Articles

Selective Inhibitors of Monoamine Oxidase. 4.[1] SAR of Tricyclic *N*-Methylcarboxamides and Congeners Binding at the Tricyclics' Hydrophilic Binding Site

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Linear [6.6.6] tricyclic moieties whose center ring is made of two atoms of differing size (here primarily thioxanth-9-ones and phenoxathiins) monosubstituted meta to the sulfur by C(O)NHMe include potent and selective inhibitors of monoamine oxidase A. Similarities with effects on SAR of acylamide and of diazapentacyclic substitution on such rings, including positional variables, the requirement for monomethylation (primary and dialkylated amides are inactive and higher monoalkylated amides show little or no potency), and that sulfur is optimally in sulfone form, suggest that binding to the enzyme occurs similarly in each series. No significantly greater rise in blood pressure was found in rats given sufficient **8** to inhibit most brain and liver MAO A and then followed by oral tyramine than was found on administration of tyramine to controls. This is in contrast to a large blood pressure rise in rats pretreated with phenelzine followed by tyramine, and in accord with the belief that an inhibitor selective for MAO A which is reversibly bound to the enzyme and therefore displaced by any ingested tyramine will not lead to the "cheese effect" (hypertension during treatment with MAO inhibitors usually caused by ingestion of foods containing tyramine).

Monoamine oxidase (MAO) (EC 1.4.3.4 amine oxidase, flavin containing) consists of two forms distinguishable by their substrate specificities[2] and their amino acid sequences.[3] Before this difference was recognized, inhibition of "MAO" was found to lead to antidepressant activity, and nonspecific inhibitors such as phenelzine, which are irreversibly bound to both forms of MAO, were clinically used as antidepressants. However, some patients developed hypertension ("cheese effect"), so clinical use of such MAO inhibitors as antidepressants was essentially abandoned. Subsequent research[4] indicated that the cheese effect was usually due to ingestion of tyramine, found especially in fermented foods such as cheeses where it is produced by the action of microorganisms on milk tyrosine, which was not destroyed by the inhibited MAO. Tyramine is a substrate of both forms of MAO. Therefore, when it was realized that inhibition of MAO A was responsible for the antidepressant effect,[5] it seemed logical to look for an inhibitor selective for MAO A, retaining the MAO B activity to destroy any ingested tyramine. As a further precaution, it would be desirable that the inhibitor be bound to the MAO A reversibly and competitively with tyramine, so that ingestion of a large amount of tyramine would lead to displacement of inhibitor from the MAO A−inhibitor complex, reactivating the MAO A to oxidize tyramine. Such a selective, reversibly bound, and tyramine-displaceable inhibitor has been our goal. Previous publications from our laboratory[1,6] have shown that the set of tricyclic compounds with the two outer rings aromatic and the center ring made up of two functions differing in size and with a hydrophilic group meta to the larger central function (termed "the hydrophilic binding site") contains many potent and selective MAO A inhibitors. The hydrophilic group reported initially was the *N*-acylamino function.[6] While this allowed for the ready synthesis of a variety of positional isomers on many tricyclic systems, the compounds **1** could not be exploited clinically because of their relationship to known *N*-arylamide carcinogens.[6] Studies were therefore instituted to learn whether other, medicinally more acceptable hydrophilic groups could replace the acylamino function and, if so, whether the MAO inhibitory activity of the resulting compounds followed the same structure to potency relationships (SAR) found for the *N*-arylacylamides **1**. A variety of five-membered rings containing two or more heterocycles (**2a**−**d**) were the first potential hydrophilic replacements for acylamino groups that were studied.[1] The SAR for potency and selectivity in inhibiting MAO A as a function of tricyclic moiety, position of substitution with respect to the middle ring larger group, and additional effect of other groups in the outer ring not substituted by the hydrophilic function were similar to the effects found earlier for the compounds**1.** Unfortunately, the seemingly best compounds of the series **2** either showed unsatisfactory pharmacokinetic properties or toxicity on chronic administration to rats. However, the similarity of SAR between these two series, and the appreciable number of compounds showing nanomolar potencies and high selectivity, made it seem worth while to search for an alternative hydrophilic

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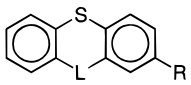
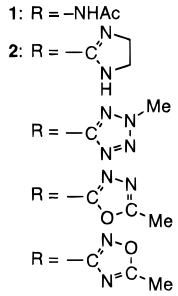


S is smaller group
L is larger group



group to substitute into the same tricyclic systems. Derivatives likely to be metabolized into aromatic carboxylic acids were selected for study, since such acids tend to be nontoxic.

Results and Discussion

Some confusion has been induced in comparisons of SAR for substitution in differing tricyclics caused by historic nomenclature requiring differing locants for identical positions of substitution with respect to the central ring components. The numbering used for the xanthone and the thioxanthone and thioxanthene systems is the historical system shown at the heading to Tables 1 and 4. Phenothiazines, as shown in the heading of Table 3, also have their own numbering system. The other tricyclics are numbered from the outer ring carbon ortho to the central element of higher atomic number, as shown for phenoxathiin in the heading for Table 2.

The tables show inhibition of rat brain MAO A and B obtained with tricyclic systems substituted by carboxylic acid functions or simple derivatives of these. In addition, a recent report[7] that some unsubstituted tricyclics had IC_{50} values in the micromolar range for, and were specific inhibitors of, MAO A led us to tabulate some of our results with unsubstituted and with simple halogenated derivatives of the tricyclics whose hydrophilic substituted derivatives are the major subject of this report. Subject to the uncertainties possibly due to the extremely low solubilities in aqueous systems of these compounds with no polar substituents, the results seem to follow one generality reported previously: where one component of the central ring is sulfur, ring sulfur in the sulfone form markedly increases potency compared to unoxidized or sulfoxide sulfur. Thus while only a little difference in the low potencies reported can be seen between the unsubstituted thioxanthone **3**, which has the sulfur in the unoxidized form, and the sulfone **4,** the unsubstituted phenoxathiins show differences analogous to those reported in our earlier work for the three degrees of oxidation of heterocyclic sulfur, with potencies increasing from the sulfoxide **49** through the sulfide **48** to the sulfone **50.** This last showed the quite respectable IC_{50} value of 50 nM. Results compatible with this progression can be seen in the 2-chlorothioxanthenes of Table 4, where the sulfone **84** has appreciable though not useful potency and selectivity**,** while the corresponding sulfide **81** and sulfoxide **83** have no detectible activity**.**

