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A large number of pyridinecarboxaldehyde (and ketone) *O*-substituted oximes were prepared by alkylating the oxime or by treating the parent aldehyde (or ketone) with an *O*-substituted hydroxylamine. Many of these were converted to the *N*-oxide. Screening revealed that many of these oxime ethers were active in preventing gastric ulcers in rats. Data on selected examples is given.

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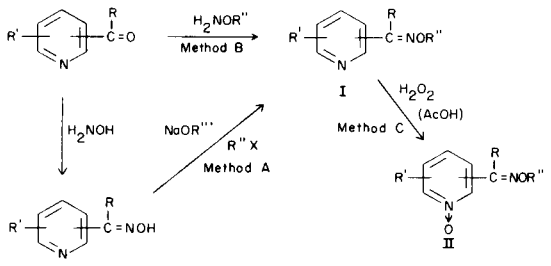
It has often been observed that the chances of finding desired biological activity is much greater in a series of compounds already known to have different (presumably unrelated) activity than in randomly chosen compounds. The pyridine oxime ether series (I and II) is a case in point. Some years ago certain of these compounds were found to be herbicides (2). Subsequently, many of the same series were found to possess central nervous system activities, especially depressant activities (3) and one, **89**, was taken to the clinic. However, the tranquilizing properties were too weak for practical use (about one-tenth to one-sixteenth of those of chlordiazepoxide). Moreover, photosensitivity was found at high doses. Still later, in our continuing search for antiulcer agents (4), compounds of this same series were discovered to prevent experimental gastric ulcers in rats. Consequently, a considerable number of new compounds of this type were prepared and selected examples were tested for prevention of exertion ulcers in rats (5).

The pyridinecarbonyl *O*-alkyloximes (I) were made by two methods (A and B) as shown in Scheme I. Many of these were converted to their *N*-oxides (II) (Method C) which were also frequently active. The compounds of this series, not previously reported, are listed in Table I.

Scheme I



Pharmacology.

Selected compounds were tested for antiulcer activity in the rat model called "exertion ulcers" as described earlier (5). In brief, the method consists of placing fasted rats in cylindrical cages rotating for three periods of 45 minutes each, separated by two rest periods of 15 minutes each. The animals were thus forced to run in these cages. They were killed two hours and 45 minutes after being placed in the cages, and found to have developed multiple gastric ulcers. These were expressed as an "ulcer index" which is the sum of: (a) percent incidence of animals with ulcers divided by 10; (b) average severity of ulcers rated from one to three; and (c) average number of ulcers per stomach. The compounds were administered orally immediately before the beginning of exertion. The results were expressed as percent change of the ulcer index by comparison to the ulcer index of the control animals. Multiple dose levels of each compound were usually adminsitered so that an ED_{50} (dose in mg./kg. reducing the ulcer index by 50%) could be estimated. Lethality (LD_{50}), the intraperitoneal dose, in mg./kg., killing 50% of the animals was determined in mice. A therapeutic ratio (LD_{50} over ED_{50}) was calculated. The higher the therapeutic ratio the more interesting the compound as regards to antiulcer application. The results are listed in Table II. From this it will be seen that numbers **2, 7, 16, 21, 22, 62, 81, 86, 89, 106,** and **111** are the most interesting having a therapeutic ratio greater than 10. In general, the *N*-oxides are less active but also less toxic than the parent amines, so that overall the *N*-oxides usually have greater therapeutic indexes. All but two of the above eleven compounds are *N*-oxides. The activities of these pyridyl oximes are of the same order as those of the *p*-aminobenzamido pyridines previously reported (4) and like them are not antichlolinergic.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and calibration against standards indicated no correction was necessary. Ir (and in many cases nmr) were determined on most of these compounds and in all cases supported the proposed structures.

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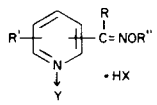
Table I
Chemistry



