ice bath was removed and the pale greenish-yellow solution was warmed to 20 ± 1 °C over 5 min by a hot water bath. The temperature was maintained at 20 ± 1 °C by a cold water bath for 2.5 h. The pale yellow solution was concentrated under reduced pressure (80 mmHg) in a water bath at 30 °C and carefully watched. Near the end of solvent removal, the instant the near colorless residue began to turn orange, the flask was removed quickly and diluted with 1 L of cold ether. Sulfuryl chloride (1 mL) was added, the mixture was stirred 0.25 h, and the orange solution was diluted with an additional 1 L of cold ether.

The ethereal solution was washed with 1 L of cold saturated sodium bicarbonate solution, which was in turn extracted with cold dichloromethane (2 × 1 L). The dichloromethane was evaporated under reduced pressure, and the residue obtained was dissolved in 200 mL of ether and added to the bicarbonate washed ether solution. The ethereal solution was extracted with cold 10% sodium bisulfite solution (2 × 1 L) and discarded. The sodium bisulfite solution was cooled in an ice bath and 25% sodium hydroxide was added slowly to attain pH 7 (ca. 100 mL), sodium

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bicarbonate (100 g) was added, and the solution was extracted with dichloromethane (5 × 1 L). Potassium carbonate (25 g) was added and the solution extracted with dichloromethane (1 L), and this was repeated with another 25 g of potassium carbonate and 1 L of dichloromethane. The combined extracts were dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure to give a brown-orange oil. Distillation through a Vigreux column (15 cm) gave 60.0 g (0.45 mol) (45%) of 3-chloro-4-oxopentanenitrile (**2n**): bp 83–93 °C (0.3 mm); ^1H NMR ($CDCl_3$) δ 4.47 (t, 1 H), 2.93 (m, 2 H), 2.40 (s, 3 H). This compound was used without further purification (Table II).

Preparation of Substituted Imidazo[1,2-*a*]pyridines. Method A. 8-Hydroxy-2-methylimidazo[1,2-*a*]pyridine (3). A mixture of 100 g (0.91 mol) of 2-amino-3-hydroxypyridine (**1a**) and 84.5 g (0.91 mol) of chloroacetone (**2b**) in 800 mL of ethanol was heated under reflux for 20 h. Most of the ethanol was removed by distillation and the residual material was dissolved in 800 mL of water. The aqueous solution was extracted with dichloromethane (4 × 120 mL). The dichloromethane extracts were combined and washed with water (100 mL). The aqueous solutions were combined, and the solution was adjusted to pH 11.5–12 by the addition of 50% sodium hydroxide (ca. 85 mL). The basic aqueous solution was extracted with dichloromethane (3 × 120 mL). The dichloromethane extracts were combined and washed with water (100 mL). The basic solution was cooled in ice and the solution was adjusted to pH 7 by the addition of 6 N hydrochloric acid (ca. 145 mL). After the solution was allowed to stand overnight, the solid that precipitated was isolated by filtration, washed with water, and dried. Recrystallization from dichloromethane–methanol gave 26.6 g (0.18 mol) (20%) of 8-hydroxy-2-methylimidazo[1,2-*a*]pyridine (**3**), mp 211–223 °C. Anal. ($C_8H_8N_2O$) C, H, N.

The substituted imidazo[1,2-*a*]pyridines **5–19**,**66**, **71**, **89**, and **104–109** (Table III) were prepared by using the procedure described above (method A).

Method B. 8-(Phenylmethoxy)imidazo[1,2-*a*]pyridine (4). With use of the method described by Paudler,[20] 8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**4**, Table III) was prepared.

Method C. 8-[(4-Fluorophenyl)methoxy]-2-methylimidazo[1,2-*a*]pyridine (20). To a stirred suspension of 15.0 g (0.10 mol) of 8-hydroxy-2-methylimidazo[1,2-*a*]pyridine (**3**) in 150 mL of *N*,*N*-dimethylformamide at 0–5 °C under nitrogen was added 5.2 g (0.11 mol) of sodium hydride in mineral oil (50%). After the mixture was stirred at 0 °C for 0.5 h, 15.3 g (0.11 mol) of *p*-fluorobenzyl chloride was added and the mixture heated on a steam bath for 0.5 h. Upon cooling, the reaction mixture was poured into ice and water (1 L) and stirred for 1 h. The solid that separates was isolated by filtration, washed thoroughly with water, and dissolved in chloroform (500 mL) and the chloroform solution dried (K_2CO_3). Following filtration, the chloroform was removed under reduced pressure to afford a solid, which was triturated in hexanes. Recrystallization from ethyl acetate–hexanes gave 18.0 g (0.07 mol) (70%) of 8-[(4-fluorophenyl)-methoxy]-2-methylimidazo[1,2-*a*]pyridine (**20**): mp 136–137 °C. Anal. ($C_{15}H_{13}FN_2O$) C, H, N.

The substituted imidazo[1,2-*a*]pyridines **21–24** (Table III) were prepared by using the procedure described above (method C).

Method D. 3-[(Dimethylamino)methyl]-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine Dihydrochloride (25). A mixture of 114.0 g (0.48 mol) of 2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**5**), 41.6 g (0.51 mol) of dimethylamine hydrochloride, and 15.2 g (0.51 mol) of paraformaldehyde in 450 mL of methanol was heated under reflux for 1.5 h with stirring. Thereafter the mixture was boiled open to the air for 0.75 h. Upon cooling to ambient temperature, the reaction mixture was acidified by the addition of concentrated hydrochloric acid (ca. 45 mL) and stirred for 18 h. The solid that formed was isolated by filtration and washed thoroughly with methanol and finally ether. After drying there was obtained 135.8 g (0.37 mol) (77%) of 3-[(dimethylamino)methyl]-1-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine dihydrochloride (**25**): mp 210–211 °C. Anal. ($C_{18}H_{21}N_3O{\cdot}2HCl$) C, H, N, Cl.

Method E. 2-Methyl-8-(phenylmethoxy)-3-[(trimethylammonio)methyl]imidazo[1,2-*a*]pyridine Iodide (26). To 132.5 g (0.36 mol) of 3-[(dimethylamino)methyl]-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine dihydrochloride (**5**) dissolved in 450 mL of hot water was added 50% sodium hydroxide to attain pH 11–12. The mixture was cooled to 0 °C and extracted with dichloromethane (3 × 150 mL). The extracts were combined and washed with brine (150 mL). The dichloromethane was removed under reduced pressure to give an oil (106.2 g), which was dissolved in 500 mL of ethanol. To the ethanol solution at 0 °C was added dropwise with stirring 56.8 g (0.4 mol) of methyl iodide and the reaction mixture stirred at ambient temperature overnight. The solid that formed was isolated by filtration and washed with ethanol (100 mL) and finally ether (300 mL). After drying, there was obtained 118.0 g (0.27 mol) (75%) of 2-methyl-8-(phenylmethoxy)-3-[(trimethylammonio)methyl]-imidazo[1,2-*a*]pyridine iodide (**26**): mp 158–163 °C. Anal. ($C_{19}H_{24}IN_3O$) C, H, N, I. This compound was used without further purification.

Method F. 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (27). A mixture of 15.5 g (0.035 mol) of 2-methyl-8-(phenylmethoxy)-3-[(trimethylammonio)-methyl]imidazo[1,2-*a*]pyridine iodide (**26**) and 1.8 g (0.037 mol) of sodium cyanide in 100 mL of *N*,*N*-dimethylformamide was heated on a steam bath for 1 h with stirring. The mixture was poured into ice/water (300 mL) and stirred for 1 h. The solid that formed was isolated by filtration, washed with water, and dried. Recrystallization from acetonitrile gave 6.9 g (0.025 mol) (70%) of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo-[1,2-*a*]pyridine (**27**): mp 163–166 °C; ^1H NMR ($CDCl_3$) δ 7.4 (m, 2 H), 6.65 (m, 2 H), 5.35 (s, 2 H), 3.94 (s, 2 H), 2.30 (s, 3 H). Anal. ($C_{17}H_{15}N_3O$) C, H, N.

