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INHIBITION OF MONOAMINE OXIDASE BY *N*-PHENACYL-CYCLOPROPYLAMINE

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Abstract—*N*-phenacyl-cyclopropylamine hydrobromide (54761) was evaluated *in vitro* and *in vivo* as a monoamine oxidase (MAO) inhibitor in rats. In contrast to 51641, which has an *o*-chlorophenoxy group in place of the phenacyl group and which is a highly selective inhibitor of type A MAO, 54761 showed a slight preference as a type B MAO inhibitor, since it inhibited phenylethylamine oxidation at slightly lower concentrations than were required to inhibit serotonin oxidation *in vitro* by rat liver MAO. Twelve analogs of 54761 with various substituents on the phenyl ring were also studied, but none was substantially more selective than 54761 as a type B inhibitor and most were preferential type A inhibitors. When 51641 and 54761 were injected into rats and MAO activity was assayed in tissue homogenates, the oxidation of serotonin in brain, heart and liver was inhibited more by 51641 than by 54761. In contrast, the oxidation of phenylethylamine was inhibited more by 54761 than by 51641 in brain and liver. In heart, however, 51641 was a more effective inhibitor of phenylethylamine oxidation than was 54761, supporting earlier evidence that phenylethylamine is destroyed in heart mainly by type A MAO. The oxidation of exogenous [^{14}C]phenylethylamine was inhibited *in vivo* more effectively by 54761, whereas the oxidation of endogenous serotonin in brain was inhibited more by 51641. Although 54761 is not as selective an inhibitor of type B MAO as some other compounds such as deprenyl, it illustrates that a large range of selectivity in MAO inhibition can exist within the *N*-cyclopropylamine series. Further, selective type B inhibition could be achieved *in vivo* 24 hr after injection of 54761 by co-administration of harmaline. Harmaline selectively protected against the inactivation of type A MAO by 54761 but permitted the inactivation of type B MAO to occur.

Monoamine oxidase (MAO; EC 1.4.3.4, amine: oxygen oxidoreductase [deaminating] [flavin-containing]) is a mitochondrial enzyme that currently is thought to exist in at least two forms distinguishable on the basis of substrate specificity and susceptibility to selective inhibitors [1]. Type A MAO preferentially deaminates substrates like serotonin and norepinephrine and is particularly susceptible to inhibition by clorgyline. Type B MAO preferentially deaminates substrates like phenylethylamine and is particularly susceptible to inhibitors like deprenyl.

Two major groups of irreversible inhibitors of MAO that have been studied are arylalkylamines with either an *N*-methyl, *N*-propargyl or an *N*-cyclopropyl configuration on the nitrogen. Clorgyline [1, 2] and deprenyl [1, 3] are selective type A and type B inhibitors, respectively, from the former class of inhibitors. In the latter group of inhibitors, Lilly 51641 has been identified as a selective type A inhibitor [4–6]. Recently an *N*-cyclopropylamine compound with slight preference as a type B MAO inhibitor was identified [7], and we are reporting here some studies comparing that compound, Lilly 54761 (*N*-phenacyl-cyclopropylamine hydrobromide), to the type A inhibitor, Lilly 51641 (*N*-[*o*-chlorophenoxyethyl]-cyclopropylamine hydrochloride).

METHODS

Male albino rats (Wistar), from Harlan Industries, Cumberland, IN, weighed approximately 150 g and were housed singly with food and water available *ad lib*. After drug treatment, the rats were killed by decapitation. Tissues were rapidly excised, frozen on dry ice, and stored at −15°. MAO activity in whole homogenates of the tissues was assayed *in vitro* with either [^{14}C]phenylethylamine (80 μM) or [^{14}C]serotonin (100 μM) as substrate [8]. The ED_{50} values and 95 per cent confidence limits for the inhibition *in vivo* of MAO were calculated by the use of the regression line in reverse according to the method of Brownlee [9]. In one experiment, [^{14}C]phenylethylamine was injected *in vivo* and the amount of unoxidized amine remaining in tissues 10 min later was determined by solvent extraction, as described previously [8]. Ring-hydroxylated metabolites such as tyramine are not extracted by this procedure; paper chromatographic analysis of extracts revealed only [^{14}C]phenylethylamine and did not detect trace amounts of other amine metabolites such as phenylethanolamine.

