Selective Inhibitors of Monoamine Oxidase (MAO). 5.[1,2] 1-Substituted Phenoxathiin Inhibitors Containing No Nitrogen That Inhibit MAO A by Binding It to a Hydrophobic Site

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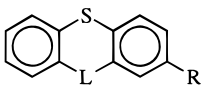
It is believed that a monoamine oxidase (MAO) inhibitor specific for MAO A, which is reversibly bound to this enzyme and displaceable by tyramine, will be an antidepressant which will not cause a rise in blood pressure when tyramine-containing foods are ingested. Some linear tricyclic compounds with a larger and a smaller group forming the central ring and with a lipophilic group ortho to the larger group (here mostly the SO_2 function of phenoxathiin 10,-10-dioxide) are reported to have the sought properties. Potency appears to require short length and relatively small cross section for the substituent. The 1-ethyl (**13**), 1-vinyl (**22**), 1-trifluoromethyl (**27**), and 1-iodo (**76**) phenoxathiin dioxides had the best profiles. Structure−activity relationships, syntheses, and a possible rationale for the selectivity of these compounds and related tricyclics are given. Compound **13** was selected for further development. A summary of pharmacological data for **13** is given.

MAO (EC 1.4.3.4, amine oxidase, flavin-containing) consists of two differing forms distinguishable by their substrate specificity[3] and their amino acid sequences.[4] Serotonin (5-HT) is specifically deaminated by MAO A, while 2-phenethylamine is relatively specifically deaminated by MAO B; these properties are used for analysis of the enzymes. Tyrosine is deaminated by both forms with similar efficiencies. Early MAO inhibitors were found to have clinically significant antidepressant and antiphobic properties. However ingestion especially of tyramine-containing foods by patients taking early MAO inhibitors led to a significant and sometimes serious increase in blood pressure ("cheese effect"), apparently due to release of norepinephrine by displacement by undestroyed tyramine and consequent vasoconstriction. Therefore clinical use of these early MAO inhibitors became extremely limited.

More recently, it has been found that inhibition of MAO A (MAO A-I) gives clinically useful antidepressant activity, while MAO B-I does not.[5] An MAO inhibitor that selectively inhibits MAO A should then have antidepressant activity while leaving the MAO B to destroy ingested tyramine, thereby minimizing the possibility of a clinical "cheese effect." Inhibitors such as moclobemide and brofaromine are reported to have such specificity.[18] Further, since the human intestinal wall, especially the duodenal mucosa, is reported[6] to have MAO A as the predominant form of its MAO, an important additional safety feature would be to have the MAO A inhibitor displaceable from the inhibited enzyme by any ingested tyramine, thus reinstating the first line of defense against dietary tyramine. Such an inhibitor, selective for MAO A inhibition, reversibly bound to the enzyme, and displaceable by tyramine, was the target of our research.

Chart 1



S is smaller group
L is larger group

We have reported in previous publications,[1,7] and earlier work cited there, the high potency and selectivity for inhibition of MAO A of a variety of tricyclic heterocyclics characterized by specific structural features: (1) The tricyclic structure included a central ring made up of a larger and a smaller moiety at least one of which was a heteroatom. In the few examples examined in which the central moieties were identical, loss of specificity for MAO A was seen. (2) A hydrophilic group was present on one outer ring para to the smaller central function. (3) In most potent compounds, a single pendant methyl group had to be present on the second or third element of this hydrophilic group.

Unfortunately, despite the lack of significant acute or chronic toxicity in animals, when the best compound resulting from the previous work (Chart 1; S = carbonyl, L = SO_2, and R = CONHMe, compound **8** of ref 1) was evaluated in humans, it showed unacceptable toxicity at high dosage. This compound was also found to have its carbonyl group almost completely reduced to the corresponding secondary alcohol function by metabolism in humans, making the thioxanthen-9-one 10,10-dioxide system seem a poor choice for further work even though the reduction appeared to be reversible in vivo. However, the desired combination of potency, selectivity for MAO A inhibition, and lack of tyramine-induced blood pressure rise found[8] for this compound and the realization that the obvious hydrophilic substituents in the

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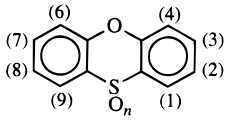
Table 1. MAO Inhibition by Phenoxathiins Monosubstituted on an Aromatic Ring



