activity 30–40 Ci/mmol; Du Pont NEN, Boston, MA) was measured as previously described.[10] Crude synaptic membranes were prepared from male Sprague-Dawley rats (Crl: CDBR) and pretreated with 0.04% Triton X-100 to remove endogenous excitatory amino acids. An aliquot (200–400 μg/mL) of membrane protein was incubated in 50 mL Tris-HCl buffer, pH 8.0, together with a final concentration of 10 nM [^{3}H]CGS 19755. Nonspecific binding was determined in the presence of 1 mM L-glutamate. Incubation was continued for 15 min at 4 °C and bound radioactivity isolated by vacuum filtration over Whatman GF/B glass fiber filters. Under these conditions, [^{3}H]CGS 19755 showed 80–85% specific binding to a single site with a K_d value of 24 nM.[10] Compounds were run at 5–10 concentrations in triplicate for IC_{50} determinations.

Other Excitatory Amino Acid Receptor Binding. Binding of CGS 19755 and its analogues to quisqualate and kainate receptors was measured by using [^{3}H]AMPA and [^{3}H]kainate as previously described.[11,12]

Behavioral Studies: NMDA Convulsion Model. Male mice (Crl: CF1BR; 18–22 g; Charles River, Wilmington, MA) were administered test compounds 30 min ip before testing for impairment of traction reflex as assessed by the ability of the mice to grasp a thin wire with their forepaws. Mice that did not bring their hindpaws up to the wire within 10 s were considered to have "lost traction", an indication of muscle relaxation.[8] Immediately following the traction test, mice were administered NMDA (154 mg/kg ip) and observed for a 30-min period for the appearance of tonic convulsions. ED_{50} values for seizure protection and traction deficit were determined by probit analysis.[24]

Acknowledgment. We acknowledge Dr. Frank Clarke for X-ray analysis of **1a** and the Analytical Support Group for spectra and analysis.

Registry No. AP-5, 76726-92-6; AP-7, 85797-13-3; CPP, 108549-42-4; TMSCN, 7677-24-9; TBDMSCl, 18162-48-6; **1a**, 110347-85-8; **1b**, 113190-92-4; **1c**, 121570-54-5; **1d**, 121524-85-4; **1e**, 113229-88-2; **1f**, 121524-86-5; **1g**, 121524-87-6; **1h**, 113229-64-4; **1i**, 121570-55-6; **1j**, 121570-56-7; **1k**, 113229-89-3; **1l**, 121570-57-8; **1m**, 121570-58-9; **1n**, 121524-88-7; **2a**, 77047-42-8; **2a** (*N*-oxide), 35469-52-4; **2d**, 121524-89-8; **2e**, 121524-90-1; **3a**, 118892-60-7; **4a**, 113190-80-0; **5a**, 113190-81-1; **5b**, 121541-51-3; **6i**, 59663-96-6; **6l**, 117423-32-2; **7i**, 117423-46-8; **7l**, 121524-92-3; **8i**, 121524-91-2; **9m**, 117423-38-8; AP-5, 76726-92-6; AP-7, 85797-13-3; CPP, 108549-42-4; NMDA, 6384-92-5; TMSCN, 7677-24-9; TBDMSCl, 18162-48-6; $Ph_3P{=}CHCHO$, 2136-75-6; $CH_2(PO_3Et_2)$, 1660-94-2; diethyl phosphite, 762-04-9; 4-picolyl chloride, 10445-91-7; imidazole, 288-32-4; 4-pyridylcarbinol, 586-95-8; 2-cyano-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]pyridine, 117423-43-5; *cis*-ethyl 1-(*tert*-butoxycarbonyl)-4-[1-(*E*)-3-(diethylphosphonoprop-2-enyl)]piperidine-2-carboxylate, 121524-93-4.

Supplementary Material Available: A table listing analysis and melting point data for **4a,b,f,g**, **6i**, and **1b–n** (2 pages). Ordering information is given on any current masthead page.

(24) Finney, D. J. *Probit Analysis*; Cambridge University Press: Cambridge, 1962.

Benzo- and Pyrido-1,4-oxazepin-5-ones and -thiones: Synthesis and Structure–Activity Relationships of a New Series of H_1 Antihistamines

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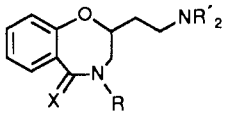
A series of novel benzo- and pyrido-1,4-oxazepinones and -thiones which represents a new structural class of compounds possessing H_1 antihistaminic activity was synthesized, and the SARs were evaluated. The antihistaminic activity was determined by blockade of histamine-induced lethality in guinea pigs. The sedative potential was determined by comparison of the EEG profiles of the compounds with those of known sedating and nonsedating antihistamines. Several of the compounds were shown to possess potent H_1 antihistaminic activity and to be free of the cortical slowing with synchronized waves and spindling activity found in the EEG of sedative antihistamines. One compound, 2-[2-(dimethylamino)ethyl]-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione (rocastine) is currently undergoing clinical evaluation as a nonsedating H_1 antihistamine.

In recent years, the search for an H_1 antihistamine which would be free from sedative side effects has been in progress. General screening of some novel compounds synthesized in these laboratories detected several compounds of the general structure I which possessed weak H_1 antagonism when tested in vitro against histamine-induced contractions of the guinea pig ileum.

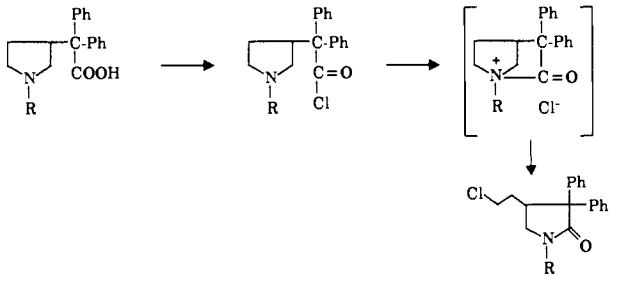


I

X = O, S
R = alkyl
R′ = alkyl

The most potent of these compounds (I: R = CH_3;R′ = CH_3; X = S) was shown to offer moderate protection against histamine-induced lethality in the guinea pig and did not produce EEG patterns in the cat which are believed to be indicative of sedation.[1] The following investigation was initiated on the basis of these findings with the goal of preparing a novel, potent nonsedative antihistamine.

Scheme I

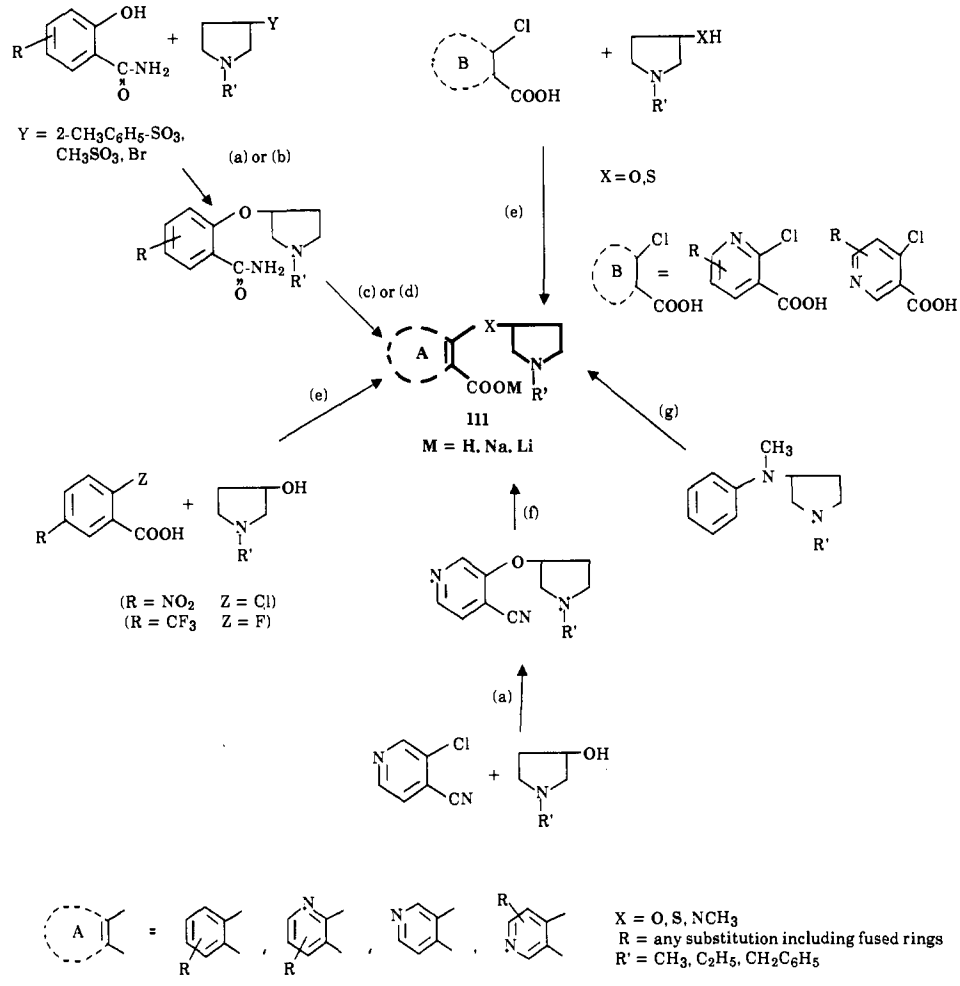


† Department of Chemical Research.
‡ Department of Pharmacology.

(1) Ruckart, R. T.; Turley, B. G.; Erdle, S. Y.; Johnson, D. N. *Pharmacologist* **1984**, *26*, 222.

0022-2623/89/1832-2178$01.50/0

Scheme II[a]



[a] (a) $NaOCH_3$/DMF; (b) NaH/DMF or DMSO; (c) NaOH/H_2O; (d) CH_3COOH/HCl/*n*-butyl nitrite; (e) 2 NaH/THF or DMF or DMSO; (f) KOH/*tert*-butyl alcohol; (g) (1) *n*-BuLi, (2) CO_2.

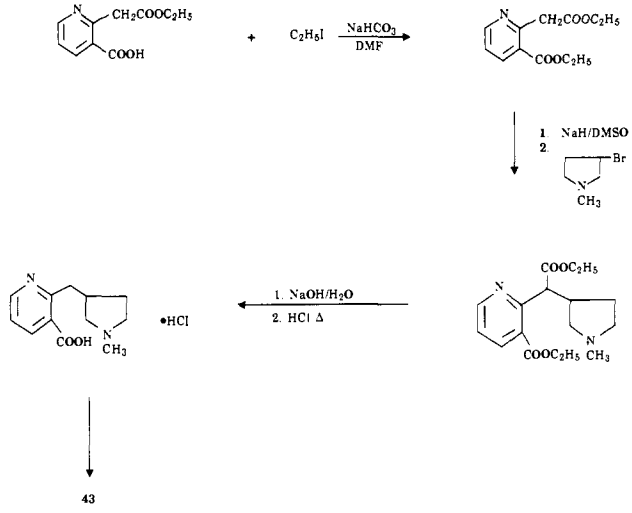
Chemistry

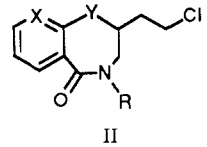
In 1963 a new rearrangement was reported from these laboratories which described the formation of a new five-membered ring when a 1-substituted 3-pyrrolidinediphenylacetic acid was converted to the corresponding acid chloride (Scheme I).[2]

Subsequently, several variations of this rearrangement which produce a variety of five- and six-membered heterocyclic rings containing a chloroethyl side chain have been reported.[3]

This paper describes yet another variation yielding seven-membered lactams, namely benzo- and pyrido-1,4-oxazepin-5-ones [II: X = CH, Y = O; X = N, Y = O, respectively] and related benzo-1,4-diazepin-5-ones (II: X = CH, Y = NCH_3), pyrido-1,4-thiazepin-5-ones (II: X = N, Y = S), and pyrido-4-azepin-5-ones (II: X = N, Y = CH_2), which also possess the chloroethyl side chain. Displacement of the chlorine by various amines gave a series of compounds which possessed H_1 antihistaminic activity. Conversion of the amides to the thioamides enhanced this activity.

Scheme III





II

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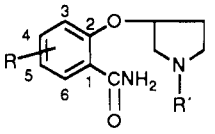
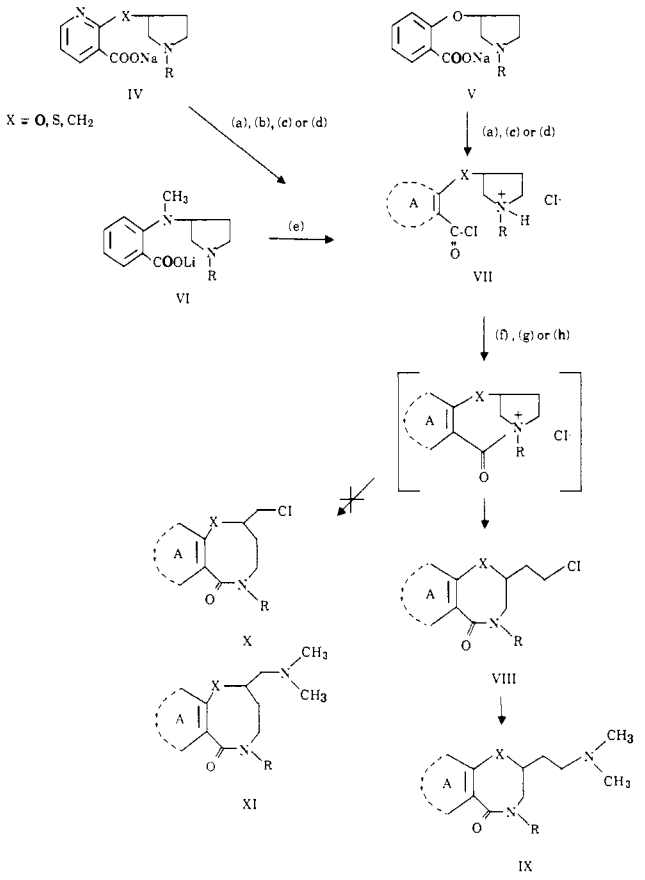
Table I. 2-[(1-Substituted-3-pyrrolidinyl)oxy]benzamides as Intermediates[a]



compd	R	R′	method of prep[b]	mp[c]	% yield[d]	recrystn solvent[e]	formula[f]
1	H	$C_6H_5CH_2$	A2	120–122	42	A, B	$C_{18}H_{20}N_2O_2$
2	H	CH_3	A2	116–118	38	A, B	$C_{12}H_{16}N_2O_2$
3	5-OCH_3	CH_3	A1	85–87	4	B	$C_{13}H_{18}N_2O_3$
4	5-Br	CH_3	A1	160–162	28	B, C	$C_{12}H_{15}BrN_2O_2$
5	4-Cl	CH_3	A1	122–123	45	B	$C_{12}H_{15}ClN_2O_2$
6	5-Cl	CH_3	A3	126–128	23	B	$C_{12}H_{15}ClN_2O_2 \cdot 0.5H_2O$
7	5-F	CH_3	A1	90–93	42	D	$C_{12}H_{15}FN_2O_2$
8		CH_3	A1	128–130	22	B	$C_{16}H_{18}N_2O_2$
9		CH_3	A1	122–129	32	B, E	$C_{16}H_{18}N_2O_2$

[a] All compounds exhibited IR, ^1H NMR, and MS spectra consistent with the assigned structures. When necessary ^{13}C NMR was used to elucidate structures. [b] For more detailed experimental procedures, see U.S. Patent 4,592,866. [c] Melting points were taken on a Thomas-Hoover apparatus in capillary tubes and are uncorrected. [d] Isolated yields; no efforts were made to optimize yields. [e] A = isopropyl ether, B = ethyl acetate, C = chloroform, D = hexane, E = isooctane, F = 2-propanol, G = water, H = ethanol, I = toluene, J = cyclohexane, K = methanol, L = dimethylformamide, M = 4-methyl-2-pentanone, and N = acetone. [f] All compounds gave C, H, and N analyses within 0.4% of theoretical values unless otherwise indicated. Solvates and acid content of salts were confirmed by ^1H NMR.

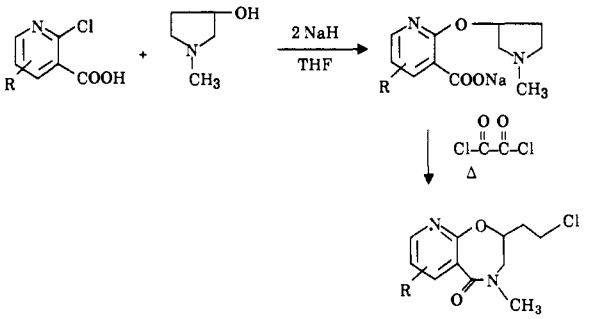
Scheme IV[a]



[a] (a) (1) $CHCl_3$, (2) HCl (pH 6–7), (3) $SOCl_2$; (b) (1) $CHCl_3$, (2) HCl (pH 6–7), (3) Ph_3P/CCl_4 (c) $SOCl_2$ (neat); (d) (1) HCl, (2) ClCOCOCl; (e) (1) $CHCl_3$, (2) $POCl_3$; (f) heat; (g) $(C_2H_5)_3N$; (h) $C_2H_5N[CH(CH_3)]_2$.

The starting acids (III) required for the rearrangement to oxazepinones, thiazepinones, and diazepinones and the standard methods used for their preparation are shown in Scheme II. The acids were obtained and used as either the crude acid or more often as the alkali metal salt. The

Scheme V

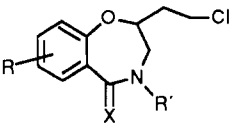


prerequisite acid for the pyrido-4-azepin-5-one (II: X = N, Y = CH_2) was prepared according to Scheme III.

In the case of the benzo compounds, the prerequisite acids were usually made from the amides (Table I), which were prepared by condensing the appropriately substituted salicylamide (preparations of novel substituted salicylamides are given in the Experimental Section) with a 3-halo-, 3-[(methylsulfonyl)oxy]-, or 3-[(tolylsulfonyl)oxy]-1-alkylpyrrolidine in dimethylformamide with sodium hydride as a base. The amides were hydrolyzed to the desired acids or the corresponding salts. Attempts to couple salicylic acid directly with the 3-substituted pyrrolidines failed.

