8 analogues in the 1–22 series containing D-Asn alone or in combination with D-Asp[3], D-Ala[2], or *N*-Me-D-Ala[2] gave detectable levels of activity at the doses tested (Table III).

This is not the only report of differential effects of certain N-terminal modifications on the biological activity of GRF analogues with varying chain lengths. Baird et al.[20] found that whereas rat GRF(1–43) was 3.9 times more potent than human GRF(1–44)NH_2, rat GRF(1–27)NH_2 and (1–33)NH_2 were 6.15 and 9.72 times more potent than the human (1–27)NH_2 and (1–33)NH_2 sequences, respectively, using rat pituitary cells in culture. The major structural difference between the human and cat peptides is the presence of His rather than Tyr in position 1 of the rat hormone (see Table I). Thus, it appears that the biological effects of side-chain characteristics of amino acids in the N-terminal region of GRF are also dependent on amino acids present at the distantly removed C-terminus. This could indicate that both regions are involved with promoting the receptor binding conformation of GRF. Since very mild conformational restraint can enhance the activity of sequences shorter than 29 residues, it might be possible to eventually design far more rigid analogues of smaller chain lengths that retain useful levels of GH releasing activity.

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Acknowledgment. We thank Etchie Yauger, Lisa Mutty, and Vienna Mackey for their expert technical assistance. This research was supported by NIH Grant AM-30167.

Registry No. **1**, 104874-07-9; **2**, 104834-33-5; **3**, 104874-08-0; **4**, 104834-34-6; **5**, 104848-48-8; **6**, 104834-35-7; **7**, 104834-43-7; **8**, 104834-36-8; **9**, 104834-37-9; **10**, 104834-38-0; **11**, 104848-62-6; **12**, 104834-39-1; **13**, 104834-40-4; **14**, 104848-63-7; **15**, 104834-41-5; **16**, 104834-42-6; GRF(1–29)NH_2, 86168-78-7; D-Ala[2](1–29)NH_2, 89453-59-8; Ac-Tyr[1](1–29)NH_2, 89453-61-2; D-Asp[3](1–29)NH_2, 89453-60-1; D-Ash[8](1–29)NH_2, 94061-38-8; D-Asp[3],D-Asn[8],Nle[27]-(1–29)NH_2, 101366-32-9; GRF(1–24)NH_2, 95415-63-7; growth hormone, 9002-72-6.

3-[(2-Ethoxyphenoxy)methyl]piperidine Derivatives. Synthesis and Antidepressant Activity[1]

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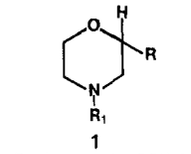
Received April 7, 1986

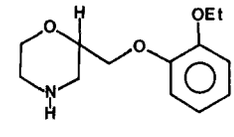
The 3-[(2-ethoxyphenoxy)methyl]piperidine derivatives **3–5** were synthesized and screened as potential antidepressant agents by the reserpine interaction test in mice and the evaluation of reuptake inhibition of biogenic amines in pig brain synaptosomal fractions. In addition, their anticonvulsant activity, tested by pentylenetetrazole antagonism, and approximate acute toxicity were evaluated. In vivo and in vitro tests showed that compounds **3** and **5** possess a biological activity comparable to that of the antidepressant drug viloxazine (**2**).

Recently, several antidepressants have been developed that are devoid of pharmacological and biochemical secondary effects typical of imipramine-like tricyclic antidepressants and of monoamine oxidase inhibitors.[1-8] Several of these new drugs reveal a common structural characteristic consisting of a morpholine ring to which an aromatic group is attached either directly or by an oxymethylene bridge, as indicated in **1**.[2,4-7]

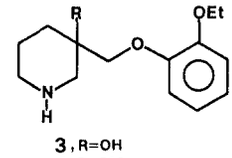
On the basis of this observation, investigations were designed to see whether the substitution of the morpholine ethereal oxygen of type 1 drugs with an alcoholic group could lead to new compounds in which the antidepressant activity is still present. We therefore synthesized 3-[(2-ethoxyphenoxy)methyl]-3-piperidinol (**3**), which exhibits in the 3-position the side chain of viloxazine (**2**),[2] one of the best known members of type 1 drugs. Subsequently, in order to evaluate the importance of the presence of the hydroxyl group in determining the activity of **3**, its 3-methoxy (**4**) and 3-desoxy (**5**) analogues were also prepared.



