Selective monoamine oxidase inhibitors. Compounds derived from phenethylamine and 1-phenoxy-2-aminopropane

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ABSTRACT 4-Alkoxyphenylalkylamines (*1—10*), 3- and 4-trifluoromethylphenethylamines (*11—14*) and 1-phenoxy-2-aminopropanes (*15—22*) were synthesized and tested for monoamine oxidase (MAO) inhibitory effects *in vitro* and after oral administration *in vivo* with particular attention to any selective effect on the A form of MAO. The compounds were, to varying degree, more potent in inhibiting the deamination of 5-hydroxytryptamine (5-HT) than phenethylamine, i.e. they are preferential MAO-A inhibitors. The most potent compounds *in vitro* were 3-(4-ethoxy-2-methylphenyl)-1-methylpropylamine (*10*) and 4-ethoxy-2-methylphenethylamine (*2*) in the 4-alkoxyphenylalkylamine series, 2-fluoro-4-trifluoromethylphenethylamine (*13*) in the trifluoromethylphenethylamine series and 1-(2-bromo-4-methylphenoxy)-2-aminopropane (*21*) in the phenoxy-2-aminopropane series. After oral administration to rats all the compounds were poor inhibitors of 5-HT deamination in brain slices. However, after intraperitoneal injection to mice, compounds *3, 10* and 4-methoxyamphetamine were quite potent in potentiating the 5-hydroxytryptophan syndrome in mice and in protecting MAO-A in the mouse forebrain against being irreversibly inhibited by phenelzine.

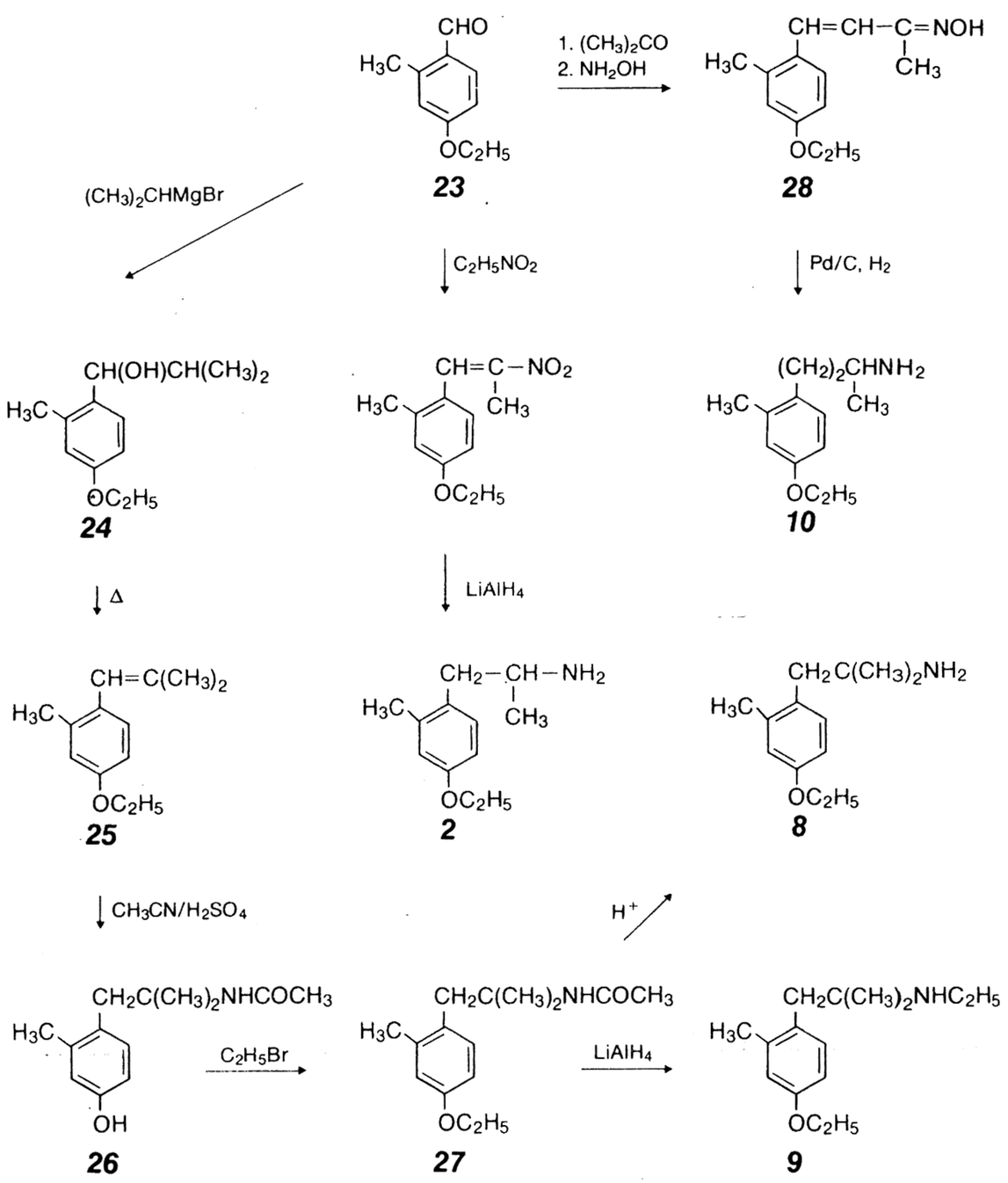
The renewed interest in selective inhibitors of the A-form of monoamine oxidase (MAO) as potential antidepressant drugs [1] has initiated search for compounds suitable for clinical use. Besides being a selective MAO-A inhibitor such a compound should act reversibly and have no or very slight interaction with orally ingested tyramine. In previous reports we have described the synthesis and pharmacological effects of 4-aminophenethylamine derivatives [2, 3], among which amiflamine [(*S*)-(+)-4-dimethylamino-2,α-dimethylphenethylamine (+)-hydrogen tartrate] has been chosen for clinical studies as a potent reversible MAO-A inhibitor. In the present study we report the synthesis and MAO inhibitory effects of compounds in three structurally related series; 4-alkoxyphenethylamines, 3- or 4-trifluoromethylphenethylamines and substituted 1-phenoxy-2-aminopropanes.

