Aliphatic Propargylamines: Potent, Selective, Irreversible Monoamine Oxidase B Inhibitors

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A series of aliphatic propargylamine derivatives has been synthesized. Some of them possess highly potent, irreversible, selective, inhibitory activity toward monoamine oxidase B (MAO-B). The potency of the inhibitors is related to chain length and substitution of a hydrogen on the terminal carbon of the aliphatic chain. MAO inhibitory activity as assessed in vitro increased as the aliphatic carbon chain length increased. Substitution of a hydrogen by hydroxyl, carboxyl, or carbethoxyl groups at the aliphatic chain terminal or replacement of the methyl group on the nitrogen atom by an ethyl group considerably reduced the inhibitory activity. Stereospecific effects were observed with the *R*-(−)-enantiomer being 20-fold more active than the *S*-(+)-enantiomer. Inhibitors with relatively short carbon chain lengths (i.e. four to six carbons) were found to be more potent than those with longer chains in inhibiting brain MAO-B activity in vivo especially after oral administration. Chronic administration of low doses of the aliphatic propargylamines caused a slight cumulative inhibition of MAO-A activity in the mouse brain. These MAO-B inhibitors appear to be nontoxic, and they do not possess an amphetamine-like moiety in their structure as is the case for deprenyl. We expect that these aliphatic propargylamines may be useful in the treatment in certain neuropsychiatric disorders.

Introduction

Monoamine oxidase (MAO, EC 1.4.3.4.) is an enzyme that oxidizes monoamine neurotransmitters and neuromodulators, as well as exogenous bioactive monoamines.[1,2] Since inhibition of MAO activity can be utilized in the treatment of depression, a large number of MAO inhibitors were synthesized in the 1960's[3] and some of them, such as phenelzine and tranylcypromine, are still used as antidepressants. The application of these latter, nonselective, irreversible MAO inhibitor antidepressants, however, is limited because they can cause a number of adverse clinical side effects, such as hepatotoxicity and severe hypertension following the ingestion of tyramine-rich foods and drinks.[4]

MAO exists in two forms, MAO-A and MAO-B,[5] and they are now known to be derived from distinctly different gene loci.[6] MAO-A and -B are differentially distributed in neuronal and non-neuronal structures.[7,8] MAO-A deaminates preferentially 5-hydroxytryptamine (5-HT) and is very sensitive to selective MAO-A inhibitors, such as clorgyline [*N*-[(2,4-dichlorophenoxy)-*N*-propyl)]-*N*-methylpropargylamine]. MAO-B deaminates preferentially 2-phenylethylamine (PE) and is very sensitive to MAO-B inhibitors, such as deprenyl [*N*-(phenylisopropyl)-*N*-methylpropargylamine].[2] Some amines, such as dopamine and *p*-tyramine, are oxidized by both MAO-A and MAO-B. Both the antidepressant and the hypertensive effects (i.e. *p*-tyramine pressor effect) are thought to be related to the inhibition of MAO-A activity. Recent drug developments have therefore concentrated on reversible MAO-A inhibitors as antidepressants (e.g. Brofaromine and Moclobemide).[9] Because neuronal MAO is type A, it seems only natural that most drug research emphasized MAO-A inhibitors. Until recently, MAO-B inhibitors have been largely ignored.

The MAO-B inhibitor deprenyl (selegiline) has been used as an effective adjuvant to L-DOPA in the treatment of Parkinson's disease.[10] It is thought to act by reducing the deamination of dopamine and reduces the requirement for L-DOPA in those cases where L-DOPA is being ingested. Recently, it has been reported that deprenyl by itself can significantly delay the onset of disability associated with early, otherwise untreated, cases of Parkinson's disease.[11,12] Deprenyl, along with other MAO inhibitors, has been shown to prevent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson-like neurotoxicity

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in animals.[13] MPTP itself is not toxic, but is converted to the distal toxin, 1-methyl-4-phenylpyridinium ion (MPP^+), by MAO-B in the brain. The exact neuroprotective mechanism by which deprenyl acts is not yet well understood. Perhaps it reduces oxidative stress (i.e. free radical formation) by decreasing oxidative deamination.[14] Deprenyl has also been claimed to be effective in the treatment of Alzheimer's disease,[15,16] depression,[17,18] and attention deficit disorder.[19] In addition it has been shown to prolong life span and improve sexual activity in rodents[20,21] and humans.[22] Unlike MAO-A inhibitors, MAO-B inhibitors do not usually cause hypertensive crises (except after ingestion of large doses chronically), and they therefore possess the potential to become very useful neuropsychiatric and geriatric drugs.

Deprenyl, a structural analog of amphetamine, is catabolized to produce desmethyldeprenyl, methamphetamine, and amphetamine;[23-25] this has caused some concern since it might cause deprenyl to become a drug subject to substance abuse. It has also been asked whether or not it is the amphetamine moiety of deprenyl that is related to its clinical efficacy. Different MAO-B inhibitors, not possessing the amphetamine moiety or amphetamine-like properties, should therefore be assessed.[26] Finally, although deprenyl is generally considered to be a safe and harmless drug, there has been at least one report indicating that after chronic use, abnormalities in liver function developed in some patients.[27]

A large number of arylalkyl and cycloaliphatic propargylamines and a few acyclic aliphatic propargylamines have been tested, a few of the former having been shown to inhibit MAO-A activity in vitro.[28-30] Two of the deprenyl-like arylalkyl analogs were tested for MAO-B inhibitory activity in vivo and shown to be very potent.[30] None of the acyclic aliphatic propargylamines have been tested for MAO-B inhibiting activity in vitro or in vivo.

Recently it has been shown that straight chain aliphatic amines (the number of carbon atoms ranging from 4 to 18) are readily metabolized by MAO-B.[31] The affinity of MAO-B for these aliphatic amines was quite high (K_m values in the low micromolar range). This high affinity of some aliphatic amines for the active site of MAO-B has now been applied in the design of some specific MAO-B inhibitors. We have described the synthesis of a series of aliphatic propargylamine derivatives, and the potency and selectivity of these compounds in vitro and in vivo in the inhibition of MAO-A and MAO-B activities have been assessed and compared with a typical MAO-B inhibitor, deprenyl, which is a drug proven to be useful in the treatment of Parkinson's disease.

Results and Discussion

Inhibition of Rat Liver Mitochondrial MAO Activities by *N*-Alkyl-*N*-methylpropargylamines in Vitro. MAO-A and MAO-B activities from rat liver mitochondrial membranes were assayed using 5-HT (5×10^{-4} M) and PE (1.9×10^{-5} M) as substrates, respectively. The aliphatic propargylamine inhibitors (from 1×10^{-10} M to 1×10^{-4} M) were preincubated with the MAO for 20 min at ambient temperature, and then the residual enzyme activities were determined. The inhibitory activities (IC_{50}) of the aliphatic propargylamine derivatives towards MAO-A and MAO-B are summarized in Table I. Some of the aliphatic propargylamines are highly selective MAO-B inhibitors with MAO-A/MAO-B ratios of their IC_{50} values ranging from 20 to 1000. The inhibition is irreversible, which is very similar to aromatic *N*-methylpropargylamine inhibitors, such as deprenyl and pargyline. Following incubation of the rat liver MAO with compound **5** (1×10^{-5} M), for example, MAO activity could not be recovered by dialysis or by gel filtration with Sephadex G-25. Compounds with longer carbon chain lengths are more active in the inhibition of MAO activity in vitro. MAO inhibitory activity appears to be correlated with the lipophilicity of these compounds. The carbon chain length of the *N*-alkyl group is not only related to the inhibitory potency, but also affects the selectivity towards MAO-A and MAO-B. The optimal carbon number of the alkyl group is six with respect to MAO-B selectivity. As can be seen in Table I, **8** exhibits the most selective inhibitory activity towards MAO-B. It is much more selective than deprenyl. Compound **7**, possessing an α-ethyl rather than an α-methyl branch, is also a quite potent MAO-B inhibitor, however, its selectivity appears to be decreased significantly. These compounds also actively inhibit the