The substituted imidazo[1,2-*a*]pyridines **28–37**, **40**, **42–49**, and **62** (Table III) were prepared by using the procedures described in methods D–F.

Method G. 3-(Cyanomethyl)-2-methyl-8-(3-pyridylmethoxy)imidazo[1,2-*a*]pyridine (38). A solution containing 5.3 g (0.026 mol) of 2-amino-3-(3-pyridylmethoxy)pyridine (1m), 4.5 g (0.34 mol) of 3-chloro-4-oxopentanenitrile (**2n**), and 2.6 g (0.026 mol) of triethylamine in 100 mL of ethanol was heated under reflux for 24 h. The volatiles were removed under reduced pressue, and the residue was dissolved in dichloromethane (100 mL). The dichloromethane solution was washed with 15% potassium carbonate (3 × 30 mL) and brine (3 × 30 mL) and dried (K_2CO_3). Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Recrystallization from acetonitrile gave 3.9 g (0.014 mol) (54%) of 3-(cyanomethyl)-2-methyl-8-(3-pyridylmethoxy)imidazo[1,2-*a*]pyridine (**38**): mp 160–163 °C. Anal. ($C_{16}H_{14}N_4O{\cdot}^1/_4H_2O$) C, H, N.

The substituted imidazo[1,2-*a*]pyridines **27**, **39**, **41**, and **54–57** (Table III) were prepared by using the procedure described in method G.

Method H. 3-(Cyanomethyl)-8-hydroxy-2-methylimidazo[1,2-*a*]pyridine (50). 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**; 40.0 g, 0.14 mol), 1,4-cyclohexadiene (50.0 g, 0.62 mol), *N*,*N*-dimethylformamide (600 mL), and palladium black (2 g) were stirred together and heated. At 45 °C a sudden exotherm occurred and the temperature rose rapidly to 75–80 °C, heating was discontinued, and the mixture was stirred for 1 h. The catalyst was removed by filtration, and the volatiles were removed in vacuo (0.1 mmHg) at 55 °C. Recrystallization from methanol–ethyl acetate gave 27.0 g (0.14 mol) (100%) of 3-(cyanomethyl)-8-hydroxy-2-methylimidazo[1,2-*a*]pyridine (**50**): mp 237–238 °C dec. Anal. ($C_{10}H_9N_3O$) C, H, N.

Method I. 3-(Cyanomethyl)-2-methyl-8-(3-thienylmethoxy)imidazo[1,2-*a*]pyridine (51). To 6.1 g (0.032 mol) of 3-(cyanomethyl)-8-hydroxy-2-methylimidazol[1,2-*a*]pyridine (**50**) in 160 mL of *N*,*N*-dimethylformamide was added 1.54 g (0.032 mol) of sodium hydride in mineral oil (50%) over 0.25 h. The mixture was stirred for 1.5 h and 5.5 g (0.032 mol) of thenyl bromide[42] was added dropwise with stirring over 1 h. After the

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addition, the mixture was stirred an additional 1 h. The volatiles were removed in vacuo, and the residue obtained was partitioned between water (100 mL) and chloroform (300 mL). The chloroform layer was separated, washed with water (100 mL), and dried ($MgSO_4$). Following filtration, the chloroform was removed under reduced pressure to give an oil. The residual oil was dissolved in chloroform (30 mL) and passed through silica gel (10 g, 60 H). Removal of the chloroform under reduced pressure gave a solid, 6.7 g. Recrystallization from ethyl acetate gave 3.2 g (0.011 mol) (34%) of 3-(cyanomethyl)-2-methyl-8-(3-thienylmethoxy)-imidazo[1,2-*a*]pyridine (**51**): mp 159–161 °C. Anal. ($C_{15}H_{13}N_3OS \cdot {}^1/_4H_2O$) C, H, N, S.

The substituted imidazo[1,2-*a*]pyridines **52** and **53** (Table III) were prepared by using the procedure described in method I.

3-(Cyanomethyl)-2-methyl-8-[*N*-methyl-*N*-(phenylmethyl)amino]imidazo[1,2-*a*]pyridine (58). To 9.8 g (0.036 mol) of 3-(cyanomethyl)-2-methyl-8-[(phenylmethyl)amino]-imidazo[1,2-*a*]pyridine (**57**) in 120 mL of *N,N*-dimethylformamide was added 5.1 g (0.036 mol) of methyl iodide and the solution was stirred at room temperature for 72 h. The volatiles were removed in vacuo, and the residue obtained was partitioned between chloroform (600 mL) and water (200 mL). The chloroform layer was separated and dried ($MgSO_4$). Following filtration, the chloroform was removed under reduced pressure to give a solid. Chromatography on silica gel eluting with chloroform gave after recrystallization from diisopropyl ether 0.4 g (0.0014 mol) (4%) of 3-(cyanomethyl)-2-methyl-8-[*N*-methyl-*N*-(phenylmethyl)-amino]imidazo[1,2-*a*]pyridine (**58**): mp 99–101 °C; mass spectrum (70 eV), calcd ($C_{18}H_{18}N_4$) 290.1531, obsd 290.1532.

***O*-(2-Methylimidazo[1,2-*a*]pyridin-8-yl) Dimethylthiocarbamate (59).** To a stirred suspension of 19.5 g (0.81 mol) of sodium hydride in mineral oil (50%) in 1 L of *N,N*-dimethylformamide was added 117 g (0.79 mol) of 8-hydroxy-2-methylimidazo[1,2-*a*]pyridine (**3**) in small portions at 5–10 °C, and the mixture was stirred an additional 2 h at room temperature. The mixture was cooled to 5 °C, and a solution of 100 g (0.81 mol) of dimethylthiocarbamoyl chloride in 250 mL of tetrahydrofuran was added dropwise over 2 h at 5–10 °C, followed by 18 h at room temperature. The solvent was removed under reduced pressure, the residue partitioned between chloroform and water, and the aqueous layer extracted with chloroform (2 × 250 mL). The combined chloroform extracts (4 L) were concentrated to 2 L and filtered through silica gel (200 g), and the column was washed with chloroform (0.5 L). The chloroform collected was removed under reduced pressure and the residue triturated with ether (3 × 500 mL) and toluene (1 × 250 mL). The solid was isolated by filtration, washed with toluene (200 mL) and acetonitrile (200 mL), and dried to give a brown solid, 52 g. Recrystallization from toluene gave 49.0 g (0.21 mol) (26%) of *O*-(2-methylimidazo-[1,2-*a*]pyridin-8-yl) dimethylthiocarbamate (**59**): mp 154–155 °C. Anal. ($C_{11}H_{13}N_3OS$) C, H, N.

***S*-(2-Methylimidazo[1,2-*a*]pyridin-8-yl) Dimethylthiocarbamate (60).** Diphenyl ether (150 mL) was heated under argon in a falsk fitted with a mechanical stirrer, a thermometer, and a flexible-neck side-arm flask containing 13.0 g (0.055 mol) of *O*-(2-methylimidazo[1,2-*a*]pyridin-8-yl) dimethylthiocarbamate (**59**). At 240 °C, **59** was added to the solvent and the mixture heated at 240–250 °C with stirring for 0.75 h. The mixture was cooled to 40–50 °C, poured cautiously into stirred hexanes (850 mL) and cooled overnight. The solid that formed was isolated by filtration, 11.6 g. Recrystallization from acetonitrile gave 7.2 g (0.031 mol) (55%) of *S*-(2-methylimidazo[1,2-*a*]pyridin-8-yl) dimethylthiocarbamate (**60**): mp 172–174 °C. Anal. ($C_{11}H_{13}N_3OS$) C, H, N.