Chemistry

The 4-alkoxyphenethylamines (*1*—*7*) in Table 1 and 4-trifluoromethylphenethylamines (*11*—*13*) in Table 2 were prepared by the reduction of the corresponding β-nitrostyrene derivatives with lithium aluminium hydride as illustrated in Scheme 1 or 2. The intermediate β-nitrostyrenes were synthesized by the condensation of the appropriate benzaldehydes with nitroethane or nitropropane in the presence of ammonium acetate. All the β-nitrostyrene derivatives were isolated as yellow oils, which could not be crystallized or distilled without decomposition and were therefore reduced without further purification. The benzaldehydes used in this work, were prepared by the formylation of the corresponding 4-alkoxybenzene derivatives according to the Vilsmeier-Haack reaction [4—7]. 2-Fluoro-4-trifluoromethylbenzaldehyde (*31*) was obtained by the reaction of dimethylformamide with the Grignard compound of 2-fluoro-4-trifluoromethylchlorobenzene (*30*, Scheme 2). This method was used earlier in the preparation of 4-trifluoromethylbenzaldehyde [8]. Compound *30* in turn was prepared by the Sandmeyer reaction of the diazonium salt of 2-chloro-5-trifluoromethylaniline (*29*).

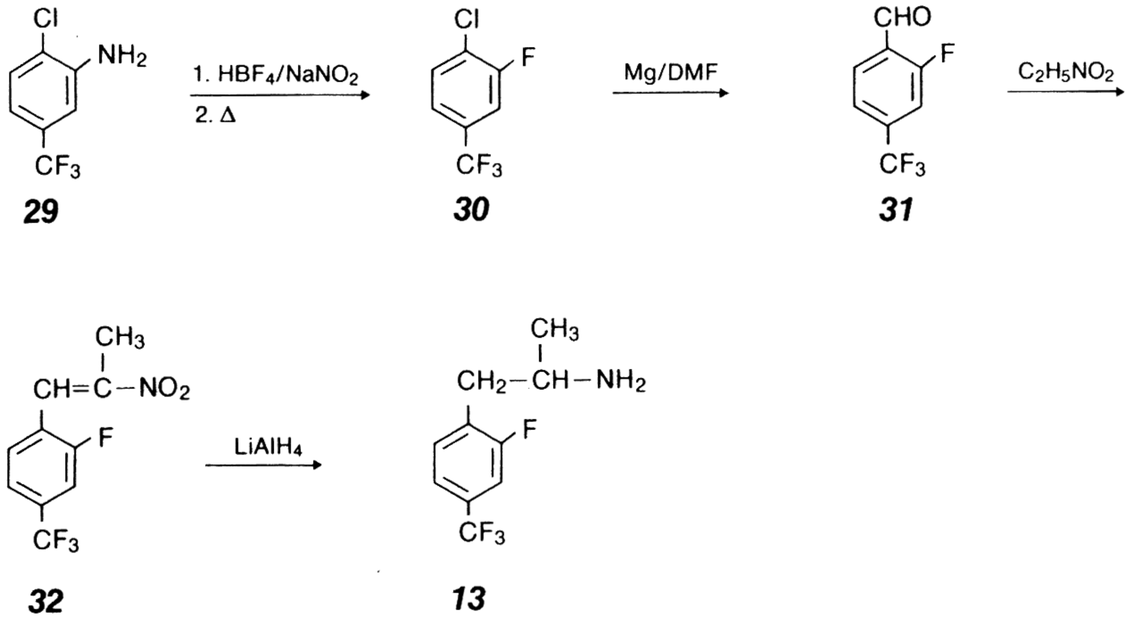
Hydrolysis and litium aluminium hydride reduction of the acetamide *27* yielded the amines *8* and *9*, respectively (Scheme 1). The preparation of *27* was accomplished by the Ritter reaction of the corresponding β,β-dimethylstyrene *25* and acetonitrile. During this reaction de-ethylation occurred and *N*[α,α-dimethyl-β-(4-hydroxy-2-methylphenyl)ethyl]acetamide (*26*) was obtained instead of *27*. The preparation of *27* was then accomplished by the ethylation of the obtained phenol *26* with ethyl bromide. The synthesis of compound *25* was achieved by the reaction of 4-ethoxy-2-methylbenzaldehyde (*23*) with isopropylmagnesium bromide followed by dehydration of the obtained benzyl alcohol *24*.

The preparation of compound *10* was accomplished by catalytic reduction of 4-(4-ethoxy-2-methylphenyl)-3-butene-2-one oxime (*28*, Scheme 1), which was



Scheme 1

prepared from the corresponding olefinic ketone by the treatment of hydroxylamine. The olefinic ketone was obtained by the condensation of 4-ethoxy-2-methylbenzaldehyde (*23*) with acetone.