Scheme IV shows the various methods of producing the intermediate acid chloride VII and effecting the rearrangement to give VIII (Tables II–IV). The alkali salt of the acid was usually suspended in chloroform and hydrogen chloride gas was introduced until the pH meter read 6. The chlorinating agent was then added. In the case of the pyridyl compounds (IV), the most frequently used method employed triphenylphosphine/carbon tetrachloride as the agent for making the acid chloride. This worked well since the resulting rearranged product could be separated from the byproduct, triphenylphosphine oxide, by a simple acid–base extraction, followed by crystallization of the lactam. A later modification consisted of preparing the sodium salt of the acid in tetrahydrofuran and treating it directly with oxalyl chloride and heat to give the rearranged product (Scheme V). In the limited

Table II. 4-Alkyl-2-(2-chloroethyl)-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-ones and -thiones as Intermediates[a]



compd	R	R′	X	method of prep[b]	mp[c]	% yield[d]	recrystn solvent[e]	formula[f]
10	H	$C_6H_5CH_2$	O	C	145–147	15	A, B	$C_{18}H_{18}ClNO_2$
11	H	CH_3	O	C	97–107	47	F, G	$C_{12}H_{14}ClNO_2$
12	H	CH_3	S	G	105–108	52	H	$C_{12}H_{14}ClNOS$
13	7-OCH_3	CH_3	O	C	98–100	23	–	$C_{13}H_{16}ClNO_3$
14	7-OCH_3	CH_3	S	G	98–100	65	H	$C_{13}H_{16}ClNO_2S$
15	7-Br	CH_3	O	C	92–94	60	A, B	$C_{12}H_{13}BrClNO_2$
16	7-Br	CH_3	S	G	118–120	72	H	$C_{12}H_{13}BrClNOS$
17	8-Cl	CH_3	O	C	85–87	59	F	$C_{12}H_{13}Cl_2NO_2$
18	8-Cl	CH_3	S	G	105–106	55	H	$C_{12}H_{13}Cl_2NOS$
19	7-Cl	CH_3	O	B	101–103	33 (crude)	F	$C_{12}H_{13}Cl_2NO_2$
20	7-Cl	CH_3	S	G	102–104	68	H	$C_{12}H_{13}Cl_2NOS$
21	7-F	CH_3	O	B	113–116	19	A	$C_{12}H_{13}ClFNO_2$
22	7-F	CH_3	S	I1	135–137	52	A	$C_{12}H_{13}ClFNOS$
23	7-NO_2	CH_3	O	DD	91–92	16	A, B	$C_{12}H_{13}ClN_2O_4$[g]
24	7-NO_2	CH_3	S	I1	153–155	57	A, I	$C_{12}H_{13}ClN_2O_3S$
25	7-CF_3	CH_3	O	F	102–103	8	A	$C_{13}H_{13}ClF_3NO_2$
26	7-CF_3	CH_3	S	I1	146–148	50	A	$C_{13}H_{13}ClF_3NOS$

[a-f] Same as footnotes in Table I. [g] C: calcd, 50.03; found, 50.51.

number of cases in which it was used, this proved to be the method of choice.

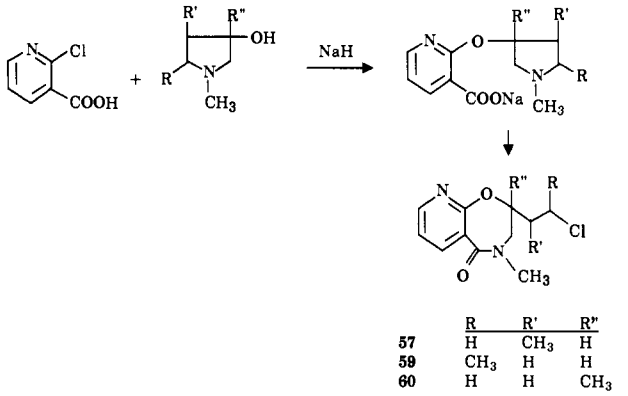
When the rearranged product was a benzoxazepinone (Scheme IV; VIII: A = benzo; X = O), and therefore neutral, the chlorinating agent of choice was thionyl chloride. The acid chlorides were generally stable at room temperature as long as the pyrrolidine nitrogen was protonated. The rearrangement was effected by heat or by addition of an organic base such as triethylamine or diisopropylethylamine.

Treatment of the 2-[(1-alkyl-3-pyrrolidinyl)methylamino]benzoic acid lithium salt (VI) with phosphorus trichloride gave an exothermic reaction which produced the benzodiazepinone (VIII: A = benzo; X = NCH_3) immediately.

As in previously reported rearrangements of this type, the pyrrolidine ring always cleaved (Scheme IV) so as to produce the smallest possible ring and a chloroethyl side chain (VIII) as opposed to producing a larger ring with a chloromethyl side chain (X). The ^1H NMR spectra of the rearranged compounds do not easily differentiate between the chloroethyl side chain (VIII, Scheme IV) and the chloromethyl side chain (X, Scheme IV). A doublet at about 3.55 ppm can be assigned to the CH_2 adjacent to the amide in VIII or the CH_2Cl in X. Likewise, a multiplet at about 3.85 ppm can be assigned to the CH_2Cl in VIII or the CH_2 adjacent to the amide in X. However, the ^1H NMR spectra of the dimethylamino analogues readily differentiate between IX and XI in several ways. First, the doublet at 3.55 ppm remains unchanged when the chloro compounds are converted to the dimethylamino compounds, which indicates the resonance must be assigned to the CH_2 adjacent to the amide of VIII and IX. Second, the multiplet at 3.85 ppm is shifted to a triplet at about 2.55 ppm, which is consistent for the amino CH_2 of IX. Therefore, the 3.85 ppm resonance of the chloro compounds must be assigned to the CH_2Cl of VIII. Last, homonuclear decoupling of the high-field multiplet (2.1 ppm) of IX collapses the 2.55 ppm triplet and perturbs the OCH resonance at 4.75 ppm. Only structure IX is consistent with these results.

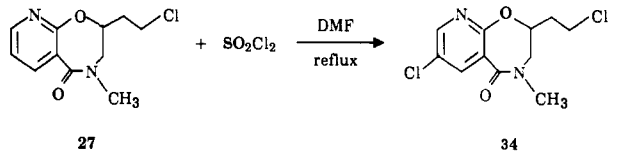
The branched side chain and methyl substitution on the 2-position of the oxazepine ring (compounds **57**, **59**, and **60**) were prepared by employing the same reaction as

Scheme VI



	R	R′	R″
57	H	CH_3	H
59	CH_3	H	H
60	H	H	CH_3

Scheme VII



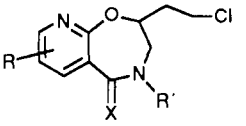
27 **34**

previously described on a properly substituted 1-methyl-3-pyrrolidinol (Scheme VI, Table V).

In general, pyridoxazepinones having substituents on the pyridine ring were prepared from the appropriately substituted *o*-chloropyridinecarboxylic acids or carbonitriles (preparations for novel pyridinecarboxylic acids and nitriles are given in the Experimental Section). In the case of **34**, however, the compound was also prepared by dropwise addition of sulfuryl chloride to a refluxing solution of the parent compound (**27**) in dimethylformamide (Scheme VII). When the reactants were combined at a lower temperature and heat subsequently applied, only trace amounts of the product were produced.

The seven-membered lactams containing the chloroethyl side chain (VIII, Scheme VIII) were converted to the corresponding thiolactams (XII) by treatment with either phosphorus pentasulfide or 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (Lawesson's reagent). Subsequent displacement of the chlorine by a primary or secondary amine gave the target compounds

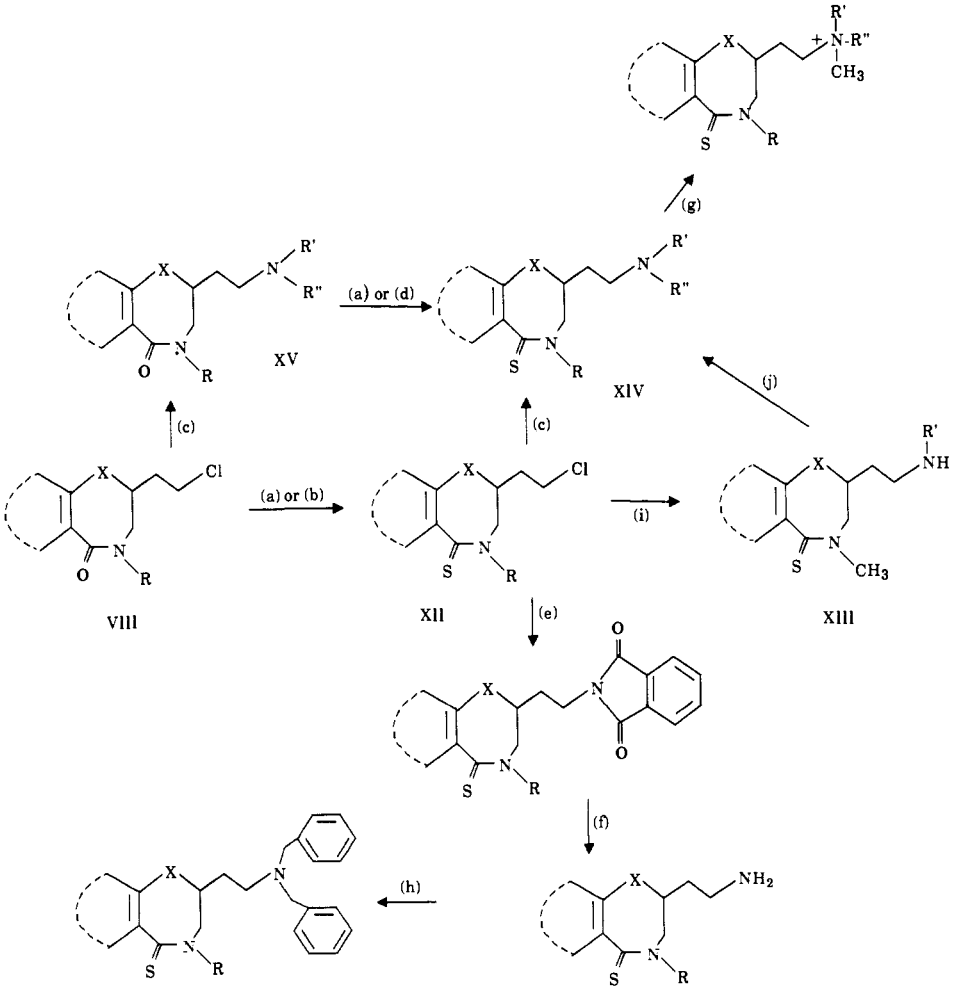
Table III. 4-Alkyl-2-(2-chloroethyl)-3,4-dihydropyrido[3,4-*f*]-1,4-oxazepin-5(2*H*)-ones and -thiones as Intermediates[a]



compd	R	R′	X	method of prep[b]	mp[c]	% yield[d]	recrystn solvent[e]	formula[f]
27	H	CH_3	O	D1	149–152	49	F	$C_{11}H_{13}ClN_2O_2 \cdot HCl$
28	H	CH_3	S	I2	134–136	44	F	$C_{11}H_{13}ClN_2OS$
29	H	$C_6H_5CH_2$	O	D2, E	160–168	16	F	$C_{17}H_{17}ClN_2O_2 \cdot HCl$
30	H	C_2H_5	O	D1	153–155	28	F	$C_{12}H_{15}ClN_2O_2 \cdot HCl$
31	H	C_2H_5	S	I2	133–135	43	F	$C_{12}H_{15}ClN_2OS \cdot HCl$
32	7-Br	CH_3	O	E	71–75	31	A	$C_{11}H_{12}BrClN_2O_2$
33	7-Br	CH_3	S	I1	138–141	56	A, I	$C_{11}H_{12}BrClN_2OS$
34	7-Cl	CH_3	O	E, F, FF	78–79	13	A	$C_{11}H_{12}Cl_2N_2O_2$
35	7-Cl	CH_3	S	H	125–127	55	F	$C_{11}H_{12}Cl_2N_2OS$
36	8-CH_3	CH_3	O	D2	73–74	29	A, G	$C_{12}H_{15}ClN_2O_2 \cdot H_2O$
37	8-CH_3	CH_3	S	H	80–86	100	A	$C_{12}H_{15}ClN_2OS \cdot H_2O$
38	7-Cl, 8-CH_3	CH_3	O	F	65–69	30	A, F	$C_{12}H_{14}Cl_2N_2O_2$
39	7-Cl, 8-CH_3	CH_3	S	I1	123–132	48	A	$C_{12}H_{14}Cl_2N_2OS$
40	7-C_6H_5	CH_3	S	CC	156–158	64	B, D	$C_{17}H_{17}ClN_2OS$

[a-f] See corresponding footnotes in Table I.

Scheme VIII[a]

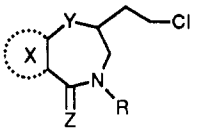


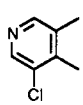
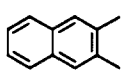
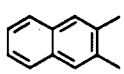
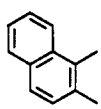
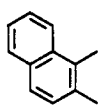
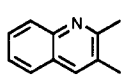
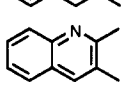
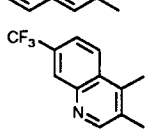
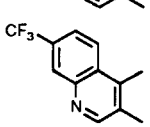
[a] (a) P_4S_{10} (sometimes K_2S added)/toluene, chloroform, or acetonitrile; (b) Lawesson's reagent/toluene; (c) HNR′R″/neat or in solvent; (d) P_4S_{10}/pyridine or toluene; (e) potassium phthalimide/DMF; (f) hydrazine/EtOH; (g) CH_3I/4-methyl-2-pentanone; (h) benzaldehyde/$NaBH_3CN$/MeOH; (i) $R'NH_2$; (j) R″Cl.

XIII and XIV. In one instance, compound **46**, (Table IV) conditions were never found whereby either of the thiating reagents would produce the thiolactam. This was presumably due to the steric effect of the chlorine in the ortho position.

An alternative route to the target compounds consists of first displacing the chloro on the side chain by an amine to give XV, with subsequent thiation of the lactam to the thiolactam (XIV). This route was generally less satisfactory since the thiation step gave increased tars and low

Table IV. Miscellaneous Chloroethyl Heterocycles as Intermediates[a]



compd	X	R	Y	Z	method of prep[b]	mp[c]	% yield[d]	recrystn solvent[e]	formula[f]
41		CH_3	S	O	D1	97–100	4	A, F	$C_{11}H_{13}ClN_2OS$
42		CH_3	S	S	H	160–162	43	B, D	$C_{11}H_{13}ClN_2S_2$
43		CH_3	CH_2	O	EE	199–202	14.5	F	$C_{12}H_{15}ClON_2 \cdot HCl$
44		CH_3	CH_2	S	I1	110–120[g]	51	A, B	
45		C_2H_5	NCH_3	O	U	78–80	42	A	$C_{14}H_{19}ClN_2O$
46		CH_3	O	O	D2	134–138	7	B	$C_{11}H_{12}Cl_2N_2O_2$
47		CH_3	O	O	T	188–190	20	A, F	$C_{11}H_{13}ClN_2O_2 \cdot HCl$[h]
48		CH_3	O	S	H	168–171	0.6	F	$C_{11}H_{13}ClN_2OS \cdot HCl$
49		CH_3	O	O	E	101–102	58 (crude)	F	$C_{16}H_{16}ClNO_2$
50		CH_3	O	S	G	166–168	35	H	$C_{16}H_{16}ClNOS$
51		CH_3	O	O	B	109–111	37	A, B	$C_{16}H_{16}ClNO_2$
52		CH_3	O	S	G	167–170	84	C	$C_{16}H_{16}ClNOS$
53		CH_3	O	O	D2	133–134	11	F	$C_{15}H_{15}ClN_2O_2$
54		CH_3	O	S	I1	114–116	52	F	$C_{15}H_{15}ClN_2OS$
55		CH_3	O	O	D2	172–174	7	F	$C_{16}H_{14}ClF_3N_2O_2 \cdot HCl$
56		CH_3	O	S	I1	135–137	73	A	$C_{16}H_{14}ClF_3N_2OS$

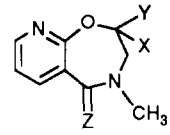
[a-f] See corresponding footnotes in Table I. [g] This compound was shown by ^1H NMR to be impure as is indicated by the melting range. The dimethylamino derivative (113) analyzed correctly. [h] C: calcd, 47.67; found, 48.33.

yields. The products required chromatography for purification whereas the former route yielded a crude thiolactam which usually crystallized readily. Thiation of the compounds containing the side-chain amino group could not be avoided, however, when the target compounds were prepared as in Scheme IX.

Scheme IX depicts a route whereby seven-membered lactams are prepared by cyclization of 1-amino- or 1-(alkylamino)-4-(dimethylamino)-2-butanol (XVI) with a properly substituted chloropyridinecarboxylic acid or ester. Although this route does not employ the rearrangement, it is interesting that a similar rearrangement was used in making the 1-alkyl-3-[(dimethylamino)ethyl]oxazolidinones (XVII),[3a] which were intermediates to the precursory 1,4-diaminobutanols (XVI). The compound (140) containing the methylene side chain was prepared by a similar cyclization route using a diaminopropanol (Scheme X).

Other members of the homologous series, compounds having a propyl side chain, were prepared by employing the cyano group to lengthen the chain (Scheme XI).

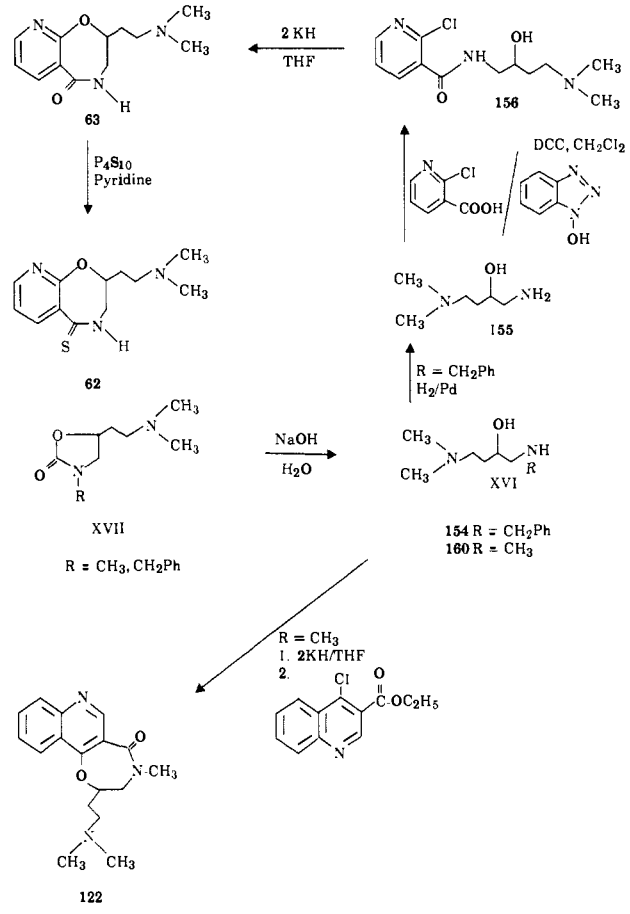
Table V. 2-(2-Chloroethyl)-3,4-dihydro-4-methylpyrido[3,4-*f*]-1,4-oxazepin-5(2*H*)ones and -thiones with Methyl Branching as Intermediates[a]



compd	X	Y	Z	method of prep[b]	mp[c]	% yield[d]	recrystn solvent[e]	formula[f]
57	$CH(CH_3)CH_2Cl$	H	O	D2	178–181	16	F	$C_{12}H_{15}ClN_2O_2 \cdot HCl$
58	$CH(CH_3)CH_2Cl$	H	S	I1	148–151	48	A, F	$C_{12}H_{15}ClN_2OS \cdot HCl$
59	$CH_2CH(CH_3)Cl$	H	O	D1	143–149	23	F	$C_{12}H_{15}ClN_2O_2 \cdot HCl$
60	CH_2CH_2Cl	CH_3	O	D2	155–158	21	F	$C_{12}H_{15}ClN_2O_2 \cdot HCl$
61	CH_2CH_2Cl	CH_3	S	I1	119–121	28	F	$C_{12}H_{15}ClN_2OS$

[a-f] See corresponding footnotes in Table I.