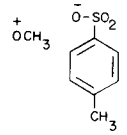
Compound No.	R	R'	Position of Oxime on ring	R''	Y (a)	HX	Method of Preparation	Crystallizing Solvent	M.p. or B.p./mm	Yield %	Molecular Formula	Analysis C	H	N	Cl
1	H	H	2	CH_3		HCl	(b)	Isopropyl Alcohol	139-140.5	59 (b)	$C_7H_9ClN_2O$	48.69 (48.70)	5.43 (5.25)	16.39 (16.23)	20.53 (20.54)
2	H	H	2	CH_3	O	Base	C	Ethyl Acetate	91.5-94	42	$C_7H_8N_2O_2$	55.12 (55.25)	5.48 (5.30)	18.31 (18.41)	
3	H	H	3	CH_3		HCl	(c)	95% Ethanol	194 dec	62 (c)	$C_7H_9ClN_2O$	48.80 (48.70)	5.37 (5.25)	16.00 (16.23)	20.50 (20.54)
4	H	H	3	CH_3	O	Base	C	Benzene	129-130	50	$C_7H_8N_2O_2$	55.37 (55.25)	5.24 (5.30)	18.18 (18.41)	
5	H	H	4	CH_3		HCl	(c)	Ethanol	216 dec	80 (c)	$C_7H_9ClN_2O$	48.87 (48.70)	5.21 (5.25)	16.18 (16.23)	20.75 (20.54)
6	H	H	3	CH_2CH_3		HCl	A	Isopropyl Alcohol	160-161	52	$C_8H_{11}ClN_2O$	51.66 (51.48)	5.69 (5.94)	14.71 (15.10)	18.95 (19.00)
7	H	H	3	CH_2CH_3	O	Base	C	Benzene--Hexane	110-112	56	$C_8H_{10}N_2O_2$	57.53 (57.82)	5.85 (6.07)	17.16 (16.86)	
8	H	H	4	CH_2CH_2Cl		HCl	A (d)	Ethanol--Ethyl Ether	151.5--152.5	43 (d)	$C_8H_{10}Cl_2N_2O$	43.24 (43.48)	4.67 (4.56)	12.42 (12.68)	
9	H	H	4	CH_2CH_2Cl	O	HCl	C	Ethanol--Ethyl Ether	104-105	88 (e)	$C_8H_{10}Cl_2N_2O_2$	40.64 (40.52)	4.01 (4.25)	12.01 (11.82)	
10	H	H	4	$CH_2CH_2CH_3$		HCl	(f)	Ethanol--Ethyl Ether	171-173	89	$C_9H_{13}ClN_2O$	53.88 (53.84)	6.41 (6.48)	13.38 (13.96)	17.64 (17.72)
11	H	H	4	$CH_2CH_2CH_3$			(g)	Ethanol--Ethyl Ether	144.5--145	74	$C_{17}H_{22}N_2O_5S$	55.52 (55.72)	5.82 (6.05)	7.61 (7.65)	
12	H	H	2	$CH_2CH{=}CH_2$		Base	A		116°/15 mm	74	$C_9H_{10}N_2O$	66.83 (66.65)	6.34 (6.22)	17.04 (17.27)	
13	H	H	2	$CH_2CH{=}CH_2$	O	HCl	C	Isopropyl Alcohol	106.5-108.5	34	$C_9H_{11}ClN_2O_2$	50.10 (50.35)	5.07 (5.17)	12.74 (13.05)	15.97 (ii) (16.52)
14	H	H	3	$CH_2CH{=}CH_2$		Base	A		66°/0.1 mm	48	$C_9H_{10}N_2O$	66.30 (66.65)	6.20 (6.22)	16.99 (17.27)	
15	H	H	3	$CH_2CH{=}CH_2$		HCl	A	Isopropyl Alcohol	138-140	91 (h)	$C_9H_{11}ClN_2O$	54.53 (54.41)	5.46 (5.58)	14.26 (14.10)	17.92 (17.85)
16	H	H	3	$CH_2CH{=}CH_2$	O	Base	C	Benzene--Hexane	74.5-76	27	$C_9H_{10}N_2O_2$	60.46 (60.66)	5.67 (5.66)	15.57 (15.72)	
17	H	H	4	$CH_2C{\equiv}CH$	O	Base	C (i)	Benzene--Hexane	84.5-85	56	$C_9H_8N_2O_2$	67.54 (67.48)	4.97 (5.03)	17.53 (17.49)	

Table I con't.

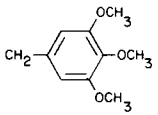
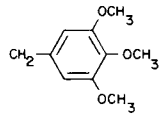
Compound No.	R	R'	Position of Oxime on Ring	R''	Y (a)	HX	Method of Preparation	Crystallizing Solvent	M.p. or B.p./mm	Yield %	Molecular Formula	Analysis C	H	N	Cl
18	H	H	3	$(CH_2)_3CH_3$		Base	A		73°/0.03 mm	70	$C_{10}H_{14}N_2O$	67.55 (67.38)	8.04 (7.92)	15.69 (15.72)	
19	H	H	3	$(CH_2)_3CH_3$		HCl	A	2-Butanone	107-109.5	86 (h)	$C_{10}H_{15}ClN_2O$	55.78 (55.94)	7.12 (7.04)	12.85 (13.05)	16.60 (16.52)
20	H	H	3	$(CH_2)_3CH_3$	O	Base	C	Benzene--Hexane	75-76.5	67	$C_{10}H_{14}N_2O_2$	61.50 (61.83)	7.33 (7.27)	14.28 (14.42)	
21	H	H	3	$C(CH_3)_3$		HCl	B	Isopropyl Alcohol--Ethyl Acetate	138-139	83	$C_{10}H_{15}ClN_2O$	56.04 (55.94)	6.94 (7.01)	12.72 (13.05)	16.53 (16.52)
22	H	H	3	$C(CH_3)_3$	O	Base	C	Ethyl Acetate	116.5-118	56	$C_{10}H_{14}N_2O_2$	61.88 (61.83)	7.33 (7.27)	14.32 (14.42)	
23	H	H	4	$CH(CH_3)CH=CH_2$		Base	A		63°/0.02 mm	43	$C_{10}H_{12}N_2O$	67.97 (68.15)	6.90 (6.87)	15.95 (15.90)	
24	H	H	4	$CH(CH_3)CH=CH_2$		HCl	A	2-Butanone	172-173		$C_{10}H_{13}ClN_2O$	56.81 (56.47)	6.02 (6.16)	13.24 (13.17)	16.74 (16.67)
25	H	H	4	$CH_2C(CH_3)=CH_2$		Base	A		77°/0.05 mm	62	$C_{10}H_{12}N_2O$	68.23 (68.15)	6.93 (6.87)	15.77 (15.90)	
26	H	H	4	$CH_2C(CH_3)=CH_2$		HCl	A	2-Butanone	126.5-127.5	75 (h)	$C_{10}H_{13}ClN_2O$	56.32 (56.47)	6.05 (6.16)	13.27 (13.17)	16.68 (16.67)
27	H	H	3	$(CH_2)_7CH_3$		Base	A		115°/0.1 mm	72	$C_{14}H_{22}N_2O$	72.05 (71.75)	9.63 (9.46)	11.71 (11.46)	
28	H	H	3	$(CH_2)_7CH_3$		HCl	A	Isopropyl Alcohol--Ethyl Acetate	113.5-115	96 (h)	$C_{14}H_{23}ClN_2O$	62.32 (62.09)	8.37 (8.56)	10.52 (10.35)	12.85 (13.09)
29	H	H	3	$(CH_2)_7CH_3$	O	Base	C	Ethyl Acetate	76.5-78	69	$C_{14}H_{22}N_2O_2$	66.98 (67.17)	8.62 (8.86)	11.01 (11.19)	
30	H	H	4	$(CH_2)_{17}CH_3$		Base	A (j)	Hexane	52.54	67	$C_{24}H_{42}N_2O$	77.02 (76.95)	11.19 (11.30)	7.35 (7.48)	
31	H	H	4	$(CH_2)_{17}CH_3$	O	Base	C	95% Ethanol	93-95	80	$C_{24}H_{42}N_2O_2$	73.47 (73.80)	10.70 (10.84)	7.19 (7.17)	
32	H	H	4			HCl	A	Ethanol--Diethyl Ether	161-162		$C_{16}H_{19}ClN_2O_4$	57.03 (56.72)	5.34 (5.65)	8.21 (8.37)	
33	H	H	4		O	Base	C	Ethyl Acetate	106-107		$C_{16}H_{18}N_2O_5$	60.56 (60.37)	5.82 (5.70)	8.98 (8.80)	
34	H	H	4	$CH_2CH=CHC_6H_5$		Base	A		155°/0.03 (k)	38	$C_{15}H_{14}N_2O$	75.52 (75.60)	5.89 (5.92)	11.88 (11.76)	
35	H	H	4	$CH(C_6H_5)_2$	O	HCl	C (1)	Isopropyl Alcohol	188-189	45	$C_{19}H_{17}ClN_2O_2$	66.98 (66.96)	4.81 (5.03)	8.02 (8.22)	9.97 (10.40)
36	H	H	4	$CH_2CH_2OC_6H_5$		Base	B (m)		142°/0.05 mm	71	$C_{14}H_{14}N_2O_2$	69.52 (69.40)	5.65 (5.82)	11.37 (11.57)	

