

## Selective Monoamine Oxidase Inhibitors.<sup>†</sup> 3. Cyclic Compounds Related to 4-Aminophenethylamine. Preparation and Neuron-Selective Action of Some 5-(2-Aminoethyl)-2,3-dihydroindoles

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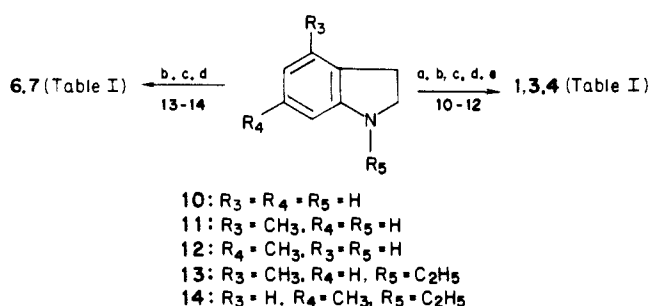
Nine 5-(2-aminoethyl)-2,3-dihydroindole derivatives were synthesized and tested as monoamine oxidase (MAO) inhibitors in vitro and in vivo. All compounds were found to be selective MAO-A inhibitors in vitro, the most active ones, 5-[1-(2-aminopropyl)]-2,3-dihydro-4-methylindole acetate (3), 5-[1-(2-aminopropyl)]-4-chloro-2,3-dihydroindole acetate (5), 5-[1-(2-aminopropyl)]-2,3-dihydro-1-ethyl-4-methylindole tartrate (6), 5-[1-(2-aminopropyl)]-2,3-dihydro-1-ethyl-6-methylindole tartrate (7), and 5-[1-(2-aminobutyl)]-4-chloro-2,3-dihydroindole acetate (9) being equipotent with amiflamine, (S)-(+)-4-(dimethylamino)-2,α-dimethylphenethylamine. Some of the compounds, 3, 6, 5-[1-(2-aminopropyl)]-2,3-dihydroindole acetate (1), and 5-[1-(2-amino-2-methylpropyl)]-2,3-dihydroindole acetate (8), were found to be very potent inhibitors of MAO in serotonergic and/or noradrenergic nerve terminals in the rat brain in vivo, inhibiting MAO within these neurons at doses <sup>1</sup>/<sub>10</sub> of those required to inhibit MAO in other neurons or cells. Compound 1 was also a potent and selective inhibitor of MAO within dopaminergic nerve terminals in vivo. This neuron selectivity is due to the uptake of these compounds by the neuronal uptake mechanisms.

The discovery of the A and B forms of monoamine oxidase (MAO) (EC 1.4.3.4.)<sup>1</sup> initiated the search for selective inhibitors of the A form of this enzyme as potential antidepressant drugs.<sup>2</sup> The transmitter amines serotonin and norepinephrine are selective substrates for MAO-A,<sup>1,3</sup> whereas some other amines, e.g. tyramine, are metabolized by both enzyme forms. Since tyramine ingested in food can cause hypertensive crises in patients treated with nonselective MAO inhibitors, it was thought that selective MAO-A inhibitors might be less harmful, since tyramine can be metabolized by MAO-B left intact. MAO-A is the predominant form in the monoaminergic neurons<sup>4,5</sup> and therefore important for the regulation of the concentrations of the transmitter amines therein. As the result of this research a number of selective and reversible MAO-A inhibitors have been developed.<sup>2</sup> It is hoped that these new MAO inhibitors will have less severe side effects than the original nonselective and irreversible MAO inhibitors.

A further advantage would be to produce selective inhibitors that inhibit intra- but not extraneuronal MAO-A. Recently it was found that amiflamine, (S)-(+)-4-(dimethylamino)-2,α-dimethylphenethylamine (FLA 336(+)), a selective and reversible inhibitor of the A form of MAO,<sup>6</sup> inhibits MAO in serotonergic and noradrenergic neurons at lower doses than required to inhibit MAO-A in other cells in the rat brain.<sup>7,8</sup> The preference of amiflamine for aminergic MAO appears to be due to accumulation of amiflamine and/or its metabolite desmethylamiflamine (FLA 788(+)) into these neurons by the membranous amine uptake mechanisms, since the preference was antagonized by the selective serotonin and norepinephrine uptake inhibitors norzimeldine and desipramine, respectively. The didesmethyl derivative of amiflamine (FLA 668(+)) was found to be a very selective inhibitor of MAO in noradrenergic neurons in the rat hypothalamus.

Since the various amine uptake mechanisms have different structural requirements for transport, it should be possible to develop selective MAO inhibitors for each aminergic neuron system.<sup>8,9</sup> In our search for neuron-selective MAO inhibitors some bicyclic analogues of amiflamine were synthesized. Since amiflamine is extensively metabolized in man by N-demethylation of the aromatic

Scheme I<sup>c</sup>



<sup>a</sup> Reagents: a = C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>Cl; b = POCl<sub>3</sub>/DMF; c = C<sub>2</sub>H<sub>5</sub>NO<sub>2</sub>; d = LiAlH<sub>4</sub>; e = H<sub>2</sub>/Pd, H<sup>+</sup>.

amine, with great interindividual variation,<sup>10</sup> this metabolism was blocked by incorporating the aromatic amine into an indoline ring system. The new compounds were tested for their MAO inhibitory effect in vitro and their potential neuron-selective action in vivo. The compounds were also examined for their ability to inhibit the synaptosomal uptake of serotonin, norepinephrine, and dopamine in vitro and to induce behavioral changes in reserpinized rats. The results of these tests are reported here.

### Chemistry

The target compounds prepared for this study are listed in Tables I and II and their synthesis outlined in Schemes I and II.

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<sup>†</sup> Part 2: reference 13.

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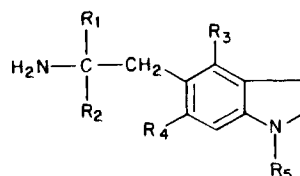
<sup>‡</sup> Department of Biochemical Neuropharmacology.