Of greater interest is the major thrust of this report, the MAO inhibition by tricyclics substituted by the hydrophilic carboxamide group. A qualitative correspondence between the results reported in this paper and those reported for the tricyclic *N*-arylacylamides[6] and for the tricyclics substituted by imidazolines and their congeners[1] earlier is clear. This includes the effects on potency both of the position of the substituent on the tricyclic system with respect to the central groups, i.e. the greatest potency is conferred by a hydrophilic substituent on an outer ring meta to the larger central ring group (most usually here SO_2) and para to the smaller, and of similarity of the effects of generalized structural details. Thus the thioxanthone dioxide **8,** which has its CONHMe meta to the large central SO_2 group, has an IC_{50} of 60 nM and is selective for MAO A, while **6**, which has its CONHMe para to the SO_2, shows only 28% inhibition of MAO A at 1000 nM. The loss of specificity with compounds of low potency which is shown here for **6** has been mentioned in our earlier papers. A similar effect of substituent position with respect to the central SO_2 group is seen when potencies of the corresponding phenoxathiin dioxides are compared. Thus **59** (*N*-methylcarboxamide function meta to sulfone, IC_{50} = 30 nM) is far more potent than **53** (*N*-methylcarboxamide ortho to sulfone, inactive) or with **62** (*N*-methylcarboxamide para to sulfone, IC_{50} = 600 nM). Incidentally, while the increased potency in going from the sulfide **7** to the sulfone **8** is evident here as expected, **58** and **59** appear to invert this order. We can give no explanation of this.

Another point of close similarity between the present series and the *N*-arylacylamide series[6] is the sharp maximum found in this series with the *N*- monomethylated amides. The C(O)NHMe substituent which confers maximum potency in the results reported here corresponds to the NHC(O)Me reported previously[6] to lead to maximum potency in the *N*-arylamide series. In the *N*-arylamides, maximum potency was found for *N*-acetylamino-substituted tricyclics, with the lower (formamido) and higher homologs less active or inactive. Similarly, as shown in this present report, the *N*-methylcarboxamides are far more potent than the otherwise identical primary amides $ArC(O)NH_2$ (compare **30** to **32** or **34** to **35** in the thioxanthone dioxide series and **57** to **59** in the phenoxathiin dioxide series. Also, as in the earlier *N*-arylacylamide paper, replacing the pendant methyl in this work with larger R groups to give ArC(O)NHR where R is Et or higher to give, for example, **10**, **11**, **12** and higher thioxanthone dioxides of Table 1 compared to **8**, led to partial or complete loss of activity at the concentrations of interest. Similar results were found in the phenoxathiin dioxide series, where not even the relatively small cyclopropyl function found in **66** could satisfactorily replace the methyl of **62**.

Other substitutions eliminating appreciable activity include dialkylation of the amide N not only by simple alkyl groups, as found for **20**, **69,** and **70** among others, but also by the *N*-methyl (**16**) and *O*-methyl (**17**) hydroxylamine amides. It is interesting that the *N*-methylamidine **46**, which is a nitrogen analog of a methylamide, has substantial potency, whereas the *N*,*N*′-dimethylamidine **47** has little, and that the *N*-methyl-3-thioamide **45** has little activity, in contrast to its

amide analog **8.** No further studies of amidines were carried out because amidines are known generally to be poorly absorbed in vivo.

Comparison of the effect of methyl groups on potency in this present methylamide series with results reported for the tricyclics whose hydrophilic function was a five-membered ring with two or more heteroatoms[1] turns out not to be a simple matter. The effect for alkyl groups greater than methyl is the same in all three series, *N*-arylacylamino, five-membered ring, and *N*-alkylarylcarboxamide, causing diminution or loss of activity for all. However, methylation of either the carbon or a nitrogen of the 2-arylimidazolines destroyed activity, unlike the effect of methyl substitution in the present and earlier series, while carbon methylation in the 1,2,4-oxadiazole and in the 1,3,4-oxadiazole series led to very potent and specific inhibitors. The 5-aryltetrazoles in the previous paper are an even more difficult case for comparison, since with these 2-methylation led to potent inhibitors while 1-methylation gave far less potent compounds. The simplest conclusion that can be suggested is that the steric requirement for binding to the enzyme at the position meta to the larger central group (in all these examples the SO_2 function) is very sensitive to small changes in the relatively rigid 5-membered rings.

The similarities in the effects of substituent position, size, and hydrophilicity on activity support the idea that the differing hydrophilic groups cause interaction between the inhibitors and the enzyme to occur with essentially identical geometries. This raises the possibility of using inhibitors based on those reported here but modified with a reactive group which can bind covalently to nearby amino acids of the enzyme. Such reactive groups might be placed in each in turn of several positions on the tricyclic system to explore the composition of the enzyme docking site of these inhibitors. Together with similar use of other specific binding sites on tricyclics which we hope to report on in future publications, a fairly broad range of probing might be available.

Compound **8** was selected for further study[8] aimed at its development as a potential antidepressant/anxiolytic. The dialysis of MAO A in rat brain homogenates which had been inhibited by **8** led to complete return of enzyme activity. As anticipated from this and the previous discussion, when conscious, unrestrained rats pretreated with **8** were given oral tyramine, the rise in blood pressure was within significance of control values up to 90 mg/kg of tyramine, while phenelzine used as positive control at equipotent MAO A inhibition in rat brain (phenelzine is approximately twice as potent as **8** in our tests) gave blood pressure increases 3−10-fold greater. Activity was shown by **8** in standard antidepressant models in rats, but no activities in a large variety of other pharmacological tests and models at high multiples of the dose of 50 mg/kg in Sprague Dawley male rats which gives 80% inhibition of rat brain MAO A and ca. 90% inhibition of rat liver MAO A. Details of methods and results have been published.[8] Unfortunately, when humans were fed large multiples of the anticipated therapeutic dose of **8** in early clinical trials, a small proportion showed an increase above pretreatment levels in their serum aminotransferases ("liver enzymes"). Increased levels of these in serum are considered markers of possible liver damage, so further work with this compound was discontinued. Parenthetically, the reduction product of **8**, the alcohol **88**, was found to be to be a major metabolite of **8.** As anticipated, the reduction of **8** to **88** was reversible and was a function of pH in vitro, favoring **8** under alkaline conditions.