2-Methyl-8-[(phenylmethyl)thio]imidazo[1,2-*a*]pyridine (61). A mixture of 10.0 g (0.043 mol) of *S*-(2-methylimidazo-[1,2-*a*]pyridin-8-yl) dimethylthiocarbamate (**60**) and 3.0 g (0.054 mol) of potassium hydroxide (86%) in 125 mL of ethanol was heated under reflux for 24 h. The mixture was cooled to room temperature and 6.9 g (0.055 mol) of benzyl chloride was added dropwise with stirring. The mixture was stirred at room temperature for 24 h, and the volatiles were removed under reduced pressure. The residue obtained was dissolved in chloroform (300 mL) and filtered through Celite. The chloroform was removed under reduced pressure to give a solid. Recrystallization from acetonitrile gave 5.2 g (0.020 mol) (47%) of 2-methyl-8-[(phenylmethyl)thio]imidazo[1,2-*a*]pyridine (**61**): mp 154–156 °C. Anal. ($C_{15}H_{14}N_2S$) C, H, N.

3-(Cyanomethyl)-2-methyl-8-[(phenylmethyl)sulfinyl]-imidazo[1,2-*a*]pyridine (63). To a solution of 10.0 g (0.034 mol) of 3-(cyanomethyl)-2-methyl-8-[(phenylmethyl)thio]imidazo-[1,2-*a*]pyridine (**62**) in 75 mL of dichloromethane was added 7.0 g (0.035 mol) of *m*-chloroperbenzoic acid (85%) in portions at 0–5 °C. The mixture was stirred for 0.5 h at room temperature, cooled to 0 °C, and filtered. The filtrate was diluted with dichloromethane (250 mL) and the dichloromethane solution was washed with 5% potassium carbonate and dried (K_2CO_3). Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Recrystallization from acetonitrile gave 3.8 g (0.012 mol) (35%) of 3-(cyanomethyl)-2-methyl-8-[(phenylmethyl)sulfinyl]imidazo[1,2-*a*]pyridine (**63**): mp 183–185 °C. Anal. ($C_{17}H_{15}N_3OS$) C, H, N.

3-(Cyanomethyl)-2-methyl-8-[(phenylmethyl)sulfonyl]-imidazo[1,2-*a*]pyridine (64). With use of the procedure described for the preparation of 3-(cyanomethyl)-2-methyl-8-[(phenylmethyl)sulfinyl]imidazo[1,2-*a*]pyridine (**63**) but with use of 2 equiv of *m*-chloroperbenzoic acid there was obtained 2.0 g (0.006 mol) (24%) of 3-(cyanomethyl)-2-methyl-8-[(phenylmethyl)sulfonyl]imidazo[1,2-*a*]pyridine (**64**): mp 200–201 °C. Anal. ($C_{17}H_{15}N_3O_2S$) C, H, N.

3-(Cyanomethyl)-2-methyl-8-phenoxyimidazo[1,2-*a*]-pyridine (65). To a stirred mixture of 25.0 g (0.17 mol) of 8-hydroxy-2-methylimidazo[1,2-*a*]pyridine (**3**) in 220 mL of *N*-methylpyrrolidone was added a solution of 8.8 g (0.135 mol) of potassium hydroxide (86%) in 80 mL of methanol. After 0.5 h, the solution was distilled under reduced pressure to remove 200 mL of solvent. Bromobenzene (21.1 g, 0.135 mol) and copper powder (0.5 g) was added and the reaction mixture was heated under reflux for 4 h in a nitrogen atmosphere. Upon cooling, the mixture was diluted with chloroform (500 mL) and filtered through Celite. The filtrate was washed with water (3 × 200 mL) and the chloroform removed under reduced pressure to a final volume (50 mL). Treatment of this solution with ether, filtration to remove the precipitated solids, and removal of ether under reduced pressure gave a solid. Chromatography on silica gel eluting with ethyl acetate/dichloromethane (1/1, v/v) gave 5.2 g (0.023 mol) (14%) of 2-methyl-8-phenoxyimidazo[1,2-*a*]pyridine, which was used without further purification.

With use of the procedures described in methods D–F, 2-methyl-8-phenoxyimidazo[1,2-*a*]pyridine was used to prepare from **3** 2.0 g (0.008 mol) (6%) of 3-(cyanomethyl)-2-methyl-8-phenoxyimidazo[1,2-*a*]pyridine (**65**): mp 137–138 °C. Anal. ($C_{16}H_{13}N_3O$) C, H, N.

2,3-Dimethyl-8-(hydroxymethyl)imidazo[1,2-*a*]pyridine (67). To a stirred suspension of 62.6 g (0.36 mol) of 2,3-dimethyl-8-formylimidazo[1,2-*a*]pyridine (**66**) in 400 mL of 2-propanol at 0 °C was added in portions 8.0 g (0.21 mol) of sodium borohydride. The reaction mixture was stirred at room temperature an additional 2 h. The excess sodium borohydride was decomposed by the addition of distilled water and the solution concentrated under reduced pressure at 50 °C. The residue obtained was dissolved in water and extracted with chloroform. The chloroform extracts were combined and dried (Na_2SO_4). Following filtration, the chloroform was removed under reduced pressure to give a solid. Recrystallization from 2-propanol gave 54.6 g (0.31 mol) (85%) of 2,3-dimethyl-8-(hydroxymethyl)-imidazo[1,2-*a*]pyridine (**67**): mp 155–158 °C. Anal. ($C_{10}H_{12}N_2O$) C, H, N.

2,3-Dimethyl-8-(phenoxymethyl)imidazo[1,2-*a*]pyridine (68). 2,3-Dimethyl-8-(hydroxymethyl)imidazo[1,2-*a*]pyridine (**67**; 22.9 g, 0.13 mol) was dissolved in 400 mL of dichloromethane. To the solution at 0 °C was added dropwise with stirring 19 mL of thionyl chloride. The reaction mixture was stirred for 1 h and the dichloromethane was removed under reduced pressure. The residue obtained was dissolved in distilled water, neutralized at 0 °C with ammonium hydroxide, and extracted with dichloromethane. The dichloromethane extracts were combined and dried (Na_2SO_4). Following filtration, the dichloromethane was removed

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under reduced pressure to give 8-(chloromethyl)-2,3-dimethylimidazo[1,-a]pyridine, mp 108–109 °C, which was used without further purification.

To a stirred suspension of 0.62 g (0.026 mol) of sodium hydride in mineral oil (50%) in 60 mL of *N,N*-dimethylformamide was added 2.4 g (0.026 mol) of phenol in small portions of 5–10 °C, and the mixture was stirred an additional 0.5 h at room temperature. The mixture was cooled to 5 °C and a solution of 5.0 g (0.026 mol) of 8-(chloromethyl)-2,3-dimethylimidazo[1,2-*a*]pyridine in 35 mL of *N,N*-dimethylformamide was added dropwise over 0.5 h, followed by 12 h at room temperature. The solvent was removed under reduced pressure, the residue partitioned between chloroform and water, and the aqueous layer extracted with chloroform. The chloroform extracts were combined and dried (Na_2SO_4). Following filtration, the chloroform was removed under reduced pressure to give an oil. Chromatography on silica gel eluting with ethyl acetate–chloroform (1:1, v/v) gave a solid. Recrystallization from ethyl acetate gave 3.8 g (0.015 mol) (58%) of 2,3-dimethyl-8-(phenoxymethyl)imidazo[1,2-*a*]pyridine (**68**): mp 108–109 °C. Anal. ($C_{16}H_{16}N_2O$) C, H, N.