**Table I.** 5-(2-Aminoethyl)-2,3-dihydroindoles

no.	mp, <sup>a</sup> °C	yield, %	formula	anal.	no.	mp, <sup>a</sup> °C	yield, %	formula	anal.
1	139–140	86	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> ·CH <sub>3</sub> COOH	C, H, N, O	6	170–171	65	C <sub>14</sub> H <sub>22</sub> N <sub>2</sub> ·C <sub>4</sub> H <sub>6</sub> O <sub>6</sub>	C, H, N
2	113–115	28	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> ·CH <sub>3</sub> COOH	C, H, N, O	7 <sup>c</sup>	173–175	51	C <sub>14</sub> H <sub>22</sub> N <sub>2</sub> ·C <sub>4</sub> H <sub>6</sub> O <sub>6</sub>	C, H, N
3	175–176	65	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> ·CH <sub>3</sub> COOH	C, H, N	8	167–168	20	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> ·CH <sub>3</sub> COOH	C, H, N, O
4 <sup>b</sup>	249–251	70	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> ·2HCl	C, H, N, Cl	9 <sup>d</sup>	125–126	14	C <sub>12</sub> H <sub>17</sub> ClN <sub>2</sub> ·CH <sub>3</sub> COOH	C, H, Cl, N, O
5	183–185	81	C <sub>11</sub> H <sub>16</sub> ClN <sub>2</sub> ·CH <sub>3</sub> COOH	C, H, Cl, N, O					

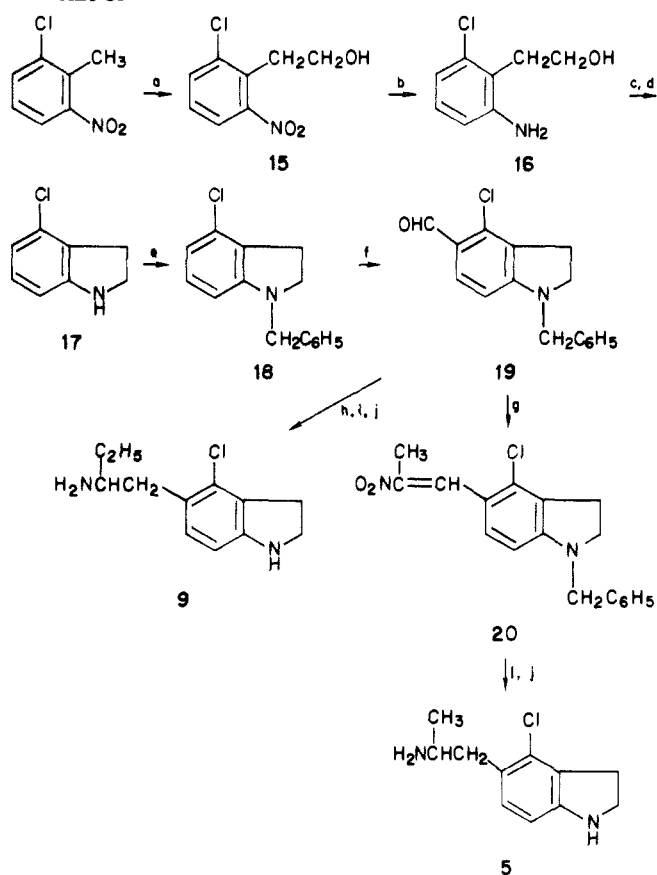
<sup>a</sup> Compounds 3–7 are recrystallized from ethanol, 8 from ethanol-isopropyl ether, and 9 from acetonitrile-isopropyl ether. Compound 1 was purified by trituration with acetone; compound 2 was crystallized from acetonitrile-ether. <sup>b</sup> N: calcd, 10.65; found, 9.90. <sup>c</sup> C: calcd, 58.68; found, 57.5. <sup>d</sup> Cl: calcd, 12.45; found, 13.2.

**Table II.** Inhibition of MAO in Vitro and in Vivo and the Amide Uptake in Vitro by Compounds 1–9



no.	R <sub>1</sub> R <sub>2</sub> R <sub>3</sub> R <sub>4</sub> R <sub>5</sub>					MAO inhibition <sup>b</sup>														
	in vitro IC <sub>50</sub> , μM <sup>a</sup>			in vivo ED <sub>50</sub> , μmol/kg po						inhib of amine uptake <sup>c</sup> IC <sub>50</sub> , μM										
	5-HT	PEA	PEA/5-HT	5-HT		NE		DA		5-HT	NE	DA								
1	CH <sub>3</sub>	H	H	H	H	5.0	>100	>20	1.8*	>28	>15	1.1*	>>34 (12%)	>31	0.8*	20	25	1.8	0.36	3.8
2	C <sub>2</sub> H <sub>5</sub>	H	H	H	H	14	800	57	11*	>65 (29%)	>6	32*	>65 (22%)	>2	26*	74	9.8	3.6	0.50	10
3	CH <sub>3</sub>	H	CH <sub>3</sub>	H	H	0.8	>500	>625	0.8*	14	>17	1.1*	29	26	4.6*	13	2.8	0.38	0.75	9.0
4	CH <sub>3</sub>	H	H	CH <sub>3</sub>	H	13	170	13	>>61 (0%)	>>61 (11%)	49*	>>61 (0%)	>>1	>61 (41%)	>>61 (16%)	–	–	>16	6.0	6.0
5	CH <sub>3</sub>	H	Cl	H	H	0.2	800	4000	1.5*	6.5	4.3	1.6*	9.2	5.8	2.2*	4.1	1.9	0.34	0.32	>10
6	CH <sub>3</sub>	H	CH <sub>3</sub>	H	C <sub>2</sub> H <sub>5</sub>	1.1	>500	>455	13*	>>22 (7%)	>2	9*	>87 (40%)	>10	10	16	1.6	1.5	7.5	>10
7	CH <sub>3</sub>	H	H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	0.33	77	233	>>27 (2%)	>27 (26%)	17*	>>44 (0%)	>3	12	17	1.4	2.2	2.5	>10	
8	CH <sub>3</sub>	CH <sub>3</sub>	H	H	H	2.8	2600	929	4.4*	>64 (21%)	>15	12*	>64 (19%)	>5	8*	36	4.5	1.9	2.7	>10
9	C <sub>2</sub> H <sub>5</sub>	H	Cl	H	H	0.63	1.45	230	9.1*	18	2.0	11*	22	2.0	12	28	2.3	0.30	1.6	>10
amifla- mine						0.8	>1000	>1250	1.1*	5.2	4.7	2.0*	8.2	4.1	3.3	4.4	1.1	0.10	0.65	>10

<sup>a</sup> Determined from log concentration-inhibition curves using a rat brain mitochondrial preparation as enzyme and [<sup>14</sup>C]serotonin (5-HT) (50 μM) and [<sup>14</sup>C]phenethylamine (PEA) (2.5 μM) as substrates. <sup>b</sup> Determined from the protection by the test compounds against the irreversible MAO inhibition produced by phenelzine. The rats were sacrificed 48 h after the phenelzine injections, and the MAO activity remaining inside (N) and outside (EN) synaptosomes prepared from hypothalamus [serotonin and norepinephrine (NE)] or striatum [dopamine (DA)] was determined as described in the Experimental Section. The ED<sub>50</sub> values were estimated from log dose-response curves. Percent inhibition at the highest dose tested is given in brackets. Asterisk indicates significant difference N vs. EN at three different doses (*p* < 0.05, Mann-Whitney U-test). <sup>c</sup> The compounds were preincubated with the synaptosomal preparations for 10 min at 37 °C and incubated for further 2 min with [<sup>14</sup>C]-5-HT + [<sup>3</sup>H]-NE (cerebral cortex) or [<sup>14</sup>C]-DA (striatum), each at 50 nM.