Scheme IX

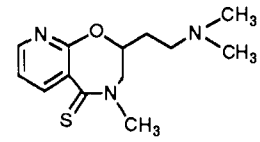


Reduction of the nitrile to the primary amine followed by thiation or dimethylation and thiation gave the desired homologues.

Two open-chain analogues, **150** and **151**, were prepared according to Scheme XII.

Structure–Activity Relationships

Compounds listed in Tables VI to IX were tested for their ability to protect guinea pigs against histamine-induced lethality. The data are reported as the percent of guinea pigs protected by a given dose of drug administered either orally (Table VI) or intraperitoneally (Tables VII–IX) at a specified time prior to a challenge with a dose of histamine equal to twice its LD_{100}. Table VI also gives the oral ED_{50} data at 1-h pretreatment and sometimes 6-h pretreatment for the more potent compounds. A few of the compounds are listed in more than one table to facilitate comparison. In the following discussion, 2-[2-(dimethylamino)ethyl]-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione (**64**) will be considered the



64

parent compound for the purpose of structural comparisons. This compound is undergoing clinical evaluation and an extensive pharmacological profile is being published elsewhere.[4]

Amide vs Thioamide. A survey of the tables (VI–IX) shows that, in all cases where a significant difference in potency exists between an amide and the corresponding thioamide, the latter is more potent. This difference is more pronounced in the more potent compounds (compare **65** vs **64**, **63** vs **62**, **71** vs **70**, **81** vs **80**, and **97** vs **96**; Table VI).

Contribution of the Aromatic Ring. Replacement of the aromatic ring nitrogen with carbon resulted in diminished potency as is seen in Table VIII by comparing **95** and **126** with **64** and **134**, respectively. This is also apparent when **96**, **98**, and **100** in Table VI are compared with thier analogues **80**, **84**, and **90**.

When the aromatic ring nitrogen is rotated from the ortho to the meta position relative to the ether linkage (**64** vs **114**; Table VII) high potency is retained, whereas when the nitrogen is para (**118**; Table VII) to the ether linkage, potency is greatly reduced.

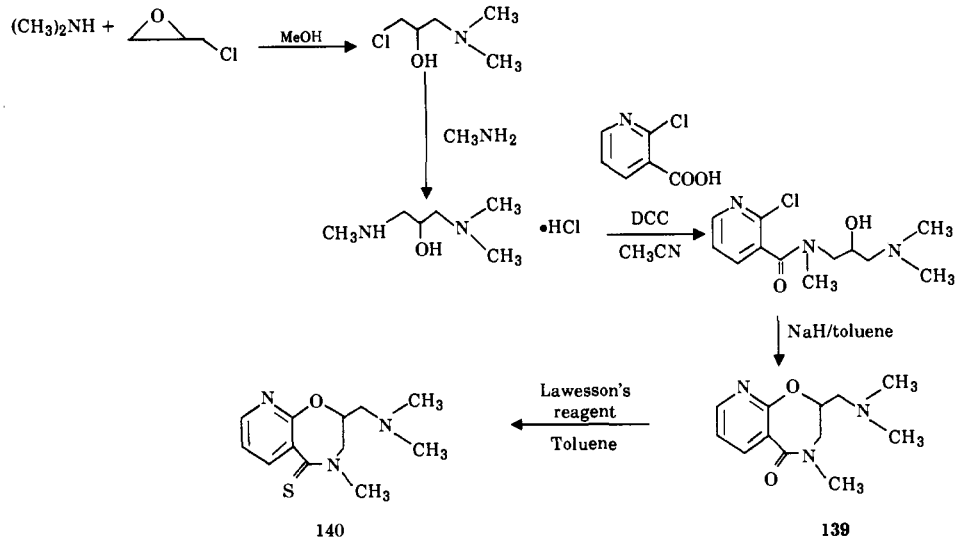
When the aromatic ring is quinoline or naphthalene, the potency is very dependent on the position of the ring junction (see **119–124**; Table VII).

Contribution of the Seven-Membered Ring and Heteroatom. A survey of Table VII shows that the oxazepine ring (**65** and **64**) is superior to the corresponding thiaoxazepine (**108** and **109**), diazepine (**110** and **111**), or azepine (**112** and **113**). The lack of activity in compounds **150** and **151** (Table IX) demonstrates the necessity of having the aliphatic ring.

Comparison of the Side-Chain Amino Group. A comparison of the side-chain amino groups in Tables VI and VIII shows that a small tertiary amine is preferable. The potency is drastically reduced in the secondary (**66** vs **64**; Table VI) and quaternary (**129** vs **64**; Table VIII) amines while the primary amine (**67**; Table VI) gave no protection at the highest test dose. There is a significant decrease in potency when the dimethylamino moiety (**64**;

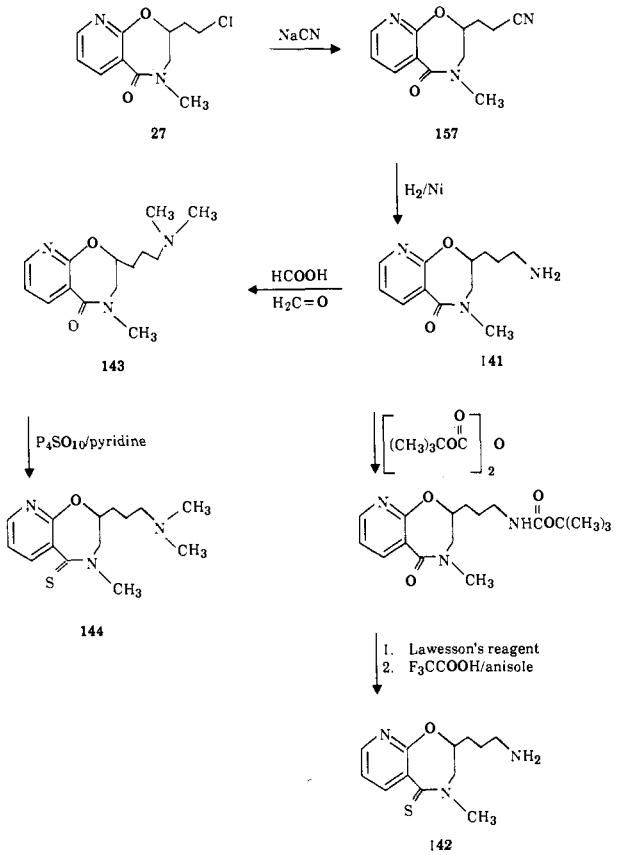
(4) Nolan, J. C.; Stephens, D. J.; Proakis, A. G.; Leonard, C. A.; Johnson, D. N.; Foxwell, M. H.; Yanni, J. M. *Agents Actions* In press.

Scheme X



140 139

Scheme XI



27 157 143 141 144 142

Table VI) is replaced by the larger diethylamine group (**69**; Table VI). The dibutylamino (**130** vs **64**; Table VIII) analogue confirms this trend by fully protecting only at the highest test dose. Likewise, the cyclic amines exhibited the same trend in potency [i.e., azetidino (**70**; Table VI) > pyrrolidino (**72**; Table VI) > piperidino (**133**; Table VIII) (This is a valid statement since compound **133** would have been even less active if administered orally.)]. Comparison of dimethylamino with azetidino (**64** vs **70**; Table VI) shows the latter confers the higher potency.

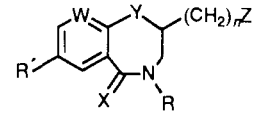
Length and Branching of the Side Chain. Table IX shows the effect of the length and branching of the side chain. Compound **140**, where the side chain contains one methylene group, exhibits no activity at the top screening dose. The ethylene chain (**64**) is optimum, and the potency of **144**, which contains three methylene groups, is severely reduced. Branching at either carbon in the side chain also reduces potency (compare **145** and **147** with **65**). A methyl attached at the 2-position of the oxazepine ring, however, has little or no effect as seen in **149** (Tables VI and IX).

Amide Nitrogen Substituent. Variations of the substituent on the amide nitrogen (Table VI) demonstrate that a methyl group (**64**) conferred greater potency than a hydrogen (**62**), ethyl (**78**), or benzyl (**79**).

Aromatic Ring Substitution. The effect of substitution on the aromatic ring may vary from insignificant to drastic depending on the substituent and its position. Comparison of **115** and **116** with **114** (Table VII) demonstrates that the attachment of a chlorine or dimethylamino moiety at position 6 renders a highly active compound inactive at the screening dose. A chlorine (**80**) or bromine (**90**) in the 7-position of the pyridooxazepine series enhances potency, as does a methyl group in the 8-position (**93**) (compare with that of **64**; Table VI); however, when the compound contains both substituents (**89**) the potency is reduced. A phenyl group in the 7-position (**94**) also reduces potency.

Table VI also shows that in the benzooxazepine series substitution in the 7-position with a bromo (**100**), chloro (**96**), fluoro (**101**), nitro (**105**), amino (**106**), or acetamido (**107**) moiety enhances the potency (compare with that of **95**) whereas a trifluoromethyl (**102**) or methoxy (**104**) moiety has little or no effect. In this series the potency is also increased by a chlorine in the 8-position (**99**).

An evaluation of the SAR data indicated that incorporation of the following features into the basic bicyclic structure should produce an antihistamine of highest potency:

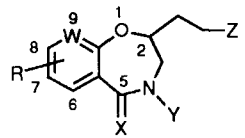


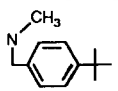
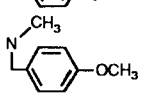
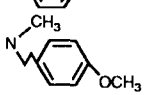
W = nitrogen, Y = oxygen, n = 2, Z = azetidino, R = methyl, X = sulfur, R' = chloro

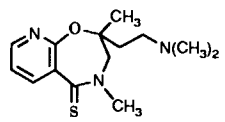
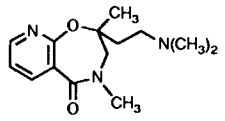
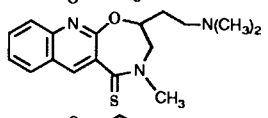
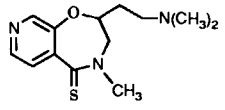
The above compound (**84**) was synthesized and was shown to be the most potent compound in the series with an oral ED_{50} of 0.02 mg/kg at 1-h pretreatment and an ED_{50} not discernibly different at 6-h pretreatment in the histamine-induced guinea pig lethality test.

The optical isomers of several key compounds have been prepared. Their absolute configuration, biological activ-

Table VI. Antihistaminic Activity of 4-Alkyl-2-(2-amino or substituted-amino)-3,4-dihydrobenzo- or -pyrido[3,4-*f*]-1,4-oxazepin-5(2*H*)-ones and -thiones Administered Orally[a]

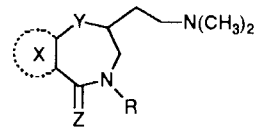


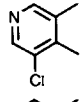
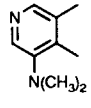
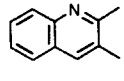
compd	W	X	Y	Z	R	method of prep[b]	mp[c]	% yield[d]	recrystn solvent[e]	formula[f,g]	protection against histamine-induced lethality in the guinea pig: % survival at 60-min pretreatment time at the following doses (mg/kg, po) 30	3	1	0.3	0.1	ED_{50}, mg/kg, po, at the following pretreatment times 1 h	6 h
62	N	S	H	$N(CH_3)_2$	H	J	172–175	19	H	$C_{12}H_{17}N_3OS \cdot 2HCl \cdot H_2O$[h]		100	33	0			
63	N	O	H	$N(CH_3)_2$	H	V	160–164	13	F	$C_{12}H_{17}N_3O_2 \cdot C_4H_4O_4$		67	0				
64	N	S	CH_3	$N(CH_3)_2$	H	L2	130–133	86	H	$C_{13}H_{19}N_3OS \cdot C_4H_4O_4$				100	50	0.12	6.0
65	N	O	CH_3	$N(CH_3)_2$	H	L2	146–184	34	F	$C_{13}H_{19}N_3O_2 \cdot 1.5C_4H_4O_4$		100	20			1.05	
66	N	S	CH_3	$NHCH_3$	H	L1	137–138	38	H	$C_{12}H_{19}N_3OS \cdot 1.5C_2H_2O_4$	100	0					
67	N	S	CH_3	NH_2	H	O	208–209	69	F	$C_{11}H_{15}N_3OS \cdot 0.5C_4H_4O_4$	0						
68	N	S	CH_3	$N(CH_3)C_2H_5$	H	L1	127–131	31	F	$C_{14}H_{21}N_3OS \cdot C_2H_4O_4$		100	60	0			
69	N	S	CH_3	$N(C_2H_5)_2$	H	L1	142–144	29	F	$C_{15}H_{23}N_3OS \cdot C_2H_2O_4$		67	33				
70	N	S	CH_3		H	M	106–122	50	F	$C_{14}H_{19}N_3OS \cdot 1.15C_4H_4O_4 \cdot 0.33C_3H_8O$[i]					100	0.04	1.0
71	N	O	CH_3		H	M	143–145	21	F	$C_{14}H_{19}N_3O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$				100	67	0.13	6.0
72	N	S	CH_3		H	K2	141–142	45	H	$C_{15}H_{21}N_3OS \cdot C_2H_2O_4$	67	80	33				
73	N	S	CH_3		H	L1	143–145	28	F	$C_{15}H_{19}N_3OS \cdot C_4H_4O_4$		100	0				
74	N	S	CH_3	$N(CH_3)CH_2C_6H_5$	H	L1	163–166	55	F	$C_{19}H_{23}N_3OS \cdot C_2H_2O_4$		100	0				
75	N	S	CH_3		H	L1	175–178	31	F	$C_{23}H_{31}N_3OS \cdot 1.5C_2H_2O_4$		100	40	0			
76	N	S	CH_3		H	L1	128–130	56	F	$C_{20}H_{25}N_3O_2S$		67	0				
77	N	S	CH_3		H	L1	75–78	37	A	$C_{21}H_{27}N_3O_2S$	100	33					
78	N	S	C_2H_5	$N(CH_3)_2$	H	K1	73–74	39	J	$C_{14}H_{21}N_3OS$		100	33				
79	N	S	$CH_2C_6H_5$	$N(CH_3)_2$	H	K1	155–156	77	F	$C_{19}H_{23}N_3OS \cdot C_2H_2O_4$		100	0				
80	N	S	CH_3	$N(CH_3)_2$	7-Cl	L1	204–206	36	A, F	$C_{13}H_{16}ClN_3OS \cdot HCl$					100	0.04	0.6
81	N	O	CH_3	$N(CH_3)_2$	7-Cl	K1	150–156	40	F	$C_{13}H_{18}ClN_3O_2 \cdot C_2H_2O_4$			100	33		0.3	28
82	N	S	CH_3	$NHCH_3$	7-Cl	L3	112–129	14	F, H	$C_{12}H_{16}ClN_3OS \cdot C_2H_2O_4$		100		0			
83	N	S	CH_3	$N(C_2H_5)_2$	7-Cl	L1	141–143	53	F	$C_{15}H_{22}ClN_3OS \cdot C_4H_4O_4$		100		20		0.39	
84	N	S	CH_3		7-Cl	M	146–150	82	F	$C_{14}H_{18}ClN_3OS \cdot C_2H_2O_4$					100	0.02	0.02
85	N	O	CH_3		7-Cl	M	169–174 dec	57	F	$C_{14}H_{18}ClN_3O_2 \cdot C_2H_2O_4$					100	0.04	0.8
86	N	S	CH_3		7-Cl	L1	172–173	70	F, H	$C_{15}H_{20}ClN_3OS \cdot C_4H_4O_4$				100	40	0.12	

87	N	S	CH_3	$N(CH_3)CH_2C_8H_5$	7-Cl	L1	188–194 dec	64	F, H	$C_{19}H_{22}ClN_3OS{\cdot}C_2H_2O_4$		100		60		0.9	
88	N	S	CH_3	$N(CH_3)_2$	7-Cl, 8-CH_3	K1	191–192	74	F	$C_{14}H_{20}ClN_3OS{\cdot}C_2H_2O_4$				67	67		
89	N	S	CH_3		7-Cl, 8-CH_3	M	162–166 dec	82	F	$C_{15}H_{20}ClN_3OS{\cdot}C_2H_2O_4{\cdot}0.5H_2O$				67	67		
90	N	S	CH_3	$N(CH_3)_2$	7-Br	K1	145–151	72	F	$C_{13}H_{18}BrN_3OS{\cdot}C_2H_2O_4$					100	0.05	2
91	N	S	CH_3		7-Br	M	161–170 dec	80	F	$C_{14}H_{18}BrN_3OS{\cdot}C_2H_2O_4$		100	60		60	0.09	0.1
92	N	S	CH_3	$N(CH_3)CH_2C_8H_5$	7-Br	L1	192–203	77	F, H			100	0				
93	N	S	CH_3	$N(CH_3)_2$	8-CH_3	L3	216–218	66	F	$C_{14}H_{21}N_3OS{\cdot}C_2H_2O_4$				100	80	0.06	>2
94	N	S	CH_3	$N(CH_3)_2$	7-C_6H_5	K1	193–196	20	H, K	$C_{19}H_{23}N_3OS{\cdot}C_2H_2O_4$		100	100	0			
95	CH	S	CH_3	$N(CH_3)_2$	H	L2	233–236	28	H	$C_{14}H_{20}N_2OS{\cdot}HCl$	100	0	0				
96	CH	S	CH_3	$N(CH_3)_2$	7-Cl	L2	150–151	–	F, G	$C_{14}H_{19}ClN_2OS{\cdot}C_2H_2O_4{\cdot}$ $0.5H_2O$		100	33				
97	CH	O	CH_3	$N(CH_3)_2$	7-Cl	L2	199–200	57	F, G	$C_{14}H_{19}ClN_2O_2{\cdot}C_2H_2O_4$		40	33	0			
98	CH	S	CH_3		7-Cl	M	121–126	47	F	$C_{15}H_{19}ClN_2OS{\cdot}C_2H_2O_4{\cdot}$ $0.5H_2O$				100	40	0.12	
99	CH	S	CH_3	$N(CH_3)_2$	8-Cl	L2	196–199	25	H	$C_{14}H_{19}ClN_2OS{\cdot}HCl$	100	100	0	0			
100	CH	S	CH_3	$N(CH_3)_2$	7-Br	L2	155–157	–	F	$C_{14}H_{19}BrN_2OS{\cdot}C_2H_2O_4{\cdot}H_2O$	100	67	0				
101	CH	S	CH_3	$N(CH_3)_2$	7-F	K1	180–182	87	F	$C_{14}H_{19}FN_2OS{\cdot}C_2H_2O_4{\cdot}$ $0.5H_2O$		100	20	0			
102	CH	S	CH_3	$N(CH_3)_2$	7-CF_3	K1	170–171	67	F	$C_{15}H_{19}F_3N_2OS{\cdot}C_2H_2O_4$	100	33					
103	CH	S	CH_3		7-CF_3	M	76–110	46	F	$C_{16}H_{19}F_3N_2OS{\cdot}C_2H_2O_4$	100	33					
104	CH	S	CH_3	$N(CH_3)_2$	7-OCH_3	L2	160–168	19	F	$C_{15}H_{22}N_2O_2S{\cdot}C_2H_2O_4{\cdot}0.5H_2O$	100	0					
105	CH	S	CH_3	$N(CH_3)_2$	7-NO_2	K1	192–194	64	K	$C_{14}H_{19}N_3O_3S{\cdot}0.75C_4H_4O_4$		67		33			
106	CH	S	CH_3	$N(CH_3)_2$	7-NH_2	Q	176–179	55	F	$C_{14}H_{21}N_3OS$		100	0				
107	CH	S	CH_3	$N(CH_3)_2$	7-$NHCOCH_3$	R	104–110	93	H	$C_{16}H_{23}N_3O_2S{\cdot}C_2H_2O_4{\cdot}H_2O$		100		0			
149													100	67	40	0.12	~6
148												67		67		0.45	
120														100	67	0.1	2.9
114													100	0			
diphen-hydramine												67	33			2.8	38
brom-pheniramine														100	40	0.08	2.5

[a-f] See corresponding footnotes in Table I. [g] $C_4H_4O_4$ = fumarate; $C_2H_2O_4$ = oxalate. [h] C: calcd, 42.10; found, 42.66. [i] C_3H_8O = 2-propanol.