2,3-Dimethyl-8-[(phenylthio)methyl]imidazo[1,2-*a*]pyridine (69). With use of the procedure described for the preparation of 2,3-dimethyl-8-(phenoxymethyl)imidazo[1,2-*a*]pyridine (**68**), treatment of 8-(chloromethyl)-2,3-dimethylimidazo[1,2-*a*]pyridine with thiophenol gave 3.6 g (0.013 mol) (50%) of 2,3-dimethyl-8-[(phenylthio)methyl]imidazo[1,2-*a*]pyridine (**69**): mp 78–79.5 °C. Anal. ($C_{16}H_{16}N_2S$) C, H, N, S.

2,3-Dimethyl-8-[(phenylsulfinyl)methyl]imidazo[1,2-*a*]pyridine (70). To a solution of 2.0 g (0.008 mol) of 2,3-dimethyl-8-[(phenylthio)methyl]imidazo[1,2-*a*]pyridine (**69**) in 60 mL of dichloromethane was added 1.3 g (0.008 mol) of *m*-chloroperbenzoic acid (85%) in portions at 0–5 °C. The mixture was stirred 0.5 h at room temperature, cooled to 0 °C, and filtered. The filtrate was diluted with dichloromethane (250 mL) and the dichloromethane solution washed with 5% potassium carbonate and dried (K_2CO_3). Following filtration, the dichloromethane was removed under reduced pressure to give an oil. Chromatography on silica gel eluting with ethyl acetate–chloroform (1:1, v/v) gave a solid. Recrystallization from ethyl acetate–hexanes gave 1.2 g (0.004 mol) (53%) of 2,3-dimethyl-8-[(phenylsulfinyl)-methyl]imidazo[1,2-*a*]pyridine (**70**): mp 144–146 °C. Anal. ($C_{16}H_{16}N_2SO$) C, H, N, S.

2-Carboxy-3-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (72). 2-Carboethoxy-3-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (**71**, 20.0 g, 0.065 mol), dissolved in 100 mL of ethanol containing 10% sodium hydroxide (100 mL), was heated under reflux for 2 h with stirring. Upon cooling, the solution was diluted with water (200 mL) and acidified with acetic acid. The solid that formed was isolated by filtration, washed thoroughly with water, and dried. Recrystallization from *N,N*-dimethylformamide gave 16.1 g (0.057 mol) (87%) of 2-carboxy-3-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**72**): mp 204–205 °C dec. Anal. ($C_{16}H_{14}N_2O_3$) C, H, N.

3-Carbamoyl-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (73). To 100 mL of thionyl chloride was added, in portions over 0.1 h with stirring, 13.2 g (0.043 mol) of 3-carboxy-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**72**). Dichloromethane (200 mL) was added and the reaction mixture was heated under reflux for 2 h. Upon cooling, the volatiles were removed under reduced pressure, and the residue obtained was dissolved in 500 mL of tetrahydrofuran. The tetrahydrofuran solution was treated with gaseous ammonia for 0.5 h at 0 °C and stirred at ambient temperature for 72 h. The solid that formed was isolated by filtration and partitioned between dichloromethane (300 mL) and 5% sodium hydroxide (500 mL). The dichloromethane layer was separated and dried (Na_2SO_4). Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Recrystallization from acetonitrile gave 3.7 g (0.013 mol) (30%) of 3-carbamoyl-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**73**): mp 225–227 °C. Anal. ($C_{16}H_{15}N_3O_2$) C, H, N.

3-Cyano-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (75). To a suspension of 4.5 g (0.013 mol) of 3-carbamoyl-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**73**) and 3.3 mL of pyridine in 100 mL of *p*-dioxane at 0 °C was added over 0.1 h with stirring 2.8 mL of trifluoroacetic anhydride. The reaction mixture was stirred at ambient temperature for 4.5 h and was added to a mixture of ice and water (400 mL). The solid that formed was isolated by filtration, washed thoroughly with water, and dried. Recrystallization from methanol gave 2.4 g (0.009 mol) (69%) of 3-cyano-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**75**): mp 170–171 °C. Anal. ($C_{16}H_{13}N_3O$) C, H, N.

2-Methyl-8-(phenylmethoxy)-3-(nitrilopropyl)imidazo-[1,2-*a*]pyridine (76). To 4.8 g (0.2 mol) of sodium hydride in mineral oil (50%) in 100 mL of *N,N*-dimethylformamide was added over 0.5 h 28.2 g (0.2 mol) of *tert*-butyl cyanoacetate. After stirring an additional 1.5 h, the reaction mixture was heated to 94 °C, and 17.5 g (0.04 mol) of 2-methyl-8-(phenylmethoxy)-3-[(trimethylammonio)methyl]imidazo[1,2-*a*]pyridine iodide (**26**) was added in four portions over 0.5 h. After heating an additional 0.5 h, the reaction mixture was poured into water (1 L). The aqueous solution was extracted with dichloromethane (3 × 150 mL), and the combined extracts were washed with water and dried (Na_2SO_4). Following filtration, the dichloromethane was removed under reduced pressure. The residue obtained was triturated sequentially with petroleum ether (250 mL) and ether (200 mL) and filtered to give a solid, 8.0 g. The solid (8.0 g) was combined with *p*-toluenesulfonic acid (0.5 g) in 40 mL of dichloromethane and the dichloromethane was removed under reduced pressure. The residue obtained was heated at 145–150 °C for 5.5 h. Upon cooling, the residue was dissolved in 200 mL of dichloromethane. The dichloromethane solution was washed with 5% sodium hydroxide (50 mL) and dried (Na_2SO_4). Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Chromatography on silica gel eluting with 1% methanol in dichloromethane gave after recrystallization from ethyl acetate 4.4 g (0.015 mol) (37%) of 2-methyl-8-(phenylmethoxy)-3-(nitrilopropyl)imidazo[1,2-*a*]pyridine (**76**): mp 130–131 °C. Anal. ($C_{18}H_{17}N_3O$) C, H, N.

2-[2-Methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridin-3-yl]propanenitrile (77). To a mixture of 5.6 g (0.02 mol) of 3-acetyl-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**74**) and 22.4 g (0.2 mol) of potassium *tert*-butoxide in 200 mL of *tert*-butyl alcohol and 200 mL of dimethoxyethane was added, dropwise with stirring over 3 h, a solution of 39.0 g (0.2 mol) of tosylmethyl isocyanide in 200 mL of dimethoxyethane. After the addition was complete, the solution was stirred for 1 h and the dimethoxyethane was removed under reduced pressure. The residue obtained was dissolved in water (1 L) and extracted with dichloromethane (2 × 200 mL). The dichloromethane extracts were combined and washed with 2 N hydrochloric acid (3 × 200 mL). The acidic aqueous washes were combined and basified by the addition of 50% sodium hydroxide. The basic aqueous solution was extracted with dichloromethane (2 × 100 mL), and the extracts were combined and dried (Na_2SO_4).

Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Chromatography on silica gel eluting with ethyl acetate–hexane (4/1, v/v) gave a solid, 0.8 g. Treatment of an ethyl acetate solution of this solid (0.8 g) with methanolic hydrogen chloride gave after recrystallization from 2-propanol 0.7 g (0.002 mol) (10%), of 2-[2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridin-3-yl]propanenitrile hydrochloride (**77**): mp 188–189 °C. Anal. ($C_{18}H_{17}N_3O$·HCl) C, H, N, Cl.