			IC_{50} (μM) or % inhib at μM					
no.	substituent	*n*	MAO A	MAO B	formula	anal.	mp (°C)	recryst[a]
1[b]	1-Me + 3-Me	0	0.61	9% @ <10	$C_{13}H_{10}OS$	CHN	64−66	
2	1-Me	1	1	0% @ 10	$C_{13}H_{10}O_2S$	CHS	140−142	EA−H
3	1-Me	2	0.03	6% @ 0.1	$C_{13}H_{10}O_3S$	CHS	155−156.4	A
4[c]	2-Me	0	15% @ 1	12% @ 1				
5[d]	2-Me	1	11% @ 1	8% @ 1				
6[c]	2-Me	2	30% @ 1	9% @ 1				
7[c]	3-Me	0	23% @ 1	13% @ 1				
8	3-Me	1	7% @ 1	7% @ 1	$C_{13}H_{10}O_2S$	CHS	123.5−124.0	A
9[c]	3-Me	2	0.2	11% @ 1				
10[c]	4-Me	2	0.8	6% @ 1				
11	1-Et	0	15% @ 0.1	0% @ 0.1	$C_{14}H_{12}OS$	CHS		liq
12	1-Et	1	64% @ 1	7% @ 1	$C_{14}H_{12}O_2S$	CHS	107−109	from oil
13[e]	1-Et	2	0.07	0% @ 0.1	$C_{14}H_{12}O_3S$	CHS	102−103; 114−116	EA−H
14	2-Et	2	0.007	0% @ 0.01	$C_{14}H12O_3S$	CHS	77−80	M
15	3-Et	0	0.3	8% @ 1	$C_{14}H_{12}OS$	CH	oil	
16	3-Et	1	0.3	2% @ 1	$C_{14}H_{12}O_2S$	CHS	91−93	EA−H
17	3-Et	2	0.006	10% @ 0.1	$C_{14}H_{12}O_3S$	CHS	86−88	EA−H
18	4-Et	2	1	9% @ 0.1	$C_{14}H_{12}O_3S$	CHS	85−88	EA−H
19	1-Pr	2	67% @ 0.1	16% @ 0.1	$C_{15}H_{14}O_3S$	CHS	143−144.5	EA−P
20	1-C_5H_{11}	2	42% @ 1	4% @ 1	$C_{17}H_{18}O_3S$	CHS	44−46	H
21	1-$CHMe_2$	2	0% @ 0.1	0% @ 0.1	$C_{15}H_{14}O_3S{\cdot}0.25H_2O$	CHS	113−115	EA−P
22[e]	1-CH=CH_2	2	0.04	0% @ 0.1	$C_{14}H_{10}O_3S$	CHS	143−145	EA−P
23	1-CMe=CH_2	2	62% @ 1	15% @ 1	$C_{15}H_{12}O_3S$	CHS	136−138	EA−P
24	1-C≡CH	2	0.1	0% @ 0.1	$C_{14}H_8O_3S$	CHS	180−181 dec	EA−P
25	1-$CH_2C_6H_4Cl$(m)	2	20% @ 1	0% @ 1	$C_{19}H_{13}O_3ClS$	CHS	104−106	EA−P
26	1-CHFMe	2	19% @ 0.1	0% @ 0.1	$C_{14}H_{11}O_3FS$	CH	129−131	A
27	1-CF_3	2	0.08	0% @ 0.1	$C_{13}H_7O_3F_3S$	CHS	174−176	EA−P
28	2-CF_3	2	8% @ 0.1	5% @ 0.1	$C_{13}H_7O_3F_3S{\cdot}0.25H_2O$	CHS	137−139	EA−H
29	1-C_2F_5	2	5% @ 0.1	0% @ 0.1	$C_{14}H_7O_3F_5S$	CHS	152−154	EA−P
30	1-CH_2NEt_2	2	24% @ 1	0% @ 1	$C_{17}H_{19}O_3NS{\cdot}HCl$	CHS	226−228	A−EA
31	1-CH_2N_3	2	66% @ 1	0% @ 1	$C_{13}H_9O_3N_3S$	CHNS	87−88	EA−H
32	1-CH_2OH	2	0.14	8% @ 1	$C_{13}H_{10}O_4S$	CHNS	142−144	A
33[e]	(+−)-1-CHMeOH	2	0.4	0% @ 1	$C_{14}H_{12}O_4S$	CHS	177−179	HOAc
34	(+)-1-CHMeOH	2	2.5	0%	$C_{14}H_{12}O_4S$		113−115	
35	(−)-1-CHMeOH	2	0.25	7% @ 3	$C_{14}H_{12}O_4S$		114−116	
36[f]	2-CHMeOH	2	26% @ 1	14% @ 1	$C_{14}H_{12}O_4S$			
37	1-CHMe(OMe)	2	ca. 2	0% @ 1	$C_{15}H_{14}O_4S$	CHS	140−141	EA−H
38	1-CHMe(OAc)	2	0% @ 0.1	0% @ 0.1	$C_{16}H16_6O_5S$	CH	141.5	EA−H
39	1-CHEtOH	2	0% @ 0.1	0% @ 0.1	$C_{15}H_{14}O_4S$	CHS	93−95	EA−P
40	1-CMe_2OH	2	0% @ 0.1	0% @ 0.1	$C_{15}H_{14}O_4S$	CHS	129−131	EA−H
41	1-$CHOHC_6H_4Cl$(m)	2	40% @ 1	0% @ 1	$C_{19}H_{13}O_4SCl$	CHS	144−146	A
42[e]	1-CH_2CH_2OH	2	0.02	7% @ 0.1	$C_{14}H_{12}O_4S$	CHS	85−87	EA−P
43	1-$CH(OH)CH_2NO_2$	2	0.2	2% @ 0.1	$C_{14}H_{11}NO_6S$	CHNS	160−162	EA−H
44	(+−)-1-$CHOHCH_2OH$	2	1.2	30	$C_{14}H_{12}O_5S$	CHS	125−127	EA−H
45[g]	(+)-1-$CHOHCH_2OH$	2	2.0	30	$C_{14}H_{12}O_5S$		137−139	see text
45A[g]	(−)-1-$CHOHCH_2OH$	2			$C_{14}H_{12}O_5S$	CHS	135−137	see text
46		2	0% @ 0.1	0% @ 0.1	$C_{17}H_{16}O_5S$	CHS	105−109	A
47	1-CHO	2	45% @ 0.1	0% @ 0.1	$C_{13}H_8O_4S$	CHS	163−165	EA−H
48	1-C(O)Me	2	ca. 2	0% @ 1	$C_{14}H_{10}O_4S$	CHS	142−144	A
49[f]	2-C(O)Me	2	1.0	5% @ 1				
50	1-$C(O)CF_3$	2	37% @ 1	0% @ 1	$C_{14}H_7O_4F_3S$	CHS	129−131	EA−H
51	1-$C(O)CH_2OAc$	2	14% @ 1	5% @ 1	$C_{16}H_{12}O_6S$	CHS	139−142	A
52	1-C(O)COOMe	2	0.6	0% @ 1	$C_{15}H_{10}0_6S$	CHS	204−206	EA
53[h]	1-COOH	2	13% @ 1	5% @ 1				
54	1-CH_2COOH	2	22% @10	0% @10	$C_{14}H_{10}O_5S$	CHS	221−223	M−W
55	1-$C(=NH)C_2H_4NEt_2{\cdot}HCl$	2	0% @ 0.1	0% @ 0.1	$C_{19}H_{22}N_2O_3S{\cdot}HCl$	CHN	150−152	Ac−EA
56	1-CHFMe	2	19% @ 0.1	0% @ 0.1	$C_{14}H_{11}FO_3S$	CHS	129−131	A
57	1-CH2PO$(OEt)_2$	2	0% @ 0.1	0% @ 0.1	$C_{17}H_{19}O_6PS$	CHS	91−93	EP−H
58	1-CH_2Br	2	0.1	0% @ 0.1	$C_{13}H_9BrO_3S$	CHSBr	142−144	EA−H
59	1-NH_2	2	58% @ 0.1	0% @ 0.1	$C_{12}H_9NO_3S$	CHN	166-167.5	A
60[i]	2-NO_2	2	80% @ 1	8% @ 1				
61[j]	1-OH	2	11% @ 0.1	0% @ 0.1	$C_{12}H8O_4S{\cdot}H_2O$			
62[k]	2-OH	0	58% @ 1	7% @ 1				
63[j]	1-OMe	2	60% @ 0.1	0% @ 0.1				
64	2-OMe	2	0.2	10% @ 1	$C_{13}H_{10}O_4S$	CHS	125−127	EA−H