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Table I. Inhibition of Rat Liver Monoamine Oxidase Activities toward Different Substrates by Some Aliphatic Propargylamines in Vitro

inhibitors[a]	PE (1.9×10^{-5} M) IC_{50}	5-HT (5×10^{-4} M) IC_{50}	ratio MAO-A/MAO-B	DA (5×10^{-4} M) IC_{50}
1	inactive[c]	inactive		inactive
2	$(1.9 \pm 0.2) \times 10^{-5}$ M	inactive		$(2.8 \pm 0.3) \times 10^{-5}$ M
3	$(1.4 \pm 0.1) \times 10^{-6}$ M	$(1.9 \pm 0.2) \times 10^{-5}$ M	12	$(4.9 \pm 0.5) \times 10^{-7}$ M
4	$(1.4 \pm 0.1) \times 10^{-6}$ M	$(9.8 \pm 0.1) \times 10^{-5}$ M	71	-
5	$(1.8 \pm 0.1) \times 10^{-7}$ M	$(1.2 \pm 0.1) \times 10^{-5}$ M	69	$(5.6 \pm 0.5) \times 10^{-6}$ M
6	$(3.7 \pm 0.1) \times 10^{-7}$ M	$(1.2 \pm 0.1) \times 10^{-4}$ M	324	-
7	$(1.8 \pm 0.1) \times 10^{-7}$ M	$(2.4 \pm 0.3) \times 10^{-6}$ M	13	-
8	$(8.2 \pm 0.2) \times 10^{-8}$ M	$(9.0 \pm 0.1) \times 10^{-5}$ M	1095	-
9	$(2.1 \pm 0.2) \times 10^{-7}$ M	$(1.9 \pm 0.1) \times 10^{-5}$ M	89	$(3.2 \pm 0.3) \times 10^{-7}$ M
10	$(2.0 \pm 0.2) \times 10^{-6}$ M	$(3.8 \pm 0.3) \times 10^{-5}$ M	19	-
11	$(1.8 \pm 0.2) \times 10^{-7}$ M	$(3.9 \pm 0.4) \times 10^{-6}$ M	22	$(2.1 \pm 0.2) \times 10^{-7}$ M
12	$(3.9 \pm 0.5) \times 10^{-8}$ M	$(1.9 \pm 0.2) \times 10^{-6}$ M	50	$(2.8 \pm 0.9) \times 10^{-7}$ M
13	inactive	inactive		inactive
14	inactive	inactive		inactive
15	inactive	inactive		inactive
16	$(1.2 \pm 0.1) \times 10^{-4}$ M	inactive		-
17	$(1.3 \pm 0.1) \times 10^{-4}$ M	inactive		-
deprenyl[b]	$(5.2 \pm 0.5) \times 10^{-8}$ M	$(3.8 \pm 0.2) \times 10^{-6}$ M	66	$(2.8 \pm 0.3) \times 10^{-7}$ M

[a] Results are the average of at least three independent experiments for each compound. The mean IC_{50} values and standard errors were estimated using a series of concentrations of the substrates according to Lineweaver–Burke plots. [b] Deprenyl (a gift from Professor Knoll, Semmelweis, Budapest) was the *l*-isomer, while the aliphatic propargylamines tested were racemic mixtures. [c] No inhibition on MAO activities was observed up to 10^{-4} M.

deamination of dopamine (DA), which is a mixed-type MAO (A and B) substrate.

When the terminal carbon is substituted with a hydroxyl group, MAO-B inhibitory activity is markedly reduced. Compounds substituted with a carboxy or carbethoxy group at the terminal carbon lose the MAO inhibitory activity completely.

Stereospecificity. As can be seen in Figure 1, the *R* stereoisomer **18** is considerably more potent than the *S* enantiomer **19** in the inhibition of rat liver mitochondrial MAO-B activity using 2-phenylethylamine as substrate. An approximately 20-fold difference was observed, which is quite similar to the stereospecific effect exhibited by deprenyl.[32] The racemic mixture of the 2-butyl analog **3** is slightly less active than the *R* enantiomer **18**. Both MAO-A and MAO-B are known to catalyze the deamination of monoamines stereospecifically, and it is the *pro-R* stereoisomer that is involved.[33,34] This *pro-R* stereospecificity of deamination is consistent with the stereospecificity of the methylpropargylamine inhibitors with respect to their MAO inhibition. We conclude that the *pro-R* 2-alkyl-*N*-methylpropargylamine isomers are the active form in the inhibition of MAO activity.

Inhibition of Mouse Brain MAO Activities by *N*-Alkyl-*N*-methylpropargylamines in Vivo. Albino Swiss mice were used in this study. The mice were injected intraperitoneally with different doses of the aliphatic propargylamines which were dissolved in 100 μL of saline. In the assessment of the acute effects the mouse brains were removed and dissected 2 h after treatment; MAO-A and MAO-B activities were then estimated. Aliphatic propargylamines with shorter carbon chain lengths (such as **3**, **4**, **5**, **6**, and **8**) appear to be more potent than do their longer chain analogs in the inhibition of brain MAO-B activity (see Table II). The relative ID_{50}/IC_{50} values with respect to these smaller propargylamines are lower, suggesting that these shorter chain length molecules are more easily adsorbed (e.g. into lipids, membranes, etc.) and/or more readily transported into the brain. In

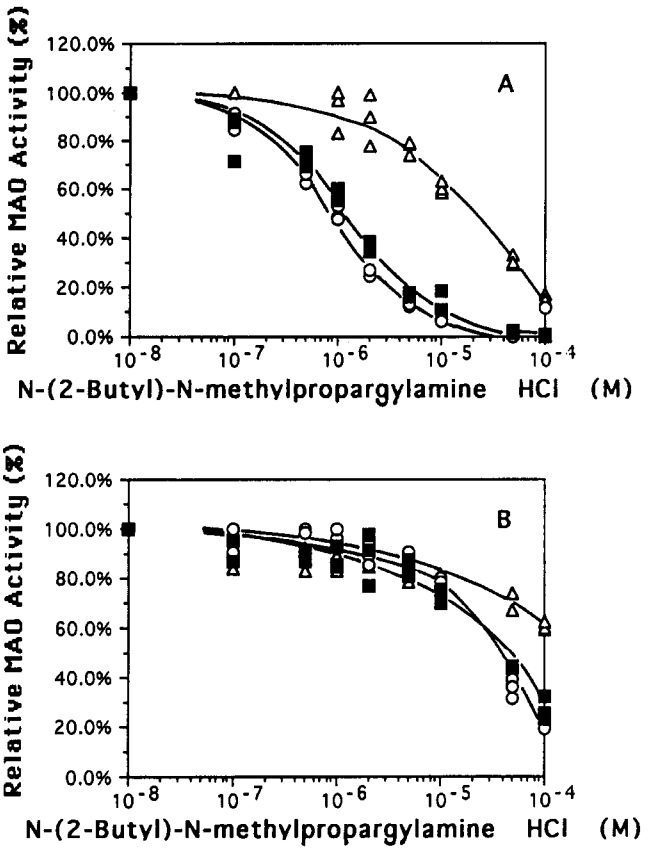

Figure 1. Stereospecific effect of *N*-(2-butyl)-*N*-methylpropargylamine hydrochloride on MAO activities. The inhibitory activity of the *R*-(−)-**18** [○] and *S*-(+)-**19** [△] enantiomers as well as the racemic mixture **3** [■] on rat liver mitochondrial MAO activities toward MAO-B substrate 2-phenylethylamine (1.9×10^{-5} M) [panel A] and MAO-A substrate 5-hydroxytryptamine (5×10^{-4} M) [panel B] were estimated as described in the Experimental Section. Results are for triplicate determinations.