Table I con't.

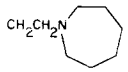
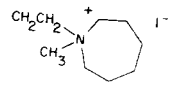
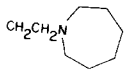
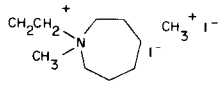
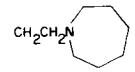
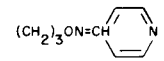
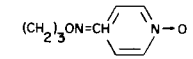
Compound No.	R	R	Position of Oxime on Ring	R''	Y (a)	HX	Method of Preparation	Crystallizing Solvent	M.p. or B.p./mm	Yield %	Molecular Formula	Analysis C	H	N	Cl
37	H	H	4	$CH_2CH_2OC_6H_5$	O	HCl	C	Isopropyl Alcohol	134-136	45	$C_{14}H_{15}ClN_2O_3$	57.04 (57.05)	4.99 (5.13)	9.67 (9.51)	11.76 (12.03)
38	H	H	2			2HCl	B (n)	Ethanol--Diethyl Ether	118-120 dec	97 (n)	$C_{14}H_{23}Cl_2N_3O$	52.51 (52.50)	7.29 (7.24)	13.18 (13.12)	
39	H	H	2				(o)	Ethanol--Diethyl Ether	119-120	99	$C_{15}H_{24}IN_3O$	46.61 (46.28)	6.17 (6.21)	11.19 (10.80)	I, 32.58 I, (32.60)
40	H	H	4			2HCl	B	Ethanol--Diethyl Ether	188-190	92 (p)	$C_{14}H_{23}Cl_2N_3O$	52.36 (52.50)	7.47 (7.24)	13.44 (13.12)	
41	H	H	4				(o)	Ethanol-Acetone	184-185	78	$C_{16}H_{27}I_2N_3O$	36.52 (36.17)	4.81 (5.12)	7.89 (7.91)	
42	H	H	4		O	2HCl	B (q)	Ethanol--Diethyl Ether	84-86	80	$C_{14}H_{23}N_3O_2$	49.73 (50.00)	7.27 (6.89)	11.72 (q) (12.50)	
43	H	H	4	CH_2COOH		Base	B	95% Ethanol	184-186 dec	66	$C_8H_8N_2O_3$	53.47 (53.33)	4.93 (4.48)	15.43 (15.55)	
44	H	H	4	CH_2COOH		Base	B (r)	Water	222 dec	73	$C_8H_8N_2O_3$	53.36 (53.33)	4.82 (4.48)	15.65 (15.55)	
45	H	H	4	CH_2COOH	O	Base	C	87% Ethanol	217-219 dec	75	$C_8H_8N_2O_4$	48.73 (48.98)	4.02 (4.11)	14.03 (14.28)	
46	H	H	4	$CH_2COOCH_2CH_3$		HCl	B (s)	Isopropyl Alcohol	188-189	85 (h)	$C_{10}H_{13}ClN_2O_3$	48.94 (49.08)	5.19 (5.35)	11.44 (11.45)	14.51 (14.99)
47	H	H	4	$CH_2COOCH_2CH_3$	O	Base	C	Ethyl Acetate--Hexane	78-79	26	$C_{10}H_{12}N_2O_4$	53.73 (53.56)	5.33 (5.40)	12.46 (12.50)	
48	H	H	4	CH_2CH_2COOH		Base	B (t)	Methanol	180-181	84	$C_9H_{10}N_2O_3$	55.79 (55.66)	5.24 (5.19)	14.28 (14.43)	

Table I con't.