Table 1 (Continued)

			IC_{50} (μM) or % inhib at μM					
no.	substituent	*n*	MAO A	MAO B	formula	anal.	mp (°C)	recryst[a]
65	1-OEt	2	13% @ 0.1	0% @ 0.1	$C_{14}H_{12}O_4S$	CHS	145−147	EA−P
66	2-OEt	2	0.04	2% @ 0.1	$C_{14}H_{12}O_4S$	CHS	123−125	EA−P
67	1-$OC_2H_4NMe_2$	2	27% @ 1	0% @ 1	$C_{16}H_{17}NO_4S\cdot HCl\cdot 0.5H_2O$	CHN	211−213	A−EA
68	1-OAc	2	10% @ 0.1	0% @ 0.1	$C_{14}H_{10}O_5S$	CHS	149−151	EA−P
69	2-OAc	2	0.5	19% @ 1	$C_{14}H_{10}O_5S$	CHS	125−127	EA−H
70	1-$SiMe_3$	2	0% @ 0.1	0% @ 0.1	$C_{15}H_{16}O_3SSi$	CH	118−119	EA−P
71	1-SMe	2	31% @ 0.1	0% @ 0.1	$C_{13}H_{10}O_3S_2$	CHS	197−199	HOAc
72	1-SPh	2	0% @ 0.1	5% @ 0.1	$C_{18}H_{12}O_3S_2$	CHS	141−143	EA−H
73	1-SO_2Ph	2	0% @ 0.1	6% @ 0.1	$C_{18}H_{12}O_5S_2$	CHS	167−169	HOAc−W
74	1-Br	2	0.06	0% @ 0.1	$C_{12}H_7O_3SBr$	CHBrS	207−208.5	EA−H
75	3-Br	2	0.02	4% @ 0.1	$C_{12}H_7O_3SBr$	CH	195−197	EA−H
76	1-I	2	0.05	0% @ 0.1	$C_{12}H_7O_3SI\cdot 0.5H_2O$	CHS	129−131	A

[a] Recrystallization solvents: A = EtOH, C = $CHCl_3$, E = Et_2O, EA = EtOAc, H = hexanes, HOAc = acetic acid, TEP = triethyl phosphate. [b] An unseparated mixture by NMR of 30% 1-methylphenoxathiin and 70% 3-methyl isomer. See Results and Discussion section of the text. [c] Suter, C. M.; Green, F. O. Phenoxathin. II. Extension of the Ferrario Reaction. *J. Am. Chem. Soc.* **1937**, *59*, 2578−2580. [d] Gruenhagen, R. H. U.S. Patent 3,071,506, Jan. 1, 1963. [e] See refs 26 and 25. [f] Paget, C. J.; Dennis, E. M.; Nelson, J.; DeLong, D. C. Antiviral Phenoxathiins and Their Analogues. Study of the Structure−Activity Relationships for Antiviral Activity and the Replacement Ability in Poliovirus Type III Dependent Variants. *J. Med. Chem.* **1970**, *13*, 620−623. [g] Each enantiomer had TLC, mass spectrum, and NMR identical to the racemic **44** and was prepared by chiral chromatography from **44**, so elemental analysis was not done. See Results and Discussion section of text. [h] Reference 22. [i] Krishna, S. Synthesis of Derivatives of Phenothioxin. *J. Chem. Soc.* **1923**, *123*, 2872−2876. [j] Kemp, D. S.; Buckler, D. R. Synthesis of 1-Methoxy-9-mercaptophenoxathiin and the Resolved 1-(*N*−(benzyloxycarbonyl)-L-alanyl)oxy)-9-(methoxycarbonyl)dithio)phenoxathiin 10-Oxide Diastereoisomers. Comments on Improved Methods for Sulfone Reduction. *J. Org. Chem.* **1989**, *54*, 3647−3663. [k] *Chem. Abstr.* Registry No. 99971-39-8; Ger. Pat 913177, June 10, 1954.

position para to the smaller central group had already been evaluated encouraged us to study other positions of ring substitution. The effect of substitutions ortho to the large group (here nearly always sulfone) was selected for initial study and is the subject of this report. The greatest portion of this work was done with phenoxathiins, which our earlier reports had shown were frequently comparable in activity to the correspondingly substituted thioxanthones.[7] Note that in Table 5 of ref 7 the top right heading structure labeled "Phenox" should be a phenoxathiin; the phenoxathiin in that table, **40**, is of high potency as indicated in the table.

