A New Class of Monoamine Oxidase Inhibitors

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Abstract: Newly synthesized compounds have been found to inhibit mitochondrial monoamine oxidase (MAO) in mouse brain and rat liver. A series of 2-acylamino-3-*tert*-aminopropiophenones acted preferentially against MAO type B (2-phenylethylamine as substrate), apparently irreversibly. 2-Decanoylamino-3-morpholinopropiophenone acted similarly *in vivo* toward the cerebral MAO, producing a dose-related inhibition. At high dose levels, MAO type A was also severely inhibited. The effects were produced rapidly and restoration of enzyme activity also appeared rapidly. The half-life for MAO type A could be estimated from the rate of enzyme reappearance to be 13 h. It is suggested that the amino ketones undergo a β-elimination reaction at the enzyme's active site, forming a reactive species (an α,β-unsaturated ketone), which reacts covalently with a nucleophilic group of the enzyme by a Michael addition. Some other related compounds, derivatives of phenylpropane, also showed inhibitory activity against MAO, particularly against type A (serotonin as substrate). The morpholino compound might have promise as a quickly effective, short-acting inhibitor of MAO type B. **Key words:** Monoamine oxidase inhibitors—Monoamine oxidase type B—2-Decanoylamino - 3 - morpholinopropiophenone—Monoamine oxidase half-life.

In the course of an attempt to develop inhibitors of glucocerebroside synthetase, analogs of ceramide were synthesized and evaluated with an *in vitro* assay. When some of the compounds were injected into mice, symptoms such as head twitches, tremor, and abduction of the hind legs were produced, indicating that these compounds have CNS effects. Subsequent tests for effects on monoamine oxidase [EC 1.4.3.4, amine:oxygen oxidoreductase (deaminating) (flavine containing)]showed that they exhibited appreciable inhibitory activity. Since some of the compounds constituted a new class of inhibitors of this enzyme, we made a more detailed study of their effects on monoamine oxidase (MAO) in rodent liver and brain, with special emphasis on the question of differential sensitivity toward the two types of enzyme, A and B (Johnston, 1968; Neff et al., 1974). It is currently of considerable interest to determine whether selective inhibition of the two types would be clinically useful in the treatment of human disorders, neurological, behavioral, or circulatory.

MATERIALS AND METHODS

2-(*N*-acylamino)-3-substituted aminopropiophenones were prepared from 2-amino-acetophenone (Wolfheim, 1914) by acylation, followed by a Mannich reaction with paraformaldehyde and a secondary amine in the presence of HCl. For example, the acetyl compound (RV-433) was made by dissolving 2.2 g (12.5 mmol) of 2-acetaminoacetophenone (Wolfheim, 1914), 0.5 g (5.5 mmol) of paraformaldehyde, and 1.5 ml (17.2 mmol) morpholine in 15 ml ethanol and adding 0.3 ml of concentrated HCl. The mixture was refluxed for 15 h; then, about 10 ml of the solvent were removed with a rotary vacuum evaporator. The mixture was diluted with 30 ml of water and adjusted with HCl to pH 3, and nonbasic impurities were removed by extracting with 45 ml of ether. The remaining material was made alkaline with ammonium hydroxide and the free base was extracted into 2 × 30 ml of

ethyl acetate. The pooled extracts were washed with saline and dried with Na_2SO_4, and the solvent was removed. The amine was converted to a crystalline salt by dissolving it in 10 ml of EtOAc and adding 2.3 g (12 mmol) of p-toluenesulfonic acid hydrate in EtOAc. The resultant precipitate was crystallized twice from methanol. The yield was 72% (4 g), m.p. 191–2°C.

Analysis: $C_{15}H_{20}N_2O_3 \cdot C_7H_8O_3S$ (mol. wt. 448.5). Calculated, 58.92% C (found 58.83), 6.29% H (6.18), 6.25% N (6.24). 2-Decanoylamino-3-morpholinopropiophenone (RV-378) was prepared similarly from 2-decanoylamino-acetophenone (m.p. 79–80°C, from benzene-hexane) but isolated as the hydrochloride (yield 62%, m.p. 137–8°C from EtOAc).

Analysis: $C_{23}H_{36}N_2O_3 \cdot HCl$ (mol. wt. 425.0). Calculated, 65.00% C (found 65.13), 8.78% H (8.82), 6.59% N (6.52).