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Table II. MAO Activities in the Mouse Brain after Intraperitoneal Administration of Aliphatic Propargylamine MAO Inhibitors

inhibitors[a]	PE (1.9×10^{-5} M) ID_{50} (μmol/kg)	5-HT (5×10^{-4} M) ID_{50} (μmol/kg)	ratio MAO-A/MAO-B	MAO-B ID_{50} (mg/kg) / IC_{50} (1×10^{-6} M)[b]
3	4.2 ± 0.6	69.7 ± 14.2	17	2.7
4	11.2 ± 1.7	478.4 ± 9.7	43	8.0
5	1.7 ± 0.5	113.9 ± 21.8	67	12.3
6	6.8 ± 1.2	>218.3	>32	18.3
7	2.7 ± 0.5	52.9 ± 5.1	20	15.2
8	1.2 ± 0.4	261.6 ± 32.4	218	14.7
9	2.6 ± 0.4	126.7 ± 13.0	49	12.4
10	75.6 ± 3.6	>491.4	>7	38.2
11	15.0 ± 3.8	144.3 ± 25.2	10	84.9
12	15.5 ± 3.5	223.4 ± 25.2	14	400.5
deprenyl	2.3 ± 0.2	142.6 ± 13.0	62	45.4

[a] Results are the average (±SEM) of three to eight animals for each ip dose, which were 0.5, 1, 2, 5, 10, 20, 50, and 100 mg/kg. Forebrains were dissected 2 h after ip administration of the drugs. MAO-A and MAO-B activities were then determined immediately. The mean ID_{50} values and standard errors were estimated from dose–response curves according to Lineweaver–Burke plots. [b] IC_{50} values are obtained from Table I.

Table III. MAO Activities in the Mouse Brain after Oral Administration of Aliphatic Propargylamine MAO Inhibitors

inhibitors	relative activity (%)[a] PE (1.9×10^{-5} M)	relative activity (%)[a] 5-HT (5×10^{-4} M)	ED_{50} (μmol/kg)[c] with respect to MAO-B
saline (6)[b]	100 ± 5	100 ± 8	
3 (6)	28 ± 2	95 ± 11	31.0 ± 0.6
4 (3)	67 ± 9	98 ± 5	140.6 ± 38.4
5 (3)	31 ± 4	89 ± 15	5.2 ± 1.0
6 (3)	72 ± 17	97 ± 13	
8			5.1 ± 0.6
9 (6)	39 ± 4	99 ± 5	
10 (3)	118 ± 14	123 ± 16	
11 (3)	104 ± 7	97 ± 8	171.1 ± 18.3
12 (6)	64 ± 8	107 ± 14	
deprenyl	40 ± 2	99 ± 11	26.3 ± 4.9

[a] Results are the mean ± standard errors for an oral dose of 10 mg/kg of each compound. Forebrains were dissected 2 h after the administration of the drugs. MAO-A and MAO-B activities were determined immediately. [b] Numbers of mice used in the experiments are indicated in parentheses. [c] Forebrains were dissected 2 hours after administration of different doses of the drugs (from 1 to 50 mg/kg). MAO-B activities were determined and ED_{50} values and standard errors were estimated from the dose–response curves according to Lineweaver–Burke plots.

Table IV. MAO Activities in Mouse Brain after Chronic Peritoneal Administration of Deprenyl and Aliphatic Propargylamine MAO Inhibitors

inhibitors	dose (mg/kg)	no. of animals	days of treatment	relative activity (%) MAO-A	relative activity (%) MAO-B
3	0.25	4	1	108 ± 5.6	117 ± 18.0
		4	13	100 ± 6.6	51 ± 3.3[a]
5	0.25	4	1	102 ± 6.4	94 ± 5.8
		4	13	89 ± 7.1	35 ± 2.3[a]
	2.0	5	1	91 ± 4.8	40 ± 2.3[a]
		5	10	49 ± 5.1[a]	19 ± 1.6[a]
		5	21	31 ± 1.5[a]	18 ± 1.2[a]
8	0.05	3	1	104 ± 5.8	55 ± 16.1[a]
		3	9	95 ± 4.5	41 ± 2.0[a]
		3	20	76 ± 9.1	37 ± 3.3[a]
	0.20	3	1	103 ± 7.1	36 ± 1.5[a]
		3	9	103 ± 8.4	35 ± 1.8[a]
		3	20	81 ± 6.8	27 ± 0.6[a]
11	0.25	4	1	85 ± 13.8	94 ± 16.7
		4	13	79 ± 8.1	70 ± 8.5[b]
deprenyl	2.0	5	1	90 ± 4.2	49 ± 14.6[a]
		5	10	73 ± 7.4[b]	32 ± 4.38[a]
		5	21	68 ± 3.8[b]	34 ± 1.6[a]

Values are means of percent of relative activities and standard errors; [a] $p < 0.01$ and [b] $p < 0.05$ in comparison to the saline-treated control groups.

comparison to the compounds with longer carbon chain lengths, they are less lipophillic, and therefore they are less likely to bind or associate with peripheral lipophillic components. Compounds with long carbon chain lengths, such as 11 and 12 may be too lipophillic to be transported. Alternatively, they may be more easily subjected to other routes of metabolism, such as β-oxidation. Several propargylamine derivatives with seven to eight carbon-branched aliphatic groups were shown in an earlier study to possess inhibitory activity towards MAO in vitro, but they were inactive in vivo.[28]

The propargylamine MAO-B inhibitors with shorter carbon chains, such as 3 and 5, were also found to be more effective in blocking MAO-B activity in the brain following oral administration than was the case for deprenyl. Table III indicates the MAO activities in the mouse brain following oral administration of the aliphatic propargylamines. These results confirm that the short-chain compounds possess superior transport properties, since, although they are moderately active in inhibiting MAO-B activity in vitro, they are even more active after oral administration in comparison to deprenyl. It is interesting to note that aliphatic propargylamines, such as 5, are more stable in aqueous solution than deprenyl. When 5 and deprenyl, dissolved in tap water, are kept on the benchtop in the laboratory, deprenyl lost 30–40% of its MAO-B inhibitory activity daily, whereas 5 remained stable over a 1-week period.

Chronic Effect on Mouse Brain MAO Activities. Two methods of chronic administration of the aliphatic propargylamine MAO inhibitors and their concomitant chronic effects on mouse brain MAO activity levels have been employed. Table IV summarizes the effects of several aliphatic propargylamine MAO inhibitors, as well as deprenyl, on mouse brain MAO activities following chronic peritoneal injection of different doses of the inhibitors. Inhibition of MAO-A and MAO-B was dependent both on the inhibitor and the doses applied. Both 3 and 5 at the low dose of 0.25 mg/kg were without effect on MAO-A and MAO-B 24 h after a single ip injection, but became inhibitors of MAO-B after 13 days of treatment. At higher doses (2 mg/kg) 5 selectively inhibited MAO-B activity. After 10 and 21 daily treatments, more inhibition of MAO-B was observed, but MAO-A had by this time also become slightly inhibited. These chronic effects on MAO-A are very similar to the effect seen with deprenyl. Compound 8 was found to be the most potent and selective MAO-B inhibitor in our series of new inhibitors and it was