Experimental Section

Chemistry. Melting points below 305 °C were determined using an electrically heated oil bath, and those above that temperature by using a block (MEL-TEMP Laboratory Devices). All melting points are uncorrected. Unless otherwise is stated, all compounds showed a single spot on UV-fluorescent silica plates (MK6F, Whatman International, Ltd.). The solvents used were EtOAc−hexanes or CH_2Cl_2−hexanes unless otherwise specified. Reactions in those few cases in which products could not be distinguished by TLC from starting materials or from simultaneously produced isomers were followed by NMR. Products were identified by elemental analysis and NMR. Preparative conditions were not optimized.

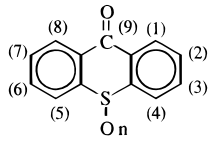
Preparation of the 9-oxothioxanthene-3-carboxylic acid amides of Table 1 proceeded from the corresponding acid chloride which was made from 2-nitroterephthalonitrile and the required aryl thiol by the procedure outlined in our previous paper[1] and the reference cited there. Amides of lower amines such as methylamine were made by cautiously adding the neat acid chloride to a stirred large excess of cooled concentrated preferably aqueous solution of amine. The resulting slurry could be filtered and the solid water washed free of a few percent of alkylammonium salt of the acid and was then essentially pure after drying. Especially the methylamides made in this way frequently were appreciably soluble in excess aqueous methylamine, so it was often expedient to concentrate either the unfiltered reaction or the first filtrate at reduced pressure (water aspirator) to remove most of the amine and then filter, or refilter, the aqueous slurry to recover the resulting solid amide. A small amount of starting acid could be recovered by acidification of the filtrate. Methylamides could also be made from the methyl esters and dry methylamine by methoxide-catalyzed reaction in dry methanol.

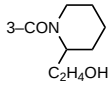
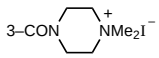
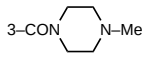
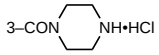
Amides of higher amines were best made from the acid chlorides and 2 equiv of amine for readily available amines, or using a small excess over 1 equiv of the reacting amine and 1 equiv of a tertiary amine such as triethylamine to scavenge the HCl. The preferred solvent was dry ethyl ether, and the amine hydrochloride almost always precipitated in filterable form. Alternatively the amine hydrochloride and any excess amine were extracted with 0.1 N or more dilute aqueous HCl and the amide recovered from its ethereal solution generally by evaporation of the ether but occasionally by cooling the solution to cause the amide to crystallize. An example of the preparation of **8** modified from ref 9 is given below. The *N*-methylthioamide (**45**) was made uneventfully from the corresponding amide (**8**) without obvious involvement of the 9-keto group, using Lawesson's reagent[10] in xylene. The same method was also used to prepare the nonmethylated thioamide corresponding to **8** (not tabulated) in poorer yield. Nitrile, the obvious side product, was not sought. Both **8** and **45** were converted by $(EtO)_3BF_4$ in toluene to *O*-ethyl and *S*-ethyl salts, respectively, and each of those added to NH_3 gave **46** or, added to $MeNH_2$, gave **47**.

The phenoxathiins of Table 2 were generally made (Scheme 1) by condensation of an *o*-hydroxythiophenol with an *o*-nitrohalobenzene, usually in a one-pot reaction without isolation of intermediate diaryl sulfide. Normally, anhydrous DMF was used as solvent with a base of low nucleophilicity such as KO-*t*-Bu or KH. Smiles rearrangement was never noted. A preparation of 3-bromophenoxathiin by this route, oxidation of that to its 10,10-dioxide, and conversion of that by the modified von Braun reaction (CuCN in DMF) to nitrile **60** is given below.

Preparation of phenoxathiins by sulfur fusion of diphenyl ethers with Friedel−Craft catalysts, while the method of choice