The piperidine analogue of RV-378 (RV-471) was also prepared: 2-decanoylamino-3-piperidinopropiophenone toluenesulfonic acid salt (yield, 30%, m.p. 87–9°C from EtOAc). On drying over P_2O_5 in vacuum at 23°C it became hygroscopic and gave an analysis indicating the presence of one molecule of water.

Analysis: $C_{31}H_{46}N_2O_6S \cdot H_2O$ (mol. wt. 576.8). Calculated: 64.56% C (found 64.97), 8.39% H (8.64), 4.86% N (4.97).

2-Decanoylamino-3-morpholino-1-phenyl-1-propanol was made from 1.7 g (4 mmol) of RV-378 in 25 ml methanol. To this was added 1.1 g of K_2CO_3 in 2 ml water, followed by 0.8 g of $NaBH_4$ in small portions over a 30-min period. After 3 h of stirring, most of the solvent was removed *in vacuo* and the residue was shaken with 10 ml of water and 75 ml of EtOAc. The organic phase was washed with 10% salt, dried over Na_2SO_4, and the solvent removed. The amine was converted to the hydrochloride with HCl in isopropanol, evaporated to dryness, and triturated with ether. The product (RV-538b) melted at 107–113°C after crystallization from chloroform-ether; yield, 1.5 g. Silica gel TLC with chloroform-methanol, 95:5 (v/v), revealed two spots very close to each other, indicating that the reduction yielded the threo- and erythro-isomers. For elemental analysis, the salt was recrystallized from EtOAc, converted to the free base with $NaHCO_3$, and purified with a silica gel column, using chloroform/methanol/ammonium hydroxide (concd.) 96:4:0.5 and 94:6:0.5 (by vol.). The melting point was 96–7°C (from hexane). This material (RV-538a) showed only the faster-moving spot with TLC.

Analysis: $C_{23}H_{38}N_2O_3$ (mol. wt. 390.6). Calculated, 70.73% C (found 70.76), 9.81% H (9.74), 7.17% N (7.13).

The infrared spectra of the compounds were obtained with the KBr pellet technique. The expected two carbonyl bands were seen in the case of the keto amides, at about 5.94 and 6.05 μm. The reduced ketone (RV-538) showed only the amide C=O band at 6.05 μm.

The preparation of other compounds tested in this study has been reported (Hyun et al., 1975) or will be reported separately.

Adult mice (Swiss-Webster, 25–30 g) from Charles River Laboratories were used. For whole homogenate studies, brains were homogenized in 5–10 volumes of 50 mM-potassium phosphate, pH 7.4. Mitochondria were prepared by homogenizing brain in 4 vol. of 0.32 M-sucrose, centrifuging at 700 g for 15 min, washing the pellet, and centrifuging the combined washings at 20,000

g for 30 min. The mitochondrial pellet was washed with sucrose and suspended in buffer as above. Monoamine oxidase was determined in the brain preparations with 0.1 mM-5-HT (serotonin) or PEA (phenethylamine) as substrates (Owen et al., 1977).

Rat liver mitochondria were prepared similarly (Hogeboom, 1955) and tested with 35 μM-[^{14}C]tyramine as substrate, in 0.2 M-phosphate, pH 7.4.

The inhibitors were tested by evaporating a solution to dryness in each test tube or adding freshly prepared aqueous solutions. Protein was determined with modified Folin reagent (Lowry et al., 1951).

RESULTS

A survey of various related compounds in tests with brain MAO (Table 1) showed that some compounds were preferentially active against MAO type A (RV-83 and 125) and some were preferentially active against MAO type B (RV-378, 470, 471, 472). A compound not shown in the table, RV-252 (N-[n-decyl]-N'-p-methoxyphenyl guanidine), was rather active at 0.2 mM against both types of MAO: 55% inhibition against 5-HT oxidation and 36% against PEA oxidation. The corresponding values obtained without preincubating the inhibitor were not much different: 61% and 28%. With some compounds, particularly the ketones, adding the substrate at the same time as the inhibitor reduced the inhibitory effect. The importance of the carbonyl group adjacent to the phenyl ring was shown by the drastically decreased inhibitory activity of the reduced compound (RV-378 versus 538).
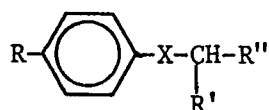
Compounds RV-472 and 470 proved difficult to purify and were not studied in detail. They were not as selective as the other keto amines with respect to inhibition of the different types of MAO. Toluenesulfonic acid, used to prepare some of the amines in crystalline form, was not itself inhibitory to MAO.