Scheme II<sup>a</sup>

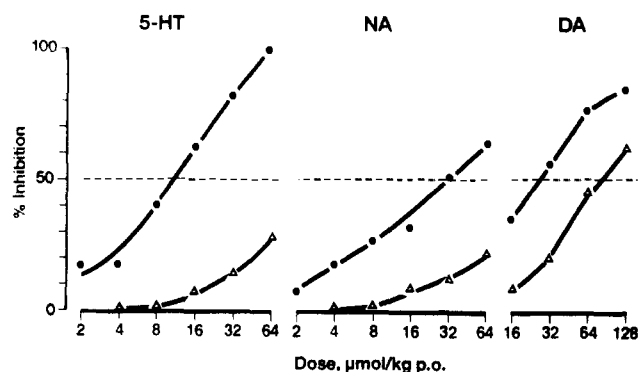
<sup>a</sup> Reagents: a =  $(\text{CH}_2\text{O})_n/\text{Me}_2\text{SO}/\text{KOH}$ ; b =  $\text{Na}_2\text{S}/\text{S}$ ; c =  $\text{SOCl}_2$ ; d =  $\text{NaOH}$ ; e =  $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}/\text{K}_2\text{CO}_3/\text{DMF}$ ; f =  $\text{POCl}_3/\text{DMF}$ ; g =  $\text{C}_2\text{H}_5\text{NO}_2$ ; h =  $\text{C}_3\text{H}_7\text{NO}_2$ ; i =  $\text{LiAlH}_4$ ; j =  $\text{H}_2/\text{Pd}, \text{H}^+$ .

The preparation of compounds 6 and 7 started from the corresponding *N*-ethyl-2,3-dihydroindoles,<sup>11</sup> 13 and 14, which were formulated by the Vilsmeier-Haack procedure and condensed with nitroethane, and the  $\beta$ -nitrostyrene obtained was reduced with lithium aluminum hydride. The method has been used in the preparation of various 4-aminophenethylamine derivatives and is described in previous papers.<sup>12,13</sup>

Compounds 1, 3, and 4 were synthesized by a similar method involving *N*-benzylation of the 2,3-dihydroindoles 10–12,<sup>11</sup> formylation, condensation with nitroethane, reduction, and debenylation by catalytic hydrogenation in the presence of palladium. Compounds 2 and 9 were prepared analogously from the condensation products of the corresponding 2,3-dihydroindole-5-carboxaldehydes and nitropropane. The preparation of compounds 1, 2, 5, 8, and 9 are described in the Experimental Section.

Compound 8 was obtained by a previously used route<sup>12</sup> involving the reaction of *N*-benzyl-2,3-dihydroindole-5-carboxaldehyde with isopropylmagnesium bromide, thermal dehydration of the benzyl alcohol, and Ritter reaction of the resulting styrene and acetonitrile. The acetamide formed was hydrolyzed with potassium hydroxide and debenzylated by means of catalytic hydrogenation.

The key intermediate to compound 5, 2-chloro-6-nitrophenethyl alcohol (15), was prepared essentially as described from 2-chloro-6-nitrotoluene and paraformaldehyde.<sup>14–16</sup> The reduction of 15 to 2-amino-6-chloro-



**Figure 1.** Inhibition of MAO inside (●) and outside (Δ) monoaminergic nerve terminals in hypothalamus (5-HT, NA) and striatum (DA) by compound 2. The test compound was given orally 1 h before the subcutaneous injection of phenelzine sulfate, and the rats were sacrificed 48 h later. The MAO activity inside and outside the monoaminergic nerve endings was determined as described in the Experimental Section.

phenethyl alcohol (16) was achieved by using sodium polysulfide.<sup>17</sup> The compound has been prepared formerly by reduction of 4-chlorooxindole with lithium aluminum hydride.<sup>18</sup> In the same work the cyclization of 16 to 4-chloro-2,3-dihydroindole (17) by means of zinc chloride is also described. In our study 16 is transformed into the corresponding phenethyl chloride, which is cyclized by means of sodium hydroxide to 17. Conversion of 17 into the desired 5 was then accomplished by the same method as described above for the preparation of compound 1.

### Pharmacology

**MAO Inhibition in Vitro.** With a rat brain mitochondrial preparation as enzyme source it was found that the new compounds inhibited the deamination of the MAO-A substrate 5-HT at much lower concentrations than those required for the inhibition of the deamination of the MAO-B substrate phenethylamine (Table II).

The structure-activity relationships indicate that substitution with a methyl or chloro group at the 4-position increased MAO-A inhibitory potency (3 and 5 vs. 1; 9 vs. 2). Such an effect, however, was not achieved when the methyl group was placed at the 6-position (4 vs. 1). The  $\alpha$ -ethyl-substituted compounds were slightly less active than their  $\alpha$ -methyl analogues (2 vs. 1; 9 vs. 5). The  $\alpha,\alpha$ -dimethyl derivative 8 was not less potent than the  $\alpha$ -methyl compound 1. Whereas the *N*-ethyl- $\alpha$ ,6-dimethyl derivative 7 was 40 times more potent than the corresponding secondary amine 4, the *N*-ethyl- $\alpha$ ,4-dimethyl derivative (6) had the same potency as the secondary amine 3. The most potent new compounds (5, 7, 9, 3, 6) were similar to amiflamine in MAO-A selectivity.

**MAO Inhibition in Vivo.** The inhibition of MAO inside and outside serotonergic, noradrenergic, and dopaminergic neurons in the rat hypothalamus and striatum in vivo was determined with the phenelzine protection technique combined with an assay that measures the deamination of low concentrations (0.1–0.25  $\mu\text{M}$ ) of <sup>14</sup>C-labeled serotonin, norepinephrine, and dopamine by synaptosomal preparations in the absence and presence of

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**Table III.** Antagonistic Effect of Norzimeldine on the Inhibition of MAO within Serotonergic Nerve Terminals in Rat Hypothalamus by Compound 8

pretreatment	MAO inhibn, %	
	N	EN
saline	58 ± 4 <sup>a</sup>	11 ± 5
norzimeldine	15 ± 3 <sup>a</sup>	10 ± 4

<sup>a</sup> *p* < 0.05 (Mann-Whitney U-test). Norzimeldine (20 mg/kg ip) was injected 30 min prior to compound 8 (8 μmol/kg sc). Phenelzine sulfate, 4 mg/kg sc, was given 30 min later, and the rats were sacrificed 48 h later. The MAO inhibition inside (N) and outside (EN) the serotonergic nerve terminals in the hypothalamus was determined with the synaptosomal technique described in the Experimental Section. The values are means ± SEM.