1
R = Ar, CH_2OAr, OCH_2Ar
R_1 = H, Alkyl group



2, Viloxazine



3, R=OH
4, R=OMe
5, R=H

Chemistry

The synthetic route to **3** and **4** is outlined in Scheme I. The treatment of 1-benzyl-3-piperidone (**6**)[9] with dimethyloxosulfonium methylide[10] afforded the epoxide **7**. Reaction of **7** with *o*-ethoxyphenol and NaOH yielded the 3-piperidinol **8**, which was catalytically hydrogenolyzed to

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[‡] Istituto Policattedra di Discipline Biologiche.
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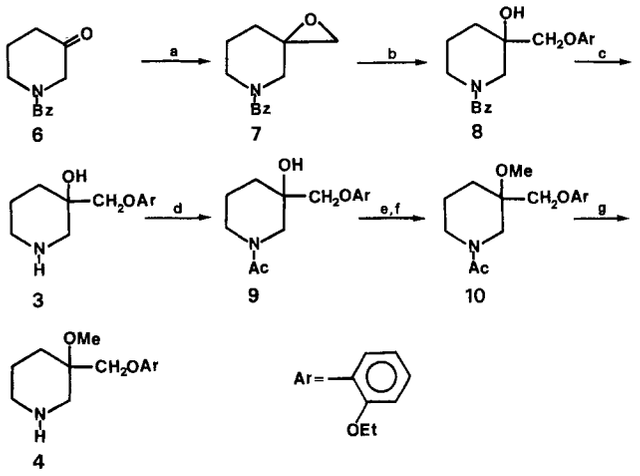
Table I. Pharmacological Activity and Approximate Acute Toxicity of Piperidine Derivatives 3–5 and Reference Drugs Viloxazine (2) and Desipramine in Orally Treated Mice

compound	LD, mg/kg po	reserpine antagonism: ED,[a] mg/kg po		pentylenetetrazole antagonism: ED,[a] mg/kg po	amphetamine antagonism: ED,[a] mg/kg po
		ptosis	hypothermia		
3	150	1.5 (0.9–3.1)	15.2 (13.5–19.1)	[50][b]	5.5 (5.1–5.9)
4	200	[25][b]	[25][b]	[50][b]	[50][b]
5	300	3.7 (2.7–5.4)	17.0 (11.1–31.0)	[50][b]	9.4 (7.4–19.7)
viloxazine (2)	600	1.5 (0.7–3.3)	4.6 (3.1–7.0)	10.3 (6.4–20.7)	15.6 (13.2–22.4)
desipramine	300	1.8 (1.0–3.4)	1.7 (0.9–3.3)	33.1 (24.5–41.4)	40.3 (29.4–65.9)

[a] In parentheses are the confidence limits for $p = 0.01$. [b] Brackets mean inactive at the screening dose.

Scheme I[a]



[a] a = Me_2SOCH_2; b = o-EtO-C_6H_4OH/NaOH; c = H_2/Pd/C; d = Ac_2O/pyr; e = NaH/toluene; f = MeI; g = HCl.

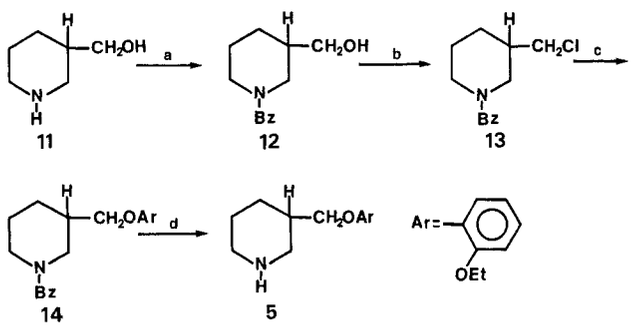
3. Acetylation of 3 with acetic anhydride, followed by treatment of the intermediate 9 with NaH and MeI and by removal of the protecting group, afforded 4. The structure of 8 was assigned on the basis of the knowledge of the importance of the steric factors in the ring-opening reactions of epoxides under basic conditions.[11] This assignment was then confirmed by the fact that 8 was recovered unchanged when submitted to oxidation with Jones reagent.

Compound 5 was synthesized as indicated in Scheme II. Treatment of 3-(hydroxymethyl)piperidine (11)[12] with benzyl chloride gave the *N*-benzyl derivative 12, which by reaction with $SOCl_2$ and anhydrous hydrogen chloride was converted to the corresponding chloromethyl derivative 13. The alkylation of *o*-ethoxyphenol with 13 in the presence of NaOH afforded 14, which by reductive debenzylation yielded 5.