Table 1. MAO Inhibition by Thioxanthones

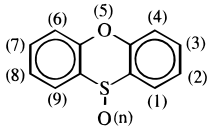


			IC$_{50}$ (μM) or % I at μM					
no.	substituent	*n*	MAO A	MAO B	formula	anal.	mp (°C)	recryst[a]
3[b]		0	Ca 0.6	27% at 10				
4[c]		2	Ca 1	12% at 10				
5[d]	2-Br	2	1	5% at 1				
6	2-CONHMe	2	28% at 1	32% at 1	$C_{15}H_{11}NO_4S$	C,H,N[b]	242−243	A−W
7	3-CONHMe	0	0.5	48% at 1	$C_{15}H_{11}NO_2S$	C,H,N,S	235−236	A−W
8[e]	3-CONHMe	2	0.06	4% at 1				
9	2,6-(CONHMe)$_2$	2	0.05	0.6	$C_{17}H_{14}O_5N_2S$	C,H,N	321−322	HOAc
10	3-CONHEt	2	Ca 0.5	9% at 1	$C_{16}H_{13}NO_4S$	C,H,N	186−186.4	IPO
11	3-CONHCHMeEt	2	11% at 1	6% at 1	$C_{18}H_{17}NO_4S$	C,H,N	175	HOAc−W
12	3-CONHt-Bu	2	18% at 1	34% at 1	$C_{18}H_{17}NO_4S$	C,H,N	196.5	HOAc
13	3-CONHC$_2$H$_4$OH	2	0% at 1	0.7% at 1	$C_{16}H_{13}NO_5S$	C,H,N	217	A
14	3-CONHCMe$_2$CH$_2$Cl	2	−6% at 1	41% at 1	$C_{18}H_{16}ClNO_4S$	C,H,N	191−192	T−SOCl$_2$
15	3-CONCMe$_2$CH$_2$OH	2	18% at 1	8% at 1	$C_{18}H_{17}NO_5S$	C,H,N	199	A
16	3-CONOHMe	2	0% at 0.1	0% at 0.1	$C_{15}H_{11}NO_5S$	C,H,N	159−161	A−H
17	3-CONHOMe	2	15% at 0.1	0% at 0.1	$C_{15}H_{11}NO_5S$	C,H,N	218−220	A−D
18	3-CONHC$_3$H$_6$NMe$_2$	2	2% at <0.5	4% at <0.5	$C_{19}H_{20}N_2O_4S$·HCl 0.5 H_2O	C,H,N	170	A
19	3-CONHCH$_2$C$_6$H$_2$-3,4,5(OMe)$_3$	2	0.5 at 1	9% at 1	$C_{23}H_{19}NO_7S$	C,H,N	235	A
20	3-CONEt$_2$	2	17% at 1	0 at 1	$C_{16}H_{13}NO_4S$	C,H,N	189	A
21		2	0 at 1	0 at 1	$C_{21}H_{21}NO_5S$	C,H,N	186	HOAc
22		2	72% at 1	51% at 1	$C_{18}H_{15}NO_4S$	C,H,N	169	A
23		2	7% at 0.1	17% at 0.1	$C_{20}H_{21}N_2O_4SI$	C,H,N	322	W
24		2	2% at 1	12% at 1	$C_{19}H_{18}N_2O_4S$	C,H,N	198−202.5	A−W or EA
25		0	7% at 10	10% at 10	$C_{20}H_{20}N_2O_2S$·HCl·0.5H_2O	C,H,N	345	A−W
26	5-Me-3-CONHMe	2	0.05	7% at 1	$C_{16}H_{13}NO_4S$	C,N,N	232−233.5	A−W
27	5-Et-3-CONHMe	2	44% at 1	5% at 1	$C_{17}H_{15}NO_4S$	C,H,N	169.5	A−W
28	7-Me-3-CONHMe	2	0.008	18% at 1	$C_{16}H_{13}NO_4S$	C,H,N	251.5−254	HOAc
29	7-*i*-Pr-3-CN	2	60% at 0.3	5% at 0.3	$C_{17}H_{13}NO_3S$	C,H,N	177	HOAc
30	7-*i*-Pr-3-CONH$_2$	2	0.7	14% at 1	$C_{17}H_{15}NO_4S$	C,H,N	235	HOAc
31	7-*i*-Pr-3-CONHMe	0	59% at 0.1	14% at 0.1	$C_{18}H_{17}NO_2S$	C,H,N	185−186	HOAc
32[e]	7-IsoPr-3-CONHMe	2	0.006	15% at 0.1	$C_{18}H_{17}NO_4S$	C,H,N	203−205	HOAc−W
33	7-OH-3-CONHMe	2	64% at 1	19% at 1	$C_{15}H_{11}NO_5S$	C,H,N	320−322.5	A
34	7-PrO-3-CONH$_2$	2	0.45	11% at 1	$C_{17}H_{15}NO_5S$	C,H,N	240−241	D−A−W
35	7-PrO-3-CONHMe	2	0.002	4% at 0.03	$C_{18}H_{17}NO_5S$	C,H,N	193	A−D−W
36	7-MeCHOAc-3-CONH$_2$·$^1/_2$H$_2$O	2	29% at 1	3% at 1	$C_{18}H_{15}NO_6S$·0.5H_2O	C,H,N,S	205−207	M−Ac−W
37	7-MeCHOH-3-CONHMe	2	0.01	0at 0.1	$C_{17}H_{15}NO_5S$	C,H,N,S	193−196	M−W
38	7-OAc-3-CONHMe	2	0.13	27% at 1	$C_{17}H_{13}NO_6S$·H_2O	C,H,N	230−231	A−W
39	7-OCH$_2$COOMe-3-CONHMe	2	0.3	5% at 1	$C_{18}H_{15}NO_7S$	C,H,N	140.2−140.7	A−W
40	7-OCH$_2$COOC$_2$H$_4$OMe	2	Ca. 1	8% at 0.1	$C_{20}H_{19}NO_8S$	C,H,N	140−141	MOX−W
41	7-NMe$_2$-3-CONHMe	2	0.03	7% at 0.1	$C_{17}H_{16}N_2O_4S$	C,H,N	213−215	A−D−W
42	5,7-Me$_2$-3-CONHMe	2	0.02	3% at 0.1	$C_{17}H_{15}NO_4S$	C,H,N	239−241	A−W
43	2,4-Me$_2$-3-CONH$_2$	0	0 at 0.1	0 at 0.1	$C_{16}H_{13}NO_2S$	C,H,N	292.5	A
44	2,4-Me$_2$-3-CONMe$_2$	2	0 at 0.1	0 at 0.1	$C_{18}H_{17}NO_4S$	C,H,N	189−191	EA−H
45	3-C(S)NHMe	2	38% at 0.1	0 at 0.1	$C_{15}H_{11}NO_3S_2$	C,H,N,S	221.2	E−W
46[f]	3-C(=NH)NHMe·HCl	2	0.06	12% at 1	$C_{15}H_{12}N_2O_3S$·HCl	C,H,N,S	315.3−317.3	A, EA, E
47	3-C(=NMe)NHMe	2	21% at 1	4% at 1	$C_{16}H_{14}N_2O_3S$	C,H,N	221−223	A

[a] Recrystallization solvents: A = ethanol; Ac = acetone; C = chloroform; D = DMF; E = ether; EA = ethyl acetate; H = hexanes; HOAc = acetic acid; IPO = 2-propanol; M = methanol; MOX = 2-methoxyethanol; P = pentane; T = toluene; W = water. [b] Aldrich Chemical Co. [c] Beaulieu, F.; Snieckus, V. Directed Metallation of Diarylsulfone 2-Amides and 2-O-Carbamates. Regiospecific General Route to Thioxanthen-9-one 10,10-Dioxides via Anionic Friedel-Crafts and Remote Fries Rearrangement Equivalents. *J. Org. Chem.* **1994**, *59*, 6508−6509. [d] Jayamma, V.; Badiger, V. V.; Nargund, K. S. Substituted Thioxanthones. *J. Karnatak Univ.* **1967**, 12, *49*; *Chem. Abstr.* **1968**, *69*, 106456t. [e] Harfenist, M.; Joyner, C. T.; Heuser, D. J. Tricyclic Compounds, Compositions Containing Them, and Their Use in Medicine. Eur. Pat. Appl. EP 150, 891. [f] Compound **47**·HCl is as tabulated. **47**·HBF$_4$: C,H,N. Mp: 228.7 °C.