**Table IV.** Behavioral Changes by the Test Compounds in Reserpinized Rats

no.	ED <sub>50</sub> <sup>a</sup> μmol/kg ip		
	5-HT	NA	DA
1	42	17	42
2	64	128	>256
3	64	128	>128
4	>61	>61	>61
5	59	59	>59
6	87	>87	>87
7	>87	87	>87
8	128	64	>256
9	28	>112	>112
amiflamine	7.5	15	>300

<sup>a</sup> The lowest dose causing a serotonin syndrome (5-HT), reversal of ptosis (NA), and increased motor activity (DA) was noted. > indicates highest dose examined without effect. Reserpine, 5 mg/kg sc, was given 18 h before the test compounds. Behavioral changes were observed during 90 min after the administration of the test compounds.

the selective amine uptake inhibitors citalopram, maprotiline, and amfonelic acid.<sup>7,9</sup> The difference between the deaminating activity in the absence and presence of the selective amine uptake inhibitor is defined as the measure of the deamination occurring within the given aminergic system. Figure 1 gives an example of the dose-response curves obtained for compound 2.

Table II shows that some of the compounds very selectively and potently inhibited MAO within the aminergic neurons. For example, compounds 1, 3, and 8 inhibited MAO inside serotonergic neurons at doses 1/10 of those required to inhibit extraneuronal MAO. High selectivity in all three amine systems was noted for compound 1. High selectivity for MAO in noradrenergic neurons was noted for compounds 3, 6, 7, and 8. Other compounds, e.g. the α-ethyl derivative 9, the N-ethyl derivative 7, and compound 4 with a methyl group at the 6-position, had very slight or no selective action in serotonergic neurons. However, the latter compound was a quite selective inhibitor of MAO in noradrenergic neurons.

Pretreatment of the rats with norzimeldine (20 mg/kg sc), a selective inhibitor of the neuronal serotonin uptake,<sup>19</sup> antagonized the inhibition of MAO by 8 within the serotonergic nerve terminals (Table III).

**Inhibition of Amine Uptake in Synaptosomes.** Since the compounds that have high selective MAO inhibitory effects in the monoaminergic neurons may be transported by the neuronal uptake mechanisms, the affinities of the compounds for serotonin, norepinephrine, and dopamine uptake sites were determined (Table II). Although this test does not differentiate between transported and non-transported inhibitors, the most potent MAO inhibitors

**Table V.** Spearman Rank Correlations between the Various Parameters Examined

	Spearman rank correl coeff, <i>r<sub>s</sub></i>						
	neuronal MAO inhibn in vivo			uptake inhibn in vitro		behavioral changes	
	5-HT	NE	DA	5-HT	NE	5-HT	NE
MAO-A inhibn in vitro	0.35	0.33	0.41	0.65*	0.12	0.27	0.29
neuronal MAO inhibn in vivo		0.81 <sup>b</sup>	0.79 <sup>b</sup>	0.70 <sup>a</sup>	0.63 <sup>a</sup>	0.71 <sup>a</sup>	0.68 <sup>a</sup>
uptake in vitro			0.89 <sup>b</sup>	0.64 <sup>a</sup>	0.48	0.58 <sup>a</sup>	0.52
behavioral changes				0.65 <sup>a</sup>	0.59 <sup>a</sup>	0.58 <sup>a</sup>	0.80 <sup>b</sup>
					0.33	0.80 <sup>b</sup>	0.42
						0.70 <sup>a</sup>	0.68 <sup>a</sup>
							0.55

<sup>a</sup> *p* < 0.05. <sup>b</sup> *p* < 0.01.

within the serotonergic neurons, 3, amiflamine, and 5, were also the most potent inhibitors of the serotonin uptake in vitro. Spearman rank tests show significant correlation between these two parameters and also between MAO-A inhibition in vitro and the inhibition of serotonin uptake, serotonin being the substrate in both cases (Table V). On the other hand, there was no correlation between the inhibition of norepinephrine uptake in vitro and inhibition of MAO within noradrenergic neurons in vivo (Table V). However, compounds with high affinity for the norepinephrine uptake sites, e.g. 5, 1, 3, and amiflamine (Table IV), were also the most potent inhibitors of MAO within the noradrenergic neurons.

Only three of the compounds (1, 3, 4) inhibited dopamine uptake in striatal synaptosomes by 50% at concentrations below 10 μM, compound 1 being the most active but having moderate potency (Table IV).

**Behavioral Changes in Reserpinized Rats.** Compounds that release monoamines cause characteristic syndromes in reserpinized rats.<sup>20</sup> Compounds that release serotonin produce a "serotonin syndrome" consisting of abduction of hind legs, wet dog shake, forepaw treadings, Straub tail, and release of porphyrins from the Harderian gland. Compounds that release norepinephrine cause reversal of the reserpine-induced ptosis. Similarly, compounds that release dopamine produce reversal of the reserpine-induced sedation. Table IV shows that most of the compounds tested produced a serotonin syndrome and reversed ptosis in reserpinized rats albeit at doses 5–10 times higher than the ED<sub>50</sub> values for MAO inhibition within the aminergic neurons. Compounds 4 and 7, which did not produce any MAO inhibition within the serotonergic nerve terminals, did not cause any serotonin syndrome. Although both these compounds inhibited MAO within noradrenergic neurons, only the more potent one (7) reversed the reserpine-induced ptosis in the dose range studied. Compound 1 caused behavioral changes, indicating a dopaminergic activity.

**Discussion**

The results obtained with the new MAO inhibitors described in this study confirm the previous conclusion<sup>7-9</sup> that it is possible to develop MAO inhibitors with a selective effect within certain monoaminergic neurons. The selectivity is most likely due to the ability of the compounds to be transported into the neurons by the membranous uptake mechanisms. Accordingly, the structure

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relationships for the inhibition of MAO within the monoaminergic neurons reflect the structural requirements for transport by the amine uptake mechanisms as well as for inhibition of MAO-A. Since the requirements for transport are not the same for all three amine pumps, it might also be possible to obtain MAO inhibitors that are selective for each aminergic system.

The findings that the compounds with H, CH<sub>3</sub>, or Cl at the 4-position (1, 3, 5, 6) were very potent and selective inhibitors of MAO within serotonergic and noradrenergic nerve terminals would suggest that these compounds are effectively transported by the uptake mechanisms in these neurons. The compounds had also quite high affinities for the uptake sites as revealed by the uptake inhibition experiments.

A methyl substituent at the 6-position, as in compound 4, abolished the selectivity for MAO within the serotonergic nerve terminals, which is in accordance with the low affinity of 4 for the serotonin uptake sites. This is probably due to lack of transport of 4 into these terminals. However, a selective inhibition of MAO in noradrenergic nerve terminals by this compound indicates uptake into catecholaminergic nerve terminals. The low in vitro activity of 4 is probably not the reason for the failure to inhibit MAO in the serotonergic neurons since compound 2 with the same in vitro potency produced a selective inhibition of MAO in these neurons. The *N*-ethyl derivative 7 with 40 times inhibitory potency for MAO-A in vitro compared with 4 also failed to inhibit MAO in serotonergic neurons but did inhibit MAO in noradrenergic neurons. These observations suggest that the methyl substituent at the 6-position abolishes the ability of the compounds to be transported by the serotonin pump and reduces transport by the norepinephrine pump. Since the affinities of 7 for the serotonin and norepinephrine uptake sites were similar, this compound may be a nontransported inhibitor of serotonin uptake and a transported inhibitor of norepinephrine uptake. The high selectivity for the  $\alpha$ -ethyl derivative 2 and of the  $\alpha,\alpha$ -dimethyl derivative 8 indicates that these compounds are transported by the amine pumps.