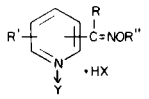
Compound No.	R	R'	Position of Oxime on Ring	R''	Y (a)	HX	Method of Preparation	Crystallizing Solvent	M.p. or B.p./mm	Yield %	Molecular Formula	Analysis C	H	N	Cl
49	H	H	4	$CH_2CH_2COOCH_2CH_3$		Base	B (u)		113°/0.03 mm	42	$C_{11}H_{14}N_2O_3$	59.45 (59.44)	6.67 (6.35)	12.70 (12.61)	
50	H	H	4	$CH_2CH_2COOCH_2CH_3$	O	Base	C	Ethyl Acetate	62-63	35	$C_{11}H_{14}N_2O_4$	55.55 (55.45)	5.79 (5.92)	11.64 (11.76)	
51	H	H	4			Base	A (v)	95% Ethanol	94-96	40	$C_{15}H_{16}N_4O_2$	63.11 (63.36)	5.78 (5.67)	20.02 (19.71)	
52	H	H	4		O	Base	C	Ethanol--Diethyl Ether	215.5-216	68	$C_{15}H_{16}N_4O_2$	56.99 (56.96)	4.94 (5.10)	17.71 (17.71)	
53	H	6-CH_3	2	$(CH_2)_2CH_3$		HCl	(w)	Ethyl Acetate	101.5-103.5	80	$C_{10}H_{15}ClN_2O$	56.32 (55.94)	7.07 (7.04)	13.19 (13.05)	16.49 (16.52)
54	H	6-CH_3	2	$CH(CH_3)_2$		Base	A		117°/15 mm	74	$C_{10}H_{14}N_2O$	67.54 (67.38)	7.76 (7.92)	15.75 (15.72)	
55	H	6-CH_3	2	$CH(CH_3)_2$		HCl	A	Ethyl Acetate	156-157.5	48 (g)	$C_{10}H_{15}ClN_2O$	55.75 (55.94)	6.98 (7.04)	12.63 (13.05)	16.63 (16.52)
56	H	6-CH_3	2	$CH(CH_3)_2$	O	HCl	C (x)	Ethyl Acetate--Diethyl Ether	100-102	60	$C_{10}H_{15}ClN_2O_2$	51.97 (52.06)	6.44 (6.55)	11.95 (12.15)	14.98 (15.37)
57	H	6-CH_3	2	$CH_2CH=CH_2$		Base	A		126°/15 mm	68	$C_{10}H_{12}N_2O$	68.14 (68.16)	6.77 (6.86)	15.90 (15.90)	
58	H	3-CH_3	4	CH_2CH_3		HCl	B	Ethanol--Diethyl Ether	170-172	80 (y)	$C_9H_{13}ClN_2O$	53.53 (53.86)	6.14 (6.53)	13.65 (13.96)	
59	H	3-CH_3	4	CH_2CH_3	O	Base	C	Ethyl Acetate--Hexane	84-86		$C_9H_{12}N_2O$	60.11 (59.98)	6.68 (6.71)	15.19 (15.55)	
60	H	3-CH_3	4	$(CH_2)_2CH_3$		HCl	A (z)	Ethanol--Diethyl Ether	159-159.5		$C_{10}H_{15}ClN_2O$	56.31 (55.94)	7.40 (7.04)	12.95 (13.05)	
61	H	3-CH_3	4	$CH_2CH=CH_2$		HCl	B (aa)	Ethanol--Diethyl Ether	141-143	61	$C_{10}H_{13}ClN_2O$	56.41 (56.47)	6.11 (6.16)	13.22 (13.17)	
62	H	3-CH_3	4	$CH_2CH=CH_2$	O	HCl	C	Ethanol--Diethyl Ether	109-111	18	$C_{10}H_{13}ClN_2O_2$	52.45 (52.52)	5.60 (5.73)	12.20 (12.25)	
63	H	3-Cl	4	$(CH_2)_2CH_3$	O	Base	(bb)	Benzene--Hexane	102.5-104	2.5 (bb)	$C_9H_{11}ClN_2O_2$	50.29 (50.36)	4.94 (5.17)	12.83 (13.05)	
64	H	6-CH=NOH	2	CH_2CH_3		Base	(cc)	Diethyl Ether	163-166	8	$C_9H_{11}N_3O_2$	55.42 (55.95)	5.66 (5.17)	21.37 (21.75)	
65	H	2-CH_3, 3-OH, 5-CH_2OH	4	$(CH_2)_2CH_3$		Base	B (dd)	Ethyl Acetate	96-97	87	$C_{11}H_{16}N_2O_3$	59.02 (58.91)	6.99 (7.19)	12.77 (12.49)	