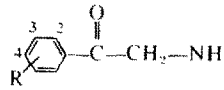
Serotonin and 5-hydroxyindoleacetic acid concentrations in whole brain were measured spectrofluorometrically by condensation with *o*-phthalaldehyde [10].

For *in vitro* studies of MAO inhibition, an enzyme preparation solubilized by ultrasonication of isolated mitochondria was assayed as described previously [6]. Radiocarbon-labeled substrates were phenylethylamine (80 μM), serotonin (100 μM), tryptamine (200 μM) or tyramine (100 μM). Inhibitors were preincubated with enzyme for 30 min prior to substrate addition. Five concentrations of each inhibitor were tested, and from a plot of per cent inhibition vs inhibitor concentration the molar con-

Table 1. Structure–activity relationships in the inhibition *in vitro* of MAO action on phenylethylamine and serotonin

X =	pI_{50} Values Serotonin (A)	Phenylethylamine (B)	Difference (A − B)
O —C—CH_2—	6.05	6.25	− 0.20
—CH_2—CH—	5.75	5.80	− 0.05
CH_3 —$CHCH_2$—	5.63	5.61	0.02
OH —SCH_2CH_2—	8.70	6.36	2.34
O —C—CH_2CH_2—	7.83	5.49	2.34
—$CH_2CH_2CH_2$—	8.00	5.28	2.72

Table 2. Influence of substituents on the inhibition *in vitro* of MAO by *N*-phenacyl-cyclopropylamines

 R =	pI_{50} Values Serotonin (A)	Phenylethylamine (B)	Difference (A − B)
None (54761)	6.05	6.25	− 0.20
3-Chloro	6.80	7.15	− 0.35
4-Chloro	6.41	6.49	− 0.08
2-Trifluoromethyl	6.51	5.50	1.01
3-Trifluoromethyl	6.68	6.49	0.19
4-Trifluoromethyl	6.19	5.36	0.83
3,4-Dihydroxy	4.90	4.07	0.83
3-Methoxy	6.62	6.28	0.34
4-Methoxy	7.48	6.64	0.84
3-Iodo	7.40	6.78	0.62
3,4-Dichloro	7.13	6.50	0.63
α-Naphthyl*	7.66	6.30	1.36
β-Naphthyl*	7.77	5.54	2.23

* Naphthyl group in place of the phenyl group.

centration producing 50 per cent inhibition was determined by interpolation. The negative logarithm of that concentration is the pI_{50} value.

The inhibitors were all synthesized in the Lilly Research Laboratories and were used as water-soluble hydrochloride or hydrobromide salts. For *in vivo* experiments, drugs were dissolved in water, and the solutions were injected at a volume of 1 ml/kg. All radioactive amines were from New England Nuclear, Boston, Mass.

RESULTS

In vitro studies. The inhibition of rat liver MAO action on serotonin (a substrate for type A MAO [1]) and phenylethylamine (a substrate for type B MAO [1]) by a group of *N*-substituted cyclopropylamines is shown in Table 1. Among the compounds having a phenyl ring connected to the nitrogen by straight- or branched-chain groups, the most selective type B inhibitor, indicated by a negative value in the "difference (A − B)" column, was *N*-phenacyl-cyclopropylamine (54761). To determine if the selectivity of this compound toward type B MAO could be further enhanced, we compared ten analogs with various aromatic substituents and the two isomeric compounds with naphthyl replacing the phenyl (Table 2). Only the 3-chloro and 4-chloro compounds resembled 54761 in having small negative values in the difference column. The remaining inhibitors showed various degrees of preference toward type A MAO, i.e. preferentially inhibited serotonin oxidation. The β-naphthyl compound showed a high degree of type A selectivity.

Compound 54761 was compared with 51641, a selective type A MAO inhibitor from the *N*-substituted cyclopropylamine series previously studied by us [5, 6], in more detail. Table 3 shows the inhibition by these two compounds of the oxidation of four substrates *in vitro*. Compound 54761 was markedly inferior to 51641 as an inhibitor of serotonin oxidation but was slightly more effective than 51641 in blocking phenylethylamine oxidation. The selectivity of 54761 was opposite to but less striking than that of 51641.