Several of the compounds tested produced a serotonin-like syndrome in reserpinized rats and reversed the ptosis induced by reserpine. Thus, these compounds, like amiflamine and  $\alpha$ -ethyltryptamine,<sup>20</sup> appear to release serotonin and norepinephrine in addition to having properties as inhibitors of MAO. The release of the transmitter amines may be coupled to the uptake of the compounds since all compounds that produced a selective inhibition of MAO within the aminergic nerve terminals also caused behavioral changes in reserpinized rats. Thus, the rank order of the potencies for inducing the serotonin syndrome was significantly correlated to those for inhibition of MAO within serotonergic (as well as noradrenergic and dopaminergic) neurons in vivo and those for inhibition of serotonin (and norepinephrine) uptake in vitro (Table V). The lack of correlation between the potencies for reversal of ptosis (a norepinephrine effect) and for the inhibition of MAO within the noradrenergic neurons may be due to the limited number of compounds tested. Only compound 1 produced an increase in the motor activity in reserpinized rats, caused a very selective inhibition of MAO within dopaminergic nerve terminals in the striatum, and had moderately high affinity for the dopamine uptake sites, indicating that this compound is transported by the dopamine uptake mechanism and also releases dopamine. These findings are theoretically interesting since they support the hypothesis that the amine releasing effect by

this type of compound is due to facilitated exchange diffusion; i.e., the release of the transmitter amine occurs via the membranous transport mechanism and is automatically coupled to the uptake of the releasing compound.<sup>21</sup>

### Experimental Section

Melting points were determined in a Mettler FP 61 melting point recorder. <sup>1</sup>H NMR spectra were recorded in a Varian EM-360 60-MHz spectrometer. The analyses were performed by the Department of Analytical Chemistry, University of Lund, Lund, Sweden. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within  $\pm 0.4\%$  of the theoretical values. The absence of precursors was examined by GC with a Carlo Erba 4300 gas chromatograph equipped with 25 m  $\times$  0.35 mm fused silica capillary column (SE 52) and a fid detector. Detailed experimental procedures are given only for selected key compounds, which will serve to illustrate the general synthetic methods employed. The intermediates were usually isolated as oils and were used directly in the next step.

**5-(2-Aminoprop-1-yl)-2,3-dihydroindole Acetate (1).** A solution of 40.6 g (0.14 mol) of *N*-benzyl-5-(2-nitropropen-1-yl)-2,3-dihydroindole in 200 mL of THF was added dropwise to a stirred mixture of 14.0 g (0.37 mol) of LiAlH<sub>4</sub> in 400 mL of dry Et<sub>2</sub>O. The mixture was stirred and heated under reflux for 2 h. After dropwise addition of 50 mL of saturated Na<sub>2</sub>SO<sub>4</sub> solution while stirring and cooling in ice, the mixture was filtered and the solvent was evaporated. The residual oil, 39.7 g, was dissolved in 50 mL of 12 N HCl and 200 mL of water and hydrogenated with H<sub>2</sub>/Pd (5%) at atmospheric pressure and approximately 50 °C. When the hydrogen uptake had stopped, the catalyst was filtered off and the filtrate was made basic with 10 N NaOH. The mixture was extracted with Et<sub>2</sub>O, and the extract was dried over Na<sub>2</sub>SO<sub>4</sub> and treated with 9 mL of AcOH. The semisolid acetate salt was triturated with acetone and collected by filtration: yield 28.4 g (86%); <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  7.1–6.7 (m, 3 H, Ar), 3.8–2.8 (m, 7 H, CH, 3 CH<sub>2</sub>), 2.0 (s, 3 H, CH<sub>3</sub>), 1.4 (d, 3 H, CH<sub>3</sub>).

***N*-Benzyl-5-(2-nitropropen-1-yl)-2,3-dihydroindole.** A mixture of 52.2 g (0.22 mol) of *N*-benzyl-2,3-dihydroindole-5-carboxaldehyde, 30 mL (0.4 mol) of nitroethane, and 15 g of ammonium acetate in 300 mL of EtOH was heated under reflux for 7 h. After cooling overnight, the precipitate was collected by filtration and washed with cool EtOH: yield 41.5 g (64%); mp 87–90 °C. Recrystallization from EtOH gave a pure compound, melting at 93–94 °C. Anal. (C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N, O.

***N*-Benzyl-2,3-dihydroindole-5-carboxaldehyde.** To a stirred solution of 250.3 g (1.19 mol) of *N*-benzyl-2,3-dihydroindole in 300 mL of DMF was added while cooling in tap water 115 mL (1.26 mol) of POCl<sub>3</sub>. The mixture was heated for 1.5 h at 100 °C, poured into 2 L of an ice-water mixture, and made basic with 10 N NaOH. After cooling overnight, the product formed was collected by filtration and recrystallized from 2 L of EtOH: yield 247.2 g (88%); mp 89–90 °C. Anal. (C<sub>18</sub>H<sub>15</sub>NO) C, H, N, O.

**5-(2-Aminobut-1-yl)-2,3-dihydroindole Acetate (2).** A mixture of 47.5 g (0.2 mol) of *N*-benzyl-2,3-dihydroindole-5-carboxaldehyde, 27 mL of 1-nitropropane, and 15 g of ammonium acetate in 500 mL of EtOH was heated for 30 h at reflux. The mixture was cooled overnight, and the precipitate was collected by filtration, washed with EtOH, and dried. The product (27.0 g) was dissolved in 80 mL of THF, and the solution was added to a stirred suspension of 11.4 g (0.3 mol) of LiAlH<sub>4</sub> in 200 mL of dry Et<sub>2</sub>O. After the mixture was stirred at reflux temperature for 1 h, 38 mL of saturated Na<sub>2</sub>SO<sub>4</sub> solution was added in portions while cooling in ice. The mixture was filtered and the solvent was evaporated. To the residual oil, 23.5 g, was added 50 mL of 12 N HCl and 200 mL of water, and the solution was hydrogenated with H<sub>2</sub>/Pd (5%) at normal pressure and about 50 °C. When the hydrogen uptake had ceased, the catalyst was removed by filtration, the filtrate was made basic with 10 N NaOH and extracted with Et<sub>2</sub>O, and the extract was dried with Na<sub>2</sub>SO<sub>4</sub>. The solution was treated with 8 mL of AcOH. The semisolid compound obtained was dissolved in water and washed with Et<sub>2</sub>O.