66	H	2-CH_3, 3-OH, 5-CH_2OH	4	$(CH_2)_2CH_3$	O	Base	C	Acetic Acid--Ethyl Acetate	182-183 dec	70	$C_{11}H_{16}N_2O_4$	55.03 (54.99)	6.75 (6.71)	11.60 (11.66)	
67	H	2-CH_3, 3-OH 5-CH_2OH	4	CH_2CH_2COOH		Base	B (dd)	95% Ethanol	204 dec	80	$C_{11}H_{14}N_2O_5$·C_2H_5OH (ee)	51.64 (51.99)	6.42 (6.71)	9.68 (9.33)	
68	H	2-CH_3 3-OH 5-$CH_2OPO_3H_2$	4	$(CH_2)_2CH_3$		Base	B (ff)	Water	200-202 dec	75	$C_{11}N_{17}N_2O_6P$	42.95 (43.42)	5.49 (5.63)	9.24 (9.21)	
69	CH_3	H	3	CH_3		HCl	B	Isopropyl Alcohol	197-199.5	83	$C_8H_{11}ClN_2O$	51.54 (51.48)	5.90 (5.94)	15.03 (15.01)	19.05 (19.00)
70	CH_3	H	3	CH_3	O	Base	C	Ethyl Acetate	123-124.5	50	$C_8H_{10}N_2O_2$	57.89 (57.82)	5.97 (6.07)	17.04 (16.86)	
71	CH_3	H	4	CH_3		Base	B		56°/0.012 mm	86	$C_8H_{10}N_2O$	64.26 (63.98)	6.48 (6.71)	18.59 (18.65)	
72	CH_3	H	4	CH_3		HCl	B	Isopropyl Alcohol	186.5-187.5	87 (h)	$C_8H_{11}ClN_2O$	51.27 (51.48)	5.96 (5.94)	14.72 (15.01)	19.13 (19.00)
73	CH_3	H	2	$(CH_2)_2CH_3$		Base	A		121°/15 mm	74	$C_{10}H_{14}N_2O$	67.20 (67.38)	7.75 (7.92)	16.01 (15.72)	
74	CH_3	H	2	$(CH_2)_2CH_3$	O	HCl	C	Ethyl Acetate	78-79.5	47	$C_{10}H_{15}ClN_2O_2$	51.75 (52.06)	6.38 (6.55)	12.11 (12.15)	15.01 (15.37)
75	CH_3	H	3	$(CH_2)_2CH_3$		Base	A		69°/0.06 mm	69	$C_{10}H_{14}N_2O$	67.52 (67.38)	7.71 (7.92)	16.34 (15.72)	
76	CH_3	H	3	$(CH_2)_2CH_3$		HCl	A	2-Butanone	150-152	96 (h)	$C_{10}H_{15}ClN_2O$	55.80 (55.94)	6.87 (7.04)	13.37 (13.05)	16.67 (16.52)
77	CH_3	H	3	$(CH_2)_2CH_3$	O	Base	C	Methyl-Cyclohexane	69.5-71	75	$C_{10}H_{14}N_2O_2$	61.69 (61.83)	7.07 (7.27)	14.70 (14.42)	
78	CH_3	H	4	$(CH_2)_2CH_3$		CHCOOH(gg) ‖ CHCOOH		Isopropyl Alcohol	102-103	59	$C_{14}H_{18}N_2O_5$	56.98 (57.13)	5.88 (6.17)	9.54 (9.52)	
79	CH_3	H	4	$CH_2CH{=}CH_2$		Base	A		68°/0.02	47	$C_{10}H_{12}N_2O$	68.27 (68.16)	6.96 (6.87)	15.86 (15.90)	
80	CH_3	H	4	$CH_2CH{=}CH_2$		CHCOOH(hh) ‖ CHCOOH		Diethyl Ether	110-111°	86 (h)	$C_{14}H_{16}N_2O_5$	57.61 (57.53)	5.69 (5.52)	9.98 (9.59)	