2-Methyl-3-(1-methyl-1-cyanoethyl)-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (78). A mixture of 16.6 g (0.06 mol) of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (**27**) and 1.43 g (0.063 mol) of sodium hydride in mineral oil (50%) in 100 mL of *N,N*-dimethylformamide was stirred at ambient temperature for 0.25 h and heated on a steam bath for 0.25 h. Upon cooling to 0 °C, the reaction mixture was treated with 8.9 g (0.063 mol) of methyl iodide. After stirring 1.5 h at ambient temperature, the reaction mixture was added to 1.43 g (0.063 mol) of sodium hydride in mineral oil (50%) in 50 mL of *N,N*-dimethylformamide. This mixture was heated on a steam bath for 0.5 h. Upon cooloing of the mixture to 0 °C, an additional 8.9 g (0.063 mol) of methyl iodide was added. The reaction mixture was stirred at ambient temperature for 1 h and added to 2.5 L of water. The aqueous solution was extracted with dichloromethane (2 × 300 mL), and the extracts were combined and dried (Na_2SO_4). Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Chromatography on silica gel eluting with dichloromethane gave after

recrystallization from isopropyl ether 1.1 g (0.004 mol) (6%) of 2-methyl-3-(1-methyl-1-cyanoethyl)-8-(phenylmethoxy)imidazo-[1,2-*a*]pyridine (**78**): mp 102–104 °C. Anal. ($C_{19}H_{19}N_3O$) C, H, N.

3-(Isocyanomethyl)-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (79). To 7.6 g (0.028 mol) of 3-(hydroxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**80**) dissolved in 250 mL of tetrahydrofuran at 0 °C was added dropwise with stirring a solution of 3.5 g (0.030 mol) of methanesulfonyl chloride and 3.87 g (0.030 mol) of *N,N*-diisopropylethylamine in 50 mL of tetrahydrofuran. After stirring at 0 °C for 1.5 h, the solution was saturated with ammonia at 0–5 °C. Methanol was added to dissolve the precipitate and the solution was left at ambient temperature overnight. The volatiles were removed under reduced pressure, and the residue was dissolved in ethyl acetate (800 mL). The ethyl acetate solution was washed with saturated sodium bicarbonate and water and dried (Na_2SO_4). Following filtration, the solvent was removed under reduced pressure to give a solid. Chromatography on silica gel eluting with 7% methanol in chloroform gave 3.5 g (0.011 mol) (40%) of 3-(aminomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine: mp 118–127 °C. Anal. ($C_{16}H_{17}N_3O$) C, H, N.

A solution of 2.2 g (0.007 mol) of 3-(aminomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine in 150 mL of ethyl formate was heated under reflux for 3 h. Upon cooling, 500 mL of ethyl acetate was added and the ethyl acetate solution washed with saturated sodium bicarbonate and water and dried (Na_2SO_4). Following filtration, the solvent was removed under reduced pressure to give 2.0 g (0.006 mol) (86%) of 3-[(formylamino)-methyl]-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine: mp 147–153.5 °C. Anal. ($C_{17}H_{17}N_3O_2$) C, H, N.

3-[(Formylamino)methyl]-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (1.0 g, 0.003 mol) was added to 60 mL of dichloromethane containing *N,N*-diisopropylethylamine (6 mL) and phosphorus oxychloride (1 mL). The mixture was stirred for 2 h and diluted with water. The dichloromethane layer was separated, washed with saturated sodium bicarbonate and water, and dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Recrystallization from acetonitrile gave 0.85 g (0.0026 mol) (85%) of 3-(isocyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (**79**): mp 156–163 °C. Anal. ($C_{17}H_{15}N_3O$) C, H, N.

3-(Hydroxymethyl)-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (80). To a suspension of 0.75 g (0.019 mol) of lithium aluminum hydride in 50 mL of anhydrous tetrahydrofuran at 0 °C was added 2.45 g (0.008 mol) of 3-carboethoxy-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**71**) in portions so that the temperature remained below 10 °C. After stirring of the mixture at 0–5 °C for an additional 1 h, 0.75 mL of water was added dropwise at 0–10 °C, followed by 0.75 mL of 15% sodium hydroxide and then 2.25 mL of water. The mixture was allowed to warm to room temperature with stirring, and the solids were removed by filtration. The solids were washed thoroughly with hot tetrahydrofuran (200 mL) and hot chloroform (4 × 150 mL). The filtrate and washings were combined and dried (K_2CO_3). Following filtration, the solvents were removed under reduced pressure to give a solid. Recrystallization from acetonitrile gave 1.34 g (0.005 mol) (65%) of 3-(hydroxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**80**); mp 132–134 °C. Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

3-(Methoxymethyl)-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (81) and 3-[(Ethylthio)methyl]-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (84). To a solution of 0.65 g (0.012 mol) of sodium methoxide and 0.81 mL (0.011 mol) of ethyl mercaptan in 40 mL of methanol was added 4.37 g (0.011 mol) of 2-methyl-8-(phenylmethoxy)-3-[(trimethylammonio)methyl]imidazo[1,2-*a*]pyridine iodide (**26**). The solution was heated under reflux for 2.5 h. Upon cooling, the solution was purged with nitrogen, and the volatiles were removed under reduced pressure. The residue was partitioned between dichloromethane (60 mL) and water (60 mL). The dichloromethane layer was saprated, washed with brine, and dried (K_2CO_3). Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Chromatography on silica gel eluting with 1% methanol in dichloromethane gave two fractions. Removal of solvent from each fraction under reduced pressure and recrystallization from diisopropyl ether gave 0.9 g (0.003 mol) (31%) of 3-(methoxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**81**) [mp 106–108 °C; anal. ($C_{17}H_{18}N_2O_2 \cdot {}^1/_2H_2O$) C, H, N] and 1.9 g (0.006 mol) (50%) of 3-[(ethylthio)methyl]-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**84**) [mp 76–78 °C; anal. ($C_{18}H_{20}N_2SO$) C, H, N, S].

3-(Ethoxymethyl)-2-methyl-8-(phenylmethoxy)imidazo-[1,2-*a*]pyridine (82). To a solution of 0.34 g (0.005 mol) of sodium ethoxide in 50 mL of ethanol was added 1.25 g (0.003 mol) of 2-methyl-8-(phenylmethoxy)-3-[(trimethylammonio)methyl]-imidazo[1,2-*a*]pyridine iodide (**26**). The solution was heated under reflux for 7 h. Upon cooling, the ethanol was removed under reduced pressure and the residue was partitioned between dichloromethane (60 mL) and 2% sodium hydroxide (60 mL). The dichloromethane layer was separated and dried (Na_2SO_4). Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Chromatography on silica gel eluting with 2% methanol in dichloromethane gave after recrystallization from 2-propanol 0.05 g (0.0002 mol) (7%) of 3-(ethoxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**82**): mp 94–96 °C. Anal. ($C_{18}H_{20}N_2O_2$) C, H, N.

2-Methyl-3-[(methylthio)methyl]-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (83). With use of the procedure described for the preparation of 3-(ethoxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**82**), treatment of 2-methyl-8-(phenylmethoxy)-3-[(trimethylammonio)methyl]-imidazo[1,2-*a*]pyridine iodide (**26**) with sodium methylmercaptide gave 5.4 g (0.018 mol) (40%) of 2-methyl-3-[(methylthio)-methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**83**): mp 88–90 °C. Anal. ($C_{17}H_{18}N_2OS$) C, H, N.