29 **30** **31** **32** **13**

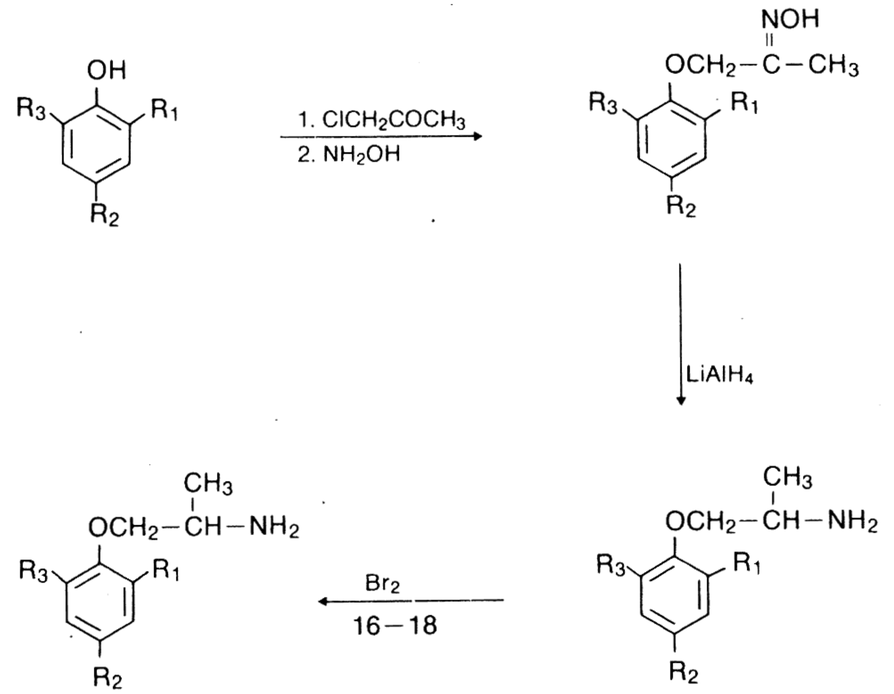
Scheme 2

3-Trifluoro-α-methylphenethylamine (*14*), earlier prepared by the reduction of the corresponding β-nitrostyrene [9], was now synthesized by the reduction of the imine adduct obtained by the reaction of 3-trifluoromethylbenzylmagnesium chloride and acetonitrile. Reduction of Grignard-nitrile adducts was previously reported [10].

The synthesis of compounds *15*—*19* (Table 3) was achieved by a general route (Scheme 3) involving *O*-alkylation of the appropriate phenols with 1-chloropropanone followed by treatment of the 1-(phenoxy)-2-propanones with hydroxylamine and reduction of the obtained ketone oximes with lithium aluminium hydride. Neither the ketones nor the oximes were isolated but used directly in the subsequent steps. Two of the compounds, *16* and *17* (Table 3) were prepared previously by hydrogenation of 1-(2,6-dimethylphenoxy)-2-propanone oxime with Raney nickel and reductive ammonolysis of 1-(4-methylphenoxy)-2-propanone, respectively [11, 12].

In an attempt to synthesize 1-(2-bromo-4-methoxyphenoxy)-2-aminopropane, by lithium aluminium hydride reduction of 1-(2-bromo-4-methoxyphenoxy)-2-propanone oxime, debromination occurred and compound *15* was obtained instead.

The bromo compounds *20*—*22* in (Table 3) were synthesized by nuclear bromination of the corresponding amines *16*—*18* in acetic acid in the presence of sodium acetate (Scheme 3).



20. $R_1=R_3=CH_3$, $R_2=Br$
21. $R_1=Br$, $R_2=CH_3$, $R_3=H$
22. $R_1=CH_3$, $R_2=Br$, $R_3=H$

15. $R_1=R_3=H$, $R_2=OCH_3$
16. $R_1=R_3=CH_3$, $R_2=H$
17. $R_1=R_3=H$, $R_2=CH_3$
18. $R_1=CH_3$, $R_2=R_3=H$
19. $R_1=R_3=H$, $R_2=CF_3$

Scheme 3

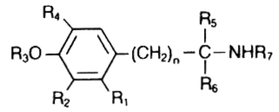
Pharmacology

4-Alkoxyphenethylamine derivatives

4-Methoxyamphetamine is a potent, selective and reversible MAO-A inhibitor *in vitro* and *in vivo* [13]. However, due to its hallucinogenic effect [14] 4-methoxyamphetamine is not a suitable MAO inhibitor for therapeutic use. In order to explore the possibility to obtain more pure MAO inhibitors some new compounds structurally related to 4-methoxyamphetamine were synthesized and tested for MAO inhibitory activities (Table 4). All compounds except *7* were *in vitro* to varying degree, more potent in inhibiting the 5-HT deamination than the phenethylamine (PEA) deamination, i.e. they are selective MAO-A inhibitors. The 4-methoxy derivative *1* was at least as potent and selective inhibitor of the 5-HT deamination (MAO-A) as 4-methoxyamphetamine. The corresponding 4-ethoxy compound *2* had the same potency as *1*. Further increase in the size of the 4-alkoxy substituent, *3* decreased the potency. Substitution at 3- and 5-positions *5*, *7* and 2-, 3- and 5-positions *6* markedly

Table 1

4-Alkoxyphenethylamines[a].