Results and Discussion

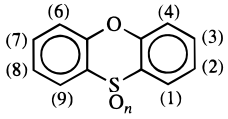
Table 1 shows the effect on selectivity for MAO A and on potency of monosubstitution on the phenoxathiin ring system primarily ortho to the sulfur. It is evident that in contrast to the substitution meta to sulfur, which required[1] a hydrophilic substituent for maximum potency (however, note an exception, the potency of **14** reported in Table 1), the greatest potency with substitution ortho to sulfur requires a lipophilic substituent (compare the potent **3**, **13**, **27**, **74**, and **76**, which have small lipophilic substituents, with, for example, **47**, **48**, **53**, **59**, **61**, and **63**, which have small but hydrophilic substituents). Comparing the relative potency due to differing lipophilic substituents in the same position ortho to sulfur, there appears to be a stringent upper limit to the linear size and possibly the cross section conferring activity and potency. Thus, **3** (1-methyl) and **13** (1-ethyl) are very potent, while their higher homologues **19** (1-propyl), **20** (1-pentyl), and **21** (1-isopropyl) have progressively lower activity. Similarly, the 1-vinyl function of **22** confers high potency, while **23**, which can be considered a methylated vinyl or methenylated ethyl analogue, is less active than either **13** or **22**. Comparison of the potent 1-trifluoromethyl (**27**) with its essentially inactive pentafluoroethyl analogue (**29**) shows a similar effect. We have no good explanation for the potency of the 1-(2-hydroxyethyl) compound **42**. It is conceivable that it extends to bring the terminal hydroxyl function near the 2-hydrophilic site shown by our earlier work.

An important observation is that none of the potent compounds reported here have a nitrogen atom. It has been stated in earlier reviews that a nitrogen atom in the molecule was necessary for MAO I activity,[9] and indeed all of our potent compounds reported in earlier work had a nitrogen at the putative binding site, as have all commercially significant MAO I. However, since these nitrogens were of widely differing basicities and anticipated charge distributions and water-binding ability, we felt that the presence of nitrogen was not necessary to allow MAO inhibition (other than for the hydrazine phenelzine, the propargyl- (pargyline), cyclopropyl-, and haloalkenylamines, and the aminoethylamides (e.g., Ro41-1049), where it is mechanistically necessary). The potency of many of the tricyclic inhibitors reported here supports our view.

One earlier generalization that applies only partially in the study reported here was that for the hydrophilic substituents conferring activity when para to the smaller central group, adding a duplicate group in the symmetrical position in the other outer ring completely destroyed activity. However, one symmetrical disubstituted compound here, **77**, the 1,9-dimethylphenoxathiin dioxide (Table 2), retained nearly as high potency as the monomethyl **3**. All activity was lost for the other 1,9-disubstituted analogues (compare **78** and **84** with **13** and **32**). The thioxanthone corresponding to **77**, **92** (4,5-dimethylthioxanthen-9-one dioxide), while not as active as its monomethyl analogue **87**, also did have appreciable activity.

A point of similarity between the structure−activity relationship (SAR) in these compounds substituted ortho to the central ring sulfur and the SAR reported in our earlier papers[1,7] for compounds substituted meta to the central ring sulfur is that as in the earlier cases, potency increases from the sulfide and sulfoxide to the sulfone form of the central sulfur for the few cases where our data allows comparison. For example, the activity attributable to the 1-methyl fraction of the sulfide

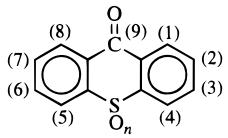
Table 2. MAO Inhibition by Phenoxathiins with Two or More Substituents on the Aromatic Rings



			IC$_{50}$ (μM) or % inhib at μM					
no.	substituent	*n*	MAO A	MAO B	formula	anal.	mp (°C)	recryst[a]
77	1,9-Me$_2$	2	0.05	8% @ 0.1	$C_{14}H_{12}O_3S$	CH	259−261	EA
78	1,9-Et$_2$	2	0% @ 0.1	0% @ 0.1	$C_{16}H_{16}O_3S$	CHS	159−161	HOAc
79	1,9-Pr$_2$	2	0% @ 0.1	0% @ 0.1	$C_{18}H_{20}O_3S$	CHS	135−137	EA−P
80	1,9-(CH$_2$NEt$_2$)$_2$	2	18% @ 1	8% @ 1	$C_{22}H_{30}N_2O_3S\cdot 2HCl\cdot 2H_2O$	CN[b]	245−247	A−EA
81	1,9-(NH$_2$)$_2$	2	0% @ 0.1	0% @ 0.1	$C_{12}H_{10}N_2O_3S$	CHN	268−270	A
82	1-Et-7-OH	2	0.11	4% @ 1	$C_{14}H_{12}O_4S$	CHS	169−171	EA−P
83	1-Et-2-OMe	2	0.6	15% @ 1	$C_{15}H_{14}O_4S$	CHS	137−139	A
84	1,9-(CH$_2$OH)$_2$	2	15% @ 1	7% @ 1	$C_{14}H_{12}O_5S$	CHS	218−222	A
85[c]	2,8-Br$_2$	2	13% @ 1	17% @ 1	$C_{12}H_6O_3Br_2S$			

[a] See Table 1, footnote a. [b] Anal. CN; H: calcd, 7.10; found, 6.52. [c] Suter, C. M.; Mckenzie, J. P.; Maxwell, C. E. Phenoxthin. I. A Comparison of the Directive Influences of Oxygen and Sulfur. *J. Am. Chem. Soc.* **1936**, *58*, 717−720.