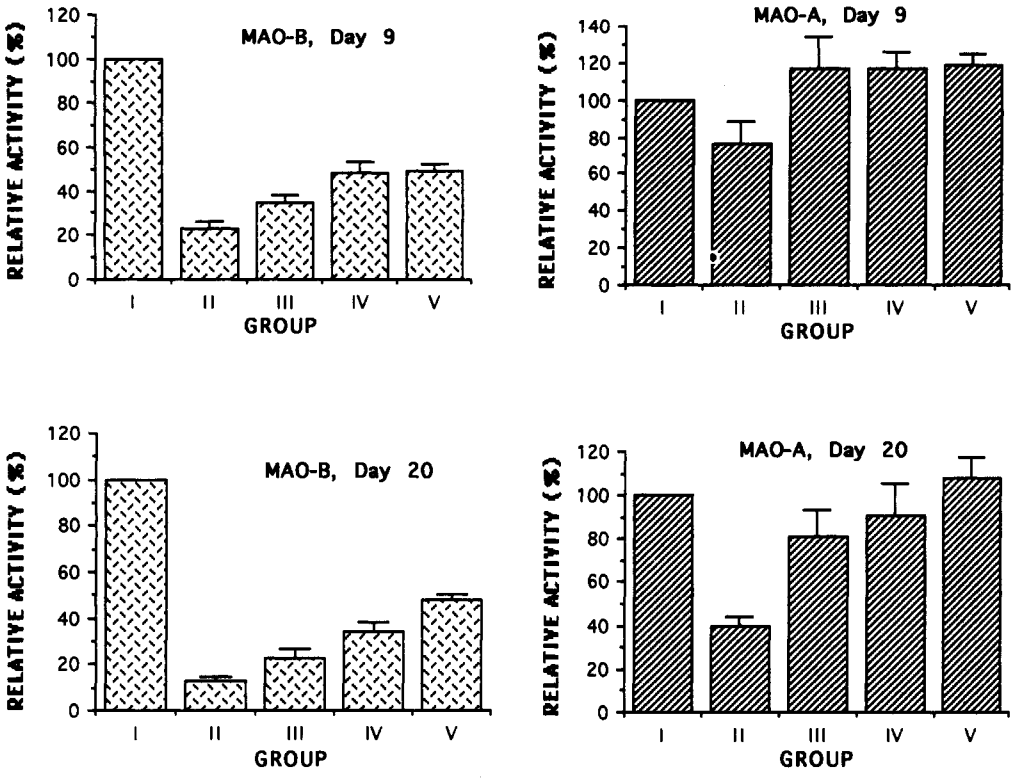


Figure 2. Effect of chronic oral administration of 5 on brain MAO activities in mouse. Compound 5 was administered via the drinking water. Group I = untreated animals; Group II = 5 (100 μg/mL) in the drinking water; Group III = 5 (100 μg/mL on day 1 and then 10 μg/mL on subsequent days); Group IV = 5 (100 μg/mL on day 1 and then 1 μg/mL on subsequent days); Group V = 5 (100 μg/mL on day 1 and then just water on subsequent days). Animals were sacrificed on day 9 and day 20, and brain MAO activities toward MAO-B substrate 2-phenylethylamine (1.9×10^{-5} M) and MAO-A substrate 5-hydroxytryptamine (5×10^{-4} M) were estimated. Results are reported as relative activity (mean ● standard error for five animals at each dosage) with respect to untreated group.

also more effective than deprenyl. At low doses (0.05 and 0.2 mg/kg) 8 selectively inhibited MAO-B but exhibited very little if any cumulative effect on MAO-A even after 20 days of treatment. We have also shown that 11, a highly potent MAO-B inhibitor in vitro, exhibited only weak potency and poor selectivity on MAO activities in vivo after 13 days of treatment.

The chronic effects of 5, on mouse brain MAO activities were also assessed following oral administration (in these experiments the drug was added to the drinking water). As can be seen in Figure 2, at lower doses (i.e. 1 and 10 μg/mL), selective inhibition of MAO-B activity was achieved, while at higher doses (100 μg/mL), MAO-A also became inhibited. A prolonged inhibition of MAO-B activity following only a single day of drug treatment was observed in group V. This result confirmed that the inhibition of MAO-B by aliphatic propargylamines is also irreversible in vivo, and the synthesis of new brain mitochondrial MAO appears to be an extremely slow process. The inhibition of both MAO-A and MAO-B activities was found to be increased with longer duration of treatment.

Toxicity. The acute toxicity of these compounds is very low. Compounds 3, 4, 5, 6, and 8 were administered orally to mice at doses up to 1000 mg/kg. This resulted in no fatality within at least the following 48 h. The aliphatic propargylamines appear to be less toxic than deprenyl, for which the LD_{50} has been reported to be 445 mg/kg in male mice (Eldepryl, report from Britania Pharmaceuticals Ltd.). In subchronic investigations 5 has been administered either intraperitoneally or orally at doses up to 10 mg/kg, and it produced no toxic or anoretic effects after 3 weeks of treatment. Compound 5 and deprenyl at such doses have failed to exhibit any apparent behavioral effects in mice.[35]

The major metabolic products of deprenyl are methamphetamine or amphetamine, which probably arise by hydroxylation and cleavage between the propargyl and amphetamine moieties. If aliphatic propargylamines are metabolized in a similar manner, 4, for instance, would be metabolized to *n*-butylamine and *N*-methyl-*n*-butylamine, which would be then deaminated by MAO-B to form *n*-butyraldehyde, and this subsequently would be oxidized to the totally nontoxic *n*-butyric acid. The aliphatic side chains of the propargyl compounds are expected to be metabolized in vivo by routes similar to those for lipids.

The above described aliphatic propargylamines do not possess an amphetamine-like residue as does deprenyl, and they therefore should not produce amphetaminergic side effects. Because they are highly selective MAO-B inhibitors, they should also not cause a hypertensive reaction following ingestion of *p*-tyramine (i.e. the "cheese effect").

Conclusion. Several aliphatic propargylamine derivatives have been synthesized and shown to be highly potent, selective, irreversible MAO-B inhibitors. These inhibitors are apparently nontoxic, and do not possess an amphetamine moiety within their structures. Some of these new inhibitors may be potentially useful in the treatment of neuropsychiatric disorders such as Parkinson's disease, and they may also exhibit neuroprotective effects.

(35) Barber, A. J.; Yu, P. H.; Boulton, A. A. New Selective Irreversible Monoamine Oxidase B Inhibitor: Comparison of Deprenyl and a New Aliphatic Propargylamine. *Proc. Can. College Neuropsychopharmacol.* 1992, 89.

Experimental Section

Preparation of Rat Liver Mitochondrial MAO. Liver mitochondrial fractions were prepared by differential centrifugation as previously described.[2] Mitochondrial membrane fragments were then obtained from the mitochondria by lysing them in chilled distilled water followed by centrifugation at 105000*g* for 30 min. The membrane preparations were further washed, twice, by suspension in water followed by centrifugation. The resultant pellets were homogenized in water by repeated ultrasonic disruption (several of 5-s duration) at 75 W peak envelope power using a needle probe tip (Braunsonic 1510, San Francisco, CA).

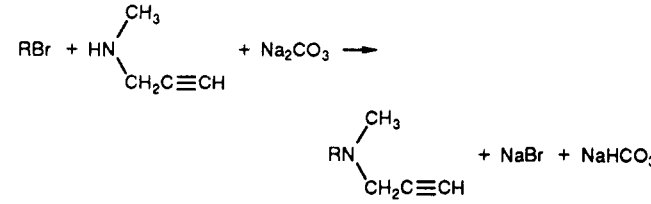
Monoamine Oxidase Assays. A radioenzymatic procedure for monoamine oxidase using ^{14}C-labeled substrates was followed as previously described.[2] The enzyme preparations were incubated at 37 °C for 30 min in the presence of 5-hydroxytryptamine (MAO-A substrate, 5×10^{-4} M, 0.1 μCi) and 2-phenylethylamine (MAO-B substrate, 1.9×10^{-5} M, 0.1 μCi) in a final volume of 200 μL. The reactions were terminated by adding 200 μL of 2 M citric acid. The oxidized products were extracted into 1 mL toluene/ethyl acetate (1:1, v/v), of which 600 μL was then transferred to a counting vial containing 10 mL of Omnifluor cocktail (New England Nuclear, Boston, MA). Radioactivity was assessed by liquid scintillation (Beckman LS-7500).