Compound	n	R_1	R_2	R_3	R_4	R_5	R_6	R_7	M.p.°C	Yield %	Recrystn. solvent [c]	Formula	Analysis
1	1	CH_3	H	CH_3	H	CH_3	H	H	183—5	6 [b]	A	$C_{11}H_{17}NO \cdot HCl$	C, H, Cl, N, O
2	1	CH_3	H	C_2H_5	H	CH_3	H	H	185—6	13 [b]	A	$C_{12}H_{19}NO \cdot HCl$	C, H, Cl, N, O
3	1	CH_3	H	$CH(CH_3)_2$	H	CH_3	H	H	144—5	65	B	$C_{13}H_{21}NO \cdot HCl$	C, H, Cl, N
4	1	CH_3	H	C_2H_5	H	C_2H_5	H	H	142—3	55	B	$C_{13}H_{21}NO \cdot HCl$	C, H, Cl, N
5	1	H	CH_3	CH_3	CH_3	CH_3	H	H	268—9	50	C	$C_{12}H_{19}NO \cdot HCl$	C, H, Cl, N
6	1	CH_3	CH_3	CH_3	CH_3	CH_3	H	H	248—9	64	D	$C_{13}H_{21}NO \cdot HCl$	C, H, Cl, N
7	1	OCH_3	H	CH_3	$(CH_2)_2CH_3$	CH_3	H	H	141—2	68	B	$C_{14}H_{23}NO_2 \cdot HCl$	C, H, Cl, N
8	1	CH_3	H	C_2H_5	H	CH_3	CH_3	H	258—9	65	C	$C_{13}H_{21}NO \cdot HCl$	C, H, Cl, N
9	1	CH_3	H	C_2H_5	H	CH_3	CH_3	C_2H_5	208—9	70	E	$C_{15}H_{25}NO \cdot HCl$	C, H, Cl, N
10	2	CH_3	H	C_2H_5	H	CH_3	H	H	153—4	68	B	$C_{13}H_{21}NO \approx HCl$	C, H, Cl, N

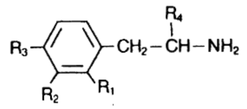
[a] Compounds 1—9.

[b] The yield was estimated from the starting materials in a three steps synthesis.

[c] A = ethanol – isopropyl ether, B = acetone, C = ethanol – ether, D = ethanol, E = acetonitirile.

Table 2

3- or 4-Trifluoromethylphenethylamines.



Compound	R_1	R_2	R_3	R_4	M.p.°C	Yield %	Formula	Analysis
11	H	H	CF_3	CH_3	198—9 [a]	55	$C_{10}H_{12}F_3N \cdot HCl$	—
12 [b]	H	H	CF_3	C_2H_5	173—4	34	$C_{11}H_{14}F_3N \cdot HCl$	C, H, Cl, N
13	F	H	CF_3	CH_3	156—7	35	$C_{10}H_{11}F_4N \cdot HCl$	C, H, Cl, N
14	H	CF_3	H	CH_3	163—4 [c]	20	$C_{10}H_{12}F_3N \cdot HCl$	—

[a] Literature [9] m.p. 200—201°C.

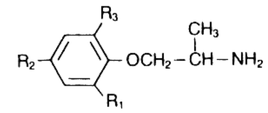
[b] Crystallized from acetone.

[c] Literature [9] m.p. 163—164°C.

diminished the inhibitory potency on the 5-HT deamination without changing the potency on the PEA deamination. The α,α-dimethyl derivative *8* was about 10 times less potent than the corresponding α-methyl derivative *2*. The corresponding *N*-ethyl compound *9* further decreased inhibitory potency. The compound *10* was the most potent compound tested in this study. This indicates that prolongation of the side chain with one methylene group increased the potency.

Table 3

1-Phenoxy-2-aminopropanes.



Compound	R_1	R_2	R_3	Recrystn. solvent [a]	M.p. °C	Yield %	Formula	Analysis
15	H	OCH_3	H	A	165—6	55	$C_{10}H_{15}NO_2 \cdot HCl$	C, H, Cl, N
16	CH_3	H	CH_3	A	200—1 [b]	65	$C_{11}H_{17}NO \cdot HCl$	
17	H	CH_3	H	B	155—6 [c]	70	$C_{10}H_{15}NO \cdot HCl$	
18	CH_3	H	H	B	148—9	53	$C_{10}H_{15}NO \cdot HCl$	C, H, Cl, N, O
19	H	CF_3	H	A	217—8	34	$C_{10}H_{12}F_3NO \cdot HCl$	C, H, Cl, N
20	CH_3	Br	CH_3	B	213—4	66	$C_{11}H_{16}BrNO \cdot HCl$	C, H, Cl, N, O
21	Br	CH_3	H	B	147—8	55	$C_{10}H_{14}BrNO \cdot HCl$	C, H, Cl, N, O
22	CH_3	Br	H	A	223—4	47	$C_{10}H_{14}BrNO \cdot HCl$	C, H, Cl, N, O

[a] A = ethanol – isopropyl ehter, B = ethanol – ether.

[b] Literature [11] m.p. 203—205°C.

[c] Literature [12] m.p. 153—154°C.

The most potent compounds were administered orally to rats and the MAO inhibition was examined by incubating hypothalamic slices from the treated rats with ^{14}C-5-HT or ^{14}C-PEA. Compared to the reference compound amiflamine the new compounds were quite weak inhibitors (Table 4).

A few of the compounds were injected intraperitoneally to mice and examined on the potentiation of the 5-hydroxytryptophan (5-HTP) induced head twitches, tremor and abduction of the hind-legs (Table 5). Compound *1* and *10* had similar potency as 4-methoxyamphetamine in this test but were less active than amiflamine. The phenelzine induced irreversible inhibition of MAO-A in the mouse brain was also potently protected by the intraperitoneal pretreatment of the mice with compound *1* or *2*. The poor effects of the alkoxyphenylalkylamines after oral administration to rats is probably due to rapid metabolism, presumably dealkylation.

Trifluoromethylphenethylamine derivatives

A few trifluoromethylphenethylamines (*11*—*14*) were synthesized and examined for MAO inhibition effect *in vitro* and after administration *in vivo* (Table 4). 2-Fluoro-4-trifluoromethyl-α-methylphenethylamine (*13*) was the most potent of these compounds in inhibiting the 5-HT deamination *in vitro*. However, the MAO-A selectivity for *13* was much less than that of the most potent compounds in the alkoxy series.