In a further comparison of these two inhibitors *in vitro*, we determined their effects in an incubation mixture containing two substrates. The simultaneous oxidation of serotonin and phenylethylamine was measured by labeling one and then the other amine with radiocarbon (Fig. 1). When the radioactive substrate was phenylethylamine, its rate of oxidation was inhibited more by 54761, but when the radioactive substrate was serotonin, 51641 was by far the more potent inhibitor. These results resemble those in Table 3, indicating that the presence of the second substrate had little influence on the properties of the inhibitors.

In vivo studies. The inhibitors 51641 and 54761 were injected into rats; then tissues were removed and homogenized for assay *in vitro* of MAO activity. Figure 2 shows that in rat brain 51641 caused nearly complete inhibition of serotonin oxidation within 1 hr, and the effect persisted almost at maximum inhibition for 8 hr. Compound 54761 had significantly less effect on serotonin oxidation by brain MAO. In contrast, 54761 was strikingly more potent in inhibiting phenylethylamine oxidation than was 51641, particularly at the longer time points. Qualitatively similar results were found in liver and heart.

In a study similar to that shown in Fig. 2, but with the post-injection interval fixed at 1 hr, various doses of 51641 and 54761 were compared as MAO

Table 3. Influence of substrate on MAO inhibition *in vitro* by 54761 and 51641

Substrate	pI_{50} Values 51641	54761	Difference 51641 − 54761
Serotonin	9.08	6.05	3.03
Tryptamine	7.42	5.87	1.55
Tyramine	6.97	6.20	0.77
Phenylethylamine	6.15	6.25	− 0.10

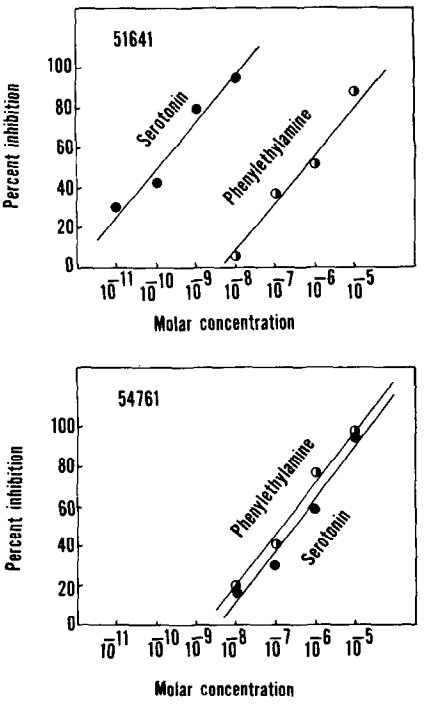


Fig. 1. Inhibition *in vitro* of MAO by 51641 (top) and 54761 (bottom) when two substrates (phenylethylamine and serotonin) are undergoing stimultaneous oxidation. Serotonin (100 μM) and phenylethylamine (80 μM) were both present in the incubation mixture. One or the other of the two amine substrates was labeled with radiocarbon, and the rate of deamination of that substrate was determined as described in Methods.