Table 3. MAO Inhibition of Some Thioxanth-9-ones



			IC$_{50}$ (μM) or % inhib at μM					
no.	substituent	*n*	MAO A	MAO B	formula	anal.	mp (°C)	recryst[a]
86	4-Me	0	1.4	0% @ 1	$C_{14}H_{10}OS$	CH	146.5	A−W
87	4-Me	2	0.06	0% @ 1	$C_{14}H_{10}O_3S$	CH	182.6	HOAc−W
88	4-Et	0	2.0	10% @ 1	$C_{15}H_{12}OS$	CHS	114.6	A−W
89	4-Et	2	0.4	2% @ 0.1	$C_{15}H_{12}O_3S$	CHS	159.1	HOAc−W
90	4-CMe$_3$	2	0% @ 0.1	5% @ 0.1	$C_{17}H_{16}O_3S$	CHS	*b*	EA−H
91	4,5-Me$_2$	0	8% @ 1	9% @ 1	$C_{15}H_{12}OS$	CHS	104.2	A−W
92	4,5-Me$_2$	2	0.3	9% @ 1	$C_{15}H_{12}O_3S$	CHS	234−235.5	HOAc
93[c]	4-Cl-1-Me	0	34% @ 1	0% @ 1	$C_{14}H_9OClS$			
94[c]	1-Cl-4-Me	0	55% @ 1	0% @ 1	$C_{14}H_9OClS$			
95	1-Cl-4-Me	2	40% @ 1	0% @ 1	$C_{14}H_9O_3ClS$	CHS	191.6	HOAc−W
96[d]	2-Cl	2	23% @ 1	15% @ 0.1				
97[d]	2-Br	2	1	11% @ 1				

[a] See Table 1, footnote a. [b] Mp: uncertain, sintered 33.5 °C, clarified 138.3 °C. [c] Archer, S.; Suter, C. M. The Preparation of Some 1-Alkylamino- and Dialkylaminoalkylaminothiaxanthones. *J. Am. Chem. Soc.* **1952**, *74*, 4296−4309. [d] Gilman, H.; Diehl, J. W. Orientation in the Thioxanthenone Nucleus. *J. Org. Chem.* **1959**, *24*, 1914−1946.

mixture **1** (**7** is essentially inactive) seems greater than that of the 1-methyl sulfoxide **2**, and both are far less potent than the sulfone **3**. Similarly, the 1-ethyl sulfone **13** is far more potent than either the sulfide **11** or sulfoxide **12**. It is interesting that in the 3-ethyl series, the sulfone **17** is also much more potent than the sulfide **15** or the sulfoxide **16** and that in the thioxanthen-9-one series of Table 3 the corresponding (note the differing ring-numbering systems) 4-methyl and 4-ethyl sulfones **87** and **89** are again more potent than the sulfides **86** and **88**. It is noteworthy that none of the variety of compounds studied in this series ortho-substituted to the central ring sulfur had appreciable MAO B inhibitory activity.

Selection of which of the several potent compounds tabulated should be further studied as a clinical candidate was based on several criteria. The monomethyl sulfone **3** was ruled out since it was partly irreversibly bound to MAO A, i.e., not completely dissociated from the enzyme in 24 h of dialysis. This irreversibility has been shown to be associated with tyramine-induced blood pressure rise,[1] and indeed, after pretreatment with this compound, the blood pressure of tyramine-fed rats rose to 36% of that induced by phenelzine pretreatment under our standard test conditions.[10] The 3-bromo sulfone **75**, while potent in vitro, showed no activity in rat brain MAO 3 h after oral administration at 20 mg/kg, the ED$_{50}$ cutoff selected. The 1-ethylphenoxathiin dioxide **13** was preferred to the 1-vinyl (**22**), the 1-trifluoromethyl (**27**), and the 1-iodo (**76**) phenoxathiin dioxides on pharmacokinetic and other grounds, since all showed low acute toxicity, all showed negligible MAO B inhibition, and none caused significant tyramine-induced blood pressure rise above vehicle control values in rats given 15 mg/kg tyramine orally after 80% inhibition of brain MAO had been established by the required dosage of inhibitor. This is in contrast to blood pressure increases found with phenelzine and moclobemide. The 2-ethyl sulfone **14** showed a slight increase in blood pressure under the test conditions.

Compound **13** had an ED$_{80}$ of 8 mg/kg in inhibition of rat brain MAO A in vivo and was active in standard antidepressant models (Porsolt test in rats, potentiation of 5-HT activities in rats and mice, and a Rhesus model of borderline personality disorder). More comprehensive data on the pharmacology of **13** have been presented

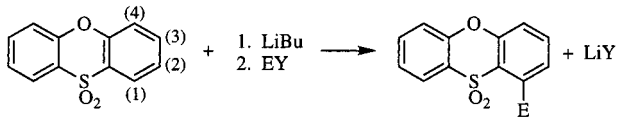
and published[11−13] (synonyms for **13** were 1370U and BW1370U87).

The detected metabolites of **13** were found to be the vinyl analogue **22**, the product of α hydroxylation **33**, the acetyl compound **48**, the product of *β* hydroxylation **42**, the product of 1,2-dihydroxylation **44**, and the carboxylic acid **54** produced by terminal oxidation of the ethyl group. Structures were determined both by physical methods[14−16] and by comparison with synthesized samples. The chirality of the potentially optically active metabolites corresponding to **33** and **44** was not determined. As can be seen from Table 1, **22** and **42** could contribute somewhat to activity, but the chiral **34** and **35**, although differing 10-fold in in vitro potency, were not sufficiently potent to affect total activity measurably at their in vivo concentrations. Incidentally, both were reversibly bound to MAO A. The difference in potency between the racemic **44** and its dextrorotatory isomer **45** seemed to make determination of the levorotatory isomer's in vitro potency pointless; the small sample was used to determine that 10 mg/kg caused 43% inhibition of rat brain MAO in vivo and that it was reversibly bound to MAO A in vitro. Since both enantiomers of **45** not only were synthesized by chiral reagent dihydroxylation[27] but also were separated from **44** by chiral chromatography (see Experimental Section), elemental analysis was only done on **45A**.

A procedure used to make **13** pentadeuterated on the ethyl group is given in the Chemistry section. The potency of the deuterated and of the proton forms of **13** was identical, but unfortunately no statistically significant results are available showing whether deuteration increased the half-life in vivo.