for phenoxathiin itself, was not applicable to the congeners that our work required. This presumably is because of nonreactivity or differing reactivity of the substituted rings. Although sulfur fusion of 4,4′-dibromodiphenyl ether was ineffective, as reported in the literature, the related reaction with molar amounts of $AlCl_3$ and $SOCl_2$ in CH_2Cl_2 gave an appreciable yield of a mixture of the expected 2,8-dibromophenoxathiin 10-oxide and the corresponding phenoxathiin.

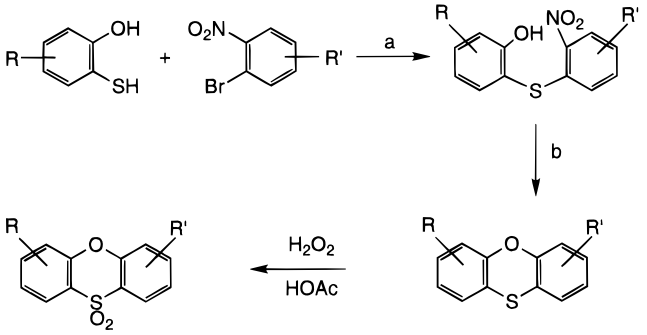
Table 2. MAO Inhibition by Phenoxathiins



			IC$_{50}$ (μM) or % I at μM					
no.	substituent	*n*	MAO A	MAO B	formula	anal.	mp (°C)	recryst[a]
48[b]		0	0.3	−2% at 0.3				
49[c]		1	24% at 1	7% at 1				
50[d]		2	0.05	3% at 1				
51[e]	1-COOH	2	13% at 1	5% at 1	$C_{13}H_8O_5S\cdot0.15H_2O$	C,H,N	205−207	HOAc
52	1-CONH$_2$	2	8% at 1	15% at 1	$C_{13}H_9NO_4S$	C,H,N	207.5−208.5	A−D−W
53	1-CONHMe	2	4% at 1	7% at 1	$C_{14}H_{11}NO_4S$	C,H,N	244−247	A
54[f]	2-CN	0	0.4	14% at 1				
55	2-CN	2	0.2	0.7% at 0.3	$C_{13}H_7NO_3S$	C,H,N	253−254.8	A−W
56[g]	2-COOH	2	9% at 1	11% at 1				
57[h]	2-CONH$_2$	2	45% at 1	11% at 1	$C_{13}H_9NO_4S$	C,H,N	290−292	A−D−W
58	2-CONHMe	0	0.02	15% at 1	$C_{14}H_{11}NO_2S\cdot0.5H_2O$	C,H,N,S	102−103	MeOH
59	2-CONHMe	2	0.03	−14% at 0.01	$C_{14}H_{11}NO_4S$	C,H,N	253−257	A−D−W
60	3-CN	2	0.06	2.5	$C_{13}H_7NO_3S$	C,H,N,S	225−227	EA−H
61	3-COOH	2	9% at 1	11% at 1	$C_{13}H_8O_5S\cdot0.3H_2O$	C,H,N	261−265	IPO−W
62	3-CONHMe	2	0.6	3.0	$C_{14}H_{11}NO_4S$	C,H,N,S	206−207	EA−H
63[i]	4-COOH	0	32% at 10	8% at 10	$C_{13}H_8O_3S$	C,H,N,S	165−168	HOAc
64	4-CONHMe	0	13% at 10	8% at 10	$C_{14}H_{11}NO_2S$	C,H,N	122−124	EA
65	1-aza-7-CONHMe	2	2% at 1	4% at 1	$C_{13}H_{10}N_2O_4S$	C,H,N	267−270	A−D−W
66	3-CONH-cyclo-Pr·0.2H$_2$O	2	NS at 0.1	10% at 0.1	$C_{16}H_{13}NO_4S$	C,H,N,S	185−187	A−W
67	3-CONHBu	2	14% at 0.1	8% at 0.1	$C_{17}H_{17}NO_4S$	C,H,N,S	135−137	EA−H
68	3-C(O)NHC$_2$H$_4$NHAc	2	0.3	11% at 0.1	$C_{17}H_{16}N_2O_5S$	C,H,N,S	235	EA
69	3-CONMe$_2$	2	0 at 0.1	10% at 0.1	$C_{15}H_{13}NO_4S$	C,H,N,S	173−175	EA−H
70	3-CONEt$_2$	2	5% at 0.1	11% at 0.1	$C_{17}H_{17}NO_4S$	C,H,N,S	105−108	EA−H
71	4-COOH	0	32% at 10	8% at 10	$C_{13}H_8O_3S$	C,H,N,S	165−168	HOAc
72	4-CONEt$_2$	0	0 at 0.1	0 at 0.1	$C_{17}H_{17}NO_2S$	C,H,N	85−87	EA−P
73	2-OC(O)NHMe	2	0.2	18% at 1	$C_{14}H_{11}NO_5S$	C,H,N	162−164	A
74	1-Ac	2	85% at 0.1	0 at 0.1	$C_{14}H_{10}O_4S$	C,H	142−144	EA−P
75[j]	2-Ac	2	52% at 1	5% at 1	$C_{14}H_{10}O_4S$	C,H	169	EA−H
76	2,7-DiAc	2	0.5	2	$C_{16}H_{12}O_5S$	C,H	223−225	A