(21) Trendelenburg, U. In *The Release of Catecholamines from Adrenergic Neurons*; Paton, D. M., Ed.; Pergamon: Oxford, 1979; p 333.

The water layer was again alkalized with 10 N NaOH and extracted with Et<sub>2</sub>O. The extract was dried and treated with 8 mL of AcOH. The resulting product was dissolved in MeCN and precipitated by the addition of Et<sub>2</sub>O. The crystallization of the still semisolid compound was effected by agitation and cooling in an ice bath; yield 6.2 g (28%).

**2-Chloro-6-nitrophenethyl Alcohol (15).** A solution of 1.5 g of KOH in 10 mL of EtOH was added to a mixture of 171.6 g (1.0 mol) of 2-chloro-6-nitrotoluene and 30 g (1.0 mol) of para-formaldehyde in 150 mL of Me<sub>2</sub>SO. The mixture was left for 3 days at room temperature, diluted with 2 L of water, neutralized with HCl, and extracted with Et<sub>2</sub>O. The extract was dried with Na<sub>2</sub>SO<sub>4</sub> and the ether was evaporated. The light yellow, crystalline product (185.5 g) was recrystallized from isopropyl ether-petroleum ether: yield 142.5 g (71%); mp 61–62 °C (lit.<sup>14</sup> mp 58–60 °C). Anal. (C<sub>8</sub>H<sub>9</sub>ClNO<sub>3</sub>) C, H, Cl, N, O.

**2-Amino-6-chlorophenethyl Alcohol (16).** To a stirred solution of 48.0 g (0.2 mol) of Na<sub>2</sub>S·9H<sub>2</sub>O and 6.4 g of sulfur in 100 mL of water and 50 mL of EtOH was added by portions 20.1 g (0.1 mol) of compound 15. The solution was boiled under reflux for 4 h, the ethanol was evaporated, and 300 mL of water was added. The mixture was extracted with Et<sub>2</sub>O. The extract was washed with water and dried with Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated. The residual oil crystallized spontaneously on standing: yield 16.9 g (98%); mp 84–85 °C (lit.<sup>18</sup> mp 82–83 °C).

**4-Chloro-2,3-dihydroindole (17).** To a solution of 86.7 g (0.5 mol) of compound 16 in 400 mL of CHCl<sub>3</sub> was added while cooling in ice 180 mL of 4 M HCl in Et<sub>2</sub>O. The mixture was treated with 75 mL of SOCl<sub>2</sub>, which was added dropwise with stirring. The mixture was allowed to warm to room temperature and then warmed for 2 h at 50 °C. The solvent was removed, and the residue was dissolved in 400 mL of water. The solution was added dropwise while stirring to 100 mL of 10 N NaOH solution. The mixture was refluxed for 15 min and extracted with ether. The extract was dried with Na<sub>2</sub>SO<sub>4</sub>, and the ether was evaporated. The residual oil, 80.6 g, was distilled: yield 60.2 g (78%); bp 160–162 °C (35 mmHg) [lit.<sup>18</sup> bp 135 °C (10 mmHg)].

**N-Benzyl-4-chloro-2,3-dihydroindole (18).** To a mixture of 60.0 g (0.39 mol) of compound 17, 62.0 g of K<sub>2</sub>CO<sub>3</sub>, and 5.0 g of KI in 100 mL of DMF was added dropwise 48 mL (0.42 mol) of benzyl chloride while stirring and heating at 100 °C. The mixture was heated at 100 °C overnight, poured into 1.5 L of water, and extracted with Et<sub>2</sub>O. The extract was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated, and the residual oil, 96.7 g, was distilled: yield 87.0 g (93%); bp 155–160 °C (1 mmHg); mp 49–51 °C. Anal. (C<sub>15</sub>H<sub>14</sub>ClN) C, H, Cl, N.

**N-Benzyl-4-chloro-2,3-dihydroindole-5-carboxaldehyde (19).** To a stirred solution of 86.7 g (0.35 mol) of compound 18 in 100 mL of DMF was added while cooling in tap water 34.0 mL (0.36 mol) of POCl<sub>3</sub>. The mixture was heated at 100 °C for 2 h and then poured into 1.5 L of an ice-water mixture and made basic with 10 N NaOH. The precipitated oil crystallized on standing. The product was filtered off and washed with water: yield 95.0 g (98%); mp 95–97 °C. Recrystallization from EtOH yielded a pure compound, mp 102–103 °C. Anal. (C<sub>16</sub>H<sub>14</sub>ClNO) C, H, Cl, N, O.

**N-Benzyl-4-chloro-5-(2-nitropropen-1-yl)-2,3-dihydroindole (20).** This compound was prepared analogously to *N*-benzyl-5-(2-nitropropen-1-yl)-2,3-dihydroindole from 94.0 g (0.34 mol) of *N*-benzyl-4-chloro-2,3-dihydroindole-5-carboxaldehyde, 43 mL of (0.6 mol) nitroethane, and 20 g of ammonium acetate in 700 mL of ethanol: yield 90.6 g (81%); mp 112–113 °C. Anal. (C<sub>18</sub>H<sub>18</sub>ClN<sub>2</sub>O<sub>2</sub>) C, H, Cl, N, O.

**5-(2-Aminoprop-1-yl)-4-chloro-2,3-dihydroindole Acetate (5).** A solution of 89.4 g (0.27 mol) of compound 20 in 300 mL of THF was added dropwise to a stirred mixture of 28.0 g (0.74 mol) of LiAlH<sub>4</sub> in 600 mL of dry Et<sub>2</sub>O. The mixture was stirred and heated under reflux for 2 h. After dropwise addition of 100 mL of saturated Na<sub>2</sub>SO<sub>4</sub> solution while stirring and cooling in ice, the mixture was filtered and the solvent was evaporated. The residual oil was dissolved in 100 mL of 12 N HCl and 400 mL of water and hydrogenated with H<sub>2</sub>/Pd (5%) at atmosphere pressure and approximately 50 °C. When the hydrogen uptake had stopped, the catalyst was filtered off and the filtrate made basic with 10 N NaOH. The mixture was extracted with Et<sub>2</sub>O,

and the extract was dried over Na<sub>2</sub>SO<sub>4</sub> and treated with 18.0 mL (0.3 mol) of AcOH. The acetate salt was collected by filtration: yield 59.5 g (81%). An analytically pure sample, melting at 189–190 °C, was obtained by recrystallization from EtOH: <sup>1</sup>H NMR (D<sub>2</sub>O + CD<sub>3</sub>OD, 4:1) δ 7.0 (d, 1 H, Ar), 6.7 (d, 1 H, Ar), 3.8–2.8 (m, 7 H, CH, 3 CH<sub>2</sub>), 2.0 (s, 3 H, CH<sub>3</sub>), 1.4 (d, 3 H, CH<sub>3</sub>).