Table VII. H_1-Antihistaminic Activity of Miscellaneous 2-(Dimethylamino)ethyl Heterocycles Administered Intraperitoneally[a]



compd	X	Y	Z	R	method of prep[b]	mp[c]	% yield[d]	recrystn solvent[e]	formula[f,g]	protection against histamine-induced lethality in the guinea pig: % survival at 30-min pretreatment time at the following doses (mg/kg, ip)			
										30	3	1	0.3
65		O	O	CH_3							100		0
64		O	S	CH_3									100
108		S	O	CH_3	K1	>250	77	F	$C_{13}H_{19}N_3OS\cdot 2HCl$[h]	67	0		
109		S	S	CH_3	K1	191–193	58	F, G	$C_{13}H_{19}N_3S_2\cdot C_2H_2O_4$	100	0		
110		NCH_3	O	C_2H_5	L2	175–178[k]	67	-	$C_{16}H_{25}N_3O$	0			
111		NCH_3	S	C_2H_5	J	92–94	46	A	$C_{16}H_{25}N_3S$	0			
112		CH_2	O	CH_3	K1	149–151	51	A, F	$C_{14}H_{21}N_3O_1\cdot 2C_4H_4O_4$	33	0		
113		CH_2	S	CH_3	K1	150–153	76	A, F	$C_{14}H_{21}N_3S\cdot C_4H_4O_4$	67	33		
114		O	S	CH_3	L2	>200 dec	11	F, H	$C_{13}H_{19}N_3OS\cdot 1.5HCl$[i]				100
115		O	O	CH_3	K1	195–196	77	F	$C_{13}H_{18}ClN_3O_2\cdot 0.5C_4H_4O_4$	0			
116		O	O	CH_3	K1	172–175	56	F	$C_{15}H_{24}N_4O_2\cdot 1.5C_4H_4O_4$	0			
117		O	O	CH_3	K1	179–181	80	F, G	$C_{13}H_{19}N_3O_2\cdot 2C_2H_2O_4\cdot 0.5H_2O$	100	67	33	
118		O	S	CH_3	J	111–114	9	F, G	$C_{13}H_{19}N_3OS\cdot 2C_2H_2O_4$	100	100	0	
119		O	O	CH_3	K1	25–30	67	F	$C_{17}H_{21}N_3O_2\cdot C_4H_4O_4\cdot 0.5H_2O$		100	0	

120		O	S	CH_3	K1	123–126	50	F	$C_{17}H_{21}N_3OS \cdot C_4H_4O_4 \cdot 0.5H_2O \cdot 0.5C_3H_8O^j$			100
121		O	S	CH_3	L2	115–118	-	F, G	$C_{18}H_{22}N_2OS \cdot C_2H_2O_4 \cdot 0.5H_2O$	100	67	67
122		O	O	CH_3	AA	214–218	10	H	$C_{17}H_{21}N_3O_2 \cdot C_2H_2O_4$	33		
123		O	O	CH_3	K1	204–205	81	F	$C_{18}H_{20}F_3N_3O_2 \cdot C_4H_4O_4$	100	0	
124		O	S	CH_3	L2	238–240	20	F, G	$C_{16}H_{22}N_2OS \cdot HCl$	100	33	

[a-j] See corresponding footnotes in Table I. [g] $C_4H_4O_4$ = fumarate; $C_2H_2O_4$ = oxalate. [h] C: calcd, 46.16; found, 45.68. [i] C: calcd, 48.78; found, 49.34. [j] C_3H_8O = 2-propanol. [k] Boiling point at 0.1 mm.

ities, and structural relationships to other antihistamines will be the subject of another publication.

Sedation Evaluation

The sedative and antihistaminic potential for a selected group of compounds was determined in cats by the method described previously.[4] The criteria for predicting sedative activity were based on the inspection of electroencephalographic tracings for periods of cortical slowing, synchrony, and spindle-type activity after each dose of test compound (0.001–20 mg/kg, iv). The antihistaminic potential was assessed by comparing the histamine (0.5 μg/kg, iv) hypotensive response before and after each dose of the test compound. Table X shows the dose at which EEG changes reflective of sedation occurred and the dose which suppressed by 50% the histamine-induced hypotensive effect. The nonsedative antihistamines astemizole[5] and loratadine[6] produced a good separation between the antihistaminic and the sedative doses. In contrast, the sedating antihistamines diphenhydramine[6] and brompheniramine[7] were essentially equipotent in producing an antihistaminic and a sedative effect. Of the compounds from this series selected for testing, only one (**96**) produced sedation below 20 mg/kg, iv. The remaining compounds appear to be free of sedative side effects, and of those tested for antihistaminic activity, all were active below 1 mg/kg, iv.

Previously reported in vitro and in vivo binding experiments[8] show that compound **64** readily penetrates the central nervous system (CNS) of mice and displaces [^{3}H]pyrilamine equally well from binding sites in guinea pig lung and cerebral cortex (20 and 19 nM, respectively). Thus the reason for the apparent lack of sedative activity for compound **64** as well as other members of the series is unclear, since it is not due to selectivity for peripheral binding sites or poor CNS penetration.

Conclusions

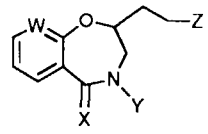
The synthesis of a novel series of (aminoethyl)benzo- and -pyridooxazepinones and -thiones exhibiting good H_1 antihistaminic activity is reported. Starting with a compound (**95**) which exhibited weak activity, extensive modification of the structure, which was guided by structure–activity studies, gave compounds of very high oral potency. Electroencephalographic studies in cats suggest that several compounds in the series would be expected to be nonsedating in humans. Compound **64** (rocastine) is undergoing clinical evaluation.

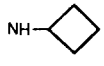
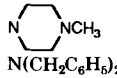
Experimental Section

Melting points were determined in open capillary tube with a Thomas-Hoover melting point apparatus or on a Fischer-Johns hot plate and are uncorrected. Elemental analyses (C, H, and N) were performed in house and were within 0.4% of the theoretical values except where noted. IR spectra were obtained on a Perkin-Elmer Model 297 spectrophotometer. ^{1}H NMR were recorded on a Varian EM-360 instrument using tetramethylsilane as an internal standard and lock. ^{13}C NMR were recorded on a Varian FT-80A instrument using tetramethylsilane as the internal standard. Structural assignments for all new compounds were consistent with spectra. Electron-impact (EI) mass spectra were obtained at 70 eV on a Hitachi RMV-6 unit and chemical-ionization spectra were obtained on a Varian MAT-44 using isobutane as the reagent gas. Analytical TLC were carried out on Analtech

(5) Nickolson, A. N.; Stone, B. M. *Br. J. Clin. Pharm.* **1982**, *13*, 199.
(6) Roth, T.; Roehrs, T.; Koshorek, G.; Sicklesteel, J.; Zorick, F. *J. Allergy Clin. Immunol.* **1978**, *5*, 366.
(7) Blamoutier, J. *Curr. Med. Res. Opin.* **1978**, *5*, 366.
(8) Bruce, G. S.; Tabor, R. D.; Haimes-Bartolf, M. D.; Kinnier, W. J. *Pharmacologist* **1984**, *26*, 222.

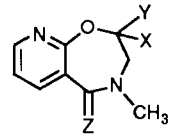
Table VIII. H_1-Antihistaminic Activity of 4-Alkyl-2-(2-amino- or substituted-aminoethyl)-3,4-dihydrobenzo- or -pyrido[3,4-*f*]-1,4-oxazepin-5(2*H*)-ones and -thiones Administered Intraperitoneally[a]

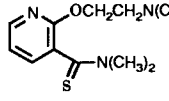
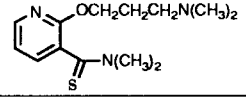


compd	W	X	Y	Z	method of prep[b]	mp[c]	% yield[d]	recrystn solvent[e]	formula[f,g]	protection against histamine-induced lethality in the guinea pig: % survival at 30-min pretreatment time at the following doses (mg/kg, ip)			
										30	3	1	0.3
64	N	S	CH_3	$N(CH_3)_2$									100
65	N	O	CH_3	$N(CH_3)_2$							100		0
95	CH	S	CH_3	$N(CH_3)_2$							100	50	0
125	CH	O	CH_3	$N(CH_3)_2$	L2	56–76	21	A	$C_{14}H_{20}N_2O_2$	62			
126	CH	S	CH_3		K2	253–253 dec	51	H, L	$C_{16}H_{22}N_2O_2S$·HCl	50			
127	CH	S	$CH_2C_6H_5$		G	236–238	20	A, I	$C_{22}H_{26}N_2O_2S$[h]	0			
128	CH	O	$CH_2C_6H_5$		K2	97–99	43	A, B	$C_{22}H_{26}N_2O_3$	0			
129	N	S	CH_3	$N^+(CH_3)_3I^-$	BB	221–225	78	M	$C_{14}H_{22}IN_3OS$	100	0		
130	N	S	CH_3	$N(n\text{-}C_4H_9)_2$	L1	208–209	47	F	$C_{19}H_{31}N_3OS$·$C_2H_2O_4$	100	33		
131	N	S	CH_3		M	152–154	21	F	$C_{14}H_{19}N_3OS$·0.5$C_4H_4O_4$	0			
132	N	S	CH_3		M	172–195	42	A, F	$C_{15}H_{21}N_3OS$·0.5$C_4H_4O_4$	0			
133	N	S	CH_3		L1	133–140	57	F	$C_{16}H_{23}N_3OS$·0.5$C_4H_4O_4$·0.5H_2O·0.5C_3H_8O[i]	100	0		
134	N	S	CH_3		K2	152–153	60	H	$C_{15}H_{21}N_3O_2S$	100	0		
135	N	S	CH_3		L1	184–185	57	F	$C_{16}H_{24}N_4OS$·2$C_4H_4O_4$·0.5H_2O	100	0		
136	N	S	CH_3	$N(CH_2C_6H_5)_2$	P	123–126	20	F	$C_{25}H_{27}N_3OS$·$C_4H_4O_4$	0			
137	N	S	CH_3		L1	163–167	54	H	$C_{14}H_{16}N_4OS$·1.5$C_2H_2O_4$	100	0		
138	N	S	CH_3		S	119–121	31	F	$C_{14}H_{16}N_4OS$	33			

[a–f] See corresponding footnotes in Table I. [g] $C_4H_4O_4$ = fumarate; $C_2H_2O_4$ = oxalate. [h] C: calcd, 69.08; found, 69.60. [i] C_3H_8O = 2-propanol.

Table IX. Antihistaminic Activity of 4-Methyl-3,4-dihydropyrido[3,4-*f*]-1,4-oxazepin-5(2*H*)-ones and -thiones Containing Various Side Chains Administered Intraperitoneally[a]



compd	X	Y	Z	method of prep[b]	mp[c]	% yield[d]	recrystn solvent[e]	formula[f,g]	protection against histamine-induced lethality in the guinea pig: % survival at 30-min pretreatment time at the following doses (mg/kg, ip)		
									30	3	0.3
139	$CH_2N(CH_3)_2$	H	O	Z	150–151	13	K, N	$C_{12}H_{17}N_3O_2 \cdot C_4H_4O_4$	0		
140	$CH_2N(CH_3)_2$	H	S	H	178–179	46	K	$C_{12}H_{17}N_3OS \cdot 0.5C_4H_4O_4$	0		
65	$CH_2CH_2N(CH_3)_2$	H	O							100	0
64	$CH_2CH_2N(CH_3)_2$	H	S								100
141	$CH_2CH_2CH_2NH_2$	H	O	Y	126–134	43	H	$C_{12}H_{17}N_3O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$	100	0	
142	$CH_2CH_2CH_2NH_2$	H	S	W	164–166	64	F	$C_{12}H_{17}N_3OS \cdot C_4H_4O_4$	67		
143	$CH_2CH_2CH_2N(CH_3)_2$	H	O	X	108–110	32	F	$C_{14}H_{21}N_3O_2 \cdot 1.5C_4H_4O_4 \cdot 0.5H_2O$	100	0	
144	$CH_2CH_2CH_2N(CH_3)_2$	H	S	J	136–138	34	F	$C_{14}H_{21}N_3OS \cdot 2C_2H_2O_4$	100	33	
145	$CH(CH_3)CH_2N(CH_3)_2$	H	O	L3	204–205	55	F	$C_{14}H_{21}N_3O_2 \cdot C_2H_2O_4$	67	0	
146	$CH(CH_3)CH_2N(CH_3)_2$	H	S	L3	211–213	65	F	$C_{14}H_{21}N_3OS \cdot C_2H_2O_4$	100	0	
147	$CH_2CH(CH_3)N(CH_3)_2$	H	O	K1	173–176	28	F	$C_{14}H_{21}N_3O_2 \cdot 2HCl$	100	0	
148	$CH_2CH_2N(CH_3)_2$	CH_3	O	L3	188–190	67	F	$C_{14}H_{21}N_3O_2 \cdot 2HCl$	67	67	67
149	$CH_2CH_2N(CH_3)_2$	CH_3	S	L3	255 dec	76	F	$C_{14}H_{21}N_3OS \cdot HCl$		100	100
150				N	224–227	32	K, F	$C_{12}H_{19}N_3OS \cdot HCl$	0		
151				N	142–144	28	M	$C_{13}H_{21}N_3OS \cdot HCl$	0		

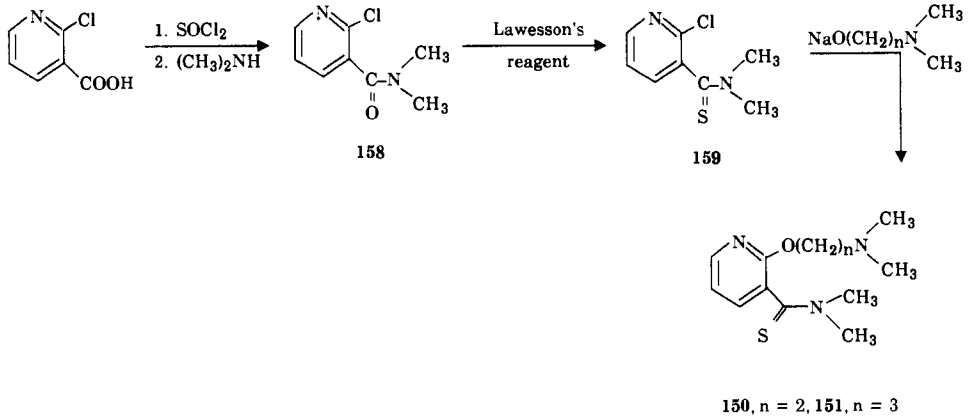
[a–f] See corresponding footnotes in Table I. [g] $C_4H_4O_4$ = fumarate; $C_2H_2O_4$ = oxalate.

Table X. EEG Effects and H_1-Antihistamine Activity in Cats

cmpd	no. of expt	dose, mg/kg, iv, required for 50% block of H_1 activity, $\bar{x} \pm SD$	dose, mg/kg, iv, required to elicit marked cortical slowing and spindling, $\bar{x} \pm SD$
64	3	0.5 ± 0.0	>20
66	3	ND[a]	>20
71	3	0.6 ± 0.4	>20
80	3	0.5 ± 0.0	>20
84	3	0.005 ± 0.005	>20
85	3	0.06 ± 0.04	>20
95	3	ND[a]	>20
96	3	ND[a]	10–20
121	2	0.5 ± 0.3	>20
astemizole	3	0.43 ± 0.12	8.0 ± 1.7
loratadine	3	0.43 ± 0.12	20 ± 0.0
brompheniramine	5	1.3 ± 1.0	1.7 ± 0.6
diphenhydramine	3	0.75 ± 0.33	0.6 ± 0.6

[a] ND = not determined.

Scheme XII



158 159

150, n = 2, 151, n = 3

Uniplate silica gel GF. HPLC separations were performed on a Waters Model 500A system using a preparative (5.5 cm × 30 cm) silica gel column.

When possible, general methods of preparation (method A–M) are illustrated by typical example; however, for compounds which do not fit into a general method (method N through miscellaneous), specific reaction conditions are given. In multistep sequences, the purity and structure of intermediates were verified spectroscopically by ^1H NMR.

Method A. Procedure 1. 3-[(1-Methyl-3-pyrrolidinyl)oxy]-2-naphthalenecarboxamide (8). To a cooled solution of 1-methyl-3-pyrrolidinol (68 g, 0.67 mol) and triethylamine (74 g, 0.73 mol) in 700 mL of dry benzene was added dropwise methanesulfonyl chloride (74 g, 0.63 mol). After stirring at room temperature for 45 min, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in 100 mL of DMF.