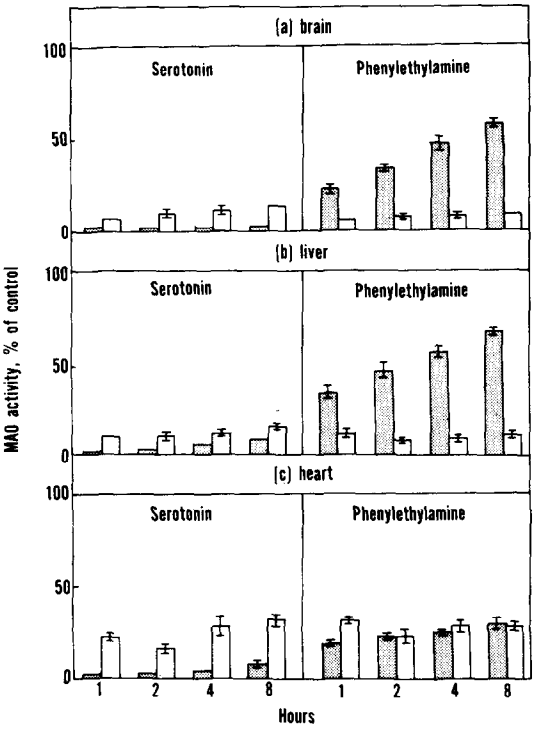


Fig. 2. Inhibition *in vivo* of MAO in (a) brain, (b) liver and (c) heart determined with phenylethylamine or serotonin as substrate after the injection of 51641 (shaded bars) or 54761 (open bars). Both compounds were injected i.p. at 30 mg/kg. Mean values ± S.E. for five rats per group are shown.

Table 4. Inhibition of MAO in rat brain *in vivo* by 51641 and 54761*

Inhibitor	Dose (mg/kg)	% Inhibition of MAO: Serotonin	% Inhibition of MAO: Phenylethylamine
51641	0.03	4 ± 1	
	0.1	26 ± 4	
	0.3	56 ± 8	
	1	84 ± 9	19 ± 2
	3		25 ± 2
	10		36 ± 2
	30		55 ± 7
ED_{50} (mg/kg)		0.24 (0.18–0.32)	25 13–49)
54761	1	5 ± 2	8 ± 3
	3	14 ± 3	28 ± 5
	10	55 ± 7	67 ± 6
	30	91 ± 1	92 ± 1
ED_{50} (mg/kg)		7.6 (6.2–9.4)	5.8 (4.9–6.9)
Ratio of ED_{50} values, 51641/54761		0.03	4.4

* Drugs were injected i.p. 1 hr before the rats were killed. MAO activity in tissue homogenates was assayed with either [^{14}C]serotonin or [^{14}C]phenylethylamine as substrate. MAO activity in μmoles substrate oxidized/min/g of tissue was calculated for controls and each treated group. There were five rats per group. Inhibition as a percentage of the control mean is shown, as are ED_{50} values (numbers in parentheses show 95 per cent confidence limits).

Table 5. Inhibition of MAO in rat liver *in vivo* by 51641 and 54761*

Inhibitor	Dose (mg/kg)	% Inhibition of MAO: Serotonin	% Inhibition of MAO: Phenylethylamine
51641	0.03	12 ± 3	
	0.1	28 ± 2	
	0.3	45 ± 3	
	1	65 ± 4	14 ± 5
	3		20 ± 2
	10		35 ± 2
	30		67 ± 2
ED_{50} (mg/kg)		0.39 (0.31–0.50)	15.5 (10.6–22.7)
54761	1	19 ± 4	21 ± 2
	3	41 ± 7	38 ± 3
	10	72 ± 4	70 ± 2
	30	91 ± 1	85 ± 2
ED_{50} (mg/kg)		4.2 (3.4–5.1)	4.6 (4.0–5.3)
Ratio of ED_{50} values, 51641/54761		0.09	3.4

* See Table 4 legend.

inhibitors. Table 4 shows ED_{50} values in mg/kg, representing the doses of 51641 and 54761 required for 50 per cent inhibition of MAO activity in brain homogenates assayed with either serotonin or phenylethylamine as substrate. Compound 51641 was 32 times more potent than 54761 in blocking serotonin oxidation by rat brain but was less than one-fourth as active as 54761 in blocking phenylethylamine oxidation. The ED_{50} for 51641 in blocking serotonin oxidation in brain was about 1/100th of its ED_{50} for blocking phenylethylamine oxidation, whereas 54761 had a slightly lower ED_{50} for blocking phenylethylamine than for blocking serotonin oxidation in brain. Qualitatively similar results were obtained for liver (Table 5). Compound 51641 was eleven times more potent than 54761 in blocking serotonin oxidation but was less than one-third as potent in blocking phenylethylamine oxidation. In heart (Table 6), 51641 was much more active than 54761 in blocking serotonin oxidation, as in the other two tissues. However, phenylethylamine oxidation was more effectively blocked by 51641 than by 54761, in contrast to the converse relative potency for inhibition in brain and liver.