**5-(2-Amino-2-methylprop-1-yl)-2,3-dihydroindole Acetate (8).** A solution of 70 mL (0.72 mol) of 2-bromopropane in 200 mL of dry Et<sub>2</sub>O was added dropwise with stirring to 16.0 g (0.66 mol) of magnesium turnings in 200 mL of Et<sub>2</sub>O under nitrogen. When all the halide had been added, the mixture was refluxed for 10 min. The solution was stirred, and 74.0 g (0.31 mol) of *N*-benzyl-2,3-dihydroindole-5-carboxaldehyde was added in portions while cooling in ice. The mixture was refluxed for 1 h, and 130 mL of 12 N HCl in 70 mL of water was added dropwise while cooling and stirring. After the addition of 1 L of water, the mixture was made basic with ammonium hydroxide and extracted with CHCl<sub>3</sub>. The extract was washed with water and dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent evaporated. The residue, 86.8 g of oil, was heated at 180 °C for 0.5 h under nitrogen, and the obtained product was dissolved in 100 mL of MeCN. To the stirred solution was added dropwise while cooling in ice 60 mL of concentrated H<sub>2</sub>SO<sub>4</sub>. The mixture was left overnight at room temperature and was then poured into 1.5 L of ice-water and neutralized with ammonium hydroxide. The semisolid product was collected and dissolved in a mixture of 150 mL of ethylene glycol, 150 mL of 2-methoxyethanol, and 25 g of KOH. The solution was refluxed for 24 h, poured into 2 L of water, and extracted with Et<sub>2</sub>O. The extract was washed with water and dried with Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated. The residue was dissolved in 300 mL of water and 70 mL of 12 N HCl. Insoluble matter was separated and the solution was hydrogenated with H<sub>2</sub>/Pd (5%) at normal pressure and about 50 °C. The catalyst was removed by filtration, and the solution was made basic with 10 N NaOH and extracted with Et<sub>2</sub>O. The extract was dried with Na<sub>2</sub>SO<sub>4</sub> and treated with 18 mL of acetic acid. The semisolid salt solidified on standing; yield 15.4 g. The crude compound was purified by recrystallization from ethanol-isopropyl ether: yield 10.4 g (20%); <sup>1</sup>H NMR (D<sub>2</sub>O + CD<sub>3</sub>OD, 5:1) δ 7.2–6.7 (m, 3 H, Ar), 3.6–2.9 (m, 6 H, 3 CH<sub>2</sub>), 2.0 (s, 3 H, CH<sub>3</sub>), 1.4 (s, 6 H, 2 CH<sub>3</sub>).

**5-(2-Aminobut-1-yl)-4-chloro-2,3-dihydroindole Acetate (9).** A mixture of 63.4 g (0.23 mol) of compound 19, 36.0 mL (0.4 mol) of nitropropane, and 15 g of ammonium acetate in 400 mL of EtOH was heated under reflux for 8 h. After cooling overnight, the precipitate was collected by filtration and washed with cool EtOH. The obtained, crude *N*-benzyl-4-chloro-5-(2-nitrobuten-1-yl)-2,3-dihydroindole was dried under vacuum. The dried product (55.0 g) was dissolved in 300 mL of THF, and the solution was added to a stirred suspension of 15.0 g (0.4 mol) of LiAlH<sub>4</sub> in 300 mL of Et<sub>2</sub>O. After the mixture was stirred at reflux temperature for 2 h, 50 mL of saturated Na<sub>2</sub>SO<sub>4</sub> solution was added in portions while cooling in ice. The mixture was filtered, and the solvent was evaporated. To the residual oil, 50.9 g, was added 75 mL of 12 N HCl and 300 mL of water, and the solution was hydrogenated with H<sub>2</sub>/Pd (5%) at atmospheric pressure and approximately 50 °C. When the hydrogen uptake had ceased, the catalyst was removed by filtration, the filtrate was made basic with 10 N NaOH and extracted with Et<sub>2</sub>O, and the extract was dried with Na<sub>2</sub>SO<sub>4</sub>. The solution was treated with 14.0 mL of AcOH, and the yielded semisolid acetate salt was separated and dissolved in 500 mL of water. The solution was washed with Et<sub>2</sub>O, made basic with 10 N NaOH, and extracted with Et<sub>2</sub>O. The extract was dried with Na<sub>2</sub>SO<sub>4</sub> and treated with 14.0 mL of AcOH. The crystallization of the still semisolid precipitate was effected by agitation with a mixture of MeCN/(*i*-Pr)<sub>2</sub>O: yield 6.5 g (14%); mp 120–125 °C. An analytically pure sample, melting at 125–126 °C, was obtained by recrystallization from MeCN/(*i*-Pr)<sub>2</sub>O.

**Monoamine oxidase inhibition in vitro** was determined with a mitochondrial preparation of rat brain as described by Ask et al.<sup>6</sup> [<sup>14</sup>C]-5-HT (50 μM) and [<sup>14</sup>C]phenethylamine (2.5 μM) were used as substrates. IC<sub>50</sub> values were estimated from log concentration curves based on at least five different concentrations of the inhibitor.

**Monoamine Oxidase Inhibition in Vivo.** The phenelzine protection method combined with the assay of the deaminating activities in crude synaptosomal preparations of hypothalamus

(serotonin and norepinephrine) or striatum (dopamine) was used for the determination of the MAO inhibition in vivo inside and outside the monoaminergic neurons.<sup>7-9</sup> In this assay low concentrations of [<sup>14</sup>C]serotonin (0.1 μM), [<sup>14</sup>C]-1-norepinephrine (0.25 μM), or [<sup>14</sup>C]dopamine (0.25 μM) were incubated with the synaptosomal preparation in the absence and presence of selective uptake inhibitors (citalopram, maprotiline, amfonelic acid).

Sprague-Dawley rats weighing 160–200 g were given the test compound orally 1 h before the injection of phenelzine sulfate (4 mg/kg sc in the hypothalamus experiments; 2.5 mg/kg sc in the striatal experiments). The rats were killed 48 h later when the effects of the test compound were presumed to have disappeared. The hypothalami or striata were rapidly dissected out, homogenized in 20 volumes of 0.25 M sucrose, and centrifuged at 800g for 10 min. After a 10-min preincubation of 50 μL of the synaptosome-rich supernatant in 925 μL of Krebs-Henseleit's buffer, pH 7.4, containing 5.6 mM glucose, 1.1 mM ascorbic acid, and 0.13 mM disodium edetate, the incubation was continued for a further 10 min at 37 °C with [<sup>14</sup>C]serotonin (0.1 μM) or [<sup>14</sup>C]dopamine (0.25 μM) in the absence or presence of 0.12 μM citalopram (5-HT) or 0.3 μM amfonelic acid (dopamine). In the [<sup>14</sup>C]norepinephrine (0.25 μM) experiments 200 μL of the hypothalamic supernatants was used in the absence and presence of maprotiline (3 μM). The deaminated products were extracted into ethyl acetate, and the monoamine oxidase activities were calculated from the radioactivities.