The degree of inhibition by the keto amines on MAO type B resulting from preincubation with brain mitochondria was found to increase with duration of exposure to the inhibitor (Fig. 1). This indicates that the inhibitors acted by causing inactivation of the enzyme. The disappearance of enzyme activity was rapid at first, then slowed somewhat. Note the lack of a lag period, indicating that the inhibition was due to the added compound, not to a metabolically produced derivative of the inhibitor.

Evidence for the irreversibility of the inhibitory action of the keto amines was obtained (Table 2) by dialyzing the mitochondria after preincubating them with the inhibitors. Dialysis prior to incubating the preparation with substrate, which should have led to the removal of the inhibitor, did not restore the activity of the enzyme.

Tyramine is considered a nonselective substrate for types A and B MAO (Neff et al., 1974). When this substrate was used with *rat liver* mitochondria,

TABLE 1. *Inhibition of mouse brain monoamine oxidases by 2-decanoylamino-3-morpholinopropiophenone and related compounds*

R—⬡—X—CH—R''
              |
              R'

Compound number	X	R	R'	R''	Percent inhibition			
					Serotonin		Phenethylamine	
RV-378	C=O	H	-NHCOC$_9$H$_{19}$	-CH$_2$N⬡O	6	(8)	51	(15)
RV-471	"	"	"	-CH$_2$N⬡	8	(8)	71	(9)
RV-472	"	"	"	-CH$_2$N⬡N-Me	19	(22)	63	(33)
RV-470	"	"	"	-CH$_2$N(Me)C$_2$H$_4$OH	30	(15)	58	(46)
RV-538b	CHOH	"	"	-CH$_2$N⬡O	9	-	9	(11)
RV-128	"	"	"	-CONHNH$_2$	35	(0)	-	(3)
RV-83	CHNHC$_{10}$H$_{21}$	"	OH	-CH$_2$OH	41	(56)	28	(23)
RV-218	CHOH	NO$_2$	-NHC$_{10}$H$_{21}$	"	12	-	-	-
RV-125	"	NH$_2$	"	"	31	(27)	20	(27)
RV-143	"	H	"	-CH$_2$NH$_2$	7	(0)	31	(38)

All compounds were tested at 0.1 mM except the last five (0.2 mM) with mitochondria and substrates at 0.1 mM. The values shown are for the degree of inhibition obtained when the inhibitors were incubated for 30 min with the mitochondria before addition of substrate and incubation for 30 min more. The values in parentheses were obtained when the inhibitor was added together with the substrate. Compounds 378, 470, and 538 were hydrochlorides, 471, 218, and 143 were toluenesulfonates, 472 was a citrate, and 83 was the hydrobromide. The control MAO activity (in nmol/mg protein/h) was 27.4 for 5-HT and 22.4 for PEA.

the keto amines were found to be much more effective inhibitors than they were in mouse brain tested with PEA or 5-HT (Table 3). All the keto amines showed rather similar inhibitory power, except for RV-433, a homologue of the decanoylamino morpholine derivative in which the acyl group was acetyl instead of decanoyl. Evidently, a lipoidal side chain in the amide position produces more effective inhibition. By way of comparison, we found 50% inhibition of tyramine deamination with 0.1 μM-phenelzine, a clinically useful MAO inhibitor.

Intraperitoneal injection of mice with isotonic saline (10 ml/kg) or with RV-378 in saline, followed by sacrifice 2 h later, showed that the compound inhibited cerebral MAO *in vivo* (Fig. 2). At the lowest dosage level tested (25 mg/kg), type B MAO in

brain was inhibited to a greater extent than was type A (35% versus 12%). As the dosage was increased, this difference decreased.

A similar *in vivo* study with a dose level of 250 mg/kg of RV-378 showed that the two types of MAO in brain were largely inactivated within 1 h (Fig. 3). Resynthesis (or reactivation) of MAO type A (the upper curve) became noticeable promptly after the minimum was reached, and the level of enzyme was almost back to normal within 24 h. The rate of synthesis or reactivation of MAO type B (lower curve) was apparently slower. The reappearance of functional MAO molecules soon after the first hour following injection indicates that the inhibitor was rapidly destroyed, sequestered, or excreted.