General Procedure of Synthesis and Characterization of *N*-Alkyl-*N*-methylpropargylamines. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Proton magnetic resonance spectra (Bruker AM300 NMR, 300 MHz) (using deuterium oxide as solvent and reported in parts per million downfield from the internal standard tetramethylsilane) are reported in the following order: propargyl group, *N*-methyl, alkyl chain, and ethyl group protons. Mass spectra (relative intensities quoted in parentheses) were obtained by electron impact mass spectrometry at 70 eV (AEI MS902S instrument equipped with a direct insertion inlet) and are characterized by a small molecular ion (typically less than 10% relative intensity) and a base peak arising by bond cleavage of the alkyl chain α to the nitrogen atom. The NMR and mass spectra were consistent with the expected structures. Elemental analyses (performed at Microanalysis Laboratories Ltd., Markham, Ontario, Canada) for carbon, hydrogen, and nitrogen were obtained for all compounds except 1, which has been previously reported. The analyses were within acceptable limits (±0.4%) except for 13, 16, and 17. Compounds 16 and 17 were viscous oils which proved to be difficult to purify, and the elemental analysis of compound 13 is consistent with a mixture of two oxalate salts, the 1:1 amine-oxalate and 2:1 amine-oxalate. Compounds 16 and 17 exhibited small amounts of proton-containing impurities in the NMR. Despite the impurities in 16 and 17, these compounds were used in the tests for MAO inhibition. Since the concentration range over which these compounds were tested was 10^{-4} M (indicating weak or no inhibition) to 10^{-10} M (strong inhibition), small amounts of impurities will not significantly affect the determination of a compound as a weak or strong inhibitor. Optical rotation measurements of the neat optically active compounds 18 and 19 were assessed using a Perkin-Elmer 141 polarimeter at 20 °C. All compounds except *N*-methylpropargylamine hydrochloride (1) and *N*-(2-heptyl)-*N*-methylpropargylamine hydrochloride (9) are new.

***N*-Methylpropargylamine Hydrochloride (1).** *N*-Methylpropargylamine (Aldrich Chemical Co., Milwaukee, WI) (1.0 g, 14 mmol) in dry ether (75 mL) was treated with a solution of ethanolic hydrochloric acid (prepared by the addition of 3.5 mL of acetyl chloride to 35 mL of ice-cold absolute ethanol) until the precipitation of white solid ceased. The precipitate was filtered and recrystallized from ethanol/ether: mp 105–106 °C. (lit.[36] mp 105–107.5 °C); yield 85%; NMR δ 3.93 (d, 2 H, propargyl, J = 2.57), 2.99 (t, 1 H, propargyl, J = 2.57), 2.79 (s, 3 H, *N*-methyl).

***N*-Methyl-*N*-(2-propyl)propargylamine Hydrochloride (2).** 2-Bromopropane (3.08 g, 25 mmol) and *N*-methylpropargylamine (3.45 g, 50 mmol) in absolute ethanol (50 mL) were heated at reflux for 48 h. The free base was isolated in ether as described for 3. On treatment of the dried ether solution of the free base with ethanolic hydrochloric acid, at first an oil separated and then white needles subsequently precipitated very slowly from the supernatant that were recrystallized from methanol/ether: mp 155–6 °C; yield 16%. The oil and the needles gave identical mass spectra: NMR δ 4.03 (dd, 2 H, propargyl, J = 2.49, 3.49), 3.09 (t, 1 H, propargyl, J = 2.57), 2.88 (s, 3 H, *N*-methyl), 3.79 (septet, 1 H, C-2, J = 6.67), 1.33, 1.36 (dd, 6 H, C-1 and C-3, J = 10.83); MS M^+ = *m/e* 111 (10%), M − CH_3 = 96 (100%). Anal. ($C_7H_{14}ClN$) C, H, N.

Scheme I. Synthesis of *N*-Alkyl-*N*-methylpropargylamine Analogues



***N*-(2-Butyl)-*N*-methylpropargylamine Hydrochloride and Oxalate (3).** A solution of 2-bromobutane (6.86 g, 50 mmol) in absolute ethanol (5 mL) was added to a gently refluxing solution of *N*-methylpropargylamine (3.46 g, 50 mmol) in absolute ethanol (45 mL) containing powdered anhydrous sodium carbonate (5.3 g, 50 mmol). After stirring under gentle reflux for 72 h, the mixture was allowed to cool and was then filtered and 45 mL of ethanol distilled off. The residue was diluted with 75 mL of ethyl ether and washed with 2 × 20 mL water. The ethereal solution was dried over anhydrous magnesium sulfate and filtered. The filtrate was then diluted to 150 mL with ether and treated with ethanolic hydrochloric acid (prepared by the addition of 50 mmol of acetyl chloride to 10 mL of ice-cold absolute ethanol). The initial, rapid precipitation was an oil which very slowly crystallized; white needles subsequently very slowly precipitated from the supernatant: mp 150–1 °C; yield 35%; NMR (see stereoisomers 18 and 19); MS M^+ = 125 (4%), M − CH_3 = *m/e* 110 (15%), [M − (CH_2CH_3)] = 96 (100%). Anal. ($C_8H_{16}ClN$) C, H, N. The oxalate salt was readily formed by the addition of the ethereal solution of the free base (prepared as described above) to a stirred solution of oxalic acid (4.5 g, 50 mmol) in anhydrous ether (500 mL): mp 123–4 °C. Similar yields of the title compound were obtained when an extra 50 mmol of *N*-methylpropargylamine was used as base instead of anhydrous sodium carbonate.

***N*-(1-Butyl)-*N*-methylpropargylamine Hydrochloride (4).** A mixture of 1-bromobutane (6.86 g, 50 mmol), *N*-methylpropargylamine (3.46 g, 50 mmol) and anhydrous sodium carbonate (5.3 g, 50 mmol) was heated for 72 h in absolute ethanol and then isolated as for 3 to give the title compound after recrystallization of the HCl salt from methanol/ether: mp 114–5 °C; yield 52%. The same compound in approximately the same yield was obtained when 1-bromobutane (50 mmol) and *N*-methylpropargylamine (100 mmol) were gently refluxed for 72 h in absolute ethanol: NMR δ 4.07 (d, 2 H, propargyl, J = 2.36), 3.09 (t, 1 H, propargyl, J = 2.54), 2.98 (s, 3 H, *N*-methyl), 3.25 (m, 2 H, C-1), 0.96 (t, 3 H, C-4, J = 7.33), 1.71 (quintet, 2 H, C-2, J = 7.95), 1.38 (sextet, 2 H, C-3, J = 7.46); MS M^+ = *m/e* 125 (4%), M − CH_3 = 110 (8%), [M − ($CH_3CH_2CH_2$)] = 82 (100%). Anal. ($C_8H_{15}ClN$) C, H, N.

***N*-(2-Pentyl)-*N*-methylpropargylamine Hydrochloride and Oxalate (5).** 2-Bromopentane (12.1 g, 80 mmol) and *N*-methylpropargylamine (11.1 g, 160 mmol) were heated at reflux for 48 h in absolute ethanol (50 mL), and the product was isolated as for 3. The hydrochloride salt precipitated from ether as an oil which did not crystallize, but was successfully crystallized from acetone/pentane: mp 94–5 °C; yield 63%. The oxalate salt, from free base prepared as above, was recrystallized from methanol/ether: mp 89–90 °C; yield 50%; NMR δ 4.05 (d, 2 H, propargyl, J = 2.44), 3.08 (t, 1 H, propargyl, J = 2.53), 2.90 (s, 3 H, *N*-methyl), 3.64 (m, 1 H, C-2), 1.32 (d, 3 H, C-1, J = 6.65), 1.65 (m, 2 H, C-3), 1.38 (m, 2 H, C-4), 0.96 (t, 3 H, C-5, J = 7.29); MS M^+ = *m/e* 139 (4%), M − CH_3 = 124 (22%), [M − ($CH_2CH_2CH_3$)] = 96 (100%). Anal. ($C_9H_{18}NCl$) C, H, N.

(36) Peters, L. R.; Hennion, G. F. Synthesis of Nortriptyline and Related Compounds. *J. Med. Chem.* **1964**, *7*, 390–392.