Table 4

Monoamine oxidase (MAO) inhibitory effects of 4-alkoxyphenethylamines (1—10), the trifluoromethylphenethylamines (11—14) and phenoxyaminopropane derivatives (15—22).

Compound	MAO inhibition				
	in vitro [a] IC_{50}, μM			in vivo [b] ED_{50}, μmol/kg p.o.	
	5-HT	PEA	PEA / 5-HT	5-HT	PEA
1	0.17	>100	>588	79	> 37
2	0.10	140	1400	> 87	>174
3	0.63	35	56	>164	NT
4	0.25	60	240	>164	NT
5	30	800	27	174	>348
6	4.0	320	80	NT	NT
7	70	110	1.4	NT	NT
8	1.0	500	500	>164	NT
9	6.2	100	16	>147	NT
10	0.024	10	417	>164	NT
11	4.5	80	18	33	>334
12	6.1	100	16	35	>315
13	1.3	54	42	39	>310
14	38	290	8	> 83	>333
15	3.0	170	57	>188	>367
16 (Mexiletine)	6.6	330	50	>183	>367
17	2.5	320	128	>198	>396
18	3.2	180	56	>198	>396
19	22	82	3.7	>156	>313
20	0.6	160	267	>136	>217
21	0.18	180	1000	142	>285
22	0.73	170	233	>142	>285
4-Methoxyamphetamine	0.44	>100	>227	NT	NT
Amiflamine	0.8	1900	2375	7	>117

[a] Deamination of ^{14}C-5-HT (2.5 μM) or ^{14}C-phenethylamine (PEA) (2.5 μM) by rat brain mitochondrial MAO in absence and presence of various concentrations of the test compounds. [b] The test compounds were given orally 2 h before the sacrifice of the rats. Slices of hypothalamus were incubated with 1×10^{-7} M of ^{14}C-5-HT for 5 min or ^{14}C-PEA for 90 s. The inhibition of the deamination was calculated in percent of the rate of the deamination in control slices. NT = not tested.

After oral administration to rats the 4-trifluoromethylphenethylamine derivatives (*11—13*) were quite potent in inhibiting the 5-HT deamination in hypothalamic slices (Table 4). This effect persisted for two days and seemed partly due to inhibition of the neuronal 5-HT uptake. A toxic effect on the 5-HT neurons like that of 4-chloroamphetamine [16] can not be excluded.

Table 5

Potentiation of the 5-hydroxytryptophan (5-HTP) syndrome and the protection of phenelzine-induced inhibition of MAO in the mouse forebrain.

Compound	5-HTP potentiation [a] ED_{50}, μmol/kg i.p.			Phenelzine [b] protection ED_{50}, μmol/kg i.p.
	Head twitches	Tremor	Abduction	
1	1.8	3.9	3.9	3.2
2	NT	NT	NT	3.5
3	60	78	38	66
4	54	62	53	NT
8	>103	41	104	NT
10	1.5	0.6	1.7	NT
11	3.0	2.1	6.3	42
12	9.5	9.0	51	NT
13	8.9	10.5	19	NT
4-Methoxyamphetamine	2.4	3.8	3.4	5.3
Amiflamine	0.2	0.5	0.6	3.7

NT = not tested.

[a] The compounds were injected i.p. 1 h prior to 90 mg/kg i.p. of 5-HTP. [b] The compounds were injected i.p. 15 min prior to the injection of 10 mg/kg i.p. of phenelzine sulfate. The animals were sacrificed 24 h later and the MAO activities in homogenates of the forebrains were determined with 50 μM 5-HT as the substrate.

The 5-HTP syndrome in mice was potentiated by the 4-trifluoromethyl derivatives, *11* being the most potent of the three compounds. Since this test does not discriminate between MAO-A inhibitors and 5-HT uptake inhibitors both these mechanisms may have been affected by these compounds.

Phenoxy-2-aminopropane derivatives

Mexiletine (*16*) has previously been shown to be a selective MAO-A inhibitor *in vitro* [15]. This was confirmed in the present study (Table 4). However, some other phenoxy derivatives were even more potent than mexiletine, the most active compound in this series was the 2-bromo-4-methyl derivative *21*. The 4-bromo derivatives *20* and *22* were also 10 times more potent than mexiletine as MAO-A inhibitors in vitro. The 4-trifluoromethyl derivative *19* was the least potent A-inhibitor in this series but tended to be more active than the other in inhibiting MAO-B.

The *in vivo* inhibition of the MAO activity was assessed with an *ex vivo* technique, in which the rats were sacrificed one hour after the oral administration. The deamination of ^{14}C-5-HT and ^{14}C-PEA by hypothalamic slices was determined [17]. All compounds in this series were quite poor inhibitors. Com-

pound *21* was the only compound which produced 50 % inhibition of the ^{14}C-5-HT deamination in the dose range examined.

Experimental

Chemistry

Melting points were determined on a Mettler FP 61 apparatus in an open capillary tube and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Model A-60 A spectrometer using tetramethylsilane as an internal standard. Microanalyses were carried out at the Department of Analytical Chemistry, University of Lund, Sweden. Where analyses are indicated by the symbols of the elements, the analytical results were within ± 0.4 % of the theoretical values. The purity of the compounds were examined by GC, on a JXR or OV-17 column or an OV-1 capillary column, and TLC on precoated plates (Merck, silica gel F_{254}).