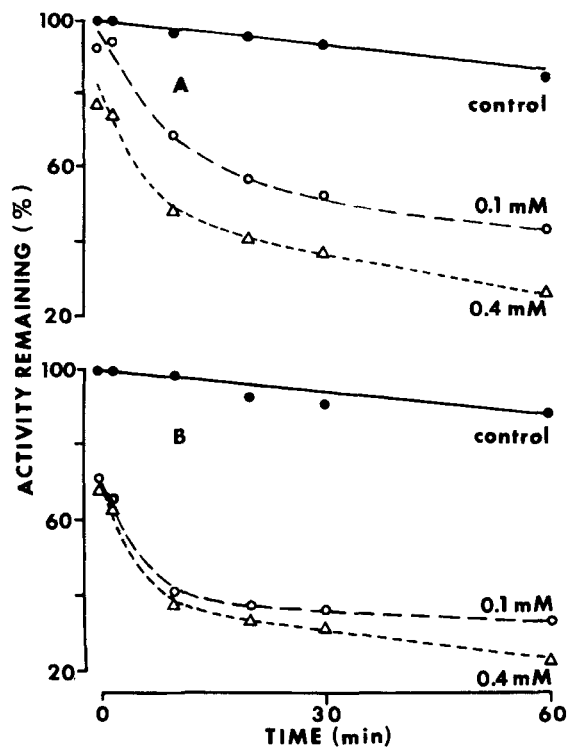Additional evidence for the rapid loss of inhibitor

FIG. 1. Effect of preincubating mouse brain MAO for different lengths of time with RV-378 (**A**) and RV-471 (**B**). The inhibitors were preincubated with mitochondria for the indicated times at the indicated concentrations; then the preparations were tested for MAO activity with 0.1 mM PEA. The control MAO activity was 21.5 nmol/mg protein/h.

TABLE 3. *Inhibition of rat liver monoamine oxidase by 2-decanoylamino-3-morpholinopropiophenone and related compounds*

Inhibitor	Basic moiety in 3-position	Concentration of amine for 50% inhibition (μM)
RV-378	morpholine	3.5
RV-471	piperidine	3.3
RV-472	N-Me-piperazine	3.5
RV-470	N-Me-ethanolamine	3.2
RV-433[a]	morpholine[a]	65
RV-538a[b]	morpholine[b]	>80

Rat liver mitochondria were preincubated with varying concentrations of inhibitor and then assayed with 35 μM-tyramine; the IC_{50} level was determined from the graphed data.

[a] This is the acetyl homolog of RV-378; [b] the reduced version of RV-378.

DISCUSSION

4-Morpholinobutyrophenone (NSD 2023) is known to be a MAO inhibitor (Squires and Lassen, 1968; Christmas et al., 1972). The latter study showed that the drug produced preferential inactivation of the type A enzyme in brain (5-HT and benzylamine as substrates) after oral administration to rats. Our most active compounds showed preferential action on the type B enzyme, which may be due to their having one less carbon atom in the aliphatic side chain and a long hydrophobic acylamino group between the ketonic and basic groups.

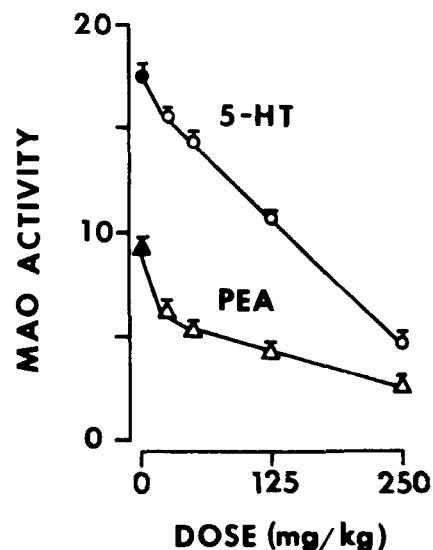Although the concentration required for strong

was obtained by assaying mixtures of brain homogenate from control and from drug-treated mice (Table 4). The brain homogenates from mice sacrificed 1 or 2 h after injecting RV-378 were mixed with an equal amount of the control brain homogenates and then assayed for MAO activity with PEA and 5-HT. The expected (mean) value was obtained with PEA, indicating that no free inhibitor remained in the drug-treated animals. In the case of 5-HT assays, the specific activity of the mixed tissues was even higher than expected.