[a] See footnote *a* of Table 1. [b] Parish Chemical Co. [c] Folsom, H. E.; Castrillón, J. The Controlled Oxidation of Organic Sulfides to Sulfoxides with the Help of *o*-Iodosylbenzoic Acid. *Synth. Commun.* **1992**, *22*, 1799−1806. [d] Kemp, D. S.; Buckler, D. R. Synthesis of 1-Methoxy-9-Mercaptopheroxathiin and the Resolved 1-((*N*-Benzyloxycarbonyl)-l-Alanyl)oxy-9-(methoxycarbonyl)dithio)phenoxathiin 10-oxide Diastereomers. Comments on Improved Methods for Sulfone Reduction. *J. Org. Chem.* **1989**, *54*, 3647−3651. [e] Shirley, D. A.; Lehto, E. A. The Metallation of Phenoxathiin 10-oxide and 10,10-Dioxide with n-Butyl Lithium. *J. Am. Chem. Soc.* **1955**, *77*, 1841−1843. [f] Batchelor, J. F.; Gorvin, J. H. Sulfur-containing Tricyclic Compounds. *Ger. Offen.* 2,344,800 1974. [g] Vasiliu, G.; Gloaba, A.; Maior, O. Condensed Heterocromatic Systems. Effect of Pyrocatechol Dichloromethylene Ether [2,2-Dichloro-1,3-benzodioxole] on Dibenzfuran, Phenoxathiin, Thianthrene and Phenoxatellurin. See: *Chem. Abstr.* **1969**, *71*, 3339u. [h] Popa, G.; Danet, A. F.; Avrigeanu, M. Determination of Some Dissociation Constants of some Heteroaromatic Monoximes. See: *Chem. Abstr.* **1977**, *86*, 105620f. [i] Gilman, H.; Van Ess, M. W.; Willis, H. B.; Stuckwisch, C. G. The Metallation of Phenoxathiin. *J. Am. Chem. Soc.* **1940**, *62*, 2606−2610. [j] Paget, C. J.; Dennis, E. M.; Nelson, J.; Delong, D. C. Antiviral Phenoxathiins and Their Analogs. 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.

Scheme 1[a]



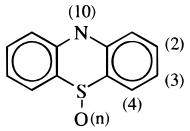
[a] (a) KOtBu in DMF, room temperature; (b) KOtBu in DMF, reflux.

3-(*N*-Methylcarbamoyl)thioxanthen-9-one 10,10-Dioxide (8). A mixture of 345.2 g of 3-carboxythioxanth-9-one 10,-10-dioxide and 1.5 kg of $SOCl_2$ was heated under reflux overnight. An additional 0.5 kg of $SOCl_2$ was then added, and refluxing continued an additional day. Excess $SOCl_2$ was then removed on a steam bath at water aspirator pressure, and the cooled residue was cautiously and slowly added with stirring to 1500 g of a cooled aqueous 40% NH_2Me solution and stirred at or below room temperature for an additional 2 days. The resulting slurry was filtered, and the solid was washed with first water and then aqueous $NaHCO_3$, leaving 328 g of off-white solid. This was recrystallized by dissolution in DMF and EtOH by addition of water to the hot solution. Two crops were taken.

Thioxanthen-9-one 10,10-Dioxide 3-*N*-Methylthioamide (45). A mixture of 9.99 g (33.2 mmol) of **8** and 20 mL of sieve-dried toluene was degassed, and 10 g (25 mmol) of Lawesson's reagent[10] was added under argon, followed by 60 mL more of toluene. The resulting suspension was heated on a steam bath with occasional shaking for 9.5 h, resulting in a yellow ball under a yellow supernatant. Removal of the toluene in vacuo (initial foaming) and addition to the residue of 80 mL of CH_2Cl_2 gave a yellow solid, which was rinsed with CH_2Cl_2 to give 12.78 g of solid, mp 212 °C. This was recrystallized from EtOH by addition of water at the boiling point, and then had mp 220.5−221.8° and a single spot at R_f 0.70 (faint spot at heavy loading at R_f 0.39), using CH_2Cl_2 on silica gel. Starting amide **8** remained at the origin under these conditions. An additional recrystallization gave 7.90 g. A small additional amount and some **8** could be separated from the initial CH_2Cl_2 solution.

Thioxanthen-9-one 10,10-Dioxide 3-Thiocarboxamide. This was prepared from the amide by modification of the

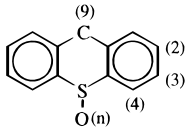
Table 3. MAO Inhibition by Phenothiazines



			IC_{50} (μM) or % I at μM					
no.	substituent	*n*	MAO A	MAO B	formula	anal.	mp (°C)	recryst[a]
77	3-CONHMe	0	0.2	13% at 10	$C_{14}H_{12}N_2OS$	C,H,N	210.8−213.8	A−W
78	3-CONHMe	2	54% at 10	15% at 10	$C_{14}H_{12}N_2O_3S$	C,H,N	361−364	D−W
79	10-Me-3-CONHMe	2	0.3	0 at 1	$C_{15}H_{14}N_2O_3S$	C,H,N	238.5	D−A−W

[a] See footnote *a* of Table 1.

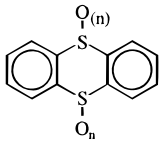
Table 4. MAO Inhibition by Thioxanthenes



	substituent			IC_{50} (μM) or % I at μM					
no.	aromatic ring	9	*n*	MAO A	MAO B	formula	anal.	mp (°C)	recryst[a]
80[b]		H/H	0	15% at 1	13% at 1				
81[c]	2-Cl	H/H	0	4% at 1	0.2% at 1				
82[d]		H/H	1	3% at 1	−33% at 1				
83[e]	2-Cl	H/H	1	0 at 1	−26% at 1				
84	2-Cl	H/H	2	2	0 at 1	$C_{13}H_9ClO_2S$	C,H,Cl,S	144	A
85	2-Br	H/H	0	13% at 1	9% at 1	$C_{13}H_9BrS$	C,H,Br,S	99.5−100	A
86	2-Br	H/H	1	3% at 1	7% at 1	$C_{13}H_9BrOS$	C,H,Br,S	142−145	A
87[f]	2-CONHMe	Bu/H	0	8% at 1	16% at 1	$C_{19}H_{21}NOS$	C,H	128−130	C−H
88[g]	3-CONHMe	H/OH	2	5	1.6	$C_{15}H_{13}NO_4S$	C,H,N	200−202	W