All the compounds mentioned above were prepared by the following general procedure. A solution of the corresponding β-nitrostyrene derivative (0.01 mol) in dry ether (100—150 ml) was added dropwise while stirring to lithium aluminium hydride (0.05 mol) in ether (100 ml). The mixture was refluxed for 7—8 h. After dropwise addition of 10 % sodium hydroxide under cooling the solid was filtered. The filtrate was dried ($MgSO_4$) and concentrated. The hydrochloride salt was prepared by treating the residue with ether – hydrogen chloride. The salt was purified by recrystallization.

The β-nitrostyrenes were prepared from the appropiate benzaldehydes as follows. A mixture of aldehyde (0.05 mol), nitroethane or nitropropane (0.06 mol) and ammonium acetate (0.06 mol) in ethanol (100—150 ml) was refluxed for 5 h under stirring. The solvent was concentrated and the residue was poured into water (200 ml) and the product was extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated to give an oil. The crude compound was used directly in the next step.

2-Fluoro-4-trifluoromethyl-α-methylphenethylamine (13)

2-Chloro-5-trifluoromethylaniline (19.6 g, 0.1 mol) was added to cold 35 % tetrafluoroboric acid (140 ml). Sodium nitrite (8.3 g, 0.12 mol) in water (10 ml) was then added dropwise under stirring. The temperature of the diazotization reaction was maintained below 15°C during the addition. After the addition, the mixture was further stirred for 30 min. The solid 5-trifluoromethyl-2-chlorophenyldiazonium fluoroborate thus formed was filtered, washed with ethanol (150 ml) and finally with ether (200 ml) [yield 22.0 g, 97 %; m.p. 218—9°C (d)]. The diazonium salt (22.0 g, 0.097 mol) was decomposed by heating at 220°C and then distilled under vacuum to give *30* as a colourless oil (yield 10.6 g, 55 %; b.p. 50—55°C/15 mm). A mixture of *30* (6.3 g, 0.032 mol) and ethyl bromide (3.49 g, 0.032 mol) was added dropwise with stirring to magnesium (1.5 g, 0.064 mol) in dry tetrahydrofuran (200 ml). The reaction mixture was refluxed for 30 min and then cooled to 25°C. While temperature was maintained, dimethyl formamide (4.7 g, 0.064 mol) was added dropwise. After being stirred at 25°C for 2 h, the mixture was poured onto ice containing concentrated sulfuric acid (1 ml). The solvent was distilled off, the product was extracted with hexane and concentrated. The residue was distilled to give *31* as a colourless oil (yield 3.0 g, 50 %, b.p. 58—60°C/15 mm). A mixture of benzaldehyde *31* (5.0 g, 0.026 mol), nitroethane (2.5 g, 0.03 mol) and ammonium acetate (2.2 g; 0.03 mol) in ethanol (80 ml) was refluxed for 5 h under stirring. The solvent was removed and the residue was washed with water and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated to give *32* as an oil (yield 5.0 g, 77 %). A solution of *32* (4.0 g, 0.016 mol) in ether (50 ml) was added dropwise to lithium aluminium hydride (1.5 g, 0.04 mol) in ether (50 ml) under stirring. The mixture was refluxed for 8 h and then decomposed by adding 10 % sodium hydroxide (20 ml). The inorganic salt was filtered, the filtrate was dried ($MgSO_4$) and acidified with hydrogen chloride – ether. The hydrochloride salt was recrystallized from acetone – ether. ^{1}H NMR of free base ($CDCl_3$) δ 1.1 (d, 3H, CH_3), 1.4 (s, 2H, NH_2), 2.7 (d, 2H, CH_2), 2.9—3.4 (m, 1H, CH), 7.1—7.5 (m, 3H, aromatic).

N-[α,α-dimethyl-β-(4-hydroxy-2-methylphenyl)ethyl]acetamide (26)

A solution of isopropyl bromide (11.4 ml, 0.12 mol) in ether (40 ml) was added dropwise with stirring to magnesium turnings (2.4 g, 0.1 mol) in ether (100 ml) under a nitrogen atmosphere. The mixture was refluxed for 15 min and cooled in an ice bath while 4-ethoxy-2-methylbenzaldehyde (8.2 g, 0.05 mol) in ehter (40 ml) was added dropwise. The reaction mixture was further refluxed for 2 h and left overnight at room temperature. Then concentrated hydrochloric acid (20 ml) in water (10 ml) was added dropwise under stirring and cooling. The mixture was diluted with water and extracted with ether, dried ($MgSO_4$) and concentrated to give *24* as an oil (5.2 g, 50 %). To a solution of *24* (5.0 g, 0.024 mol) in toluene (75 ml) a catalytic amount of *p*-toluenesulfonic acid (0.1 g) was added. The mixture was refluxed for 1 h. Water, formed during the reaction, was separated by Dean-Stark apparatus. The reaction mixture was washed with water, the organic layer was dried (Na_2SO_4) and concentrated in vacuo to give *25* as an oil (4.1 g, 90 %). Concentrated sulfuric acid (2.5 ml) was added dropwise with stirring to a solution of *25* (3.8 g, 0.02 mol) in acetonitrile (5 ml) at 0°C. After overnight stirring at room temperature the mixture was poured in cold water and extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated to provide a residue, which on crystallization from toluene gave *26*. Yield 2.2 g (50 %); m.p. 154—6°; ^{1}H NMR (DMSO-d_6) δ 1.2 (s, 6H, CH_3) 1.9 (s, 3H, $NCOCH_3$), 2.3 (s, 3H, $ArCH_3$), 2.9 (s, 2H, CH_2), 6.4—7.0 (m, 3H, aromatic).