To compare the blockade of amine oxidation *in situ* by these two selective inhibitors, we injected ^{14}C-labeled phenylethylamine into rats and determined the amount of the amine remaining unoxidized after 10 min (Fig. 3). Phenylethylamine concentration was increased significantly by 54761 in all tissues. The effect of 51641 was much less in all tissues; phenylethylamine concentration in the 51641-treated group differed significantly from control only in the lung. Next, we compared the effects of 51641 and 54761 on the oxidation of endogenous serotonin by measuring serotonin and 5-hydroxyindoleacetic acid (5-HIAA) concentrations in brain (Table 7). In the first experiment, equal doses of 51641 and 54761 were compared. Serotonin elevation and 5-HIAA lowering were greater after 51641 than after 54761. In the second experiment, various doses of 51641 and 54761 were compared. The

Table 6. Inhibition of MAO in rat heart *in vivo* by 51641 and 54761*

Inhibitor	Dose (mg/kg)	% Inhibition of MAO: Serotonin	% Inhibition of MAO: Phenylethylamine
51641	0.03	5 ± 5	3 ± 4
	0.1	37 ± 11	22 ± 8
	0.3	74 ± 7	45 ± 6
	1	89 ± 6	56 ± 5
ED_{50} (mg/kg)		0.16 (0.12–0.23)	0.57 (0.34–0.96)
54761	1	4 ± 5	8 ± 4
	3	3 ± 8	20 ± 6
	10	47 ± 11	48 ± 7
	30	87 ± 1	76 ± 1
ED_{50} (mg/kg)		9.9 (7.1–14.0)	9.9 (7.4–13.3)
Ratio of ED_{50} values, 51641/54761		0.02	0.06

* See Table 4 legend.

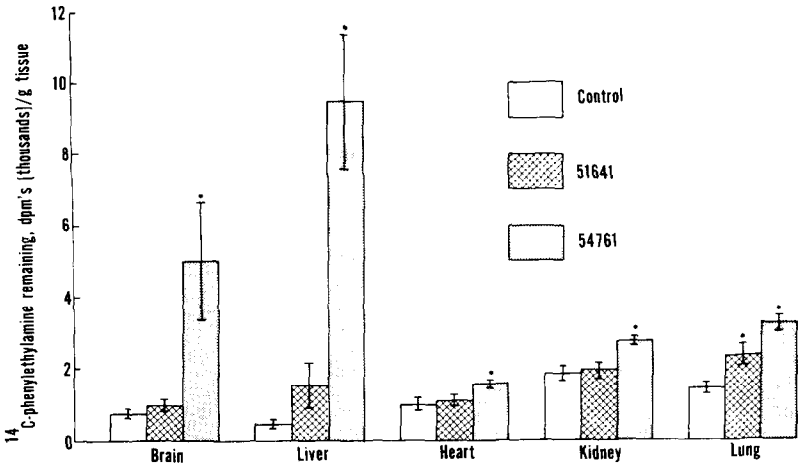


Fig. 3. Protection against the *in vivo* oxidation of [^{14}C]phenylethylamine by 51641 and 54761. [^{14}C]phenylethylamine (10 mg/kg, i.p.) was injected 10 min before the rats were killed and 8 hr after the MAO inhibitors, which were injected at 30 mg/kg, i.e. The amount of unoxidized [^{14}C]phenylethylamine remaining after 10 min was determined as described previously [8]. Mean values ± S.E. for five rats per group are shown. * Significant changes from control ($P < 0.05$).

increase in serotonin was greater after all doses of 51641, including the 5 mg/kg dose, than after any dose of 54761, including the 20 mg/kg dose. In the third experiment, the time courses of serotonin and 5-HIAA changes after equal doses of 51641 and 54761 were compared. Again, the increase in serotonin and the increase in 5-HIAA were greater after 51641 than after 54761.