2-Methyl-3-[(methylsulfinyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (85). To a solution of 4.3 g (0.014 mol) of 2-methyl-3-[(methylthio)methyl]-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (**83**) in 200 mL of dichloromethane was added 3.1 g (0.015 mol) of *m*-chloroperbenzoic acid (85%) in portions at 0–5 °C. The reaction mixture was stirred for 2 h at room temperature, washed with 5% sodium bicarbonate, and dried (Na_2SO_4). Following filtration, the dichloromethane was removed under reduced pressure to give an oil. Chromatography on silica gel eluting with 4% methanol in dichloromethane gave after recrystallization from ethyl acetate–hexanes 4.1 g (0.013 mol) (90%) of 2-methyl-3-[(methylsulfinyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**85**): mp 125–126 °C. Anal. ($C_{17}H_{18}N_2O_2S \cdot {}^1/_2H_2O$) C, H, N.

2-Methyl-3-[(methylsulfonyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (86). With use of the procedure described for the preparation of 2-methyl-3-[(methylsulfinyl)-methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**85**) but with use of 2 equiv of *m*-chloroperbenzoic acid there was obtained 1.1 g (0.003 mol) (58%) of 2-methyl-3-[(methylsulfonyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**86**): mp 165–166 °C. Anal. ($C_{17}H_{18}N_2O_3S$) C, H, N.

3-Chloro-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (87). To 10.0 g (0.042 mol) of 2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**5**) dissolved in 200 mL of glacial acetic acid was added at once 60 mL (0.06 mol) of 0.001 M chlorine in glacial acetic acid. The mixture was stirred for 0.25 h. The solid that formed was isolated by filtration, washed thoroughly with ether, and dried. Recrystallization from methanol–ethyl acetate gave 6.9 g (0.022 mol) (52%) of 3-chloro-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**87**): mp 195–197 °C. Anal. ($C_{15}H_{13}Cl \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

3-Bromo-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (88). To 5.0 g (0.021 mol) of 2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**5**) dissolved in 120 mL of glacial acetic acid was added dropwise with stirring 4.0 g (0.025 mol) of bromine. The mixture was stirred at ambient temperature for 1 h and poured into water (300 mL). The aqueous solution was basified with 2 M sodium hydroxide and extracted with ethyl acetate (2 × 300 mL). The combined extracts were dried (Na_2SO_4). Following filtration, the solvent was removed under reduced pressure to give a solid. Chromatography on silica gel eluting with chloroform and recrystallization from 1-chlorobutane–hexanes gave 1.33 g (0.004 mol) (20%) of 3-bromo-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**88**): mp 106–107 °C. Anal. ($C_{15}H_{13}BrN_2O$) C, H, N.

3-(Carboxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (90) and 3-(Carbamoylmethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (91). A solution of 6.0 g (0.022 mol) of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**), 10 mL of 15% sodium hydroxide, 50 mL of water, and 70 mL of methanol was heated under reflux for 3 h. The methanol was removed by distillation in vacuo and the solid that formed was isolated by filtration. Recrystallization from methanol gave 2.3 g (0.008 mol) (36%) of 3-(carbamoylmethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**91**): mp 219–221 °C. Anal. ($C_{17}H_{17}N_3O_2$) C, H, N.

Acidification of the filtrate to pH 6 by the addition of 6 N hydrochloric acid gave a solid that was isolated by filtration. Recrystallization from water gave 2.1 g (0.007 mol) (34%) of 3-(carboxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**90**): mp 122–126 °C. Anal. ($C_{17}H_{16}N_2O_3$) C, H, N.

2-Methyl-3-[(methylcarbamoyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (92). A suspension of 22.0 g (0.07 mol) of 3-(carboxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**90**) and 16.0 g (0.077 mol) of *N,N'*-dicyclohexylcarbodiimide in dichloromethane (1 L) was saturated with gaseous methylamine, and the resultant mixture was stirred in a closed flask overnight. The reaction mixture was filtered and the isolated solid was washed thoroughly with dichloromethane. The dichloromethane washings and filtrate were combined, washed with 10% sodium hydroxide (1 × 100 mL) and water (2 × 150 mL), and dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Recrystallization from acetonitrile gave 6.5 g (0.021 mol) (30%) of 2-methyl-3-[(methylcarbamoyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**92**): mp 167–169 °C. Anal. ($C_{18}H_{19}N_3O_2$) C, H, N.

2-Methyl-3-[(dimethylcarbamoyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (93). With use of the procedure described for the preparation of 2-methyl-3-[(methylcarbamoyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**92**), treatment of 3-(carboxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**90**) with *N,N'*-dicyclohexylcarbodiimide and dimethylamine gave 1.2 g (0.004 mol) (22%) of 2-methyl-3-[(dimethylcarbamoyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**93**): mp 165–167 °C. Anal. ($C_{19}H_{21}N_3O_2$) C, H, N.

2-Methyl-8-(phenylmethoxy)-3-(thiocarbamoylmethyl)imidazo[1,2-*a*]pyridine (94). A stirred mixture of 1.0 g (0.004 mol) of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**) and pyridine (2 mL) was cooled to −20 °C and hydrogen sulfide was bubbled into the suspension for 0.25 h. Triethylamine (0.5 mL) was added and the tightly stoppered flask was warmed to room temperature and the mixture stirred overnight. The reaction mixture was poured into water (25 mL) and the precipitate isolated by filtration and dried. Recrystallization from *N,N*-dimethylformamide/water gave 0.62 g (0.002 mol) (50%) of 2-methyl-8-(phenylmethoxy)-3-(thiocarbamoylmethyl)imidazo[1,2-*a*]pyridine (**94**): mp 190–192 °C dec. Anal. ($C_{17}H_{17}N_3OS$) C, H, N.

2-Methyl-3-[(methylthiocarbamoyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (95). A mixture of 8.0 g (0.026 mol) of 2-methyl-3-[(methylcarbamoyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**92**) in 316 mL of dimethoxyethane was heated at 70 °C. To the warm solution was added 6.1 g (0.021 mol) of phosphorus pentasulfide. The reaction mixture was stirred at 70 °C under a nitrogen atmosphere for 8 h. Upon cooling, the solvent was removed under reduced pressure. The residue obtained was partitioned between dichloromethane (200 mL) and water (200 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 100 mL). The dichloromethane extracts were combined, washed with water (1 × 100 mL), and dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Recrystallization from acetonitrile gave 4.55 g (0.014 mol) (54%) of 2-methyl-3-[(methylthiocarbamoyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**95**): mp 215–217 °C. Anal. ($C_{18}H_{19}N_3OS$) C, H, N, S.

3-[(Dimethylthiocarbamoyl)methyl]-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (96). With use of the procedure described for the preparation of 2-methyl-3-[(methylthiocarbamoyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**95**), treatment of 2-methyl-3-[(dimethylcarbamoyl)methyl]-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**93**) with phosphorus pentasulfide gave 2.2 g (0.006 mol) (38%) of 3-[(dimethylthiocarbamoyl)methyl]-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**96**): mp 199–201 °C dec. Anal. ($C_{19}H_{21}N_3OS$) C, H, N, S.

3-(Amidinomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine Hydrochloride (97). A 600-mL capacity pressure reactor, equipped with a magnetic stirring bar, was charged with 10.0 g (0.036 mol) of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**), 7.72 g (0.014 mol) of ammonium chloride, and 175 mL of anhydrous liquid ammonia. The mixture was placed in a heating bath and maintained at 100 °C for 80 h. Upon cooling, the reactor was vented and the liquid ammonia was allowed to evaporate. The residue obtained was treated with 200 mL of ethanol and filtered and the ethanol was removed under reduced pressure. Several recrystallizations of the solid obtained from acetonitrile gave 0.84 g (0.003 mol) (8%) of 3-(amidinomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**97**): mp 191–193 °C dec. Anal. ($C_{17}H_{18}N_4O\cdot HCl\cdot {}^7/_8NH_4Cl\cdot 1.5H_2O$) C, H, N, Cl.