To a cooled suspension of NaH (10.8 g, 0.45 mol) in 75 mL of DMF was added dropwise a solution of 3-hydroxy-2-naphthalenecarboxamide (84 g, 0.45 mol) in 400 mL of DMF. The above prepared sulfonate was added dropwise, and the reaction mixture stirred and heated at reflux for 16 h. The cooled solution was diluted with 1 L of H_2O and extracted twice with 500-mL portions of $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and extracted twice with 500-mL portions of 3 N HCl. The H_2O extracts were made alkaline with 50% NaOH and extracted three times with 500-mL portions of $CHCl_3$. After drying ($MgSO_4$), the $CHCl_3$ was evaporated under reduced pressure, affording 27.4 g (22%) of a pale yellow solid, which was recrystallized from EtOAc, mp 128–130 °C.

Procedure 2. *o*-[(1-Benzyl-3-pyrrolidinyl)oxy]benzamide (1). To a suspension of 4.3 g (0.11 mol) of $NaNH_2$ in 60 mL of dry toluene was added 19.3 g (0.11 mol) of 1-benzyl-3-pyrrolidinol at a rate to maintain a temperature of 35 °C. Stirring was continued at room temperature for 3 h. To the ice-bath cooled (20–30 °C) mixture was rapidly added dropwise 19 g (0.1 mol) of *o*-toluenesulfonyl chloride. Stirring was continued at room temperature for 2.5 h and the mixture was allowed to stand overnight. The toluene was washed twice with H_2O, dried (Na_2SO_4), and concentrated.

To a suspension of 5.4 g (0.1 mol) of NaOMe in 50 mL of DMF was added 13.6 g (0.1 mol) of salicylamide in 75 mL of DMF at a rate to maintain a temperature of 50 °C. After stirring for 15 min, the above prepared sulfonate in 25 mL of DMF was added dropwise and the solution was heated at reflux for 5 h. The material was partitioned between 500 mL of EtOAc and 500 mL of H_2O. The EtOAc was extracted with dilute HCl. The aqueous acid phase was basified with dilute NaOH and extracted with EtOAc. The organic layer was dried and concentrated, and the residue was crystallized twice from $(i\text{-Pr})_2O$/EtOAc to give 12.5 g (42%) of 1, mp 120.5–122 °C.

Procedure 3. 5-Chloro-2-[(1-methyl-3-pyrrolidinyl)oxy]-benzamide (6). To a cooled suspension of NaH (2.4 g, 0.1 mol) in 50 mL of DMF was added dropwise at a rate such that the temperature did not exceed 20 °C 5-chlorosalicylamide (17 g, 0.1 mol) dissolved in 50 mL of DMF. A solution of 3-bromo-1-methylpyrrolidine (16.7 g, 0.1 mol) in 50 mL of DMF was added dropwise, and the reaction mixture was stirred and heated at reflux for 19 h. The cooled solution was diluted with 250 mL of H_2O and extracted twice with 250-mL portions of $CHCl_3$. The $CHCl_3$ was extracted three times with 500-mL portions of 3 N HCl. The aqueous extracts were made alkaline with 50% NaOH and extracted with EtOAc. Drying ($MgSO_4$) and evaporation of the EtOAc under reduced pressure afforded 6 g (23%) of product as a beige solid. Recrystallization from EtOAc afforded analytically pure crystals, mp 126–128 °C.

Method B. 2-(2-Chloroethyl)-3,4-dihydro-4-methylnaphth[2,1-*f*]-1,4-oxazepin-5(2*H*)-one (51). HCl(g) was bubbled into a solution of 8 g (0.03 mol) of **9** in 40 mL of AcOH for 2 min. While cooling in an ice bath, 6.1 g (0.06 mol) of *n*-butyl nitrite was added slowly beneath the surface of the liquid at 12–15 °C (about 10 min required). The solution was stirred at 25 °C for 18 h and heated on a steam bath for 3 h. The solution was concentrated by rotary evaporation. The residue was dissolved in 60 mL of 1,1,2,2-tetrachloroethane followed by azeotroping at 0.5 mm/steam temperature.

The residue was dissolved in $CHCl_3$ (75 mL), treated with 7 g (0.06 mol) of $SOCl_2$, and heated at reflux for 12 h. The solution was extracted with H_2O (tested acidic) followed by diluted NaOH, dried (Na_2SO_4), and concentrated. The residue was crystallized twice from $(i\text{-Pr})_2O$/EtOAc to afford 3.2 g (37%) of **51**, mp 109–111 °C.

Method C. 7-Bromo-2-(2-chloroethyl)-3,4-dihydro-4-methyl-1,4-benzoxazepin-5(2*H*)-one (15). To a solution of NaOH (9.6 g, 0.24 mol) in 200 mL of H_2O was added 37 g (0.12 mol) of 4 in one portion and the mixture was heated at reflux for 18 h. The pH was adjusted to 6.7 with concentrated HCl, and the solution was concentrated under reduced pressure. The residue was boiled in 250 mL of *i*-PrOH for 1 h and filtered. The filtrate was concentrated, dissolved in $CHCl_3$, treated with $SOCl_2$ (28.3 g, 0.24 mol), and heated at reflux for 5 h. On cooling (15 °C, ice bath), Et_3N (26.6 g, 0.26 mol) was added dropwise at such a rate that the temperature of the reaction mixture did not exceed 25 °C. The reaction was stirred at room temperature for 1 h, washed consecutively with 3 N HCl, 15% NaOH, and H_2O. After drying ($MgSO_4$), the $CHCl_3$ was evaporated under reduced pressure, affording 23 g (60%) of a brown solid. A portion was recrystallized from EtOAc/$(i\text{-Pr})_2O$, mp 92–94 °C.

Method D. Procedure 1. 2-(2-Chloroethyl)-2,3-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepin-5(*H*)-one Hydrochloride (27). To a suspension of 96 g (50% in oil, 2.0 mol) of NaH in 2 L of DMSO at 50 °C and under N_2 was added dropwise at a rate to maintain 55–60 °C a solution of 150 g (0.96 mol) of 2-chloronicotinic acid and 97 g (0.96 mol) of 1-methyl-3-pyrrolidinol in 1.5 L of DMSO. (Cooling with an ice bath was required occasionally.) The reaction mixture was stirred for 1.5 h at 60 °C. After cooling to room temperature, ~2 L of EtOAc was added and the mixture was filtered, affording 185 g of crude 2-[(1-methyl-3-pyrrolidinyl)oxy]-3-pyridinecarboxylic acid sodium salt.

HCl(g) was bubbled into a suspension of 150 g (0.61 mol) of the above sodium salt in 1 L of $CHCl_3$ until a pH meter reading of 6 was attained. To the stirred mixture was added 350 g (1.34 mol) of triphenylphosphine and 350 g (2.3 mol) of CCl_4. The resulting cloudy solution was stirred at reflux for 1.5 h and 100

mL of EtOH was added (no heating). The solution was stirred for 1 h while it was cooled in an ice bath and 200 mL of isooctane was added. The solution was extracted four times with a total of 800 mL of dilute HCl. The combined acid extract was made basic with NaOH and extracted with $CHCl_3$. The $CHCl_3$ was dried (Na_2SO_4) and concentrated. The residue was dissolved in 500 mL of *i*-PrOH and 500 mL of $(i\text{-Pr})_2O$ and made acidic with ethereal HCl to give 82 g (49%) of crystalline material, mp 148–151 °C. Recrystallization from *i*-PrOH raised the melting point to 149–152 °C.

Procedure 2. 6-Chloro-2-(2-chloroethyl)-3,4-dihydro-4-methylpyrido[3,4-*f*]-1,4-oxazepin-5(2*H*)-one (46). To a suspension of 2.1 g (60% in oil, 0.052 mol) of NaH in 125 mL of DMF, heated at 60 °C, under a N_2 blanket was added dropwise at such a rate to maintain 60 °C a solution of 2.65 g (0.026 mol) of 1-methyl-3-pyrrolidinol and 5.0 g (0.026 mol) of 3,5-dichloropyridine-4-carboxylic acid in 40 mL of DMF. Subsequent to this addition, the mixture was heated to 75 °C for 3 h. The solvent was removed by rotary evaporation (60 °C, 5 mmHg). The entire solid residue was suspended in 150 mL of CH_2Cl_2 and HCl(g) was added until the pH meter read 3. To the resulting mixture was added 15 g (0.057 mol) of triphenylphosphine and 15 g of CCl_4 and the mixture was heated at reflux. After 1 h, 7.5 g (0.029 mol) of triphenylphosphine and 7.5 g of CCl_4 were added. Another 7.5 g (0.029 mol) of triphenylphosphine and 15 g of CCl_4 were added 1 h later. After stirring for 1 h, 20 mL of Et_3N was added dropwise. The reaction mixture was washed with 6 × 50 mL of 3 N HCl, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. To the residue was added EtOAc, which caused much tarry material to separate from the solution, leaving the desired product and triphenylphosphine oxide in solution. The mixture was chromatographed by column chromatography using silica gel as the stationary phase and EtOAc as the eluent. Similar fractions were combined, and EtOAc was removed by rotary evaporation, yielding 0.6 g (7%) of white crystals, mp 134–138 °C.

Method E. 7-Bromo-2-(2-chloroethyl)-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepin-5(2*H*)-one (32). To a suspension of 51.2 g of 60% NaH in oil (1.28 mol) in 1 L of THF heated at reflux and under N_2 was added a solution of 144 g (0.61 mol) of **166** and 61.6 g (0.61 mol) of *N*-methyl-3-pyrrolidinol in 1 L of THF dropwise at reflux (1 h). Heating was continued at reflux with vigorous agitation for 1.5 h. After cooling, approximately 5 mL of H_2O was added and the mixture soon solidified. (Additional THF was added to aid in stirring.) The mixture was filtered, washed with several portions of THF, and dried at 50 °C (0.5 mmHg) overnight, giving 190 g of crude sodium salt.

The entire quantity of crude sodium salt (190 g) was added slowly to 1 kg of $SOCl_2$ while cooling in an ice bath. The reaction mixture was stirred for 10 min at 10 °C and 10 min at room temperature. $SOCl_2$ was removed by rotary evaporation at 65 °C (30 mmHg) and the residue was azeotroped twice with toluene. The residue was taken up in CH_2Cl_2 (1 L) and diisopropylethylamine was added slowly until the solution just turned basic (pH paper). The mixture was stirred for 1 h at room temperature and washed successively with 1 N HCl (2 × 200 mL), dilute NaOH (2 × 200 mL), and H_2O (100 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The black residue was triturated five times with 5% toluene in $(i\text{-Pr})_2O$ to give 60 g (31%) of light brown crystals. A sample was recrystallized from $(i\text{-Pr})_2O$ to give an analytically pure sample, mp 71–75 °C.

Method F. 2-(2-Chloroethyl)-3,4-dihydro-4-methyl-7-(trifluoromethyl)-1,4-benzoxazepin-5(2*H*)-one (25). To a suspension of 30 g of 60% NaH in oil (0.75 mol) in 600 mL of THF under N_2 and heated at reflux was added dropwise at a rate to maintain good reflux a solution of 74.5 g (0.36 mol) of 2-fluoro-5-(trifluoromethyl)benzoic acid (**161**) and 36.18 g (0.36 mol) of *N*-methylpyrrolidinol in 200 mL of THF. (Mild external heating was required.) The reaction mixture was stirred at reflux for 1.5 h. After cooling to room temperature, the solid was filtered and washed with THF, affording 85 g of crude 2-[(1-methyl-3-pyrrolidinyl)oxy]-5-(trifluoromethyl)benzoic acid sodium salt.

To a suspension of 81 g (0.26 mol) of the above sodium salt in 600 mL of benzene at 10 °C was added 35 g (0.27 mol) of oxalyl chloride. The mixture was stirred mechanically at ~10 °C for 2.5 h and 5–7 mL of DMF was added slowly followed by 20.0 g (0.16 mol) of oxalyl chloride. After 30 min, diisopropylethylamine was added to basify the mixture.

The reaction mixture was extracted with 1 N NaOH (3 × 300 mL) followed by 1 N HCl (3 × 200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give 25 g of crude material. Recrystallization from $(i\text{-Pr})_2O$ gave 15 g of pure crystals, mp 102–103 °C. A second and third crop were collected, bringing the total yield to 19 g (8.2%).

Procedure G. 8-Chloro-2-(2-chloroethyl)-3,4-dihydro-4-methyl-1,4-benzoxazepine-5(2*H*)-thione (18). A mixture of P_4S_{10} (23 g, 0.12 mol) and 23 g of K_2S ground together was added to a solution of 17 (43 g, 0.16 mol) in 400 mL of dry toluene. The reaction mixture was stirred and heated at reflux for 24 h. The mixture was filtered hot, and the filtrate was concentrated under reduced pressure, affording 25.5 g (55%) of an orange oil, which solidified on standing at room temperature. Recrystallization from EtOH afforded an analytical sample, mp 105–106 °C.

Method H. 2-(2-Chloroethyl)-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-thiazepine-5(2*H*)-thione (42). A suspension of 4.8 g (0.012 mol) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) and 4.3 g (0.017 mol) of **41** in 100 mL of toluene was heated at reflux for 3 h. The reaction mixture was washed twice with (1 N) NaOH. The organic layer was concentrated and the residue was subjected to HPLC using silica gel as the stationary phase and eluting with 1:1 EtOAc/hexane. Like fractions were combined and concentrated by rotary evaporation to give 2.9 g (43%) of yellow crystals, mp 160–162 °C.

Method I. Procedure 1. 7-Bromo-2-(2-chloroethyl)-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione (33). To a solution of 5.0 g (0.016 mol) of **32** in 25 mL of CH_3CN was added 2.07 g (0.005 mol) of P_4S_{10}. The mixture was heated at reflux for 3 h. The reaction mixture was diluted with 100 mL of toluene and filtered. The filtrate was washed with 3 × 50 mL of saturated $NaHCO_3$ and 50 mL of H_2O, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to 5–10 mL. Crystallization ensued and 3.0 g of crystals were collected. The mother liquor was concentrated, giving an additional 1.0 of crystals. The two crops were combined and recrystallized from $(i\text{-Pr})_2O$ to give 3 g (56%) of yellow, analytically pure crystals, mp 138–141 °C.

Procedure 2. 2-(2-Chloroethyl)-2,3-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepine-5(4*H*)-thione (28). A solution of 59 g (0.25 mol) of **27** in 1500 mL of $CHCl_3$ was treated with 41.5 g (0.095 mol) of P_4S_{10} and the mixture was heated at reflux for 18 h. The mixture was filtered and the filtrate was extracted with dilute NaOH. The organic layer was concentrated and the residue was dissolved in 250 mL of boiling *i*-PrOH. On cooling, 28 g (44%) of solid was obtained. Recrystallization from *i*-PrOH gave an analytically pure sample, mp 134–136 °C.

Method J. 4-Ethyl-2-[2-(dimethylamino)ethyl]-1,2,3,4-tetrahydro-4-methyl-5*H*-1,4-benzodiazepine-5-thione (111). A mixture of 14 g (0.045 mol) of **110** and 11.1 g (0.05 mol) of P_2S_5 in 100 mL of dry pyridine was heated at reflux (solution occurred) with stirring for 5 h. The solution was concentrated (ca. 2.5 mm/100 °C) and the residue was partitioned between dilute NaOH and $CHCl_3$. The organic phase was dried (Na_2SO_4) and concentrated. The residue was crystallized three times from $(i\text{-Pr})_2O$ to give 6 g (46%) of **111**, mp 92–94 °C.

Method K. Procedure 1. 7-Chloro-2-[2-(dimethylamino)ethyl]-3,4-dihydro-4,8-dimethylpyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione Ethanedioate (88). To 60 mL of freshly collected Me_2NH was added 3.0 g (0.01 mol) of **39**. The reaction flask was sealed tightly and left standing at room temperature for 2 days. After cooling, the flask was opened and the solvent was evaporated in a stream of air. The crude crystalline residue was taken up in ~100 mL of CH_2Cl_2, washed with 2 × 50 mL of 1 N NaOH, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The residue was treated with oxalic acid in *i*-PrOH to afford 3.0 g (74%) of yellow crystals, mp 191–192 °C.

Procedure 2. 3,4-Dihydro-4-methyl-2-(2-morpholinoethyl)-1,4-benzoxazepine-5(2*H*)-thione Hydrochloride (126). A solution of 20.4 g (0.08 mol) of **12** in 60 mL of morpholine was heated at reflux 5 h and concentrated. The residue was partitioned between dilute NaOH and $CHCl_3$. The $CHCl_3$ was dried (Na_2SO_4) and concentrated. The HCl salt was crystallized from 4-

methyl-2-pentanone/DMF and recrystallized twice from EtOH/DMF to give 14 g (51%) of yellow crystals, mp 253–256 °C dec.

Method L. Procedure 1. 7-Bromo-3,4-dihydro-4-methyl-2-[2-[methyl(phenylmethyl)amino]ethyl]pyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione Ethanedioate (92). To a suspension of 5.0 g (0.015 mol) of **33** in 40 mL of absolute EtOH was added 3.6 g (0.030 mol) of benzylmethylamine. The reaction mixture was heated at reflux and after 3 h an additional 1.8 g (0.015 mol) of benzylmethylamine was added and heating was continued for 24 h. The solvent was removed by rotary evaporation at 60 °C (30 mm) followed by 75 °C (0.5 mm) for 1 h. The residue was taken up in 100 mL of CH_2Cl_2, washed with dilute NaOH (2 × 50 mL) and H_2O (50 mL), dried (Na_2SO_4), filtered, concentrated by rotary evaporation, and subjected to high vacuum at 75 °C for 2 h. The residue was treated with oxalic acid in *i*-PrOH/EtOH to give 5.9 g (77%) of yellow crystals, mp 192–203 °C dec.

Procedure 2. 2-[2-(Dimethylamino)ethyl]-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione (*E*)-2-Butenedioate Ethanol (2:1) Hemihydrate (64). A sample of 15 g (0.058 mol) of **28** was added to 32.8 g (0.29 mol) of 40% aqueous dimethylamine in 100 mL of EtOH in a steel bomb and the mixture was heated to 100 °C with mild stirring for 18 h. The cooled solution was partitioned between $CHCl_3$ and dilute NaOH. The organic layer was dried (Na_2SO_4) and concentrated. The residue was treated with 7 g of fumaric acid in *i*-PrOH. The resulting crystals were recrystallized from the same solvent to give **19** g (86%) of yellow crystals, mp 105–129 °C. A 5-g sample was recrystallized from 95% ethanol to give 3 g of analytically pure crystals, mp 105–118 °C.