Finally, we attempted to enhance the slight selectivity of 54761 by combining it with a selective short-acting reversible inhibitor of MAO, harmaline. The ability of reversible inhibitors to protect against inactivation of the enzyme by irreversible MAO inhibitors has previously been reported [11–13]. However, the idea of using a selective reversible inhibitor to modify the selectivity of an irreversible inhibitor appears not to have been explored. In a preliminary experiment, we injected harmaline at 30 mg/kg i.p. and measured MAO activity in rat brain 8 hr later using either phenylethylamine or serotonin as substrate, as in Table 4. The inhibition was 85 ± 3 per cent with serotonin as substrate and 23 ± 4 per cent with phenylethylamine as substrate, demonstrating the previously reported [14] selectivity of harmaline as a type A MAO inhibitor. Compound 54761 given at 30 mg/kg

Table 7. Effect of 51641 and 54761 on 5-hydroxyindole concentrations in rat brain*

Experimental group	Dose (mg/kg)	Time interval (hr)	Brain 5-hydroxyindoles (μg/g)	
			Serotonin	5-HIAA
(1) Control			0.67 ± 0.03	0.52 ± 0.01
51641	30	5	1.08 ± 0.04 (+ 61%)	0.39 ± 0.02 (− 25%)
54761	30	5	0.86 ± 0.03 (+ 28%)	0.46 ± 0.02 (− 12%)
(2) Control			0.68 ± 0.01	
51641	5	5	0.88 ± 0.03 (+ 29%)	
	10		0.92 ± 0.01 (+ 35%)	
	20		0.99 ± 0.03 (+ 46%)	
54761	5	5	0.72 ± 0.02	
	10		0.72 ± 0.02	
	20		0.84 ± 0.03 (+ 24%)	
(3) Control			0.52 ± 0.02	0.49 ± 0.01
51641	30	1	0.77 ± 0.03 (+ 48%)	0.35 ± 0.02 (− 29%)
	30	2	0.96 ± 0.03 (+ 85%)	0.31 ± 0.01 (− 37%)
	30	4	0.93 ± 0.04 (+ 79%)	0.36 ± 0.02 (− 27%)
	30	8	0.91 ± 0.01 (+ 75%)	0.41 ± 0.01 (− 14%)
54761	30	1	0.74 ± 0.02 (+ 42%)	0.39 ± 0.01 (− 20%)
	30	2	0.78 ± 0.04 (+ 50%)	0.45 ± 0.02
	30	4	0.79 ± 0.02 (+ 52%)	0.46 ± 0.01 (− 6%)
	30	8	0.74 ± 0.04 (+ 42%)	0.43 ± 0.02 (− 12%)

* Drugs were injected i.p. Mean values ± S.E. for five rats per group are shown. Percentage changes are given in parentheses for all values that differed significantly ($P < 0.05$) from the corresponding control group. 5-HIAA was not determined in experiment 2.

Table 8. Inhibition of MAO in rat brain 24 hr after the injection of 54761 alone or in combination with harmaline*

Treatment group	MAO activity (nmoles/g/min)	
	Serotonin	Phenyl-ethylamine
Control	164 ± 5	71 ± 3
54761	48 ± 1 (−71%)	14 ± 0.5 (−81%)
Harmaline	172 ± 2	76 ± 1
54761 + Harmaline	154 ± 4	24 ± 1 (−66%)

* Harmaline and 54761 were injected at 30 mg/kg, i.p. Mean values ±S.E. for five rats per group are shown. Percentage changes are given in parentheses in all cases where the differences from control were statistically significant ($P < 0.05$).

i.p. gave 84 ± 1 and 87 ± 1 per cent inhibition of serotonin and phenylethylamine oxidation, respectively, at 8 hr. We then measured MAO inhibition in another experiment at a longer interval, 24 hr, so that the effect of harmaline had disappeared [15]. Table 8 illustrates the enhanced selectivity of 54761 with these conditions. Compound 54761 alone caused 71 per cent inhibition of serotonin oxidation and 81 per cent inhibition of phenylethylamine oxidation. MAO activity in rats treated with harmaline alone was not significantly different from that of the control group with either substrate. In rats given 54761 and harmaline, MAO activity with serotonin as substrate was not significantly inhibited, but MAO activity with phenylethylamine as substrate was inhibited significantly and almost as much as in rats given 54761 alone. Thus, in the latter group of rats the slight selectivity seen with 54761 alone was greatly accentuated by co-administration of harmaline.