N-(1-Pentyl)-N-methylpropargylamine Oxalate (6). 1-Bromopentane (12.1 g, 80 mmol) and N-methylpropargylamine (11.1 g, 160 mmol) were refluxed in absolute ethanol (75 mL) for 72 h and then worked up as above to give (after addition to 80 mmol of oxalic acid in ether) the title compound after recrystallization from methanol/ether: mp 101–3 °C; yield 60%; NMR δ 4.05 (t, 2 H, propargyl, J = 2.34), 3.09 (t, 1 H, propargyl, J = 2.53), 2.95 (s, 3 H, N-methyl), 3.30, 3.18 (two mirror image multiplets, 1 H each, C-1), 1.71 (m, 2 H, C-2), 1.35 (m, 4 H, C-3 and C-4), 0.89 (t, 3 H, C-5, J = 7.04); MS M^+ = m/e 139 (3%), [M – C_4H_9] = 82 (100%). Anal. ($C_{11}H_{19}NO_4$) C, H, N.

N-Methyl-N-(3-pentyl)propargylamine Hydrochloride (7). A mixture of 3-bromopentane (7.55 g, 50 mmol), N-methylpropargylamine (3.46 g, 50 mmol) and anhydrous sodium carbonate (5.3 g, 50 mmol) in ethanol (50 mL) was refluxed with stirring for 5 days. After allowing to cool, the mixture was filtered and most of the ethanol was distilled off. The residue was taken up in ether (75 mL) and washed with water (2 × 25 mL). The ether solution was dried over magnesium sulfate and then distilled to give a clear, colorless liquid. The hydrochloride salt was recrystallized from ethanol/ether to give white crystals, mp 119–120 °C; yield 15%; NMR δ 4.03 (dd, 2 H, propargyl, J = 2.26, 7.29), 3.07 (t, 1 H, propargyl, J = 2.52), 2.87 (s, 3 H, N-methyl), 3.35 (quintet, 1 H, C-3, J = 6.19), 1.76 and 1.67 (each a multiplet, 2 H, C-2 and C-4), 1.00 (t, 6 H, C-1 and C-5, J = 6.19); MS M^+ = m/e 139 (4%); [M – (CH_2CH_3)] = 110 (100%). Anal. ($C_{11}H_{19}NO_4$) C, H, N.

N-(2-Hexyl)-N-methylpropargylamine Hydrochloride (8). 2-Bromohexane was prepared from 2-hexanol by reaction with thionyl chloride/thionyl bromide in a manner similar to that described for the preparation of 2-bromobutane from 2-butanol.[37] 2-Bromohexane (16.5 g, 100 mmol), N-methylpropargylamine (6.92 g, 100 mmol) and anhydrous sodium carbonate (10.6 g, 100 mmol) were refluxed in absolute ethanol (125 mL) for 7 days. The cool reaction mixture was filtered and most of the ethanol distilled. The residue was taken up in ether (150 mL) and washed with water (2 × 50 mL). After drying the ether solution over magnesium sulfate, sufficient ethanolic hydrochloric acid was added to convert all the product to its hydrochloride salt (which did not precipitate). Rotary evaporation of the resulting solution gave 12 g (63%) of a dark brown, very viscous liquid which was decolorized by boiling with activated charcoal in acetone. The pale brown acetone filtrate (200 mL) was treated with hexane until the solution became cloudy (200 mL required). A viscous oil precipitated. The supernatant was decanted and hexane (50 mL) added to give again a cloudy solution. Again a viscous oil precipitated. This process was repeated several times until the supernatant no longer became cloudy on the addition of more hexane. The first two or three viscous oil precipitates crystallilzed with difficulty, the next few crystallized on air drying and standing, while the later precipitations were white crystals: mp 98–99 °C; yield 50%; NMR δ 4.03 (d, 2 H, propargyl, J = 2.38), 3.07 (t, 1 H, propargyl, J = 2.52), 2.87 (s, 3 H, N-methyl), 1.33 (d, 3 H, C-1, J = 6.67), 3.64 (m, 1 H, C-2), 1.60 and 1.72 (two multiplets, 1 H each, C-3), 1.35 (m, 4 H, C-4 and C-5), 0.90 (t, 3 H, C-6, J = 6.88); MS M^+ = m/e 153 (2%), [M – CH_3] = 138 (10%), [M – C_4H_9] = 96 (100%). Anal. ($C_{10}H_{20}ClN$) C, H, N.

N-(2-Heptyl)-N-methylpropargylamine Hydrochloride (9). 2-Bromoheptane (7.16 g, 40 mmol) and N-methylpropargylamine (5.52, 80 mmol) were gently refluxed for 48 h in absolute ethanol (50 mL). The reaction mixture was processed as for 3 followed by recrystallization of the HCl salt from acetone/hexane): mp 115–6 °C (lit.[38] mp 126–8 °C); yield 66%; NMR δ 4.04 (d, 2 H, propargyl, J = 2.56), 3.08 (t, 1 H, propargyl, J = 2.44), 2.87 (s, 3 H, N-methyl), 1.33 (d, 3 H, C-1, J = 6.57), 3.63 (m, 1 H, C-2), 1.60 and 1.70 (two multiplets, 1 H each, C-3), 1.36 (m, 6 H, C-4, C-5, C-6), 0.89 (t, 3 H, C-7, J = 6.57); MS M^+ = m/e 167 (5%), M – CH_3 (23%), [M – (C_5H_{11})] = 96 (100%). Anal. ($C_{11}H_{22}ClN$) C, H, N.

N-(1-Heptyl)-N-methylpropargylamine Hydrochloride (10). 1-Bromoheptane (3.58 g, 20 mmol) and N-methylpropargylamine (2.76 g, 40 mmol) were refluxed in absolute ethanol for 48 h. The product was isolated as for 9. The hydrochloride salt separated immediately on treatment with ethanolic HCl as medium-brown crystals and as white crystals after recrystallization from methanol/ether: mp 124–5 °C; yield 84%; NMR δ 4.05 (t, 2 H, propargyl, J = 2.24), 3.10 (t, 1 H, propargyl, J = 2.51), 2.98 (s, 3 H, N-methyl), 3.31 and 3.19 (two mirror image multiplets, 1 H each, C-1), 1.75 (m, 2 H, C-2), 1.37 and 1.31 (dd, 8 H, C-3, C-4, C-5, C-6, J = 3.93, 12.67), 0.89 (t, 3 H, C-7, J = 6.79); MS M^+ = m/e 167 (18%), M – [C≡CH] = 142 (15%), [M – (C_6H_{13})] = 82 (100%). Anal. ($C_{11}H_{22}ClN$) C, H, N.

N-(2-Decyl)-N-methylpropargylamine Hydrochloride (11). 2-Bromodecane (8.84 g, 40 mmol) and N-methylpropargylamine (5.52 g, 80 mmol) were heated in absolute ethanol (50 mL) for 72 h to give, after treatment of the isolated free base with 40 mmol of ethanolic hydrochloric acid and recrystallization from methanol/ether, the salt of the title compound as pale brown crystals: mp 130–1 °C; yield 55%; NMR δ 4.01 (d, 2 H, propargyl, J = 2.30), 3.07 (t, 1 H, propargyl, J = 2.37), 2.86 (s, 3 H, N-methyl), 1.29 (d, 3 H, C-1, J = 6.67), 3.62 (m, 1 H, C-2), 1.59 and 1.72 (two multiplets, 1 H each, C-3), 1.31 (m, 12 H, C-4 to C-9), 0.85 (t, 3 H, C-10, J = 6.77); MS M^+ = m/e 209 (1%), M – CH_3 = 194 (33%), [M – (C_8H_{17})] = 96 (100%). Anal. ($C_{14}H_{28}ClN$) C, H, N.