N-[α,α-*dimethyl*-β-(4-*ethoxy*-2-*methylphenyl*)*ethyl*]*acetamide (27)*

Powdered sodium hydroxide (0.4 g; 0.01 mol) was added to a stirred solution of *26* (2.0 g, 0.009 mol) in ethanol (30 ml). Ethyl bromide (1.1 g, 0.01 mol) was then added dropwise. Reaction mixture was refluxed for 4 h. The salt thus separated, was filtered and the filtrate was concentrated. The residue was treated with water and extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated. The crude product thus obtained, was crystallized from diisopropyl ether – petroleum ether. Yield 1.7 g, (76 %); m.p. 72—3°C; ^{1}H NMR ($CDCl_3$) δ 1.2—1.5 (m, 9H, CH_3), 1.3 (s, 2H, CH_2), 1.9 (s, 3H, $NCOCH_3$), 2.3 (s, 3H, $ArCH_3$), 3.9 (q, 2H, OCH_2), 5.2 (broad, 1H, NH), 6.5—7.1 (m, 3H, aromatic). *Anal.* ($C_{15}H_{23}NO_2$): C, H and N.

4-Ethoxy-2,α,α-*trimethylphenethylamine (8)*

A solution of *27* (1.0 g, 0.004 mol) in ethanol (20 ml) and concentrated hydrochloric acid (5 ml) was refluxed for 72 h. Ethanol was removed. The residue was poured in water, basified with sodium hydroxide and extracted with ether. The ether layer was dried ($MgSO_4$) and acidified with hydrogen chloride – ether. The hydrochloride salt thus obtained was recrystallized from ethanol – ether. ^{1}H NMR of free base ($CDCl_3$) δ 1.1 (s, 6H, CH_3), 1.3 (s, 2H, NH_2), 1.4 (t, 2H, CH_2), 2.3 (s, 3H, $ArCH_3$), 2.7 (s, 2H, $ArCH_2$), 4.0 (t, 2H, OCH_2), 6.5—7.3 (m, 3H, aromatic).

N-Ethyl-4-ethoxy-2,α,α-*trimethylphenethylamine (9)*

A solution of *27* (1.0 g, 0.004 mol) in tetrahydrofuran (25 ml) was added dropwise while stirring to lithium aluminium hydride (0.3 g, 0.007 mol) in tetrahydrofuran (20 ml). The reaction mixture was refluxed for 6 h. After the addition of 10 % sodium hydroxide (5 ml) the mixture was filtered. The filtrate was dried ($MgSO_4$) and evaporated. The residue was acidified with hydrogen chloride – ether and the hydrochloride salt was recrystallized from acetonitrile. ^{1}H NMR of free base ($CDCl_3$) δ 0.9—1.5 (m, 12H, CH_3) 2.3 (s, 3H, $ArCH_3$), 2.4—2.9 (m, 4H, NCH_2 and $ArCH_2$), 4.0 (q, 2H, OCH_2), 6.5—7.1 (m, 3H, aromatic).

4-(4-Ethoxy-2-methylphenyl)-3-butene-2-one oxime (28)

Aqueous 10 % sodium hydroxide (10 ml) was added to a solution of *23* (8.2 g, 0.05 mol) in acetone (50 ml). After stirring for 4 h the reaction mixture was poured in water and extracted with ether. The solvent was removed and the oil was dissolved in ethanol (100 ml). To the solution was added hydroxylamine hydrochloride (3.48 g, 0.05 mol) and sodium acetate (4.92 g, 0.06). After refluxing the mixture for 4 h, water (500 ml) was added. The solid thus obtained was filtered and recrystallized from ethanol. Yield 7.0 g (64 %); m.p. 122—4°C. ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.3 (s, 3H, $ArCH_3$), 3.9 (q, 2H, CH_2), 6.3—7.5 (m, 6H, H, OH, & aromatic). *Anal.* ($C_{13}H_{17}NO_2$): C, H and N.

3-(4-Ethoxy-2-methylphenyl)-1-methylpropylamine (10)

10 % Pd/C (0.5 g) was added to a solution of *28* (4.0 g, 0.018 mol) in acetic acid (30 ml) and concentrated hydrocloric acid (1 ml). The mixture was hydrogenated at NTP for 6 h and the catalyst was filtered off. The filtrate was diluted with water and made basic with 15 % sodium hydroxide. The product was extracted with ether, dried ($MgSO_4$) and acidified with hydrogen chloride – ether. The hydrochloride salt was recrystallized from acetone. ^{1}H NMR of free base ($CDCl_3$) δ 1.0 (d, 3H, CH_3) 1.2—1.5 (m, 5H, CH_3 & NH_2), 1.6—2.0 (m, 2H, CH_2), 2.2 (s, 3H, $ArCH_3$), 2.3—3.0 (m, 2H, $ArCH_2$) 3.1—3.6 (m, 1H, CH) 3.9 (q, 2H, OCH_2), 6.5—7.2 (m, 3H, aromatic).

3-Trifluoromethyl-α-methylphenethylamine (14)

m-Trifluoromethylbenzyl chloride (64.2 g, 0.33 mol) in ether (200 ml) was added dropwise to magnesium (8.0 g, 0.33 mol) with a crystal of iodine in ether (100 ml). Acetonitrile (13.5 g, 0.33 mol) was added dropwise to the obtained Grignard reagent (*m*-trifluoromethylbenzylmagnesium chloride). The mixture was refluxed for 2 h. A slurry of lithium aluminium hydride (12.6 g, 0.33 mol) in tetrahydrofuran (100 ml) was added slowly to the reaction mixture and again refluxed for 18 h and then decomposed by 20 % sodium hydroxide solution. The solid was filtered and the filtrate was dried ($MgSO_4$), concentrated and distilled *in vacuo* to give an oil. The hydrochloride salt was prepared by treating the oil with excess of ether – hydrogen chloride and recrystallized from acetone.