3-(2-Imidazolinylmethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (98). An intimate mixture of 1.0 g (0.0036 mol) of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**) and 0.84 g (0.0036 mol) of ethylenediamine *p*-toluenesulfonate[43] in an argon atmosphere was placed in an oil bath preheated to 150 °C. The molten mixture was heated at 150 °C for 1 h and at 160 °C for an additional 0.5 h. Upon cooling, the mixture was dissolved in water and basified by the addition of 2.5 N sodium hydroxide. The alkaline solution was extracted with chloroform. The combined extracts were washed with water and dried (Na_2SO_4). Following filtration, the chloroform was removed under reduced pressure to give a solid. Chromatography on silica gel eluting with acetone–methanol (60/40, v/v) gave after recrystallization from acetonitrile 0.58 g (0.0018 mol) (50%) of 3-(2-imidazolinylmethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**98**): mp 157–160 °C. Anal. ($C_{19}H_{20}N_4O$) C, H, N.

3-(Acetoxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (99). To 1.35 g (0.005 mol) of 3-(hydroxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**80**) and 0.5 g (0.005 mol) of triethylamine dissolved in 20 mL of dichloromethane was added dropwise with stirring 0.39 g (0.005 mol) of acetyl chloride. The mixture was stirred at ambient temperature for 3 h and poured into 50 mL of water. The dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The extracts were combined and dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Recrystallization from dichloromethane–ether gave 1.24 g (0.004 mol) (80%) of 3-(acetoxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**99**): mp 133–136 °C. Anal. ($C_{18}H_{18}N_2O_3$) C, H, N.

With the use of the procedure desdribed above, the substituted imidazo[1,2-*a*]pyridines **100–103** (Table III) were prepared.

3-(Hydroxymethyl)-8-(phenylmethoxy)-2-(trifluoromethyl)imidazo[1,2-*a*]pyridine (110). With use of the procedure described for the preparation of 3-(hydroxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**80**), 3-(hydroxymethyl)-8-(phenylmethoxy)-2-(trifluoromethyl)imidazo[1,2-*a*]pyridine (**110**) was prepared (Table III).

3-(Cyanomethyl)-8-(phenylmethoxy)-2-(trifluoromethyl)imidazo[1,2-*a*]pyridine (111). To a stirred suspension of 8.4 g (0.026 mol) of 3-(hydroxymethyl)-8-(phenylmethoxy)-2-(trifluoromethyl)imidazo[1,2-*a*]pyridine (**110**) in 250 mL of acetonitrile was added 4.0 g (0.026 mol) of phosphorus oxychloride. After the mixture was stirred for 2 h at ambient temperature, the volatiles were removed under reduced pressure, and the residue obtained was dissolved in 200 mL of ethanol, saturated with hydrogen chloride. The solution was heated on a steam bath for 0.25 h and the ethanol removed under reduced pressure. The residue obtained was suspended in 200 mL of acetonitrile and treated with 4.7 g (0.072 mol) of potassium cyanide and 18-crown-6

(43) Oxley, P.; Short, W. F. *J. Chem. Soc.* **1947**, 497.

(0.5 g). The mixture was stirred 18 h at room temperature and the solvent removed under reduced pressure. The residue was partitioned between chloroform and the 5% potassium carbonate. The chloroform layer was separated and dried (K_2CO_3). Following filtration, the chloroform was removed under reduced pressure to give a solid. Chromatography on silica gel eluting with dichloromethane gave, after recrystallization from ethyl acetate–hexanes, 0.6 g (0.002 mol) (8%) of 3-(cyanomethyl)-8-(phenylmethoxy)-2-(trifluoromethyl)imidazo[1,2-*a*]pyridine (111): mp 176–179 °C. Anal. ($C_{17}H_{21}F_3N_3O$) C, H, N.

Single-Crystal X-ray Analysis of 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (27). **Crystal data**: $C_{17}H_{15}N_3O$ (**27**), mol wt 277.3, monoclinic, a = 9.994 (4) Å, b = 13.629 (6) Å, c = 12.789 (5) Å, β = 122.88 (1)°, U = 1462.9 Å^3, Z = 4, d_{calcd} = 1.259 g cm^{-3}. Absorption coefficient for Cu Kα radiation (λ = 1.5418 Å), μ = 6.6 cm^{-1}. Space group $P2_1/d$ (C^4) uniquely established by the systematic absences: $0k0$ when $k \neq 2n$, $h0l$ when $l \neq 2n$.

Crystallographic Measurements. Oscillation and Weissenberg photographs (Cu Kα radiation) and precession photographs (Mo Kα radiation, λ = 0.7107 Å) provided preliminary unit-cell parameters and space group information. Intensity data from a crystal of dimensions ca. 0.14 × 0.35 × 0.70 mm were recorded on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu Kα radiation; θ–2θ scans, θ_{max} = 67°) as described previously.[44] From a total of 2697 independent measurements (hkl), those 1923 reflections for which $I > 2.0\sigma(I)$ were retained for the structure analysis and corrected for the usual Lorentz and polarization effects. Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles for 40 reflections widely separated in reciprocal space.

Structure Analysis. The structure was solved by direct methods by use of the MULTAN76[21] series of programs. Approximate positions for all non-hydrogen atoms were obtained from an E map derived by use of that set of phase angles that gave the highest combined figure-of-merit. Full-matrix least-squares refinement of atomic positional and isotropic thermal parameters reduced R[22] from a value of 0.31 for the initial model to 0.14 in a few cycles. Hydrogen atom positions were then calculated and confirmed to coincide with positive regions in a difference Fourier synthesis. Continuation of the least-squares iterations, during which hydrogen atom positional and isotropic thermal parameters were varied in addition to positional and anisotropic thermal parameters for the non-hydrogen atoms, led to convergence at R = 0.051. Final atomic positional and thermal parameters are given in Tables V–VII.[23]

Atomic scattering factors used in all structure-factor calculations were those for carbon, nitrogen, and oxygen from ref 45 and for hydrogen from ref 46. In the least-squares calculations, $\sum w\Delta^2$ ($\Delta = ||F_o| - |F_c||$) was minimized with weights, w, assigned according to the scheme: $w = 1$ when $|F_o| \leq 12.0$, and $w = 12.0/|F_o|$ when $|F_o| > 12.0$.

Biology. Pylorus-Ligated Rat. Charles River CD (outbred albino) male rats, 150–200 g of body weight, were employed for gastric secretion studies using the pylorus-ligation technique. Rats that fasted for 24 h were anesthetized with a short-acting barbiturate anesthetic, Brevital. While under surgical level anesthesia, the abdomen was opened and a ligature was securely tied around the pylorus. The stomach was returned to the abdomen and the incision was closed with autoclips. Test compounds were dissolved in a 2.5% Tween 80 solution and were administered intraperitoneally in doses of 0.5 mL/200 g of body weight. Four hours after drug administration, the animals were killed and the stomachs were removed. The contents of the stomachs were collected, and the volume was recorded. An aliquot was removed and the acid concentration was determined by automatic titration against 0.1 N NaOH to a pH end point of 7.0. The acid output (AO) was calculated by multiplying the volume of gastric content in liters times the acid concentration in milliequivalents per liter, yielding AO values in milliequivalents/4 h. Six rats were used for each test compound and eight rats for the control. Percent inhibition was calculated as follows: 100 – [100 × (mean test AO/mean control AO)]. Results were statistically analyzed by the Student's t test. The mean plus or minus standard error (SE) acid output in our control studies using this procedure was 0.61 ± 0.04 mequiv/4 h. The intrperitoneal dose of cimetidine that produced a 50% inhibition of the 4-h acid output in the pylorus-ligated rat (ED_{50}) was 26.1 (12.8 – 50.9) mg/kg.[12]