N-(2-Dodecyl)-N-methylpropargylamine Hydrochloride (12). 2-Bromododecane (5.3 g, 21 mmol) and N-methylpropargylamine (3.45 g, 50 mmol) were heated at reflux in absolute ethanol (50 mL) for 48 h. After treatment of the isolated product as the free base with ethanolic hydrochloric acid, the title compound was obtained after recrystallization from acetone/pentane: mp 128–130 °C; yield 30%; NMR δ 4.05 (d, 2 H, propargyl, J = 1.98), 3.11 (t, 1 H, propargyl, J = 2.36), 2.86 (s, 3 H, N-methyl), 1.30 (m, 19 H, C-1 and C-4 to C-11), 3.61 (m, 1 H, C-2), 1.56 and 1.78 (two multiplets, 1 H each, C-3), 0.89 (t, 3 H, C-12, J = 6.75); MS M^+ = m/e 237 (0.5%), M – CH_3 = 222 (10%), [M – ($C_{10}H_{21}$)] = 96 (100%). Anal. ($C_{16}H_{32}ClN$) C, H, N.

N-(3-Carboxy-1-propyl)-N-methylpropargylamine Oxalate (13). A mixture of ethyl 4-bromobutyrate (19.5 g, 100 mmol), N-methylpropargylamine (6.92 g, 100 mmol), and anhydrous sodium carbonate (10.6 g, 100 mmol) was refluxed with stirring in 115 mL of absolute ethanol for 7 days. After allowing to cool, the mixture was filtered and the filtrate was rotary evaporated to dryness. The residue was taken up in ether (150 mL), washed with water (3 × 50 mL), and dried over magnesium sulfate, and the solvent was removed by rotary evaporation to give 14.2 g (78%) of a viscous liquid which was used without further purification. The viscous ester was hydrolyzed with a solution of potassium hydroxide (7.0 g) in tert-butyl alcohol (125 mL) at 20 °C for 20 h. The solution was evaporated to dryness, and the residue was taken up in water (100 mL), then neutralized to pH 6.5–7.0 with hydrochloric acid, and rotary evaporated to dryness again. The semisolid residue was allowed to dry further by leaving uncovered for 48 h and then was triturated in ice-cold methanol and filtered immediately from the nearly insoluble potassium chloride. The filtrate was rotary evaporated at 30 °C to give 12.8 g of a brownish viscous liquid (83%), the mass spectrum of which revealed it to be the title compound as the free base. The oxalate salt was prepared by dissolving the product (3.64 g, 23 mmol) in methanol (15 mL), adding it to a solution of oxalic acid in methanol (25 mL), and then diluting with 300 mL of ether. The oxalate was a viscous liquid which crystallized with difficulty and then recrystallized from methanol/ethyl acetate to give white plates: mp 73–5 °C; yield 50%; NMR δ 4.07 (dd, 2 H, propargyl, J = 2.30), 3.10 (t, 1 H, propargyl, J = 2.54), 2.99 (s, 3 H, N-methyl), 3.25 and 3.34 (two mirror image multiplets, 1 H each, C-1), 2.00 (m, 2 H, C-2), 2.50 (t, 2 H, C-3, J = 7.13); MS M^+ = m/e 155 (2%); [M – (C≡CH)] = 130 (3%); [M – ($HOOCCH_2CH_2$)] = 82 (100%). Anal. $C_{18}H_{28}N_2O_8$ (2:1 salt) or $C_{10}H_{15}NO_6$ (1:1 salt) C, H, N. Calcd (1:1 salt): C, 54.00, H 7.05, N 7.00; calcd (2:1 salt): C = 48.98, H 6.17, N 5.71; found: C 51.12, H 7.25, N 6.94.

N-(5-Carbethoxy-2-pentyl)-N-methylpropargylamine Hydrochloride (14). Ethyl 4-acetylbutyrate was prepared by esterification of 4-acetylbutyric acid. Selective reduction of the ketone to the secondary alcohol was achieved by the dropwise addition of a solution of sodium borohydride (4.94 g, 130 mmol)

(37) Frazer, M. J.; Gerrard, W.; Machell, G.; Shepherd, B. D. Formation of Alkyl Bromides by Thionyl Bromide. *Chem. Ind.* **1954**, 931–932.

(38) Boissier, J. R.; Ratouis, R. Nouvelles N-Propynyl Alcoylamines et leurs Sels et Procede de Preparation. French Pat. No. 1,453,844, 1966.

in dilute sodium hydroxide (prepared by diluting 7 mL of 10% sodium hydroxide with 63 mL water) to an ice-cold, stirred solution of the above ester (53.65 g, 340 mmol) in methanol (350 mL). After stirring at 20 °C for 16 h, most of the methanol was removed by rotary evaporation at 40 °C. The cold residue was diluted with cold water (350 mL) and then extracted immediately with ether (3 × 150 mL). After drying over anhydrous magnesium sulfate, the ether was evaporated to give the reduced product, a hydroxy ester, as a pale yellow liquid in 60% yield. Treatment of a chloroform solution (500 mL) of the hydroxy ester (31.8 g, 200 mmol) with bromotrimethylsilane (61.2 g, 400 mmol) at 50 °C for 27 h (procedure adapted from Jung and Hatfield[39]), followed by washing of the cold reaction mixture with 5% sodium bicarbonate (2 × 150 mL), drying over anhydrous sodium sulfate and rotary evaporation of the solvent at 35 °C gave ethyl 5-bromohexanoate.

A solution of ethyl 5-bromohexanoate (38.8 g, 188 mmol), *N*-methylpropargylamine (13.0 g, 188 mmol) and anhydrous sodium carbonate (20 g, 190 mmol) in 250 mL absolute ethanol was stirred under reflux for 6 days. The cooled reaction mixture was filtered with suction and then rotary evaporated to dryness at 45 °C. The residue was taken up in ether (150 mL) and washed with water (3 × 50 mL). The ether layer was dried over magnesium sulfate, filtered, and rotary evaporated to give 9.6 g of a brownish viscous oil. The hydrochloride salt was prepared by the addition of ethanolic hydrochloric acid to an ethereal solution of the free base: mp 113 °C; yield 45%; NMR δ 4.02 (s, 2 H, propargyl), 3.09 (t, 1 H, propargyl, J = 2.54), 2.88 (s, 3 H, *N*-methyl), 1.35 (d, 3 H, C-1, J = 4.82), 3.65 (m, 1 H, C-2), 1.64 (m, 2 H, C-3), 1.73 (m, 2 H, C-4), 2.45 (t, 2 H, C-5, J = 5.69), 4.17 (quartet, 2 H, ethyl CH_2, J = 7.17), 1.27 (t, 3 H, ethyl CH_3, J = 7.17); MS M^+ = m/e 211 (0.5%), M − CH_3 = 196 (15%), [M − (OCH_2CH_3)] = 166 (30%), [M − ($CH_2CH_2CH_2COOCH_2CH_3$)] = 96 (100%). Anal. ($C_{12}H_{22}ClNO_2$) C, H, N.

***N*-(5-Carbethoxy-1-pentyl)-*N*-methylpropargylamine Oxalate (15).** A mixture of ethyl 6-bromohexanoate (25.2 g, 112 mmol), *N*-methylpropargylamine (7.74 g, 112 mmol), and anhydrous sodium carbonate (11.9 g, 112 mmol) was refluxed with stirring in absolute ethanol (115 mL) for 7 days. After filtration and rotary evaporation, the residue was taken up in ether (150 mL) and washed with water (3 × 50 mL). The ether solution was dried over magnesium sulfate, filtered, and rotary evaporated to give 16.8 g of a brownish viscous oil. The oxalate salt was prepared as a white crystalline solid by the addition of an ethereal solution of the title compound to an ether solution of oxalic acid: mp 74–7 °C; yield 71%; NMR δ 4.05 (t, 2 H, propargyl, J = 2.20), 3.09 (t, 1 H, propargyl, J = 2.52), 2.95 (s, 3 H, *N*-methyl), 3.18 and 3.30 (two mirror image multiplets, 1 H each, C-1), 1.38 (m, 2 H, C-2), 1.63 (m, 2 H, C-3), 1.73 (m, 2 H, C-4), 2.40 (t, 2 H, C-5, J = 7.34), 4.15 (quartet, 2 H, ethyl CH_2, J = 7.14), 1.23 (t, 3 H, ethyl CH_3, J = 7.17); MS M^+ = m/e 211 (0.5%), [M − (OCH_2CH_3)] = 166 (35%), [M − ($COOCH_2CH_3$)] = 138 (8%), [M − ($CH_2COOCH_2CH_3$)] = 124 (6%), [M − ($CH_2CH_2COOCH_2CH_3$)] = 110 (6%), [M − ($CH_2CH_2CH_2COOCH_2CH_3$)] = 96 (8%); [M − ($CH_2CH_2CH_2CH_2COOCH_2CH_3$)] = 82 (100%). Anal. ($C_{14}H_{23}NO_6$) C, H, N.