Two questions remain unanswered by this and our previous publications: The first is the question of the origin of the extremely specific inhibition of MAO A by these tricyclic inhibitors despite their noncovalent binding (as shown by the examples of complete restoration of activity on dialysis of the enzyme−inhibitor complex). Our working hypothesis has been that the activity involves noncovalent binding to the flavin prosthetic group by these inhibitors.[17] This tentative explanation was invoked to account for the fact that many different tricyclics with differing electron densities led to active compounds, a result rationalized most simply by assuming that the binding is a polarizability phenomenon. It is certain that the mechanism, even if not this, differs from that responsible for the MAO inhibitory activity of the propargylamine inhibitors, which involves covalent bonding at the flavin moiety,[31] and for the MAO inhibition of the aminoethylamide inhibitors such as Ro41-1049, which are apparently deaminated by the appropriate MAO to the aldehyde which then forms an adduct that initially reacts reversibly (aldehyde−ammonia or Schiff base?) with the enzyme.[18] However, a rationale for the specificity for MAO A of our tricyclics is more difficult to suggest, especially when the short "reach" of the substituents on these inhibitors is considered in connection with the fact that probably 18 amino acids, including the five amino acid sequence containing the cysteine whose sulfur binds the flavin of the FAD prosthetic group of MAO, are identical for both MAO A and MAO B.[19] A possible answer is based on the reported difference in position of the enzymes in situ. MAO B is believed to be near the mitochondrial membrane, while MAO A is associated with lipids and, unlike MAO B, loses its enzyme activity when separated from its lipid matrix.[20] Thus conceivably, the specific MAO A inhibition may be due to our tricyclic inhibitors separating MAO A from its associated lipids, a factor not important to retention of MAO B activity. It may be pertinent that in the aminoethylamide series, the literature states that "the presence of a more bulky aromatic part led to a shift of the [inhibitory] selectivity from MAO B to MAO A."[21]

Scheme 1



EY = MeI → **3**, **77**; EtI → **13**, **78**; PrI → **19**, **79**; C_5H_{11} Br → **20**; CH_2O → **32**, **84**; MeCHO → **33**; EtCHO → **39**; Me_2CO → **40**; m-ClC_6H_4CHO → **41**; Me_2NCHO → **47**; $(COOMe)_2$ → **52**; CO_2 → **53**; $BrCH_2COOEt$ → → **54**; $B(OMe)_3$ → → **61**; $ClSiMe_3$ → **70**; $(MeS-)_2$ → **71**; $(PhS-)_2$ → **72**; Br_2 → **74**; I_2 → **76**.

Our work was not designed to study these questions and cannot cast more light on them. It was designed to produce clinical trial candidates and in **13** offered a compound which seems to meet the target of a potent and selective inhibitor of MAO A whose enzyme binding is reversed by tyramine, with no significant potentiation of tyramine-induced increase in blood pressure over control values.

Summary

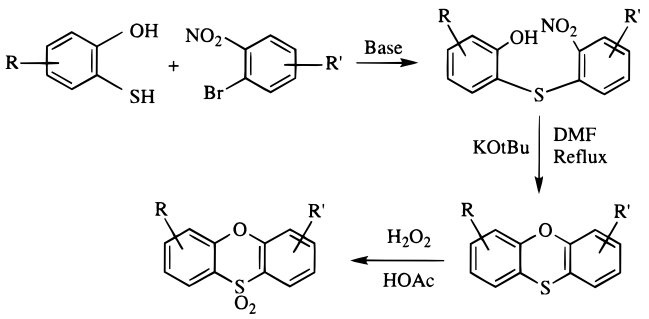
Linear tricyclic compounds whose central ring is composed of a larger and a smaller heteroatom (here mostly phenoxathiin 10,10-dioxides) substituted ortho to the sulfone function by a lipophilic group include compounds which are potent selective inhibitors of monoamine oxidase A and therefore are potential antidepressants. Monosubstitution by a group of relatively short length and small cross section (Me, Et, CF_3, I) is most likely to yield potent compounds. Reversibility of the formation of the enzyme−inhibitor complex by dialysis was used to predict lack of tyramine-induced blood pressure rise (the "cheese effect") which had halted past clinical use of older, nonselective MAO inhibitors. As predicted, no significant increase in blood pressure over control values has been found in rats dosed with tyramine after treatment with the candidate MAO A inhibitor **13** (1-ethylphenoxathiin 10,10-dioxide).

Experimental Section

Chemistry. Melting points were determined using an electrically heated oil bath and are uncorrected. All reported compounds showed a single spot on UV-fluorescent silica gel plates (MK6F, Whatman International, Ltd.) using EtOAc−hexanes or CH_2Cl_2-hexanes unless otherwise stated. Products were identified by elemental analyses and by NMR and in most cases mass spectra. Preparative conditions were not optimized.

Most of the 1-substituted phenoxathiin 10,10-dioxides were made by the action of electrophiles on the lithio derivative of phenoxathiin 10,10-dioxides[22] as shown in Scheme 1, followed if necessary by further reactions. The monocarboxylic acid made in this way by Shirley and Lehto[22] had a low melting point raised markedly on recrystallization. Later studies showed that it was contaminated by 1,9-disubstituted product.[23] Our preparations of **13** by direct ethylation of lithiophe-

Scheme 2



In nitro compound R' = 5-Br → **75**

noxathiin 10,10-dioxide showed some 1,9-diethyl compound **78** and small amounts of additional ethylation products presumably ethylated in the 4- or 6-position ortho to oxygen as well as in the 1-position. Chromatography to yield large amounts of **13** suitable for clinical trial seemed less efficient than the alternative of preparing the more readily purified 1-(1-hydroxyethyl)phenoxathiin 10,10-dioxide (**33**) by reaction of lithiophenoxathiin dioxide with acetaldehyde and subsequently removing the benzylic hydroxy group by reduction with hydrogen and Pearlman's palladium hydroxide on carbon catalyst.[24] This procedure produced a very small proportion of dihydro derivatives of **13**, identified as such by mass spectral molecular weight. Detailed preparations of **13**, **22**, **33**, **42**, **44**, and **48** have been published;[25,26] some slightly modified procedures are given below.