The 1-(phenoxy)-2-aminopropanes (*15*—*22*) were prepared by the general procedure examplified by the synthesis of *19* given below:

1-(4-Trifluoromethylphenoxy)-2-aminopropane (19)

A mixture of 4-trifluoromethylphenol (5.0 g, 0.03 mol), 2-chloropropanone (4.0 ml, 0.05 mol), sodium iodide (0.5 g) and anhydrous potassium carbonate (5.0 g) in acetone (50 ml) was refluxed overnight under stirring. The solid was filtered and the solvent was evaporated. The residual oil was dissolved in ether and the solution was washed with 2 M sodium hydroxide. The ether was evaporated and to the residue was added a solution of hydroxylamine hydrochloride (4.2, 0.04 mol) and sodium acetate trihydrate (10.0 g) in water (50 ml) and ethanol (50 ml). The mixture was refluxed for 3 h and then poured into water (500 ml). The product was extracted with ether, the extract was dried (Na_2SO_4) and the solvent was evaporated. The crude oxime (7.2 g, 0.03 mol) was dissolved in dry ether (50 ml) and the solution was added dropwise with stirring to lithium aluminium hydride (2.5 g) in dry ether (100 ml). The mixture was refluxed for 5 h and saturated sodium sulfate solution (10 ml) was added under cooling and stirring. The solid was filtered and the filtrate was dried (Na_2SO_4) and acidified with hydrogen chloride – ether. The hydrochloride salt was filtered and recrystallized from ethanol – diisopropyl ether. ^{1}H NMR (D_2O) δ 1.7 (d, 3H, CH_3), 4.0—4.8 (m, 3H, CH & CH_2), 7.0—8.1 (m, 4H, aromatic).

1-(4-Bromo-2,6-dimethylphenoxy)-2-aminopropane (20)

A solution of bromine (2.2 ml, 0.043 mol) in acetic acid (50 ml) was added to a mixture of *16* (8.6 g, 0.04 mol) and anhydrous sodium acetate (10.0 g) in acetic acid (100 ml). The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in water (300 ml). The solution was made alkaline with sodium hydroxide and extracted with ether. The extract was dried (Na_2SO_4) and acidified with hydrogen chloride – ether. The precipitated hydrochloride salt was filtered and recrystallized from ethanol – ether. ^{1}H NMR (D_2O) δ 1.4 (d, 3H, CH_3), 2.1 (s, 1H, $ArCH_3$), 3.4—4.3 (m, 3H, CH_2 & CH), 7.1 (s, 2H, aromatic).

Similarly, bromination of the amines *17* and *18* with excess of bromine in presence of sodium acetate yielded compound *21* and *22* respectively. Bromination with equivalent amount of bromine gave impure products containing starting material.

Pharmacology

Male Sprague-Dawley rats weighing 180—220 g and male albino mice (NMRI) weighing 18—22 g were used. The compounds were dissolved in distilled water or 0.9 % NaCl and were administered orally or intraperitoneally as indicated in the text.

MAO inhibition. The deamination of ^{14}C-5-HT (2.5 μM) and ^{14}C-PEA (2.5 μM) by a rat brain mitochondrial preparation was determined as described previously [8]. Different concentrations of the test compounds were added to the incubation medium and the concentrations producing 50 % inhibition (IC_{50}) were determined from log concentration inhibition curves.

The *in vivo* potencies of the test compounds were determined after oral administration to rats as described previously [17]. The rats were sacrificed 2 hours after the administration and slices of the hypothalamus were incubated with ^{14}C-5-HT[1] (1×10^{-7}) for 5 min or with ^{14}C-PEA[2] (1×10^{-7} M) for 90 s in a saline-bicarbonate buffer at pH 7.4. The inhibition of the deamination was calculated in percent of the deamination of the substrates by slices from control animals. Four rats were used per dose of the test compound. The doses producing 50 % inhibition (ED_{50}) were determined from log dose response curves.

For a few compounds the protection against the phenelzine-induced long-lasting inhibition of MAO in the mouse forebrain was determined. Different doses of the test compounds were injected intraperitoneally 15 min before the intraperitoneal injection of phenelzine sulfate (10 mg/kg). The mice were sacrificed 24 h later. The forebrain of each mouse was homogenized in 10 volumes of ice-chilled 0.11 M sodium phosphate buffer, pH 7.4. An aliquot of 0.1 ml of the homogenate was added to 0.875 ml of the sodium phosphate buffer and 25 μl of the substrate ^{14}C-5-HT (final concentration 10 μM). Incubation was performed for 10 min and stopped by addition of 1.0 ml 1 M HCl. The ^{14}C-5-hydroxyindoleacetic acid formed was extracted into 6 ml ethyl acetate. The percent protecting effects of the test compounds against the phenelzine-induced MAO inhibition were calculated from the values obtained from saline injected control animals (a), from animals injected with phenelzine (b) and from animals injected with the test compounds 15 min before the phenelzine injection (c) according to the formula:

$$\frac{c - b}{a - b} \times 100.$$

The potentiation of the 5-hydroxytryptophan (5-HTP) syndrome (head twitches, tremor and abduction of hind legs) was tested according to the method described previously [2].

[1] 5-Hydroxytryptamine[side chain-2-(^{14}C)]creatinine sulphate (sp. act. 58 mCi/mmol). Radiochemical Centre, Amersham, U.K.

[2] Phenethylamine[ethyl-1-^{14}C]hydrochloride (sp. act. 48.7 mCi/mmol). New England, Nuclear, Boston, MA.

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