Heidenhain Pouch Dog. Mongrel dogs, weighing between 12 and 18 kg, were surgically prepared with Heidenhain pouches. Any one dog that was fasted for 18 h was used for experimentation 1 day a week. Compounds were dissolved in 3 mL of 0.4% methylcellulose/saline solutions for intravenous studies and in 5 mL for oral studies. A dose of histamine of 0.4 g/kg per min was found to produce 50–60% maximal acid output, and this dose of histamine was selected as the most appropriate stimulant. The gastric secretions were collected at 30-min intervals for 0.5–1 h before the start of the infusion of histamine and for 4 and 5 h thereafter. The volume of each 30-min collection was recorded, and an aliquot was used for titration to determine the acid concentration. The AO was calculated by multiplying the volume times the acid concentration. One hour after the start of the histamine infusion, the test compound was given either intravenously or orally by gavage. The respective 30-min acid outputs were summated for 3 h after drug administration. The AO collected over the 3-h period after drug administration was divided by the 3-h AO collected in control experiments. This value times 100 yields the percentage of control AO. Percent inhibition = 100 – percent of control. Unless otherwise noted in Table IV, each compound was tested in a single dog. Each animal served as its own control because the response to a set dose of histamine depends upon the size of the pouch, and the pouch size is not constant across animals. In our laboratories, the mean plus or minus SE for acid output in control studies was 10.56 ± 1.15 mequiv/3 h. The doses inhibiting histamine-stimulated gastric acid secretion by 50% (ED_{50}) were calculated by linear regression analysis. The intravenous dose of cimetidine required to reduce acid output to 50% of control value (ED_{50}) was 0.66 (0.16–2.60) mg/kg, while the oral dose (ED_{50}) was 1.25 (0.58–2.52) mg/kg.[12]

Cytoprotective Activity in Rats. Rats were fasted and deprived of water for 20 h prior to experiments. Each test drug in 0.4% methylcellulose/saline vehicle was given to individual rats orally 30 min prior to oral administration of 1 mL of absolute ethanol. One hour after ethanol, the rats were sacrificed and the stomachs excised. After the stomach was opened along the greater curvature, the length of each linear hemorrhagic lesion induced by ethanol was measured and totalled for each stomach. Results are expressed as the mean lesion length per rat for each treatment group. The doses inhibiting ethanol-induced lesions by 50% (ED_{50}) were calculated by linear regression analysis. The estimated oral ED_{50} values for carbenoxolone and PGE_2 against ethanol-induced lesions were 30 and less than 0.1 mg/kg,[12] respectively.

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Registry No. **1a**, 16867-03-1; **1b**, 24016-03-3; **1c**, 79707-17-8; **1d**, 81066-59-3; **1e**, 81066-60-6; **1f**, 81066-62-8; **1g**, 96428-80-7; **1h**, 81066-61-7; **1i**, 81066-65-1; **1j**, 79707-19-0; **1k**, 96428-81-8; **1l**, 81066-63-9; **1m**, 96428-82-9; **1n**, 96428-83-0; **1o**, 79707-48-5; **1p**, 91848-85-0; **1q**, 96428-84-1; **1r**, 54768-59-1; **1s**, 85230-39-3; **1t**, 79707-12-3; **1u**, 7521-41-7; **2a**, 2032-35-1; **2b**, 78-95-5; **2c**, 816-40-0; **2d**, 19967-55-6; **2e**, 814-75-5; **2f**, 815-52-1; **2g**, 815-48-5; **2h**, 694-28-0; **2i**, 822-87-7; **2j**, 1694-29-7; **2k**, 609-15-4; **2l**, 54260-84-3; **2m**, 4544-43-8; **2n**, 79707-09-8; **3**, 79707-11-2; **4**, 96428-16-9; **5**, 79707-53-2; **6**, 96428-17-0; **7**, 96428-18-1; **8**, 96428-19-2; **9**, 96428-20-5; **10**, 96428-21-6; **11**, 96428-22-7; **12**, 96428-23-8; **13**, 96444-45-0; **14**, 96444-53-0; **14**·2HCl, 96444-46-1; **15**, 96452-98-1; **16**, 96428-94-3; **16**·HCl, 96428-24-9; **17**, 85333-29-5; **17**·HCl, 85333-11-5; **18**, 85333-07-9; **19**, 85230-40-6; **20**, 79707-10-1; **21**, 96428-25-0; **22**, 96428-26-1; **23**, 96428-27-2; **24**, 96428-28-3; **25**, 79707-24-7; **25**·2HCl, 96428-29-4; **26**, 79707-59-8; **27**, 76081-98-6; **28**, 91849-01-3; **29**, 91849-06-8; **30**, 96428-30-7; **31**, 79707-26-9; **32**, 91849-02-4; **33**, 96444-47-2; **34**, 96428-31-8; **35**, 96428-32-9; **36**,

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Supplementary Material Available: Tables of fractional atomic coordinates and thermal parameters (Tables V–VII), bond lengths and angles (Table VIII), torsion angles (Table IX), and least-squares planes (Table X) and unit cell dimensions for **27** (8 pages). Ordering information is given on any current masthead page.

Psychotomimetic *N*-Methyl-*N*-isopropyltryptamines. Effects of Variation of Aromatic Oxygen Substituents

David B. Repke,*† Douglas B. Grotjahn,‡ and Alexander T. Shulgin§

P.O. Box 991, Los Altos, California 94022, P.O. Box 1279, Berkeley, California 94701, and 1483 Shulgin Road, Lafayette, California 94549. *Received May 29, 1984*

Eight *N*-methyl-*N*-isopropyltryptamines (MIPTs) possessing various aromatic oxygen substituents were prepared, characterized, and evaluated for hallucinogenic activity in man. In at least two instances (the Ar H and the Ar 5-OCH_3, **1** and **4**) the unsymmetrical nitrogen substitution led to a substantial increase in potency as well as oral activity when compared to the symmetrical dimethyl homologues. Qualitatively, 4-hydroxy-*N*-methyl-*N*-isopropyltryptamine (**2**) was the most interesting in overall effect, producing a classic hallucinogenic profile. The 5-methoxy congener **4** resulted in a state characterized by heightened conceptual stimulation lacking in visual phenomena. Other members of the series exhibited diminished effects.

Over the past two decades, considerable synthetic and pharmacological effort has been expended in studies directed to the "fine-tuning" of hallucinogenic phenethylamines and tryptamines. The basic goal of this research has been to gain a better understanding of the human structure–activity relationships of these substances. This has been accomplished in some measure by producing a succession of subtle molecular changes in a parent compound such as psilocin,[1-3] *N*,*N*-dimethyltryptamine,[4-6] or mescaline.[7-9] With the phenethylamines the principle modality of variation has been the substitution pattern of the aromatic ring.[8-11] Within the tryptamine family, however, the major chemical alterations have involved changes in the amine alkyl substituents. This has been partly due to the relative ease of synthetic manipulation at this site and also because substantial biological differences can be attributed to even minor changes in these substituents. For example, DMT and 5-methoxy-DMT are active only when administered parenterally. However, lengthening and/or branching of the *N*-alkyl groups of these molecules produces orally active compounds.[4,5,7-12] Other human and animal studies with potential tryptamine hallucinogens have shown that an abrupt loss of activity occurs with *N*,*N*-di-*n*-butyl substitution,[13,14] apparently

† Los Altos.
‡ Berkeley.
§ Lafayette.

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