TABLE 2. *Activity of monoamine oxidase (type B) in dialyzed and undialyzed mouse brain mitochondria pretreated with inhibitor*

Inhibitor	Dialyzed enzyme (nmol/h/mg protein)	Undialyzed enzyme (nmol/h/mg protein)
None	25.1	21.7
RV-378	6.4 (75)	7.8 (64)
RV-471	7.2 (71)	7.8 (64)

Mitochondria were incubated for 30 min with inhibitor at 0.1 mM, then assayed directly or dialyzed overnight against two changes of 5 mM-potassium phosphate, pH 7.4. MAO type B was assayed with 0.1 mM-PEA as substrate. The numbers in parentheses indicate the degree of inhibition (percent) compared with the mitochondria that had not been treated with inhibitor.

FIG. 2. Effect of varying doses of RV-378 on mouse brain MAO activity. Mice were injected intraperitoneally with saline (10 ml/kg) or the indicated dose of inhibitor and killed 2 h later. Enzyme activity was determined in mouse brain homogenates using 0.1 mM-PEA or 5-HT. Each point represents the mean activity (nmol/mg protein/h) ± s.e.m. of five mice. The open symbols denote a significant difference compared with saline-treated mice at the 0.001 level (Student's *t*-test).
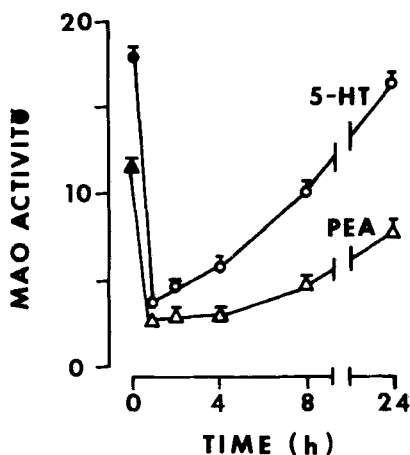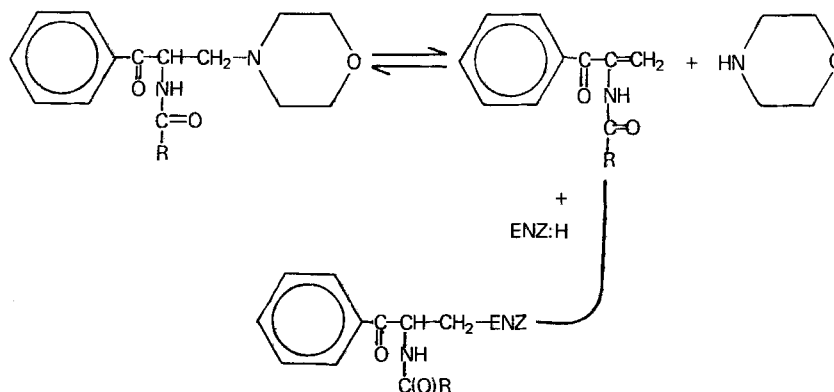
FIG. 3. Time course of MAO inhibition after treatment of mice with RV-378. Mice were injected as in Fig. 2 (250 mg/kg) and sacrificed at the times indicated. Enzyme activity was determined in brain homogenates with PEA or 5-HT. Each point represents the mean activity ± S.E.M. of five to nine mice. Open symbols denote a significant difference compared with the saline-treated controls at the 0.001 level.

The ketone group might act additionally by facilitating binding of the inhibitor to the active site by formation of a Schiff base with an amino group.

The idea that the keto amines react covalently with the enzyme is also supported by the finding that preincubation, before substrate addition, produces greater inhibition of the enzyme (Table 1). Evidently, the inhibitor and PEA competed for entrance into the active site that has the type-B specificity. In the case of the type-A reactive site, 5-HT seemed to compete effectively when the inhibitor was at a low concentration.

The failure of the keto amine to inactivate *all* of the MAO in the incubation tube, even with prolonged incubation without substrate (Fig. 1), could be due to spontaneous breakdown of the inhibitor in the medium followed by nonspecific reactions with various nucleophilic groups. However, another explanation is that a less easily inhibited form of MAO type B may be present in the preparation; this is indicated by the initially rapid decline in enzyme activity (Fig. 1) followed by a lower rate of decline. (A similar curve is seen in a semilog plot of the data; if a single reaction were involved, one would see a straight line.) The first phase may be due to a more sensitive form of the enzyme.