[a] See footnote *a*, Table 1. [b] Commercially available. [c] Muren, J. F.; Bloom, B. M. Thioxanthene Psychopharmacological Agents. I. 9-(3-Aminopropyl)thioxanthene-2-sulfonamides. *J. Med. Chem.* **1970,** *13*, 14−16. [d] Hildich, T. P.; Smiles, S. Intramolecular Rearrangements of Diphenylmethane o-Sulphoxide. *J. Chem. Soc.* **1911,** *99*, 145−160. [e] Andersen, K. K.; Cinquini, M.; Papanikolaou, E. The Synthesis and Stereochemistry of TriarylsulfoniumSalts. *J. Org. Chem.* **1970**, *35*, 706−710. [f] Chauhan, P. M. S.; Iyer, R. N.; Shankhdhar, V.; Guru, P. Y.; Amiya, B. Process for Preparation of 2,7-Diamidinoxanthene and -thioxanthene. *Chem. Abstr.* **1992**, *117*, 48338c. [g] Major metabolite of **8**, Table 1. Not preincubated with enzyme to minimize conversion to **8** before test.

Table 5. MAO Inhibition by Thianthrenes



			IC_{50} (μM) or % I at μM					
no.	substituent	*n*	MAO A	MAO B	formula	anal.	mp (°C)	recryst[a]
89	2-CONHMe	0/0	79% at 0.1	0 at 0.1	$C_{14}H_{11}NOS_2$	C,H,N	173−175	EA
90	2-CONHMe	2/0	74% at 0.1	0 at 0.1	$C_{14}H_{11}NO_3S_2$	C,H,N,S	236−238	A
91	3-CONHMe	2/0	0 at 0.1	0 at 0.1	$C_{14}H_{11}NO_3S_2$	C,H,N,S	202−204	A
92	2-CONHMe	2/2	0 at 0.1	0 at 0.1	$C_{14}H_{11}NO_5S_2$	C,H,N,S	215−217	M

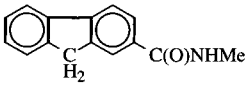
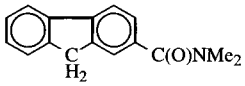
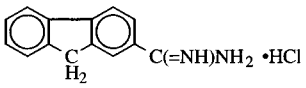
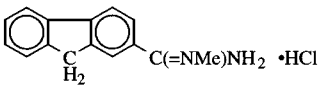
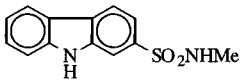
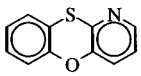
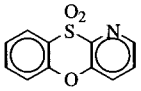
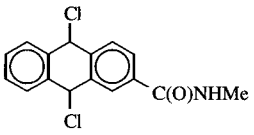
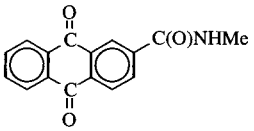
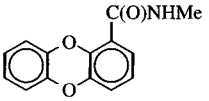
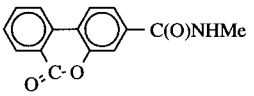
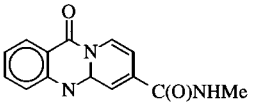
[a] See footnote *a*, Table 1.

method used to prepare **45**, notably using much larger EtOH volumes for recrystallizations. A yield of 22% of theory was obtained, and much starting amide was found, mp 226−228.3 °C. Anal. ($C_{14}H_9NO_3S_2$) C, H, N, S.

3-Cyanophenoxathiin 10,10-Dioxide (62). (1) 3-Bromophenoxathiin and its 10,10-Dioxide. A solution in 1200 mL of sieve-dried DMF of 30 g (0.238 mol) of 2-hydroxythiophenol was stirred for 30 min with strict exclusion of air with 54.7 g (0.487 mol) of KO-*t*-Bu. Addition of 70.1 g (0.25 mol) of 2,5-dibromonitrobenzene to the stirred reaction under N_2 was followed by 20 min of stirring, and the reaction was then heated under reflux overnight. After removal of most of the DMF by vacuum distillation, the residue was partitioned between 2 L of water and three 800 mL portions of CH_2Cl_2. Concentration of the nonaqueous phase was followed by crude chromatography (5% CH_2Cl_2 in petroleum ether, 12 cm diameter × 26 cm long silica gel column). The residue of removal of solvent from the main fraction was 42.3 g showing ca. 6.7 aromatic H on NMR. This was oxidized by dissolution in 500 mL of acetic acid, addition of 100 mL of 30% H_2O_2, and warming slowly first for 1.5 h at 45° C and then for 1 h at 75 °C. A slight exotherm was noted in the early heating. The cooled reaction was diluted with 2 L of water, and the resulting solid was removed by filtration, washed with water, and dried, yielding 45.77 g of solid.

(2) 3-Cyanophenoxathiin 10,10-Dioxide (60). A mixture of 10.44 g (33.6 mmol) of 3-bromophenoxathiin 10,10-dioxide, 3.61 g (40.3 mmol calculated as monomer) of CuCN, and 25 mL of dried DMF were stirred and heated under reflux (N_2) for 3 days. The cooled product was stirred at 80 °C for 2 h with 110 mL of 1 N aqueous HCl and 20 g of $FeCl_3$, cooled, and partitioned between an additional 200 mL of water and 3 × 200 mL portions of CH_2Cl_2. The organic layers were washed successively with 400 mL each of 0.1 N HCl, water, and 0.1 N