(a) Indicates no group on the N. (b) Prepared in indicated yield from known free base (6) in 2-propanol by acidification with anhydrous hydrogen chloride. (c) Prepared in indicated yield from known free base (6) in absolute ether by acidification with ethanolic hydrogen chloride. The slightly low H analysis on compound **5** is the best obtained. (d) Prepared by Method A using sodium methoxide and 2-chloroethyl tosylate on 4-pyridinecarboxaldehyde oxime. The yield is calculated for distilled free base, b.p. 100-110°/0.2 mm. A sample was converted to the hydrochloride **8** for analysis. (e) The yield was calculated for impure hydrochloride, m.p. 87-91°. Repeated recrystallizations were required to obtain the pure hydrochloride. (f) Prepared by Dr. Alan J. Lemin in these laboratories from known free base (2) in ether by acidification with anhydrous hydrogen chloride. (g) 4-Formyl-1-methoxypyridinium *p*-toluenesulfonate *O*-propyloxime. See specific preparation in Experimental. (h) Yield calculated from distilled free base. (i) Prepared by method C from 4-pyridinecarboxaldehyde *O*-propargyloxime [P. L. Carter, G. T. Newbold and D. R. Saggers, South African Patent 68-02,699 (1968); *Chem. Abstr.*, **71**, P3143a (1969)]. (j) The crude product was purified by conversion to the hydrochloride and recrystallization from 2-propanol. The still impure product was converted back to free base and recrystallized first from aqueous methanol and finally from hexane. (k) The distilled free base was an oil which crystallized on standing, m.p. 53-55°. (l) Prepared by Method C from 4-pyridinecarboxaldehyde ***O*-benzhydryloxime** (3a). (m) Prepared by Method B using *O*-(2-phenoxyethyl)hydroxylamine hydrochloride (3a). (n) Prepared by Method B using 1-[2-aminooxyethyl)azepine [L. A. Paquette, *J. Org. Chem.*, **29**, 3543 (1964)]. The yield is based on distilled free base, b.p. 147°/0.35 mm, n_D^{25} = 1.5410. This was converted to the dihydrochloride for analysis. (o) The methiodide salts were prepared by refluxing the free bases of **38** and **40** with an excess of methyl iodide in ethanol for 40 minutes. After four recrystallizations it was found by analysis that **38** had given a monomethiodide (**39**) and **40** had given a dimethiodide (**41**). (p) The yield is based on distilled free base, b.p. 148°/0.25 mm, n_D^{25} = 1.5446. This was converted to the hydrochloride for analysis. (q) Prepared by Method B from 4-pyridinecarboxaldehyde *N*-oxide and 1-(2-aminooxyethyl)azepine (*loc. cit.*, footnote (n)] and converted to the dihydrochloride in ether with ethanolic hydrogen chloride. Although other specifications were good a satisfactory N analysis was not obtained. (r) Prepared by Method B in water at room temperature using the appropriate aldehyde and (aminoxy)acetic acid hemihydrochloride. (s) The free base was prepared by Method B and distilled, b.p. 100°/0.05 mm, yield 59%. (t) Prepared in water from 4-pyridinecarboxaldehyde and β-aminoxypropionic acid hydrochloride at room temperature. (u) Prepared in water using ethyl β-aminooxypropionate at room temperature. (v) Prepared by Method A using 1,3-dibromopropane. (w) Prepared from the free base (2) in ethyl acetate by acidification with ethanolic hydrogen chloride. (x) Prepared from **55** by Method C and converted to the hydrochloride in ethyl acetate with ethereal hydrogen chloride. (y) The yield is based on distilled free base, b.p. 92°/1.8 mm, n_D^{25} = 1.5269. This was converted to the hydrochloride for analysis. (z) Crude free base has been reported, prepared by Method B (3c). (aa) Prepared by Method B using *O*-allylhydroxylamine hydrochloride [A. C. Cope and P. H. Towle, *J. Am. Chem. Soc.*, 71, 3427 (1949)]. (bb) The overall yield from 3-chloro-4-acetoxymethylpyridine was 2.5% (see Experimental). (cc) Prepared by Mr. Gay Smith in these laboratories (see Experimental). (dd) Prepared by Method B from pyridoxal hydrochloride in water at room temperature. The product separated from the reaction mixture on standing in the refrigerator overnight. (ee) Ir and analysis show this to be an ethanol solvate. A sample was rigorously dried in high vacuum. Calcd. for $C_{11}H_{14}N_2O_5$: N, 11.02. Found: 11.00. (ff) Prepared by Method B from pyridoxal-5-phosphate (from Farmochimica Cutolo-Colosi, Naples, Italy) in water at room temperature. The product separated from the reaction mixture. Calcd. for $C_{11}H_{17}N_2O_6P$: P, 10.18. Found: P, 10.15. (gg) The maleic acid salt was prepared from distilled free base (3d). (hh) The maleic acid salt was prepared from **79** in ether. (ii) The best Cl analysis obtained was slightly low, probably because of the very hydroscopic nature of this salt.

Table II

Antiulcer Activity



Compound No. (a)	R	R'	Position os Oxime on Ring	R''	Y (b)	HX	LD_{50}	ED_{50}	Therapeutic Ratio
1	H	H	2	CH_3		HCl	316	50	6.3
2	H	H	2	CH_3	O	Base	1000	87	11.5
3	H	H	3	CH_3		HCl	300	100	3.0
4	H	H	3	CH_3	O	Base	1000	inact.	
81 (6)	H	H	4	CH_3		Base	650	35	18.6
82 (3c)	H	H	4	CH_3	O	Base	650	inact.	
6	H	H	3	CH_2CH_3		HCl	316	50	6.3
7	H	H	3	CH_2CH_3	O	Base	562	55	10.2
93 (7)	H	H	4	CH_2CH_3		Base	200	40	5.0
84 (3c)	H	H	4	CH_2CH_3	O	Base	650	75	8.7
85 (2)	H	H	2	$(CH_2)_2CH_3$		Base	416	65	6.4
86 (3c)	H	H	2	$(CH_2)_2CH_3$	O	Base	533	50	10.7
87 (2)	H	H	3	$(CH_2)_2CH_3$		Base	200	inact.	
88 (3c)	H	H	3	$(CH_2)_2CH_3$	O	Base	316	50	6.3
10	H	H	4	$(CH_2)_2CH_3$		HCl	237	50	4.7
89 (3c)	H	H	4	$(CH_2)_2CH_3$	O	Base	650	50	13.0
90 (3c)	H	H	3	$CH(CH_3)_2$	O	Base	256	50	5.1
91 (3c)	H	H	4	$CH(CH_3)_2$	O	Base	300	90	3.3
12	H	H	2	$CH_2CH{=}CH_2$		Base	562	70	8.0
13	H	H	2	$CH_2CH{=}CH_2$	O	HCl	562	inact.	
15	H	H	3	$CH_2CH{=}CH_2$	O	HCl		45	
16	H	H	3	$CH_2CH{=}CH_2$	O	Base	562	50	11.2
92 (8)	H	H	4	$CH_2CH{=}CH_2$		Base	600	55	5.5
93 (3c)	H	H	4	$CH_2CH{=}CH_2$	O	HCl	650	80	8.1
17	H	H	4	$CH_2C{\equiv}CH$	O	Base	650	100	6.5
19	H	H	3	$(CH_2)_3CH_3$		HCl	178	50	3.5
20	H	H	3	$(CH_2)_3CH_3$	O	Base	178	50	3.6
94 (9)	H	H	4	$(CH_2)_3CH_3$		Base	200	60	3.3
95 (3c)	H	H	4	$(CH_2)_3CH_3$	O	Base	200	50	4.0
94 (c)	H	H	4	$CH(CH_3)CH_2CH_3$		Base	200	75	2.7
21	H	H	3	$C(CH_3)_3$		HCl	422	30	14.1
22	H	H	3	$C(CH_3)_3$	O	Base	562	45	12.5
23	H	H	4	$CH(CH_3)CH{=}CH_2$		Base	200	60	3.3
97 (3c)	H	H	4	$CH(CH_3)CH{=}CH_2$	O	HCl	533	75	7.1
25	H	H	4	$CH_2C(CH_3){=}CH_2$		Base	533	75	7.1
98 (3c)	H	H	4	$(CH_2)_4CH_3$	O	Base	167	30	5.6
99 (2)	H	H	2	$(CH_2)_2$ | $CH(CH_3)_2$		Base	200	inact.	
100 (2)	H	H	3	$(CH_2)_2$ | $CH(CH_3)_2$		Base	167	55	3.0
101 (3c)	H	H	3	$(CH_2)_2$ | $CH(CH_3)_2$	O	Base	200	45	4.4
102 (c)	H	H	4	$(CH_2)_5CH_3$		Base	200	75	2.7
103 (3c)	H	H	4	$(CH_2)_5CH_3$	O	Base	167	40	4.2
104 (c)	H	H	4	C_6H_{11} (d)		Base	1000	inact.	