Procedure 3. 2-[2-(Dimethylamino)ethyl]-3,4-dihydro-4,8-dimethylpyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione Ethanedioate (93). To 40 mL of dimethylamine was added a solution of 4.9 g (0.018 mol) of **37** in 15 mL of MeOH. The flask was sealed and allowed to stand at room temperature for 3 days. The solvent was evaporated in a stream of air and the syrupy residue was dissolved in CH_2Cl_2 which was washed twice with 1 N NaOH and once with H_2O, dried (Na_2SO_4), filtered, and concentrated on the rotary evaporator. The residual syrup was treated with oxalic acid in *i*-PrOH to give 5.5 g (83%) of yellow crystals, which melted at 215–216 °C.

Method M. 2-[2-(1-Acetidinyl)ethyl]-7-chloro-3,4-dihydro-4,8-dimethylpyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione Ethanedioate Hemihydrate (89). To a solution of 3.0 g (0.01 mol) of **39** in 20 mL of DMSO was added ~5 g of Na_2CO_3 and 1.4 g (0.0245 mol) of azetidine. After stirring of the reaction mixture for 2 days at room temperature, an additional 0.3 g (0.005 mol) of azetidine was added and the stirring was continued for 3 days. The reaction mixture was poured in 300 mL of H_2O and extracted with 2 × 100 mL of benzene. The combined benzene extracts were washed with 3 × 75 mL of H_2O, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation at 50 °C. The residue was treated with oxalic acid in *i*-PrOH, which afforded 3.5 g (82%) of yellow, analytically pure crystals, mp 162–166 °C dec.

Method N. 2-[2-(Dimethylamino)ethoxy]-*N*,*N*-dimethyl-3-pyridinecarbothioamide Hydrochloride (150). A 2.3-g (0.026 mol) sample of 2-(dimethylamino)ethanol in DMF was added dropwise to 1.1 g (0.029 mol) of 60% NaH/mineral oil suspended in 100 mL of DMF. After stirring of the mixture for 0.5 h, 4.7 g (0.024 mol) of **158** was added. The mixture was stirred at 75 °C for 6 h, cooled, and treated with 100 mL of H_2O. The solution was extracted 10 times with 100 mL of $(i\text{-Pr})_2O$. The ether was concentrated to 100 mL and extracted with dilute HCl. The acid layer was made basic with NaOH and extracted with $CHCl_3$ which was dried (Na_2SO_4) and concentrated. The residue was dissolved in 4-methyl-2-pentanone and made acidic with *i*-PrOH/HCl. The resulting crystals were recrystallized from a mixture of MeOH/*i*-PrOH to give 2.4 g (32%) of **150**, mp 224–227 °C.

Method O. 2-(2-Aminoethyl)-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione (*E*)-2-Butenedioate (2:1) (67). To a suspension of 12.15 (0.033 mol) of **152** in 150 mL of absolute EtOH was added 2.08 g (0.035 mol) of an 85% solution of hydrazine hydrate in H_2O. The mixture was heated to reflux for 2 h. After cooling to room temperature, solid phthalylhydrazide was removed by filtration. EtOH was removed by rotary evaporation and the residue partitioned between 180 mL $CHCl_3$ and 50 mL of dilute aqueous NaOH. The organic layer was washed with dilute aqueous NaOH (3 × 30 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The crude oil was treated with fumaric acid in *i*-PrOH, which yielded 6.70 g (68.7%) of pale-yellow crystals, mp 208–209 °C.

Method P. 2-[2-[Bis(phenylmethyl)amino]ethyl]-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione (*E*)-2-Butenedioate (136). To a solution of 3.16 g (0.013 mol) of **67** in ~25 mL of dry MeOH was added methanolic HCl to pH 5–6 (pH paper), followed by ~2–3 g of 3-Å molecular sieves, 6.89 g (0.065 mol) of benzaldehyde and 2.04 g (0.0325 mol) of $NaBH_3CN$. The pH was again adjusted to pH 7 (pH paper) with methanolic HCl. After 6 h of stirring at room temperature, TLC (eluting with 6% NEt_3 in MeOH) indicated what appeared to be exclusively monoalkylated product. To the reaction mixture was then added 1.0 g (0.009 mol) benzaldehyde, and the mixture was stirred overnight at room temperature. The reaction mixture was filtered and concentrated by rotary evaporation. The residue was taken up in $CHCl_3$ (100 mL) and the organic phase was washed with dilute aqueous NaOH (2 × 30 mL). The organic phase was concentrated by rotary evaporation. The residue was dissolved in 100 mL of dilute HCl, which was subsequently washed with EtOAc (2 × 30 mL), made basic with dilute aqueous NaOH, and extracted with $CHCl_3$ (4 × 30 mL). The combined $CHCl_3$ extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue contained both the mono- and dialkylated product as indicated by TLC and ^1H NMR.

To the 3.0 g of crude product which was dissolved in 30 mL of dry MeOH were added methanolic HCl to pH 4–5 (pH paper), 10.0 g (0.094 mol) of benzaldehyde, and 2.00 g (0.0319 mol) of $NaBH_3CN$. To the neutral (pH paper) reaction mixture was added ~1 g of 3-Å molecular sieves. The reaction mixture was stirred for 6 days at room temperature.

After filtration, the solvent was removed by rotary evaporation (70 °C, H_2O aspirator). The residue was dissolved in ~100 mL of $CHCl_3$ and washed with dilute aqueous NaOH (2 × 50 mL). The $CHCl_3$ was removed by rotary evaporation and the residue was dissolved in 100 mL of dilute aqueous HCl. The aqueous acidic layer was washed with EtOAc (2 × 50 mL). The combined EtOAc extracts were further extracted with dilute HCl (2 × 30 mL) and all acid layers were combined. (The product appeared to be somewhat soluble in EtOAc.) The combined aqueous acidic extracts were made basic with concentrated NaOH solution and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ layer was dried (Na_2SO_4), filtered, and concentrated by rotary evaporation (70 °C, H_2O aspirator). The 3.0 g of crude product was dissolved in hot *i*-PrOH and treated with fumaric acid to give 1.40 g (20.2%) of crystalline material, mp 123–126 °C.

Method Q. 7-Amino-2-[2-(dimethylamino)ethyl]-3,4-dihydro-4-methyl-1,4-benzoxazepine-5(2*H*)-thione (106). To 7.0 g (0.023 mol) of **105** was added 250 mL of 23% $(NH_4)_2S$ in H_2O. Enough EtOH was added to dissolve the starting compound (~50–60 mL). The reaction mixture was heated at reflux for 5 h. After cooling, the reaction mixture was acidified with concentrated HCl. The EtOH was removed by rotary evaporation at 70 °C. The remaining aqueous solution was washed with $CHCl_3$ (3 × 100 mL), filtered, cooled with ice, and made just basic with 50% NaOH. The H_2O layer was then extracted with $CHCl_3$ (3 × 100 mL), which was dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The residue was crystallized from *i*-PrOH to give 3.5 g (55%) of yellow crystals, mp 176–179 °C.

Method R. *N*-[2-[2-(Dimethylamino)ethyl]-2,3,4,5-tetrahydro-4-methyl-5-thioxo-1,4-benzoxazepin-7-yl]acetamide Ethanedioate Monohydrate (107). To 3.5 g (0.0125 mol) of **106** was added 30 mL of acetic anhydride and the mixture was swirled until dissolution occurred. Excess acetic anhydride was removed by rotary evaporation and the residue was taken up in 100 mL of CH_2Cl_2, washed successively with 2 × 50 mL of 1N KOH and 50 mL of H_2O, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The crude residue was treated with oxalic acid in EtOH to give 5.0 g (93%) of yellow, analytically pure crystals, mp 104–110 °C.

Method S. 3,4-Dihydro-4-methyl-2-[2-(1*H*-pyrazol-1-yl)-ethyl]pyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione (138). To a

suspension of 2.16 g (0.054 mol) of NaH in 20 mL of DMF was added dropwise a solution of 2.92 g (0.043 mol) of pyrazole in 10 mL of DMF. The resulting solution was then added dropwise to a solution of 10.0 g (0.039 mol) of **28** in 30 mL of DMF. The reaction flask was sealed and stirred overnight at room temperature.

The solvent was removed by rotary evaporation (90 °C, 30 mm) and the residue was taken up in 200 mL of $CHCl_3$, which was subsequently washed with H_2O (2 × 50 mL) followed by dilute aqueous NaOH (50 mL). The organic layer was then dried (Na_2SO_4), filtered, and concentrated by rotary evaporation and the residue was crystallized twice from *i*-PrOH to give 3.45 g (31%) of yellow crystals, mp 119–121 °C.

Method T. 2-(2-Chloroethyl)-3,4-dihydro-4-methylpyrido[4,3-*f*]-1,4-oxazepin-5(2*H*)-one Hydrochloride (47). A mixture of **153** free base (49 g, 0.11 mol), 125 mL of *t*-BuOH, and 34 g (0.6 mol) of KOH was stirred at room temperature for 88 h and diluted with 150 mL of toluene. The mixture was filtered and the filtrate was concentrated by rotary evaporation.

The residue was dissolved in $CHCl_3$ (mild cooling was required) and the pH adjusted to 6 by passing HCl(g) into the solution. The resulting mixture was concentrated by rotary evaporation and azeotroped once with 400 mL of toluene at high vacuum. The residue was dissolved in 400 mL of $CHCl_3$ and 63 g of triphenylphosphine was added followed by 70 g of CCl_4. The solution was stirred at reflux for 2 h and another 30 g of triphenylphosphine was added. After an additional hour at reflux, another 78 g of CCl_4 and 63 g of triphenylphosphine were added and reflux was continued for 4 h. The solution was extracted with dilute NaOH and concentrated. The residue was partitioned between toluene and dilute HCl and the organic phase was extracted five times with dilute HCl. The combined acid extract was made basic with NaOH and extracted with $CHCl_3$, which was dried (Na_2SO_4) and concentrated. The residue was chromatographed on a 7 × 25 cm column of silica gel eluting with acetone. Like fractions were combined to give 5.8 g (20%) of crystalline material. Treatment of a small sample in *i*-PrOH/$(i\text{-Pr})_2O$ with Et_2O/HCl afforded the HCl salt, mp 188–190 °C.

Method U. 2-(2-Chloroethyl)-4-ethyl-1-methyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (45). To 206 g (1 mol) of 1-ethyl-*N*-methyl-*N*-phenyl-3-pyrrolidineamine was added 660 mL (1.05 mol) of 15% *n*-BuLi in hexane. The solution was heated at reflux for 2 h and poured onto solid CO_2. The CO_2/hexane mixture was allowed to evaporate overnight, leaving a dry, yellow solid. To a solution of this solid in $CHCl_3$ was added dropwise with stirring, 1 mol of PCl_3. (The temperature rose to reflux during addition and remained there throughout most of the addition.) Upon completion of this addition, the mixture was stirred for 1 h and cautiously quenched with H_2O. The resulting mixture was made basic with NaOH and the $CHCl_3$ was separated, dried (Na_2SO_4), and concentrated. The residue was crystallized from $(i\text{-Pr})_2O$ to give 112 g (42%), mp 75–79 °C.

Method V. 2-[2-(Dimethylamino)ethyl]-3,4-dihydropyrido[3,2-*f*]-1,4-oxazepin-5(2*H*)-one (*E*)-2-Butenedioate (63). An 8.0-g (0.026 mol) sample of **156** free base was partitioned between $CHCl_3$ and dilute NaOH. The $CHCl_3$ was dried (Na_2SO_4) and concentrated, and the residue was azeotroped once with 80 mL of benzene. A solution of the residue in 20 mL of THF was added slowly to a stirred suspension of 8.3 g (0.052 mol) of 35% KH/mineral oil in 80 mL of THF. The mixture was stirred at reflux for 4 h, cooled, and treated with 10 mL of *i*-PrOH. The solution was partitioned between $(i\text{-Pr})_2O$ and dilute HCl. The acid layer was made basic with NaOH and extracted four times with $CHCl_3$. The $CHCl_3$ was concentrated and the residue was subjected to HPLC (silica, 90% EtOH/10% Et_3N). The desired fractions were concentrated and the residue (1.3 g) was treated with 0.7 g of fumaric acid in 25 mL of *i*-PrOH to give 1.2 g of title compound (13%), mp 160–164 °C.

Method W. 2-(3-Aminopropyl)-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione (*E*)-2-Butenedioate (142). To a solution of 15.0 g (0.064 mol) of 141 in 50 mL of CH_2Cl_2 was added 15.24 g (0.07 mol) of di-*tert*-butyl dicarbonate. The solution was stirred for 30 min at room temperature. The solvent was removed by rotary evaporation and the crude *tert*-butyl carbamate was purified by HPLC on a silica gel column, eluting with EtOAc to give 15 g (0.045 mol, 70.3%) of the protected amine as an oil. To a solution of 13.5 g (0.04 mol) of this oil in dry toluene was added 8.16 g (0.02 mol) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide. The reaction mixture was heated to 80 °C for 2 h. An additional quantity (2.0 g, 0.005 mol) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide was added and the heating was continued for 1 h. Another 4.0 g (0.01 mol) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide was added and the heating was continued for 5 h. After cooling, the toluene was decanted, washed with dilute aqueous NaOH (5 × 30 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. *i*-PrOH was added to the residue, resulting in precipitation of an impurity, After filtration, *i*-PrOH was removed by rotary evaporation and the residue was purified by HPLC on a silica gel column, eluting with 1% MeOH/99% $CHCl_3$. Approximately 6 g (0.017 mol, 42.6%) of material was collected and treated with 100 mL of a solution of trifluoroacetic acid/anisole/CH_2Cl_2, 40/10/50, v/v/v for 30 min. The solvent blend was removed by rotary evaporation and the residue was taken up in 150 mL of CH_2Cl_2. The organic phase was washed with dilute aqueous NaOH (3 × 40 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The residue was treated with fumaric acid in *i*-PrOH, which yielded 4.0 g (0.011 mol, 64%) of the salt. Recrystallization from *i*-PrOH afforded an analytical sample, mp 164–166 °C.

Method X. 2-[3-(Dimethylamino)propyl]-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepin-5(2*H*)-one (*E*)-2-Butenedioate (2:3) Hemihydrate (143). To a sample of **141** (5.0 g, 0.021 mol) was added, while the sample cooled in a water bath, an 88% aqueous solution of formic acid (20 g, 0.383 mol). To the resulting solution was added a solution of 37% aqueous formaldehyde (inhibited with 13% MeOH) (10.7 g, 0.131 mol). The resulting solution was heated on a steam bath for 5.5 h. After cooling, dilute aqueous HCl (100 mL) was added and the solution was evaporated to dryness. The residue was dissolved in H_2O (50 mL), neutralized with dilute aqueous KOH, and extracted with $CHCl_3$ (4 × 50 mL). The $CHCl_3$ extracts were combined, dried (Na_2SO_4), and concentrated by rotary evaporation. The resulting residue was treated with fumaric acid in hot *i*-PrOH and yielded 3.0 g (31.8%, 0.0067 mol) of the salt, which was recrystallized twice from *i*-PrOH, mp 108–110 °C.

Method Y. 2-(3-Aminopropyl)-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepin-5(2*H*)-one Ethanedioate Hemihydrate (141). A 5-g (0.022 mol) sample of **157** free base in 150 mL of EtOH was treated with about 1.5 g of Raney Ni. The mixture was hydrogenated in a Parr apparatus at 60 °C and 40 psi. The mixture was cooled and filtered. The filtrate was concentrated and the residue was treated with 3.9 g of oxalic acid in 130 mL of boiling *i*-PrOH containing 2 mL of H_2O. The hot solution was filtered and allowed to cool. The resulting solid was recrystallized from EtOH to give 3 g (43%), mp 126–134 °C.

Method Z. 2-[(Dimethylamino)methyl]-2,3-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepin-5(4*H*)-one (*E*)-2-Butenedioate (139). (This compound was made by a three-step procedure.) Dimethylamine (40% solution, 22.6 g, 0.2 mol) was added dropwise with stirring to a solution of epichlorohydrin (16 mL, 0.2 mol) in MeOH (100 mL) at 5 °C. After 2 h at 5 °C, a chilled solution of $MeNH_2$ (40% solution, 86 mL, 1 mol) was added and stirring continued at 5 °C for 1 h and then at room temperature overnight. The solvents were evaporated and the clear oil was subjected to high vacuum at 75 °C for 1.5 h to give 28.23 g (~84% yield) of 1-(dimethylamino)-3-(methylamino)-2-propanol hydrochloride.

To a stirred mixture of the above hydrochloride (24.1 g, 0.143 mol) and 2-chloronicotinic acid (22.6 g, 0.143 mol) in 150 mL of MeCN and 60 mL of H_2O was added in four portions a solution of dicyclohexylcarbodiimide (DCC, 33 g, 0.16 mol) in 90 mL of MeCN. (After the addition of the second portion, an ice bath was necessary for maintaining the temperature at room temperature.) After 2.5 h, an additional 10 g of 2-chloronicotinic acid was added. After an additional hour, 15 g of DCC in 200 mL of MeCN was added and the reaction mixture was left to stir at room temperature overnight. Concentrated HCl was added to the reaction mixture to pH 2 to convert the excess DCC to dicyclohexylurea and the white solid was removed by filtration and rinsed with aqueous MeCN. The filtrate and washings were evaporated to a paste, which was partitioned between CH_2Cl_2 and aqueous

K_2CO_3. The H_2O layer was extracted two more times with CH_2Cl_2. The CH_2Cl_2 solutions were back-washed with brine, dried (Na_2SO_4), and evaporated to give 56 g of oil. This oil was chromatographed on 250 g of silica gel eluting with MeOH to give 26.97 g of crude 2-chloro-*N*-[3-(dimethylamino)-2-hydroxypropyl]-*N*-methylbenzamide as an oil.

The 26.97 g of the above compound was dissolved in 200 mL of toluene, heated to distill out about 40 mL of solvent, and then refluxed with a Dean–Stark trap for 0.5 h. NaH (50% suspension in mineral oil, 15 g, 0.3 mol) was added portionwise to the toluene solution at room temperature. The mixture was heated at reflux for 20 min, cooled, treated with *i*-PrOH and Celite, and filtered. The filtrate was acidified with HCl solution in *i*-PrOH. The resultant precipitate was collected by filtration, rinsed, and dried under N_2 to give 11 g of hygroscopic product. Some second and third crop material was obtained from the mother liquor and washings. All three crops were combined and dissolved in H_2O; the solution was made basic with an excess amount of K_2CO_3 and extracted three times with CH_2Cl_2; the CH_2Cl_2 solutions were washed with saturated NaCl, dried over $MgSO_4$, treated with charcoal, filtered, and evaporated to give 8.8 g of **139** as a brown oil.

A 1.9-g sample of the oil was treated with fumaric acid in MeOH/acetone. One recrystallization from the same gave 1.4 g of white solid, mp 150–151 °C.