***N*-(6-Hydroxy-1-hexyl)-*N*-methylpropargylamine Hydrochloride (16).** *N*-(5-Carbethoxy-1-pentyl)-*N*-methylpropargylamine (free base of **15** 10.6 g, 50 mmol) was dissolved in *tert*-butyl alcohol (200 mL), and powdered sodium borohydride (4.75 g, 125 mmol) was added. The solution was stirred, brought to a gentle reflux, and treated very slowly (over 45 min) with methanol (40 mL, 1 mol). After stirring for another hour under reflux, the solution was allowed to cool and then the reaction was quenched with water (90 mL). Most of the methanol and *tert*-butyl alcohol were removed by rotary evaporation leaving an aqueous residue which was extracted with chloroform (75 mL). After drying over anhydrous sodium sulfate, the chloroform solution was rotary evaporated to give 7.6 g (90%) of crude title compound (selective reduction procedure adapted from Soai et al.[40]). The hydrochloride salt separated as a yellow-brown viscous oil, the attempted crystallization of which was unsuccessful: yield 60%; NMR δ 4.05 (d, 2 H, propargyl), 3.09 (t, 1 H, propargyl), 2.97 (s, 3 H, *N*-methyl), 3.20 and 3.32 (two mirror image multiplets, 1 H each, C-1), 1.39 (m, 2 H, C-2), 1.70 (m, 6 H, C-3, C-4, C-5), 2.41 (dt, 2 H, C-6, J = 2.41, 4.73). Impurities with total integration equivalent to two protons were observed; as a result, the elemental analysis was not within ±0.4%. The mass spectrum exhibited no molecular ion, but a mass of m/e 82 (due to cleavage α to the nitrogen atom) was the base peak. No masses due to starting material or to reduction of the propargyl group were present. The NMR and MS are consistent with the structure of the title compound.

***N*-(6-Hydroxy-2-hexyl)-*N*-methylpropargylamine Hydrochloride (17).** Ethyl 5-bromohexanoate (preparation described for synthesis of **14**) (42.8 g, 192 mmol) was selectively reduced by lithium aluminum hydride (7.3 g, 192 mmol)/aluminum chloride (25.5 g, 192 mmol) in ether (500 mL) at −30 °C (procedure adapted from Nystrom, 1959[41]). 5-Bromohexan-1-ol was isolated in 55% yield from the reaction mixture following decomposition of the lithium and aluminum complexes by the consecutive addition of water (7.3 mL), 10% sodium hydroxide (7.3 mL), and water (22 mL). The product (9.7 g, 53.6 mmol) was stirred under reflux with *N*-methylpropargylamine (3.7 g, 53.6 mmol) and sodium carbonate (5.68 g, 53.6 mmol) in absolute ethanol (50 mL) for 15 days. The crude product was isolated by filtration followed by rotary evaporation of the solvent. The hydrochloride salt was obtained as a pale brown viscous liquid which darkened on standing. Decolorization and attempted crystallization from acetone or ethanol and ether were not successful: overall yield 5%; NMR δ 3.90 (m, 2 H, propargyl), 2.95 (t, 1 H, propargyl), 2.73 (s, 3 H, *N*-methyl), 3.50 (m, 1 H, C-2), 1.1–1.7 (m, 9 H, C-1, C-3, C-4, C-5), 2.69 (2 H, C-6); MS M^+ = m/e 169 (5%), M − CH_3 = 154 (10%), [M − ($HOCH_2CH_2CH_2CH_2$)] = 96 (100%). Impurities with total integration of about two protons were observed in the NMR spectrum. The elemental analysis was not within acceptable limits.

***(R)*-(−)-*N*-(2-Butyl)-*N*-methylpropargylamine Hydrochloride and Oxalate (18).** A solution of (*R*)-(−)-*sec*-butylamine (Aldrich Chemical Co., 4.86 g, 67 mmol, $[\alpha]^{19}_D$ −7.5° neat) in dichloromethane (150 mL) containing triethylamine (8.4 g, 83 mmol) and 4-(dimethylamino)pyridine (860 mg, 7 mmol) was cooled in an ice–water bath and treated with methyl chloroformate (7.05 g, 75 mmol). After stirring for 2 h, the solution was diluted with an equal volume of dichloromethane and washed successively with water (80 mL), 0.1 N hydrochloric acid (2 × 80 mL), and water (80 mL). After drying over anhydrous magnesium sulfate, the solution was rotary evaporated to dryness to give the carbamate in 100% yield. This was reduced by adding an ethereal solution of it to a stirred suspension of lithium aluminum hydride (3.6 g, 95 mmol) in ether (185 mL). The mixture was stirred at 30 °C for 3 h, then treated successively with water (3.6 mL), 10% sodium hydroxide (3.6 mL), and water (10 mL) and stirred for another hour. Following filtration of the lithium and aluminum salts, the filtrate was dried over anhydrous magnesium sulfate and filtered again. To the dried filtrate were added sodium carbonate (7.2 g, 68 mmol) and propargyl bromide (8.1 g, 68 mmol). The mixture was stirred under reflux for 48 h, allowed to cool, and filtered. The filtrate was washed with water (2 × 75 mL), dried, and filtered, and the solvent was evaporated at 25 °C. The product was distilled at atmospheric pressure to give a clear colorless liquid, bp 138–142 °C. The oxalate salt was recrystallized from methanol/ether to give white crystals, mp 112–4 °C; the hydrochloride salt was obtained as white needles, mp 149–151 °C. The optical rotation of the free base (neat) was −20.4°. NMR δ 4.04 (d, 2 H, propargyl, J = 2.52), 3.06 (t, 1 H, propargyl, J = 2.55), 2.87 (s, 3 H, *N*-methyl), 1.31 (d, 3 H, C-1, J = 6.68), 3.53 (m, 1 H, C-2), 1.61 and 1.79 (two mirror image multiplets, 1 H each, C-3), 0.98 (t, 3 H, C-4, J = 7.42); MS M^+ = m/e 125 (10%);

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M – CH_3 = 110 (20%); [M – (CH_2CH_3)] = 96 (100%). Anal. (oxalate) ($C_{10}H_{17}NO_4$) C, H, N.

(*S*)-(+)-*N*-(2-Butyl)-*N*-methylpropargylamine Hydrochloride and Oxalate (19). The procedure follows exactly that of the *R*-enantiomer, starting with (*S*)-(+)-*sec*-butylamine (Aldrich Chemical Co., 4.75 g, 65 mmol, $[\alpha]^{19}_D$ +7.5° neat). The product was obtained as the oxalate salt and recrystallized from methanol/ether: mp 118–120 °C and as the hydrochloride salt, mp 152–3 °C. The optical rotation of the free base (neat) was +20.1°. NMR δ 4.03 (d, 2 H, propargyl, J = 2.48), 3.07 (t, 1 H, propargyl, J = 2.54), 2.86 (s, 3 H, *N*-methyl), 1.32 (d, 3 H, C-1, J = 6.75), 3.53 (m, 1 H, C-2), 1.60 and 1.78 (two mirror image multiplets, 1 H each, C-3), 0.98 (t, 3 H, C-4, J = 7.41); MS M^+ = m/e 125 (6%); M – CH_3 = 110 (11%); [M – (CH_2CH_3)] = 96 (100%). Anal. (oxalate) ($C_{10}H_{17}NO_4$) C, H, N.

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