Table II con't.

Compound No. (a)	R	R'	Position of Oxime on Ring	R''	Y (b)	HX	LD_{50}	ED_{50}	Therapeutic Ratio
28	H	H	3	$(CH_2)_7CH_3$		HCl	422	60	7.0
29	H	H	3	$(CH_2)_7CH_3$	O	Base	178	80	2.2
105 (c)	H	H	4	$(CH_2)_7CH_3$		Base	422	50	8.4
106 (3c)	H	H	4	$(CH_2)_{11}CH_3$	O	Base	650	50	13.0
30	H	H	4	$(CH_2)_{17}CH_3$		Base	1000	inact.	
31	H	H	4	$(CH_2)_{17}CH_3$	O	Base	1000	inact.	
107 (3a)	H	H	4	$CH(C_6H_5)_2$		HCl	650	80	8.1
53	H	6-CH_3	2	$(CH_2)_2CH_3$		HCl	562	100	5.6
55	H	6-CH_3	2	$CH(CH_3)_2$		HCl	562	inact.	
56	H	6-CH_3	2	$CH(CH_2)_2$	O	HCl	562	125	4.5
57	H	6-CH_3	2	$CH_2CH{=}CH_2$		Base	562	90	6.2
108 (2)	H	6-CH_3	2	$(CH_2)_2CH(CH_3)_2$		Base	300	inact.	
58	H	3-CH_3	4	CH_2CH_3		HCl	178	70	2.5
60	H	3-CH_3	4	$(CH_2)_2CH_3$		HCl	562	85	6.6
61	H	3-CH_3	4	$CH_2CH{=}CH_2$		HCl	178	55	3.2
62	H	3-CH_3	4	$CH_2CH{=}CH_2$	O	HCl	1000	60	16.7
72	CH_3	H	4	CH_3		HCl	422	> 90	
109 (3d)	CH_3	H	4	CH_3	O	Base	650	120	5.4
73	CH_3	H	2	$(CH_2)_2CH_3$		Base	562	inact.	
74	CH_3	H	2	$(CH_2)_2CH_3$	O	HCl		inact.	
76	CH_3	H	3	$(CH_2)_2CH_3$		HCl	316	100	3.1
77	CH_3	H	3	$(CH_2)_2CH_3$	O	Base	178	45	4.0
110 (3d)	CH_3	H	4	$(CH_2)_2CH_3$		Base	200	50	4.0
111 (3d)	CH_3	H	4	$(CH_2)_2CH_3$	O	Base	625	54	12.0
80	CH_3	H	4	$CH_2CH{=}CH_2$		$(=CHCOOH)_2$	562	63	8.9

(a) Number from Table I unless other reference is given in parentheses. (b) O indicates *N*-oxide if present. (c) Sample obtained from Dr. F. Roschig G.M.b.H., Ludwigshafter (Rhine), Germany. (d) Cyclohexyl.

The following examples are representative of the methods used to prepare these compounds. See Table I for details and variations from the examples.

Method A. 3-Pyridinecarboxyaldehyde *O*-Ethyloxime Hydrochloride (**6**).

To a rapidly stirred solution of sodium ethoxide, from 11.5 g. (0.1 mole) of sodium and 400 ml. of absolute ethanol, was added, dropwise, 61.0 g. (0.5 mole) of 3-pyridinecarboxaldehyde oxime. Then 54.0 g. (0.5 mole) of bromoethane was added during 10 minutes and the mixture was stirred under reflux for 2.5 hours. After cooling the mixture was poured into 1.5 l. of water and extracted with methylene chloride. The extract was washed with water and saturated sodium chloride, dried over magnesium sulfate, filtered, and evaporated. This free base was distilled yielding 56.6 g. (75.5%) of nearly colorless oil, b.p. 52°/0.06 mm. Ir, nmr and analyses support the structure but indicate appreciable impurities.

This free base was dissolved in absolute ether and a slight excess of hydrogen chloride gas was passed in. The resulting crystalline solid (73 g.) was recrystallized twice from 2-propanol yielding 48.3 g. (52%, overall) of white crystals, m.p. 160-161°.

Method B. 3-Pyridinecarboxaldehyde *O*-*t*-Butyloxime Hydrochloride (**21**).