Method AA. 2-[2-(Dimethylamino)ethyl]-3,4-dihydro-4-methyl-1,4-oxazepino[6,7-*c*]quinolin-5(2*H*)-one Ethanedioate (122). To a suspension of 19.4 g (0.172 mol) of KH (35% in mineral oil) in 150 mL of THF was rapidly added dropwise 12.4 g (0.086 mol) of the free base of **160**. After 10 min, 20 g (0.086 mol) of 3-(ethoxycarbonyl)-4-chloroquinoline was added over a period of 30 min. The mixture was stirred overnight at room temperature and partitioned between H_2O (add carefully) and $(i\text{-Pr})_2O$. The aqueous layer was extracted twice with $(i\text{-Pr})_2O$. The aqueous layer was extracted continuously for 18 h with $CHCl_3$. The $CHCl_3$ was dried (Na_2SO_4) and concentrated. The residue was chromatographed on the Waters 500 HPLC using silica gel as the stationary phase and 97% ethanol/3% triethylamine as the eluent. The fractions containing material of molecular weight 299 were combined and concentrated, yielding 4 g (15.6%) of an oil. Treatment of the oil with oxalic acid in EtOH gave the salt melting at 214–218 °C.

Method BB. 2-(2,3,4,5-Tetrahydro-4-methyl-5-thioxopyrido[3,2-*f*]-1,4-oxazepin-2-yl)trimethylethanaminium Iodide (129). To a solution of 2.66 g (0.01 mol) of **64** free base in 4-methyl-2-pentanone (15 mL) was added a solution of 1.4 g (0.01 mol) of methyl iodide in 15 mL of 4-methyl-2-pentanone. The resulting solid was collected by filtration and recrystallized from EtOH/4-methyl-2-pentanone (1:1) to give 2.5 g (78%) of title compound, mp 221–225 °C.

Method CC. 2-(2-Chloroethyl)-3,4-dihydro-4-methyl-7-phenylpyrido[3,2-*f*]-1,4-oxazepine-5(2*H*)-thione (40). (This compound was prepared in a series of three steps.) To a suspension of 22.7 g (60% in oil, 0.57 mol) of NaH in 400 mL of THF, under an N_2 blanket and heated at reflux, was added, at a drop rate to maintain good reflux, a solution of 63 g (0.27 mol) of **164** and 27.2 g (0.27 mol) of *N*-methylpyrrolidinol in 350 mL of THF (occasional external heating was required). The mixture was heated at reflux for 4 h and 2.5 g (60% in oil, 0.063 mol) of NaH was cautiously added to complete the reaction. Heating was continued for another 2 h. After cooling, 3–6 mL of H_2O was added and the resultant precipitate was collected, washed with THF, and dried to give 97 g of crude 2-[(1-methyl-3-pyrrolidinyl)oxy]-5-phenyl-3-pyridinecarboxylic acid sodium salt.

The entire portion of the above sodium salt was added to 400 mL of $SOCl_2$ (reaction is slightly exothermic) and stirred at room temperature for 10 min. The $SOCl_2$ was removed by rotary evaporation and the residue azeotroped once with toluene. The residue was suspended in 600 mL of CH_2Cl_2 and diisopropylethylamine was cautiously added until the solution was basic to a piece of moistened pH paper. The reaction solution was washed with 1 N HCl (3 × 200 mL) and 1 N NaOH (3 × 200 mL), dried (over Na_2SO_4), filtered, concentrated by rotary evaporation, taken up in toluene, charcoaled twice, and concentrated by rotary evaporation. The residue (60 g) was taken up in EtOAc and passed through a short bed of silica gel using 25% hexane/75% EtOAc. Similar fractions were combined to give ~25 g of crude (95% min purity) 2-(2-chloroethyl)-3,4-dihydro-4-methyl-7-phenylpyrido-[3,2-*f*]-1,4-oxazepin-5(2*H*)-one as an oil.

To 12.5 g (0.04 mol) of the above oil was added 125 mL of toluene and 16 g (0.04 mol) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide. The reaction mixture was heated at reflux for 4 h. After standing overnight, the toluene was decanted, washed with 1 N NaOH (3 × 100 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The residue was further purified by column chromatography using silica gel as the stationary phase and eluting with EtOAc/hexane 1:1, (v/v). Like fractions were combined and concentrated, giving 8.5 g (0.026 mol, 64%) of desired product, mp 156–158 °C.

Method DD. 2-(2-Chloroethyl)-3,4-dihydro-4-methyl-7-nitro-1,4-benzoxazepin-5(2*H*)-one (23). To a suspension of 109 g (60% in oil, 2.73 mol) of NaH in 800 mL of THF under N_2 and at reflux was added a solution of 250 g (1.24 mol) of 2-chloro-5-nitrobenzoic acid and 125 g (1.24 mol) of *N*-methyl-3-pyrrolidinol in 1 L of THF at such a rate as to maintain good reflux. The reaction mixture was heated at reflux for 3 h. After cooling, concentrated HCl was added until the reaction mixture was neutral. Approximately 500 mL of *i*-PrOH was added, the reaction mixture was filtered to remove NaCl, and the filtrate was concentrated by rotary evaporation to give approximately 350 g of crude 2-[(1-methyl-3-pyrrolidinyl)oxy]-5-nitrobenzoic acid sodium salt.

To 30 g (0.11 mol) of the crude sodium salt was added 100 mL of $SOCl_2$. After 10 min of stirring at room temperature, the $SOCl_2$ was removed by rotary evaporation. Another 30 mL of $SOCl_2$ was added and removed by rotary evaporation. The residue was azeotroped once with toluene and taken up in 200 mL of CH_2Cl_2. To the reaction mixture was added diisopropylethylamine until the mixture was just basic to a piece of moistened pH paper. The reaction mixture was washed with 1 N HCl (3 × 100 mL), H_2O (100 mL), and 1 N NaOH (3 × 200 mL), dried (Na_2SO_4), filtered, concentrated by rotary evaporation, decolorized with NuChar S-N twice in toluene, and concentrated by rotary evaporation. The crude residue was crystallized from $(i\text{-Pr})_2O$/EtOAc to give 5 g (16%) of light yellow crystals, mp 91–92 °C.

Method EE. 8-(2-Chloroethyl)-6,7,8,9-tetrahydro-6-methyl-5*H*-pyrido[3,2-*c*]azepin-5-one Monohydrochloride (43). (This compound was prepared in a series of four steps.) To a mixture of 54 g (0.26 mol) of 3-carboxy-2-pyridineacetic acid ethyl ester[9] and 24.4 g (0.29 mol) of sodium bicarbonate in 300 mL of DMF was added 60.8 g (0.39 mol) of ethyl iodide. The mixture was stirred at 50 °C for 24 h, cooled to 25 °C, and treated with 300 mL of H_2O. The H_2O solution was extracted three times with $(i\text{-Pr})_2O$ and the organic phase was extracted with dilute HCl. The combined acid extracts were made basic with NaOH and extracted with $(i\text{-Pr})_2O$. The ether layer was dried (Na_2SO_4) and concentrated, and the residue was distilled at 128–130 °C (0.5 mm) to give 47 g (70%) of 3-(ethoxycarbonyl)-2-pyridineacetic acid ethyl ester as an oil.

To a suspension of 8 g (0.2 mol) of 60% NaH/mineral oil in 500 mL of DMSO was added dropwise at room temperature 40 g (0.17 mol) of the above oil in 40 mL of DMSO. After stirring a few min, 30 g (0.18 mol) of 3-bromo-1-methylpyrrolidine was added and the solution was stirred at room temperature for 1 h followed by heating at 60 °C for 7 h. The resulting solution was extracted nine times with 200-mL portions of $(i\text{-Pr})_2O$ (no H_2O was used). The combined $(i\text{-Pr})_2O$ extracts were extracted three times with dilute HCl. The combined acid washings were made basic with Na_2CO_3 and extracted twice with $(i\text{-Pr})_2O$. The organic extract was dried (Na_2SO_4) and concentrated by rotary evaporation to give 40 g of 2-[3-(ethoxycarbonyl)-2-pyridinyl]-2-(1-methyl-3-pyrrolidinyl)acetic acid ethyl ester as an oil.

A solution of 12 g (0.3 mol) of NaOH in 150 mL of H_2O was added to 37 g of the above oil and the mixture was stirred at 65 °C for 1 h. The resulting solution was extracted six times with 75-mL portions of $CHCl_3$. The aqueous layer was adjusted to pH 4 with concentrated HCl, heated at reflux for 1 h, and concentrated by rotary evaporation. The residue was stirred for 15 min in 150 mL of boiling MeOH and the mixture was filtered. The filtrate

(9) Amos, D. E.; Dudde, W. D. *J. Chem. Soc.* **1974**, *1*(5), 705.

was concentrated by rotary evaporation and the residue was dissolved in 150 mL of $CHCl_3$ and concentrated by rotary evaporation to give 25 g of 2-(1-methyl-3-pyrrolidinylmethyl)-3-pyridinecarboxylic acid hydrochloride as a glass. The infrared spectra of the residue gave an acid carbonyl peak (1700 cm). The mass spectra (CI) showed a peak for a mass of 320. The 60-MHz proton NMR spectrum is as follows: δ 8.45 (dd, 1 H, H-6, J = 5.0 Hz, J = 2.0 Hz), 8.10 (dd, 1 H, H-4, J = 10.0 Hz, J = 2.0 Hz), 7.35 (s, $CHCl_3$), 7.15 (dd, 1 H, H-5, J = 5.0 Hz, J = 10.0 Hz), 2.95–3.80 (complex m, 7 H, 2 CH_2s α to N, bridge CH_2, 1 CH), 2.75 (s, 3 H, CH_3), 1.70–2.40 (br m, 2 H, CH_2 β to N).

The above crude acid hydrochloride (24 g, 0.094 mol) was dissolved in 200 mL of CH_2Cl_2 and treated dropwise with 18 g (0.14 mol) of oxalyl chloride. The resulting mixture was stirred at room temperature for 1.5 h (solution occurred) and treated dropwise with 36 g (0.28 mol) of *N,N*-diisopropylethylamine while cooling to 20–30 °C. The mixture was stirred 2 h and extracted with diluted NaOH. The NaOH solution was extracted three times with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated by rotary evaporation. The residue was purified by HPLC using a silica column and eluting with EtOAc to give 7 g (14.5% overall) of **43**. A small amount was crystallized as the HCl salt from *i*-PrOH, mp 199–202 °C.

Method FF. 7-Chloro-2-(2-chloroethyl)-3,4-dihydro-4-methylpyrido[3,2-*f*]-1,4-oxazepin-5(2*H*)-one (34). While a solution of **27** (10 g, 0.036 mol) in DMF (150 mL) was heated at reflux, SO_2Cl_2 (20 g, 0.148 mol) was added dropwise over a period 40–50 min. The reaction was allowed to stir at reflux for 30 min and was cooled, and the contents of the flask were partitioned between H_2O (150 mL) and benzene (150 mL). The benzene layer was saved and the H_2O layer extracted with an additional amount of benzene (2 × 50 mL). The benzene extracts were combined and washed with dilute KOH (2 × 50 mL) followed by dilute HCl (2 × 50 mL). The benzene layer was dried (Na_2SO_4) and concentrated by rotary evaporation, yielding 2.61 g of crude material. The crude material was recrystallized from $(i\text{-Pr})_2O$ to give 1.25 g (0.0045 mol, 12.6%) of off-white crystals, mp 78–79 °C.

Miscellaneous Procedures. 2-[2-(2,3,4,5-Tetrahydro-5-thioxopyrido[3,2-*f*]-1,4-oxazepin-2-yl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (152). To a solution of **28** (1.00 g, 0.0038 mol) in DMF (20 mL) was added potassium phthalimide (1.43 g, 0.0078 mol). The mixture was heated at 100 °C for 6 h with stirring. The DMF was removed by rotary evaporation at high vacuum and the residue was taken up in $CHCl_3$ (100 mL). The organic layer was washed with 2 N KOH (2 × 30 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The crude oil (1.2 g) was recrystallized from *i*-PrOH, giving 0.95 g (68%) of pale white crystals, mp 172–173 °C.

3-[(1-Methyl-3-pyrrolidinyl)oxy]-4-pyridinecarbonitrile (*E*)-2-Butenedioate (1:2) (153). A solution of 55 g (0.55 mol) of 1-methyl-3-pyrrolidinol in 55 mL of dry DMF was added dropwise to a suspension of NaH (22 g of 60% in oil, 0.58 mol) in 300 mL of DMF. The mixture was stirred at room temperature for 1 h and 73 g (0.53 mol) of 3-chloro-4-cyanopyridine in 200 mL of DMF was added dropwise with mild cooling to maintain a temperature of 30–40 °C. The solution was stirred for 3 h and an equal volume of H_2O was added. The solution was made acidic with dilute HCl and extracted with $(i\text{-Pr})_2O$. The aqueous layer was made basic with NaOH and extracted five times with $CHCl_3$. The extracts were combined, dried (Na_2SO_4), and concentrated. The residue was treated with fumaric acid in 2-PrOH/H_2O (10:1, v/v) to give 51 g (21%) of title compound. Recrystallization of an aliquot from 4-methyl-2-pentanone gave an analytically pure sample, mp 172–174 °C.

4-(Dimethylamino)-1-[(phenylmethyl)amino]-2-butanol (*Z*)-2-Butenedioate (1:2) (154). To a solution of 300 mL of EtOH, 130 mL of H_2O, and 102 g of 50% NaOH was added 64 g (0.27 mol) of 3-benzyl-5-[2-(dimethylamino)ethyl]-2-oxazolidinone,[3a] and the solution was heated at reflux for 3 h. The resulting mixture was stirred in an ice bath and acidified with concentrated HCl. The solution was made basic with NaOH and extracted with $CHCl_3$. The $CHCl_3$ was dried (Na_2SO_4) and concentrated, leaving 49 g (86%) of oil.

A 3-g (0.014 mol) sample of the oil was treated with 3.2 g (0.028 mol) of maleic acid in 40 mL of *i*-PrOH. The resulting solid was recrystallized from *i*-PrOH/H_2O to afford 4.7 g of title compound, mp 135–137 °C.

1-Amino-4-(dimethylamino)-2-butanol (*Z*)-2-Butenedioate (1:2) (155). A solution of 46 g (0.2 mol) of **154** in 200 mL of absolute EtOH was treated with about 5 g of 20% $Pd(OH)_2$ on carbon. The mixture was hydrogenated at 40 psi and 65 °C in a Parr apparatus for 4 h. The mixture was filtered and the filtrate was concentrated. The residue was distilled to give 19 g (63%) of an oil, 115–122 °C (15 mm). Treatment of the base with maleic acid in *i*-PrOH gave the dimaleate salt, mp 121–124 °C.

2-Chloro-*N*-[4-(dimethylamino)-2-hydroxybutyl]-3-pyridinecarboxamide Hydrochloride (156). To a suspension of 11.9 g (0.076 mol) of 2-chloronicotinic in 200 mL of CH_2Cl_2 was added 10.2 g (0.076 mol) of 1-hydroxybenzotriazole, 10 g (0.076 mol) of **155** free base, and 15.6 g (0.076 mol) of DCC. The resulting solution was stirred at room temperature for 6 h and allowed to stand for 66 h. The resulting mixture was filtered and the filtrate was concentrated by rotary evaporation. The residue was shaken with a mixture of dilute HCl and $(i\text{-Pr})_2O$. The resulting three-phase system (1 solid, 2 liquid) was filtered and the solid was discarded. The aqueous layer was separated, made basic with NaOH, and extracted three times with $CHCl_3$. The combined $CHCl_3$ extracts were combined, dried (Na_2SO_4), and concentrated. The residue was dissolved in *i*-PrOH and acidified with ethereal HCl. The resulting precipitate was dissolved by heating and adding MeOH. The crystals obtained on cooling were recrystallized from EtOH to give 9.6 g (41%), mp 182–192 °C

2,3,4,5-Tetrahydro-4-methyl-5-oxopyrido[3,2-*f*]-1,4-oxazepine-2-propanenitrile (157). To a solution of **27** free base (86 g, 0.37 mol) in toluene (150 mL) was added tetrabutylammonium bromide (9 g, 0.027 mol). Saturated aqueous KCN (100 mL) was then added, and the mixture was stirred mechanically at reflux. After 2 h, additional tetrabutylammonium bromide (3 g, 0.009 mol) and saturated aqueous KCN (20 mL) were added, and the mixture was stirred for 0.75 h at reflux. The reaction mixture was extracted with EtOAc (3 × 50 mL) and the organic layer was dried (Na_2SO_4) and concentrated by rotary evaporation to $^1/_3$ the original volume. Upon cooling crystallization occurred. The crystals were filtered and washed with several portions of EtOAc and $(i\text{-Pr})_2O$ to afford 30 g (35%) of off-white crystals, mp 104–105 °C. Recrystallization from EtOAc did not raise the melting point.

2-Chloro-*N*,*N*-dimethyl-3-pyridinecarboxamide (158). A suspension of 50 g (0.32 mol) of 2-chloronicotinic acid was treated with 81 g (0.68 mol) of $SOCl_2$, stirred at room temperature for 48 h, and heated at reflux for 8 h. The solution was concentrated and the residue was dissolved in 150 mL of dry toluene, which was removed on the rotary evaporator. The residue was dissolved in 50 mL of $CHCl_3$ and slowly added to a stirred solution of 28 g (0.62 mol) of dimethylamine in 300 mL of $CHCl_3$ while cooling in an ice bath. The solution was stirred for 1 h and extracted with dilute NaOH. The organic layer was dried (Na_2SO_4) and concentrated. The residue was crystallized from 70% $(i\text{-Pr})_2O$/30% EtOAc to give 43 g (73%) of 158, mp 66–68 °C.

2-Chloro-*N*,*N*-dimethyl-3-pyridinecarbothioamide (159). To a suspension of 25 g (0.055 mol) of P_4S_{10} in 125 mL of $CHCl_3$ was added 25 g (0.135 mol) of **158**. The mixture was heated at reflux for 18 h and filtered. The filtrate was concentrated and the residue was crystallized from 90% $(i\text{-Pr})_2O$/10% EtOAc to give 7 g (32%) of **159**, mp 93–95 °C.