An alternative method of synthesis of phenoxathiins is given in Scheme 2. This is especially useful for preparing halophenoxathiins substituted in other than the 1-position and their 10,10-dioxides which could be converted by lithium exchange with lithium alkyls at low temperatures to derivatives substituted in other than the 1-position. No migration of lithium to the 1-position was noticed under our conditions. Potassium *tert*-butoxide was usually used as base to form the thiolate for the preparation of the sulfide in the first step, especially for convenience on small-scale preparations. Careful exclusion of air was necessary to maximize yields.

Monolithiation of Phenoxathiin 10,10-Dioxide. A 12-L flask equipped with a stirrer, thermometer, addition funnel, and nitrogen demand system was purged with nitrogen, and a solution of 414 g of phenoxathiin 10,10-dioxide in 3.7 L of peroxide-free tetrahydrofuran (previously dried over 4A molecular sieves) was prepared and cooled in a dry ice−acetone bath to below −60 °C. A 1.6 M solution of butyllithium in hexane (1181 mL) was added at a rate which allowed the internal temperature to remain at or below −55 °C (temperatures above about −35 °C led to rapid degradation of yields). These conditions were also satisfactory on a smaller scale. All subsequent reactions were (also) run under an inert atmosphere.

1-(1-Hydroxyethyl)phenoxathiin 10,10-Dioxide (33). Dropwise addition of 20.37 g (0.46 mol) of chilled acetaldehyde to lithiophenoxathiin dioxide solution prepared from 44 g (0.19 mol) of phenoxathiin 10,10-dioxide at −50 °C during 45 min was followed by allowing spontaneous warming to room temperature. After removal of solvent under reduced pressure, the resulting yellow-orange residue was stirred overnight with 360 mL of 0.5 N HCl and filtered, and the solid was washed with water and then 1.5 L of ethanol. The resulting solid was sufficiently pure for synthetic use; an analytical sample was prepared (Table 1).

(+)1-(1-Hydroxyethyl)phenoxathiin 10,10-dioxide (34) was made by reducing **48** with excess of (*S*)-Alpine-Borane (Aldrich Chemical Co.), decomposing the product with 1 N HCl, and chromatographing a CH_2Cl_2 extract of the product with CH_2Cl_2 containing MeCN increased in 1% increments to 10%. The slower material was an oil with an odor resembling α-pinene, which was again chromatographed using 500-mL portions of CH_2Cl_2−MeCN increasing by 1% increments to 8% MeCN. From 1.06 g of starting **48**, 0.41 g of **34** was isolated, with $[\alpha]^{20}_D = +13.8°$ and $[\alpha]^{20}_{365} = +40.5°$, both in $CHCl_3$. Its optical purity was found to be 90% by chromatography using a Chiralcel OJ column.

(−)1-(1-Hydroxyethyl)phenoxathiin 10,10-dioxide (35) was made similarly using (*R*)-Alpine-Borane and was 75% pure as determined with the Chiralcel OJ column.

1-Ethylphenoxathiin 10,10-Dioxide (13) from 33. A solution of 590.2 g (2.14 mol) of **33** in 5.4 L of acetic acid containing 250 mL of 70% perchloric acid was treated under nitrogen with 65 g of Pearlman's catalyst[24] (Aldrich Chemical Co.) and then hydrogenated under pressure slightly above atmospheric. Catalyst was then removed by filtration, and the filtrate was diluted with 4 volumes of water. After remaining overnight, the resulting white solid was removed by filtration, rinsed with water, dried, and recrystallized. Two forms differing in melting point were obtained, as tabulated.

1-Pentadeuterioethylphenoxathiin 10,10-Dioxide. a. 1-Trideuterioacetylphenoxathiin 10,10-dioxide was prepared by stirring 15.0 g of 1-acetylphenoxathiin 10,10-dioxide (**48**) with 30 mL of D_2O, 150 mL of dry DMF, and 0.6 g of potassium *tert*-butoxide under argon for 5 h. The reaction mixture was then transferred to a round-bottom flask with DMF and 25 mL more of D_2O, and solvents were removed in vacuo. The resulting orange solid was transferred with 40 mL of D_2O to a fritted glass funnel, filtered, and dried in vacuo. NMR showed 0.12 methyl proton by integration and comparison with the aromatic multiplet. Recrystallization from ethyl acetate−hexanes after Darco G60 treatment gave 12.44 g of pearly platelets.

b. Reduction to Pentadeuterio-13. The above trideuterioacetyl material, 5.48 g, was reduced with Pearlman's catalyst[24] (Aldrich Chemical Co.) and deuterium in DOAc made by cautiously mixing 150 mL of acetic anhydride and 30 mL of "98.8% D" D_2O and, when no reaction was evident, adding 3 drops of CF_3COOH followed by stirring with exclusion of moisture for 1 h at room temperature and then overnight at 50 °C. The product of the usual workup showed 0.1 alkyl H by NMR, mp 115.2 °C. Anal. ($C_{14}H_7D_5O_2S$). Use of HOAc as solvent in this reduction gave nondeuterated **13**.

1-Ethylphenoxathiin (11) was made by reduction of 1.07 g (4.11 mmol) of **13** with 20.5 mL of 1 M DIBAL (Aldrich Chemical Co.) in toluene and an additional 25 mL of toluene under reflux for 5 h, followed by decomposition of excess DIBAL with acetone (exotherm) and purification by column chromatography using hexanes as solvent and silica gel as stationary phase. TLC (hexanes) and proton NMR with correct integration values as well as elemental analysis were used as criteria of purity for the 220 mg of liquid product obtained as the faster moving eluate fraction.