Table 6. MAO Inhibition by Miscellanous Aromatic Amides and Related Compounds

No.	Substituent	n	IC_{50} (μM) or % I at μM		Formula	Anal.	MP	Recryst[a]
			MAO A	MAO B				
93			53% @ 1	0 @ 1	$C_{15}H_{13}NO$	C,H,N	187.5-189.7	A-W
94			10% @ 10	16% @10	$C_{16}H_{15}NO$	C,H,N	140.2-140.7	A-W
95			0.3	3% @ 1	$C_{14}H_{12}N_2$•HCl	C,H,N	297.2-298.2	A-EA-E
96			60% @ 1	15% @ 1	$C_{15}H_{14}N_2$•HCl	C,H,N	255.5-261.5(dec)	A-EA-E
97			0 @ 1	0 @ 1	$C_{13}H_{12}N_2O_2S$	C,H,N.S	203-204	A-W
98[b]			Ca. 0.1	4% @ 1				
99[b]			0.6	6% @ <10[a]				
100			0.13	42% @ 0.5	$C_{16}H_{11}Cl_2NO$	C,H,N,Cl	254-255	D-T
101			63% @ 1	66% @ 1	$C_{16}H_{11}NO_3$	C,H,N	227.3-229.3	A-W
102[c]			4% @ 1	12% @ 1	$C_{14}H_{11}NO_3$ •25 H_2O • 0.14 C_6H_{14}		200-201	A-W
103			15% @ 1	0 @ 0.1	$C_{15}H_{11}NO_3$	C,H,N	268.1	IPO-W
104			0 @ 0.1	0 @ 0.1	$C_{14}H_{11}N_3O_2$	C,H,N	>?230	D-W

[a] See footnote *a*, Table 1. [b] Elliott, A. J.; Eisenstein, N.; Iorio, L. C. Central Nervous System Activity of 7-Substituted 1-Azaphenoxathiin Analogs and Their Oxidation Products. *J. Med. Chem.* **1980**, *23*, 333−335. [c] Elemental analyses indicated $H_2O \cdot {}^1/_7$ hexanes after chromatography using 1 EA:4 hexanes. Hexane was confirmed by both ^1H and ^{13}C NMR. This sample was used for biological testing. Activity was too low to merit retesting with a recrystallized sample.

NaOH. TLC (CH_2Cl_2) showed a major spot and three minor faster moving spots readily separated on a short silica gel column. Evaporation of solvent left nitrile suitable for saponification to the acid. A small amount was recrystallized from hot ethyl acetate−hexanes for elemental analysis and testing.

2-Phenoxathiinyl Methylcarbamate 10,10-Dioxide (73). A solution of 210 mg (0.85 mM) of 2-hydroxyphenoxathiin 10,10-dioxide and 1 g (excess) of diisopropylethylamine was stirred with 75 mL of 50% by volume of EtOAc−CH_2Cl_2, and 72.4 mg (1.3 mM) of methyl isocyanate in 20 mL of the same solvent mixture was added. After having been stirred an additional 2 h, the reaction was warmed in vacuo to remove volatiles, and the resulting solid was recrystallized from ethanol.

Phenothiazine-3-*N*-methylcarboxamide (77). (1) 3-Bromophenothiazine. A solution of 5.4 g of "98.5%" NaOH pellets in 278 mL of 95% EtOH was added to a solution of 46.55 g (0.127 mol) of 2-(acetylamino)phenyl 5-bromo-2-nitrophenyl sulfide in 570 mL of acetone under N_2, and the reaction mixture was stirred and heated under reflux for 3 h and let cool. An additional solution of 6 g of NaOH in 305 mL of 95% EtOH was added, and heating resumed for 45 min. The dark reaction was concentrated in vacuo to one-third of its volume and added to about 3 volumes of water. The resulting salmon-

colored solid was removed by filtration, rinsed with water, and dried. It weighed 33.9 g, had mp 180−181.6 °C, and was sufficiently pure for synthetic use, showing no detectible uncyclized sulfide by TLC.

(2) Phenothiazine-3-carboxylic Acid. A solution of 250 mL of 1.5 M BuLi in hexane was added during 20 min to a stirred mixture of 36.7 g (0.132 mol) of 3-bromophenothiazine in 700 mL of dry THF cooled in a dry ice bath under N_2 and maintained below −70 °C during the reaction and for an additional 45 min. The contents of the flask were then poured into excess dry ice and 200 mL of dry Et_2O and left an additional 20 min. After mechanical removal of remaining dry ice, the residue was partitioned between an additional 500 mL of Et_2O and repeated portions of 0.2 M aqueous Na_2CO_3. Acidification of the aqueous solutions led to 22.85 g of mostly yellow plus a little dark solid, with some odor resembling that of valeric acid. Recrystallization from EtOH−water gave yellow prisms melting with darkening about 248 °C. Anal ($C_{13}H_9NO_2S$) C, H, N.

(3) Phenothiazine-3-*N*-methylcarboxamide (77). A solution of 3.26 g (1.34 mmol) of the 3-carboxylic acid in 100 mL of dry, peroxide-free THF was stirred with 0.305 g (1.88 mmol) of carbonyldiimidazole for 30 min. A 29 mL portion of a 33% solution of $MeNH_2$ in ethanol was added under N_2 in one portion, and stirring wa continued overnight. The reaction mixture was poured into 1600 mL of water and stirred for 3 h, and the resulting 1.59 g of orange solid was filtered off, rinsed with water, and dried. Two recrystallizations from EtOH−water gave 1.19 g with mp 210.8−213.8 °C. TLC with Et_2O on silica gel visualized by long-wavelength UV showed a faint spot at the origin and an intensely fluorescent spot at R_f 0.19.

Phenothiazine-3-carboxylic Acid 5,5-Dioxide. Oxidation of 4.1 g (16.9 mmol) of phenothiazine-3-carboxylic acid in HOAc by excess 30% H_2O_2 added in increments during 5 days at 80−90 °C yielded 2.75 g of orange solid only slightly soluble in HOAc. It was recrystallized from EtOH−water and darkened but did not melt at 360 °C. Anal. ($C_{13}H_9NO_4S$) C, H, N.

Phenothiazine-3-*N*-methylcarboxamide 10,10-Dioxide (77). A mixture of 2.39 g of phenothiazine-3-carboxylic acid 10,10-dioxide (8.36 mmol) and 10 mL of $SOCl_2$ was heated under reflux ($CaCl_2$ tube) for 2.5 h and then left overnight. Distillation in vacuo left a residue which was scraped into 100 mL (excess) of aqueous 33% $MeNH_2$ with stirring. After an additional 4 h of stirring, followed by filtration, water washing, and drying of the resultant off-white solid, 1.6 g was obtained. This was dissolved in 50 mL of DMSO at 100 °C by adding 150 mL of hot water and then cooling, giving 1.45 g of product.

Biological Methods. The methods used were given in detail in the previous paper.[1] 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.

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