DISCUSSION

The results presented here complement the data of Murphy *et al.* [7] and of Glenn *et al.* [16, 17] showing that 54761 and 51641 differ in their selectivity as MAO inhibitors. Murphy *et al.* [7] had taken advantage of the fact that mouse neuroblastoma cells have predominantly type A MAO, whereas human platelets have predominantly type B MAO. They observed that 54761 was a better inhibitor of the platelet enzyme whereas 51641 was a better inhibitor of the neuroblastoma enzyme. Glenn *et al.* [16] found that 51641 was a better inhibitor than 54761 of MAO in peritoneal exudate cells from guinea pigs with tryptamine as substrate. Our results show that 54761, both *in vitro* and *in vivo*, was slightly more effective than 51641 in blocking phenylethylamine, whereas 51641 was much more effective than 54761 in blocking serotonin oxidation.

One feature of the inhibition by 51641 shown in Fig. 2 deserves comment. The inhibition of phenylethylamine oxidation by 51641 in brain and liver did not persist for as long a time as did the inhibition of serotonin oxidation. An earlier report by Egashira *et al.* [18] may be relevant to this observation. These workers found that another selective type A inhibitor, clorgyline, reacted irreversibly *in vitro* at a much slower rate with type B MAO than with type A MAO. The diminishing inhibition of phenylethylamine oxidation *in vivo* by 51641 thus may represent a reversible interaction of that inhibitor with type B MAO, whereas the long-lasting inhibition of serotonin oxidation probably represents irreversible inhibition of type A MAO. In the heart, inhibition both of phenylethylamine and of serotonin oxidation was long-lasting, and this fact is compatible with emerging evidence that phenylethylamine oxidation as well as serotonin oxidation in rat heart may occur via type A MAO [19]. The data in Table 6 showing that 51641 is a more potent inhibitor of phenylethylamine oxidation than is 54761 in heart (but not in brain or liver—Tables 4 and 5) are also consistent with the idea that phenylethylamine oxidation in heart occurs via type A MAO.

Compound 54761 appears to be the first MAO inhibitor in the *N*-cyclopropylamine series reported to inhibit type B MAO preferentially. Its selectivity is not as great as that reported for deprenyl [20, 21], a compound that we did not have available for direct comparative studies. By co-administration with harmaline, however, the selectivity of inhibition by 54761 at longer times can be enhanced. Thus, it may be useful in experiments of this sort for evaluating physiological roles of type B MAO. The fact that type B inhibitors as well as type A inhibitors exist both in the *N*-cyclopropylamine and *N*-propargylamine series of MAO inhibitors suggests that the major determinant of selectivity is the other substituent on the nitrogen, whereas the cyclopropyl and the propargyl functions may confer irreversibility to those inhibitors. The propargyl compounds have been shown to be "suicide substrates" leading to irreversible inactivation of the catalytic site on MAO [22], whereas the mechanism of irreversible inactivation by the cyclopropyl compounds has yet to be worked out.

Although there is now compelling evidence that dopamine is a type A substrate in rat brain [23–26], recent evidence suggests that type B MAO may be primarily responsible for the destruction of dopamine in human brain [27, 28]. If so, then selective type B inhibitors are of potential therapeutic importance in the treatment of diseases like Parkinsonism in which enhancement of dopaminergic neural function is beneficial. Compound 51641 is much more active than 54761 in potentiating the hyperirritability syndrome in mice produced by injection of L-dopa and presumably mediated by brain dopamine [5]. However, that test may not be predictive of L-dopa enhancement or anti-Parkinsonism efficacy in humans. Earlier clinical trials (H. W. Gillen, personal communication) indicated that 51641 alone had modest anti-Parkinsonism activity, but that it enhanced the hypertensive action of L-dopa when given in combination. The increase in blood pressure may have been due to potentiation of peripheral actions of catecholamines that normally would have been oxidized by type A MAO. If dopamine in human brain is oxidized by type B MAO, then an inhibitor like 54761 might be more appropriate for enhancing L-dopa effectiveness in Parkinson's disease.

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