Compound R 951, the propiophenone derivative of norpethidine, resembles our keto amines in possessing a tertiary amine group at the 3-position. However, it is an analgesic and, thus, does not seem to have significant anti-MAO activity (Janssen and Van Bever, 1977). It is possible that the two bulky substituents at the distal end of the piperidine group block binding to the active site of MAO. Another similar compound, L-51988 (Murphy et al., 1978), is also an aminopropiophenone, in which the amine group is cyclopropylamine. It is active against both types of MAO, tested in neuroblastoma and platelets, particularly toward type A. This difference suggests that the long-chain acylamino group in our series is a major source of the preference for MAO type B activity.

It is possible to calculate the half-life for MAO in brain with the method suggested by Price et al.

inhibition *in vitro* was relatively large for our compounds compared with available MAO inhibitors, they were not remarkably less effective *in vivo*. For example, pargyline is generally used at the 50 or 100 mg/kg dosage with rats and iproniazid at the 100 mg/kg level. We obtained strong effects with about 50 mg/kg (Fig. 2).

Comparison of the activities of the morpholino ketone (RV-378) with the morpholino alcohol (RV-538) supports the idea that the carbonyl group facilitates conversion of RV-378 to a reactive species that is responsible for the MAO inhibition. Aromatic β-keto amines are known to undergo spontaneous breakdown in aqueous solution (Schönenberger et al., 1969), forming the secondary amine and the substituted acrylophenone. The latter reactive product, the formation of which might be facilitated by the active site of MAO, would be expected to react with nearby nucleophilic groups in the enzyme (Andrisano et al., 1967):

TABLE 4. *Effect of mixing brain homogenates from control and inhibitor-treated mice*

Brain source	Monoamine oxidase activity (nmol/h/mg protein) Phenethylamine	Hydroxytryptamine
Saline-injected control	11.5	18.5
Drug-injected (after 1 h)	3.9	3.6
Mixture with control	8.0 (7.7)	14.1 (11.1)
Drug-injected (after 2 h)	3.9	4.8
Mixture with control	7.5 (7.7)	13.2 (11.7)

Mice were injected with saline or with RV-378 (250 mg/kg) and killed after 1 or 2 h. The mixed homogenates were assayed by mixing one-half the usual amount of each. The predicted activity, shown in parentheses, was calculated by averaging the activities found with control and drug-treated homogenates.

(1962). This method, which was also used by Davis and Agranoff (1968) and by Hara and Radin (1979), is based on the assumptions that the rate of enzyme resynthesis (following its inactivation by an inhibitor) is not affected by the loss of the enzyme molecules, that the excess inhibitor is removed from the organ fairly quickly, and that the newly detected enzyme activity during the recovery period is due to the synthesis of new enzyme molecules rather than to the removal of the inhibitory moiety (perhaps by a displacement reaction). The calculated half-life for type A MAO is 13 h, a rather rapid turnover rate. Because of the greater complexity of MAO type B (Fig. 3), this calculation is inappropriate.

When pargyline was used in the above manner to determine the half-life of brain MAO, longer half-lives were obtained, using PEA and 5-HT as substrates (Maitre et al., 1976). However, when several physiological consequences of MAO inhibition were followed as a function of time, rapid recovery was observed, from which these authors concluded that a second MAO pool exists, possessing a half-life of only 12−18 h. Goridis and Neff (1971) have also observed a slow turnover rate, using the same drug and tyramine as substrate. In the case of MAO in rat liver mitochondria, Erwin and Deitrich (1971) found half-lives closer to our value: 1.8 or 3.5 days.

Squires and Lassen (1968) have pointed out that the time required for half-restoration of brain MAO is very much dependent on the nature of the "irreversible" inhibitor used. This discrepancy could be attributed to different rates of enzyme reactivation, but it could also be attributed to a variable degree of sequestering of each inhibitor in a relatively protected subcellular site and gradual release at a rate sufficient to inactivate some of the newly formed MAO molecules. The latter interpretation is supported by the finding that rats given labeled pargyline accumulated a significant fraction of the labeled material in the liver lysosomes (not a MAO site) and that the radioactivity left the lysosomes very slowly (Erwin and Deitrich, 1971). Several studies have shown that lysosomes tend to take up

and store basic compounds, into which category MAO inhibitors fall.

Some of the compounds found to exhibit anti-MAO activity (Table 1) are also excellent inhibitors of β-glucosidases (Hyun et al., 1975), which are apparently sensitive to some of the structural features that characterize many MAO inhibitors. However, tests with mouse liver homogenates and the prominent MAO inhibitors phenelzine and pargyline at 0.3 mm did not show any reciprocal inhibition of glucosidase activity.

ACKNOWLEDGMENT

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