The MAO inhibition inside and outside the amine neurons was estimated from the protection against the irreversible action of phenelzine as described by Green and El Hait.<sup>22</sup> The percent inhibition produced by the reversible inhibitors was calculated according to the formula

$$\left[ 1 - \frac{\ln(100/t)}{\ln(100/p)} \right] \times 100$$

in which *t* is the MAO activity in the synaptosomes from the animals treated with the test compound + phenelzine and *p* is that from the rats treated with saline + phenelzine, the activity expressed in percentage of that in the control animals. The ED<sub>50</sub> values were estimated from log dose-response curves based on at least three doses with four rats in each dose group.

**Inhibition of the Synaptosomal Uptake of Monoamines.** Crude synaptosome preparations from rat cerebral cortex and striatum were made by homogenizing the tissues in 10 volumes of ice-cold 0.32 M sucrose with all-glass Potter-Elvehjem's homogenizers. The homogenates were centrifuged at 800g at +2 °C for 10 min. The supernatants were centrifuged at 12000g at +2 °C for 10 min, and the pellets were rehomogenized in 0.32 M sucrose to the original volume. The incubation of the preparations with [<sup>14</sup>C]serotonin + [<sup>3</sup>H]norepinephrine (cerebral cortex) or [<sup>14</sup>C]dopamine (striatum) with final concentrations of 50 nM of each amine was performed in a Micronic PPN Storage-Block-96 (Flow Laboratories) with 8 × 12 wells using two rows at each incubation. Four to five different concentrations of two test compounds in duplicates were examined at each incubation. Fifty

microliters of the synaptosomal preparation, 400 μL of the Krebs-Henseleit's buffer, pH 7.4, containing 5.6 mM glucose, 1.1 mM ascorbic acid, 0.13 mM disodium edetate, and 50 μM pargyline, and 25 μL of the inhibitor or distilled water were added to the wells. The solutions were mixed by vortexing the block for 10 s. After 10-min preincubation at 37 °C in a water bath, 25 μL of the solutions of the radioactively labeled amines was added to the two rows with a Titertec Multichannel Pipette, type 12-Channel (Flow Laboratories). The reaction was immediately started by vortexing the block for 10 s on a Super-Mixer, and the incubation was continued for 2 min at 37 °C. The uptake reaction was stopped by filtration and washing for 15 s with ice-cold 0.15 M NaCl through a Whatman GF/B glass filter paper in a 24-channel Cell Harvester (Brandel) using the standard harvesting probe. The filters were left to dry in room temperature for about 1 h. The punched filters were transformed to counting vials, 10 mL of the scintillation liquid (Aquasol, NEN) was added, and vials were shaken and allowed to stand for 1 h before counting. The radioactivity was measured in a Packard Tri Carb liquid scintillation photometer. The active uptake of the amines was defined as the difference between the accumulation of the radioactivity in the absence (quadruplicates) and the presence (quadruplicates) of selective uptake inhibitors, determined at each incubation. These inhibitors were citalopram (0.3 μM) for the serotonin uptake, maprotiline (1 μM) for the norepinephrine uptake, and amfonelic acid (0.3 μM) for the dopamine uptake in striatal synaptosomes. The inhibition was calculated in percent of the active uptake. The IC<sub>50</sub> values were obtained from log concentration-response curves.

**Behavioral Studies in Reserpinized Rats.** Reserpine, 5 mg/kg sc, was injected 18 h before the oral administration of the test compound. Behavioral changes (abduction of hind legs, wet dog shake, forepaw treading, Straub tail, ptosis) were observed for 1 h after the administration of the test compound.<sup>20</sup> The lowest doses causing these changes were noted.

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**Registry No.** 1, 102493-63-0; 1-CH<sub>3</sub>CO<sub>2</sub>H, 102493-64-1; 1 (R<sub>5</sub> = CH<sub>2</sub>Ph), 102493-62-9; 2, 102493-66-3; 2-CH<sub>3</sub>CO<sub>2</sub>H, 102493-67-4; 3, 102493-84-5; 3-CH<sub>3</sub>CO<sub>2</sub>H, 102493-85-6; 4, 102493-91-4; 4-2HCl, 102493-86-7; 5, 102493-74-3; 5-CH<sub>3</sub>CO<sub>2</sub>H, 102493-75-4; 5 (R<sub>5</sub> = CH<sub>2</sub>Ph), 102493-73-2; 6, 102493-87-8; 6-tartrate, 102493-88-9; 7, 102493-89-0; 7-tartrate, 102493-90-3; 8, 102493-92-5; 8-CH<sub>3</sub>CO<sub>2</sub>H, 102505-28-2; 8 (R<sub>5</sub> = CH<sub>2</sub>Ph), 102493-79-8; 9, 102493-82-3; 9-CH<sub>3</sub>CO<sub>2</sub>H, 102493-83-4; 9 (R<sub>5</sub> = CH<sub>2</sub>Ph), 102493-81-2; 9 (R<sub>3</sub> = H, R<sub>5</sub> = CH<sub>2</sub>Ph), 102493-93-6; 10 (R<sub>5</sub> = CH<sub>2</sub>Ph), 6037-73-6; 15, 102493-68-5; 16, 100376-53-2; 16 (chloroethyl), 102493-69-6; 17, 41910-64-9; 18, 102493-70-9; 19, 102493-71-0; 19 (R<sub>3</sub> = H), 63263-84-3; 20, 102493-72-1; 20 (R<sub>3</sub> = H), 102493-61-8; H<sub>3</sub>CC-H<sub>2</sub>NO<sub>2</sub>, 79-24-3; H<sub>3</sub>C(CH<sub>2</sub>)<sub>2</sub>NO<sub>2</sub>, 108-03-2; PhCH<sub>2</sub>Cl, 100-44-7; H<sub>3</sub>CCHBrCH<sub>3</sub>, 75-26-3; *N*-benzyl-5-(2-nitrobuten-1-yl)-2,3-dihydroindole, 102493-65-2; *N*-benzyl-5-(1-hydroxy-2-methylprop-1-yl)-2,3-dihydroindole, 102493-76-5; *N*-benzyl-5-(2-methylpropen-1-yl)-2,3-dihydroindole, 102493-77-6; *N*-benzyl-5-(2-methyl-2-acetylamino-prop-1-yl)-2,3-dihydroindole, 102493-78-7; *N*-benzyl-4-chloro-5-(2-nitrobuten-1-yl)-2,3-dihydroindole, 102493-80-1; 1-chloro-2-methyl-3-nitrobenzene, 83-42-1; monoamine oxidase, 9001-66-5; paraformaldehyde, 9002-81-7.

(22) Green, A. L.; El Hait, A. S. *Biochem. Pharmacol.* 1980, 29, 2781.