1-Acetylphenoxathiin 10,10-Dioxide (48) from 33. A mixture of 29.83 g (0.14 mol) of pyridinium chlorochromate (Aldrich Chemical Co.), 25.2 g of 4A molecular sieves, 13.92 g (0.05 mol) of **33**, and 580 mL of CH_2Cl_2 was stirred for 21 h and then filtered through a 4-cm deep layer of Kieselguhr which removed color. The apparatus and Kieselguhr were rinsed with EtOAc and the solutions combined and chromatographed on silica gel, using EtOAc−hexanes and collecting arbitrary fractions. Evaporation of solvent gave solids melting between 124.5 and 142 °C. The higher-melting residues were recrystallized from hot EtOAc by adding hexanes to incipient turbidity, yielding 9.70 g melting at 144.0 °C, and the lower-melting residues gave an additional 1.16 g melting at 142.4 °C. Recrystallization from EtOAc−pentane gave material giving a single spot on TLC using 1:1 EtOAc−pentane and the correct elemental analysis, proton NMR, and mass spectrum molecular ion.

1-Vinylphenoxathiin 10,10-Dioxide (22) from 33. A slurry of 1.06 g (3.84 mmol) of **33**, 60 mL of dried CH_2Cl_2, and 0.730 mL (10 mmol) of $SOCl_2$ was heated under reflux protected from atmospheric moisture for 3.5 h. Volatile materials were then distilled off on a hot water bath at water aspirator pressure, and then 10 mL of ethanol was added and similarly removed. The residual solid was recrystallized from

ethanol, the resulting mother liquors were evaporated down, and the residue was recrystallized from EtOAc−pentane. The combined products were again recrystallized fron EtOAc−pentane to yield 0.310 g of **22**.

1-(1-Methylvinyl)phenoxathiin 10,10-dioxide (23) was made by an analogous method.

1-Ethinylphenoxathiin 10,10-dioxide (24) was made by adding excess Br_2 to 4.2 g (16.3 mmol) of the 1-vinyl compound **22** in 100 mL of CH_2Cl_2, evaporating off solvent after 10 min, taking up the residue in dried THF, and stirring that solution with 7.6 g (67 mmol) of potassium *tert*-butoxide with exclusion of air. After 20 min the black reaction mixture was poured into water, acidified with 1 N HCl, and extracted with CH_2Cl_2. Evaporation of solvent and two recrystallizations of the resulting solid from ethyl acetate by addition of pentane gave 1.42 g of light-yellow solid.

1-(Trifluoromethyl)phenoxathiin 10,10-dioxide (27) was made by heating a mixture of 2.06 g (5.75 mmol) of 1-iodophenoxathiin 10,10-dioxide hemihydrate (**76**), 3.13 g (4 equiv) of sodium trifluoroacetate, 2.19 g (2 equiv) of cuprous iodide, and 45 mL of *N*-methylpyrrolidone. After a brief incursion to 220 °C, the reaction mixture was kept at 160 °C for 2 h and poured onto 500 mL of ice−water. The resulting solids were filtered off and extracted with first acetone and then CH_2Cl_2. The solution was extracted with 1 N NaOH and then 1 N HCl and dried, and solvent was removed to leave a dark solid. Chromatography using 3:1 hexanes−EtOAc gave 140 mg of a faster moving fraction whose mass spectrum indicated that it was recovered **76**, 235 mg of desired product, and traces of what appeared to be **29**.

2-(Trifluoromethyl)phenoxathiin 10,10-dioxide (28). A mixture of 0.87 g (3.11 mmol) of 2-bromophenoxathiin, 1.18 g (6.23 mmol as CuI) of cuprous iodide, 1.69 g of sodium trifluoroacetate, 25 mL of DMF, and 10 mL of toluene was heated, removing vapor to 152.4 °C. After 1.5 h the reaction mixture was cooled and partitioned between $CHCl_3$ and water. The organic portion was dried under high vacuum to remove DMF, oxidized with excess H_2O_2 in HOAc at 80 °C, and extensively chromatographed first with 1:1 CH_2Cl_2 and petroleum ether and then with 1:1 EtOAc and hexanes. The final product still had a minor additional TLC spot.

1-(Pentafluoroethyl)phenoxathiin 10,10-dioxide (29) was made by the method used to prepare **27** from **76** and sodium pentafluoropropionate in poor yield.

1-(1,2-Dihydroxyethyl)phenoxathiin 10,10-Dioxide (44) from 22. The product of heating under reflux of 10.1 g (0.0366 mol) of **33**, 200 mL of CH_2Cl_2, and 20 mL of $SOCl_2$ for 12 h followed by addition of 6 mL more of $SOCl_2$ and another 6 h of reflux had solvent removed in a hot water bath under reduced pressure and then had two 88-mL portions of 97% formic acid added and removed in vacuo sequentially. The residue was dissolved in 100 mL of 97% formic acid and stirred at room temperature for 12 h after addition of 4.5 mL of 30% hydrogen peroxide and for an additional 5 h after 5 mL more of 30% hydrogen peroxide had been added. The reaction was then heated on a steam bath until the solids were dissolved, cooled to room temperature, and diluted with 1 L of water, and the supernatant liquid was decanted from an oily residue.

The separate enantiomers of **44**, **45**, and **45A** were prepared using OsO_4 and H_2O_2 with the Corey chiral ethylenediamine catalyst,[27] giving for the levorotatory isomer **45A** $[\alpha]^{20}_D = -56.3°$ found (second peak) to be 93% optically pure by chromatography on Chiralcel OJ. Chromatography of racemic **44** on a semipreparative Pirkle column Regis 1010DPG gave 99% material with $[\alpha]^{20}_D = -63.4°$.

Biological Methods. The methods used were given in detail in previous papers.[1,2] They involved a radiometric procedure using [^{3}H]serotonin and [^{14}C]phenethylamine. The MAO assays were performed in triplicate at each concentration of the putative inhibitor. The percent inhibition showed SEM variation within 5% of mean values. IC_{50} values were obtained by plotting mean values vs log of inhibitor concentration and estimating visually from these plots. Dialysis of MAO−inhibitor complexes, used as a screening test for likely reversibility which would minimize tyramine-induced blood pressure rise, was described earlier.[7] The whole animal antidepressant tests mentioned followed literature methods.[28−30]

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