To a solution of 14.7 g. (0.137 mole) of 3-pyridinecarboxaldehyde and 17.1 g. (0.137 mole) of *O*-*t*-butylhydroxylamine hydrochloride, in 125 ml. of ethanol was added, with stirring, 17.2 g. (0.21 mole) of sodium acetate in 55 ml. of water. After refluxing for 4 hours the mixture was poured into 350 ml. of ice-water and the oily product was extracted with ether. After drying over magnesium sulfate, filtering and evaporating, the product was distilled yielding 21.1 g. (85%) of colorless oil, b.p. 109°/15 mm. Ir supported the structure but analysis indicated it was slightly impure.

A solution of 11 g. (0.062 mole) of this free base in absolute ether was acidified with a slight excess of hydrogen chloride gas giving 13.0 g. (98% based on the free base) of white crystals, m.p. 136-138°.

Method C. 3-Pyridinecarboxaldehyde *O*-Ethyloxime 1-Oxide (**7**).

A solution of 7.5 g. (0.05 mole) of the above free base of **6** and 8.1 ml. of 30% hydrogen peroxide in 41 ml. of acetic acid was kept at 70° overnight and then evaporated *in vacuo* below 55°. Water was added and evaporated, then ethanol was added and evaporated, and the residue was dissolved in 5% aqueous sodium bicarbonate. The product was extracted with several protions of methylene chloride and dried over magnesium sulfate. Filtration and evaporation gave 7.1 g. of solid which was recrystallized from benzene-hexane yielding 4.62 g. (55.5%) of white crystals, m.p. 110-112°.

4-Formyl-1-methoxypyridinium *p*-Toluenesulfonate *O*-Propyloxime (**11**).

A mixture of 5.0 g. (0.0278 mole) of 4-pyridinecarboxaldehyde *O*-propyloxime 1-oxide (free base of **10**) (**2**) and 5.2 g. (0.0278

mole) of methyl *p*-toluenesulfonate was heated at 100-110° for 30 minutes. The product was recrystallized from ethanol-ether and dried yielding 7.5 g. (73.5%) of white needles, m.p. 144.5-145°

3-Chloro-4-methylpyridine *N*-Oxide (**112**).

A solution of 33.7 g. (0.264 mole) of 3-chloro-4-methylpyridine and 45 ml. of 30% hydrogen peroxide in 250 ml. of acetic acid was heated overnight at 70°. The solvent was evaporated *in vacuo*, water was added and evaporated *in vacuo* then ethanol was added and evaporated. The crystalline residue was recrystallized from ethanol-ether yielding 32.6 g. of white solid, m.p. 125.5-127.5°. A sample for analysis had m.p. 128-128.5°.

Anal. Calcd. for C_6H_6ClNO: C, 50.19; H, 4.21; N, 9.76. Found: C, 50.10; H, 4.35; N, 9.71.

3-Chloro-4-acetoxymethylpyridine (**113**).

A solution of 190 g. (1.32 moles) of (**112**) and 600 ml. of acetic anhydride in 400 ml. of dioxane was cautiously stirred and warmed until an exothermic reaction started and the solution turned red. The flask was immediately cooled with an ice-methanol bath. After the reaction had subsided the solution was stirred under reflux for 2 hours and the solvent evaporated *in vacuo*. The product was distilled, b.p. 111°/8 mm, yielding 78 g. (32%) of pale yellow liquid. This was crystallized from hexane giving 17.5 g. of white crystals, m.p. 47-52°. A sample for analysis was recrystallized from benzene-hexane, m.p. 53-54°.

Anal. Calcd. for $C_8H_8ClNO_2$: C, 51.76; H, 4.34; N, 7.55. Found: C, 51.68; H, 4.06; N, 7.38.

3-Chloro-4-pyridinecarboxaldehyde *O*-Propyloxime *N*-Oxide (**63**).

A solution of 91 g. (0.49 mole) of (**113**) and 93 ml. of 30% hydrogen peroxide in 500 ml. of acetic acid was heated at 70° overnight. The solvent was removed *in vacuo*. Water was added and evaporated *in vacuo* followed by similar treatment with absolute ethanol. The resulting crude *N*-oxide was treated with 300 ml. of acetic anhydride and refluxed for 1.5 hours. Removal of the excess acetic anhydride gave crude 3-chloro-4-(diacetoxymethyl)pyridine as a brown oil. This was hydrolyzed to the 3-chloro-4-pyridinecarboxaldehyde by treatment with 300 ml. of 6*N* hydrochloric acid at 90° for 1.5 hours. Most of the excess hydrochloric acid was evaporated *in vacuo* and the residue was basified with ice-cold dilute sodium hydroxide and extracted with methylene chloride. The extract was dried, filtered and evaporated. Distillation of the residue yielded 6 g. (8.6%) of pale yellow liquid, b.p. 93°/6 mm., showing the aldehyde band in ir. This was converted to (**63** Table I) by methods B and C. The overall yield from **113** was 2.5%.

2,6-Pyridinedicarboxaldehyde, *O*-Ethyloxime, Oxime (**64**).

To a solution of 66.08 g. (0.4 mole) of 2,6-pyridinedicarboxaldehyde dioxime and 46.4 g. of sodium hydroxide in 280 ml. of water was slowly added with stirring and cooling 128 ml. of diethyl sulfate. After standing at room temperature overnight the mixture was extracted with ether and the extract was washed with water. After drying and evaporating a solid was obtained. Recrystallization from ether yielded 7 g. (8%) of white solid, m.p. 163-166°. Ir and analysis showed this to be the *O*-monoethyloxime (**64**).

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