4-(Dimethylamino)-1-(methylamino)-2-butanol (*Z*)-2-Butenedioate (1:2) (160). Crude 5-[2-(dimethylamino)ethyl]-3-methyl-2-oxazolidinone hydrochloride[3a] (containing 1 equiv of Me_2NH·HCl, 160 g, 0.55 mol) and 50% NaOH were dissolved in 90% EtOH (528 mL) and stirred at reflux for 90 min. At completion of the reaction, CO_2(g) was bubbled into the hot reaction mixture for 40 min. The resulting mixture was cooled overnight at room temperature. The solid was removed by filtration and the filter cake was rinsed twice with EtOH. The filtrate and washings were evaporated to an oil, which was then azeotropically dried with toluene. $MgSO_4$ was added and the mixture was filtered. The filtrate was evaporated to a brown oil (72 g, 90% crude yield). A portion of this oil (10.0 g, 0.0685 mol) was dissolved in boiling *i*-PrOH. A solution of maleic acid (15.89 g, 0.137 mol) in boiling *i*-PrOH (15 mL) was added. Upon cooling, product oiled

out of solution. More *i*-PrOH (30 mL) was added, and upon standing at room temperature, the salt crystallized. The solid was filtered, washed with *i*-PrOH and $(i\text{-Pr})_2O$, and triturated in Et_2O overnight. The solid was filtered and dried under vacuum to give 13.9 g of **160**, mp 93–98 °C.

2-Fluoro-5-(trifluoromethyl)benzoic Acid (161). To a solution of 99 g (0.6 mol) of *p*-fluorobenzotrifluoride in 750 mL of THF at −60 °C and under N_2 was added dropwise 256 mL of 2.5 M *n*-BuLi in hexane (0.64 mol) over a 1-h period. The reaction mixture was stirred at −70 to −60 °C for 4 h and poured over a large excess of dry ice. After 15 min the excess dry ice was evaporated by mild heating and the solvent was removed by rotary evaporation. The residue was taken up in 500 mL of H_2O and 30 mL of 1 N NaOH and washed with EtOAc (2 × 300 mL). The aqueous phase was acidified with concentrated HCl and extracted into EtOAc (2 × 300 mL). The combined organic extracts were washed with H_2O (500 mL) followed by brine (300 mL), dried (Na_2SO_4), and concentrated by rotary evaporation. The crude residue was crystallized from hexane to give 80 g (64%) of white crystals, mp 100–100.5 °C.

5-Chloro-2-hydroxy-6-methyl-3-pyridinecarboxylic Acid (162). To a solution of 15.7 g of 50% aqueous NaOH and H_2O (18.2 mL) was added 10 g (0.065 mol) of 2-hydroxy-6-methylnicotinic acid. When the acid had dissolved, 200 mL of 5.25% aqueous NaOCl was added rapidly through a dropping funnel. The temperature was not moderated (slight exotherm did occur). The entire mixture was stirred at room temperature for 18 h. The reaction mixture was then filtered and acidified with concentrated HCl. The precipitate was recrystallized from *i*-PrOH/Et_2O to afford 6 g (49%) of crystals, mp 291–294 °C.

2,5-Dichloro-6-methyl-3-pyridinecarboxylic Acid (163). A mixture of 5 g (0.027 mol) of **162** and 35 g of phenylphosphonic dichloride was heated to 135 °C for 1.5 h. After cooling, the reaction solution was poured carefully into H_2O (250 mL) and stirred for 1 h. The H_2O was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with H_2O (2 × 100 mL), dried (Na_2SO_4), filtered, concentrated by rotary evaporation, taken up in toluene, treated with charcoal, and concentrated by rotary evaporation. The crude residue was crystallized from hexane to give 1.7 g (31%) of beige crystals, mp 123–138 °C dec.

2-Chloro-5-phenyl-3-pyridinecarboxylic Acid (164). A mixture of 191 g (0.98 mol) of phenylphosphonic dichloride and 66 g (0.31 mol) of 5-phenyl-2-pyridone-3-carboxylic acid[10] was heated at 135 °C for 2 h. After cooling, the reaction mixture was poured into 1.5 L of H_2O followed by 1 L of THF to partially solubilize the precipitate formed. While moderating the temperature with ice, 1 L of H_2O was added to complete the precipitation. The precipitate was collected by filtration to give 67 g (0.29 mol, 93%) of crude product. A sample was recrystallized from *i*-PrOH to give white crystals, mp 239–240 °C.

5-Bromo-2-hydroxy-3-pyridinecarboxylic Acid (165). To a solution of 10 g (0.07 mol) of 2-hydroxynicotinic acid in 16.8 g of 50% NaOH (0.21 mol) diluted with 25 mL of H_2O was added 200 mL of a NaOBr solution prepared by adding 13.6 g (0.17 mol) of Br_2 to a solution of 20.16 g of 50% NaOH (0.25 mol) in H_2O (125 mL) at 0 °C and then diluted to 400 mL with H_2O. After 24 h of stirring at room temperature, another 100-mL portion of the above NaOBr solution was added and the reaction solution was stirred for another 24 h. The reaction solution was cooled in an ice bath and acidified carefully with 12 N HCl. The precipitate was collected by filtration and recrystallized from *i*-PrOH to give 97 g (63.5%) of product. A sample was further recrystallized from 95% EtOH, affording analytically pure material, mp 245 °C.

5-Bromo-2-chloro-3-pyridinecarboxylic Acid (166). A mixture of 15 g (0.069 mol) of **165** was added to 75 mL of $SOCl_2$ and 3 mL of DMF and the solution was heated at reflux for 30 min. After cooling, the $SOCl_2$ was removed by rotary evaporation and the residue was poured into H_2O (1 L) with vigorous agitation. The precipitate was collected and the mother liquor was condensed to $^1/_2$ the volume, yielding additional precipitate. The precipitates were combined and recrystallized twice from toluene to give 6 g (37%) of material, mp 174–177 °C.

3,5-Dichloro-4-pyridinecarboxylic Acid (167). To a solution of 4.96 mL (0.036 mol) of diisopropylamine in 200 mL of THF at −65 °C under an N_2 blanket was added dropwise 14.9 mL (0.037 mol) of 2.5 M *n*-BuLi in hexane. After 20 min, a solution of 5 g (0.034 mol) of 3,5-dichloropyridine in 30 mL of THF was added at −70 to −60 °C. The reaction mixture was stirred at −70 °C for 30 min, poured onto a large excess of dry ice, and allowed to evaporate overnight at room temperature. The residue was taken up in dilute NaOH (100 mL), washed with CH_2Cl_2 (3 × 30 mL), and filtered. The filtrate was acidified to pH 2 (pH paper) with dilute HCl to precipitate the product. After cooling, the precipitate was collected and recrystallized from EtOAc/hexane, giving 1.9 g (0.01 mol, 29%) of white crystals, mp 231–235 °C dec.

2-Chloro-3-quinolinecarboxylic Acid (168). (Note: The entire reaction sequence was carried out at −70 to −60 °C.) To a solution of 21.3 mL (0.15 mol) of diisopropylamine in 300 mL of dry THF under a N_2 blanket was added 61.6 mL of 2.7 M *n*-BuLi in hexane (0.165 mol). After 20 min, a solution of 20 g (0.12 mol) of 2-chloroquinoline in 60 mL of THF was added dropwise. Twenty minutes subsequent to this addition, the entire reaction mixture was poured onto a large excess of dry ice. The solvent was removed by rotary evaporation and the residue was taken up in H_2O (300 mL), made basic with dilute NaOH, and washed with $(i\text{-Pr})_2O$ (3 × 50 mL). The aqueous layer was filtered and made acidic (pH ~4 to 5) with dilute HCl. The precipitate was collected, washed with H_2O, *i*-PrOH, and $(i\text{-Pr})_2O$, and dried, giving 15.4 g (0.007 mol, 62%) of white crystals, mp 190–10 °C dec.

4-Chloro-7-(trifluoromethyl)-3-quinolinecarboxylic Acid (169). (Note: The entire reaction sequence was carried out between −70 and −60 °C.) To a cooled solution of 15.8 mL (0.11 mol) of diisopropylamine in 250 mL of THF under a blanket of dry N_2 was added 44 mL of 2.7 M *n*-BuLi in hexane. The solution was stirred for 20 min and a solution/suspension of 25 g (0.11 mol) of 4-chloro-7-(trifluoromethyl)quinoline in 125 mL of THF was added dropwise. After 20 min, the solution (deep red) was poured onto a large excess of dry ice and the solvent was allowed to evaporate overnight at room temperature. The residual solvent was removed by rotary evaporation and the residue was taken up in dilute NaOH (800 mL). Treatment with $CHCl_3$ (75 mL) resulted in the precipitation of the sodium salt of **169**, which was collected, washed with 1 L of $CHCl_3$, and suspended in H_2O (500 mL). The suspension was stirred while it was acidified with 6 N HCl (pH 2, pH paper). The solid was collected and washed with H_2O (500 mL). After drying, 16.2 g (0.059 mol, 53%) of white solid was collected, mp 310 °C.

Pharmacology. Histamine-Induced Lethality in Guinea Pigs. Female, English short-hair guinea pigs (250–500 g) were obtained from Hazelton Research Products, Denver, VA. The animals were fasted overnight prior to testing. Drugs were administered intraperitoneally or orally, by gavage, to the animals at various times prior to the histamine challenge. Histamine was injected intravenously (1.2 mg of histamine/kg). Survival of the animals (at 24-h postchallenge) was indicative of antihistaminic activity. For screening purposes, there were a minimum of three guinea pigs per treatment group and the results are reported as the percent (%) protected. If multiple tests were run at the same dose, results were pooled. Our experience indicates that the probability of survival without treatment is less than 1%. Using this (1% survival), the probability of one out of three surviving randomly is approximately 0.03. This is the maximum p = value for all data reported (therefore $p < 0.03$). To determine ED_{50} values, groups of 5–10 guinea pigs per treatment were used and ED_{50}s were calculated by the method of Litchfield and Wilcoxon[11] or by a computer probit analyses method.

Sedation Studies in Cats. Adult mongrel cats of both sexes were anesthetized with halothane and stainless steel electrodes placed in the exposed calvarium so that the tips rested on the dura over the frontal, parietal, and occipital lobes bilaterally. A common electrode was placed in a frontal sinus. Cannulae were placed in a cephalic vein and a femoral artery for drug admin-

(10) Oostveen, E. A.; Van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas.* **1974**, *93*(8), 233.

(11) Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.

istration and blood-pressure recording, respectively. The trachea was cannulated for artificial ventilation. Prior to removal of the anesthetic, wound edges and pressure points were infiltrated with lidocaine. The animal was immobilized with gallamine and supplemented as necessary.

Monopolar EEG recordings and lead II EKG tracings were made on a Grass electroencephalograph at 5- or 10-min intervals with increasing doses of test drugs (0.1, 0.3, 0.5, 1, 3, 5, 10, and 20 mg/kg, iv) given at 25-min intervals. Arterial blood pressure was continuously recorded on a separate polygraph. In addition to determining the effects of the test drug on the spontaneous EEG, its effects on histamine (0.5 μg/kg, iv) induced hypotension were determined 5, 10, and 20 min after each dose of test drug.

The dose of test drug producing a >50% inhibition of the histamine response was considered the antihistaminic dose while the dose of test drug producing marked slowing and spindling of the EEG (synchrony) was considered the sedative dose.

At the end of each experiment, the animal was euthanized (T-61 or FP-3).

Registry No. **1**, 23123-01-5; **2**, 28490-67-7; **3**, 91832-81-4; **4**, 91832-78-9; **5**, 91832-77-8; **6**, 91832-79-0; **7**, 117449-72-6; **8**, 91832-72-3; **9**, 91832-80-3; **10**, 91832-93-8; **11**, 91832-91-6; **12**, 91833-09-9; **13**, 91833-07-7; **14**, 91833-20-4; **15**, 91833-01-1; **16**, 117449-76-0; **17**, 91832-98-3; **18**, 91833-12-4; **19**, 91833-03-3; **20**, 91833-18-0; **21**, 117450-08-5; **22**, 117450-09-6; **23**, 117450-04-1; **24**, 117450-07-4; **25**, 117450-15-4; **26**, 117450-17-6; **27**, 91832-96-1; **27** (free base), 91832-97-2; **28**, 91833-10-2; **29**, 121675-01-2; **30**, 91833-26-0; **31**, 91833-29-3; **32**, 117449-98-6; **33**, 117450-00-7; **34**, 91833-30-6; **35**, 91833-31-7; **36**, 117450-01-8; **37**, 117450-03-0; **38**, 117450-13-2; **39**, 117450-14-3; **40**, 117450-10-9; **41**, 91847-43-7; **42**, 91847-44-8; **43**, 116120-63-9; **44**, 117657-10-0; **45**, 117449-95-3; **46**, 117449-96-4; **47**, 91833-15-7; **48**, 91833-23-7; **49**, 91832-95-0; **50**, 91833-11-3; **51**, 91833-05-5; **52**, 91833-14-6; **53**, 121675-02-3; **54**, 121675-03-4; **55**, 117449-91-9; **56**, 117449-93-1; **57**, 104612-83-1; **58**, 104612-94-4; **59**, 117449-86-2; **60**, 117449-83-9; **61**, 117449-85-1; **62**, 104353-47-1; **62** (free base), 104353-48-2; **63**, 104353-46-0; **63** (free base), 91837-11-5; **64**, 91833-50-0; **64** (free base), 91833-49-7; **65**, 91833-48-6; **65** (free base), 91833-47-5; **66**, 91837-02-4; **66** (free base), 91837-01-3; **67**, 117446-78-3; **67** (free base), 117446-77-2; **68**, 117474-76-7; **68** (free base), 117474-75-6; **69**, 91836-93-0; **69** (free base), 91836-92-9; **70**, 121675-04-5; **70** (free base), 117449-59-9; **71**, 117449-58-8; **71** (free base), 117449-57-7; **72**, 91836-95-2; **72** (free base), 91836-94-1; **73**, 117449-56-6; **73** (free base), 117449-55-5; **74**, 91837-00-2; **74** (free base), 91836-99-6; **75**, 117474-84-7; **75** (free base), 117427-81-3; **76**, 117427-83-5; **77**, 117427-82-4; **78**, 91836-98-5; **79**, 121675-06-7; **79** (free base), 121675-05-6; **80**, 121675-07-8; **80** (free base), 91837-16-0; **81**, 91837-06-8; **81** (free base), 91837-05-7; **82**, 117474-64-3; **82** (free base), 117474-63-2; **83**, 117474-70-1; **83** (free base), 117474-69-8; **84**, 117474-66-5; **84** (free base), 117474-65-4; **85**, 117474-46-1; **85** (free base), 117474-45-0; **86**, 117474-62-1; **86** (free base), 117474-61-0; **87**, 117474-72-3; **87** (free base), 117474-71-2; **88**, 117474-86-9; **88** (free base), 117427-85-7; **89**, 117474-88-1; **89** (free base), 117427-87-9; **90**, 117474-58-5; **90** (free base), 117474-57-4; **91**, 117474-60-9; **91** (free base), 117474-59-6; **92**, 117474-68-7; **92** (free base), 117474-67-6; **93**, 117450-24-5; **93** (free base), 117450-23-4; **94**, 117474-82-5; **94** (free base), 117427-78-8; **95**, 91833-40-8; **95** (free base), 91833-41-9; **96**, 91833-69-1; **96** (free base), 91833-68-0; 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**139**, 104353-41-5; **139**, 104353-40-4; **140**, 104377-49-3; **140** (free base), 104377-48-2; **141**, 91833-80-6; **141** (free base), 91833-79-3; **142**, 117446-93-2; **142** (free base), 117446-92-1; **143**, 91837-13-7; **143** (free base), 91837-12-6; **144**, 91837-15-9; **144** (free base), 91837-14-8; **145**, 104610-99-3; **145** (free base), 104610-98-2; **146**, 104611-09-8; **146** (free base), 104611-08-7; 1-benzyl-3-pyrrolidinol, 775-15-5; salicylamide, 65-45-2; 1-ethyl-*N*-methyl-*N*-phenyl-3-pyrrolidinamide, 117449-70-4; 1-(dimethylamino)-3-(methylamino)-2-propanol hydrochloride, 117450-19-8; 2-chloro-*N*-[3-(dimethylamino)-2-hydroxypropyl]-*N*-methylbenzamide, 121675-22-7; 3-(ethoxycarbonyl)-4-chloroquinoline, 13720-94-0; 2-chloro-5-nitrobenzoic acid, 2516-96-3; 3-(ethoxycarbonyl)-2-pyridineacetic acid ethyl ester, 35968-82-2; 2-(3-(ethoxycarbonyl)-2-pyridinyl)-2-(1-methyl-3-pyrrolidinyl)acetic acid ethyl ester, 116120-61-7; 2-(1-methyl-3-pyrrolidinylmethyl)-3-pyridinecarboxylic acid hydrochloride, 116120-62-8; 3-carboxy-2-pyridineacetic acid ethyl ester, 35969-51-8; **147**, 117449-38-4; **147** (free base), 104611-11-2; **148**, 117449-32-8; **148** (free base), 117499-33-9; **149**, 117449-34-0; **149** (free base), 117449-35-1; **150**, 121675-18-1; **150** (free base), 121675-20-5; **151**, 121675-19-2; **151** (free base), 121675-21-6; **152**, 121675-24-9; **153**, 91832-83-6; **154**, 121675-26-1; **155**, 121675-28-3; **155** (free base), 104353-36-8; **156**, 104353-35-7; **157**, 91833-25-9; **158**, 52943-21-2; **159**, 121675-29-4; **160**, 121675-23-8; **161**, 115029-23-7; **162**, 117449-75-9; **163**, 117449-74-8; **164**, 117449-73-7; **165**, 104612-36-4; **166**, 29241-65-4; **167**, 13958-93-5; **168**, 73776-25-7; **169**, 89524-63-0; 1-methyl-3-pyrrolidinol, 13220-33-2; 3-hydroxy-2-naphthalenecarboxamide, 3665-51-8; 5-methoxysalicylamide, 28534-37-4; 5-bromosalicylamide, 6329-74-4; 4-chlorosalicylamide, 37893-37-1; 5-fluorosalicylamide, 56874-97-6; 1-hydroxy-2-naphthalenecarboxamide, 62353-80-4; 5-chlorosalicylamide, 7120-43-6; 3-bromo-1-methylpyrrolidine, 10603-45-9; 2-chloronicotinic acid, 2942-59-8; 3,5-dichloropyridine-4-carboxylic acid, 13958-93-5; 3-chloro-4-cyanopyridine, 68325-15-5; 3-benzyl-5-[2-(dimethylamino)ethyl]-2-oxazdinone, 121675-27-2; 5-[2-(dimethylamino)-ethyl]-3-methyl-2-oxazolidinone hydrochloride, 51045-12-6; p-fluorobenzotrifluoride, 402-44-8; 2-hydroxynicotinic acid, 609-71-2; 3,5-dichloropyridine, 2457-47-8; 2-chloroquinoline, 612-62-4; 4-chloro-7-(trifluoromethyl)quinoline, 346-55-4; 2-[1-methyl-3-pyrrolidinyloxy]-5-phenyl-3-pyridinecarboxylic acid sodium salt, 117450-21-2; 2-(2-chloroethyl)-3,4-dihydro-4-methyl-7-phenylpyrido[3,2-*f*]-1,4-oxazepin-5(2*H*)-one, 117450-12-1; 2-hydroxy-6-methylnicotinic acid, 38116-61-9.