Pharmacology

Compounds 3–5 were screened for their antidepressant activity in mice by using as primary tests the antagonism to reserpine-induced palpebral ptosis and hypothermia and amphetamine antagonism. In addition, their approximate acute toxicity was evaluated, together with their ability to prevent maximal extensor seizures induced in mice by pentylenetetrazole (Table I).

Scheme II[a]



[a] a = $BzCl/K_2CO_3$; b = $HCl/CHCl_3/SOCl_2$; c = o-EtO-C_6H_4OH/NaOH; d = H_2/Pd/C.

Table II. In Vitro Reuptake Inhibition in Pig Occipital (NE), Frontal (5-HT), and Striatal (DA) Synaptosomes by Piperidine Derivatives 3–5, Viloxazine (2), and Desipramine

compound	IC_{50},[a] μM		
	[^{3}H]NE	[^{3}H]-5-HT	[^{3}H]DA
3	0.66 (±0.07)	65 (±3)	20 (±4)
4	1.3 (±0.1)	110 (±10)	68 (±7)
5	0.97 (±0.08)	95 (±5)	62 (±3)
viloxazine (2)	0.22 (±0.01)	20 (±5)	38 (±4)
desipramine	0.0032 (±0.0008)	0.42 (±0.05)	6.1 (±0.3)

[a] Concentrations necessary for 50% inhibition are means ± SEM of four determinations.

In common with the reference standard drugs viloxazine (2) and desipramine, compounds 3 and 5 showed clearcut reserpine antagonism, in the presence of a selective inhibition of cerebral NE reuptake. The 3-methoxy derivative 4 at the screened doses was found to be devoid of the biological activities investigated.

At variance with the reference standard drugs, no antagonism was observed to pentylenetetrazole-induced symptoms for 3–5.

As far as the approximate acute toxicity is concerned, all the compounds tested proved to be more toxic than viloxazine (2) and equally as toxic (i.e., 5) as or more toxic (i.e., 3 and 4) than desipramine.

Compounds 3–5 were also submitted to in vitro evaluation for possible reuptake inhibition of biogenic amines in synaptosomal fractions from the occipital and frontal cerebral cortex and the striatum nucleus of pig (Table II). The results obtained from these tests showed that the piperidine derivatives 3–5 possess a potency comparable to that of the reference compound viloxazine (2) and that the 3-methoxy analogue 4 is the least active of the series. Like viloxazine (2), compounds 3–5 were more potent on NE than on DA or 5-HT uptake inhibition. At variance with 2, 3–5 showed an inhibiting activity slightly higher on DA than on 5-HT uptake.

In vivo and in vitro tests showed that compounds 3 and 5 possess a biological activity comparable to that of viloxazine (2). The similar activity shown by 3 and 5 would

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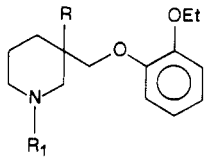
Table III. 3-[(2-Ethoxyphenoxy)methyl]piperidine Derivatives



compound	R	R_1	mp or bp (mmHg), °C	recrystn solvent	yield,[a] %	formula[b]	^{1}H NMR, δ
3	OH	H	82–83	PE[c]	92	$C_{14}H_{21}NO_3$	($CDCl_3$) 1.43 (t, 3, J = 7.2 Hz, CH_2CH_3), 3.88 (s, 2, OCH_2COH), 4.06 (q, 2, J = 7.2 Hz, CH_2CH_3)
3·HCl	OH	H	132–133	EtOH/Et_2O		$C_{14}H_{22}ClNO_3$	(D_2O) 1.46 (t, 3, J = 7.2 Hz, CH_2CH_3), 4.08 (s, 2, OCH_2COH), 4.21 (q, 2, J = 7.2 Hz, CH_2CH_3)
4	OMe	H	123–125 (0.017)		18[d]	$C_{15}H_{23}NO_3$	($CDCl_3$) 1.42 (t, 3, J = 7.2 Hz, CH_2CH_3), 3.42 (s, 3, OCH_3), 3.96 (s, 2, OCH_2CO), 4.09 (q, 2, J = 7.2 Hz, CH_2CH_3)
4·$H_2C_2O_4$	OMe	H	87–89	MeOH/Et_2O		$C_{17}H_{25}NO_7$	(D_2O) 1.39 (t, 3, J = 7.2 Hz, CH_2CH_3), 3.36 (s, 3, OCH_3), 3.96 and 4.29 (2 d, 2, J = 11.5 Hz, OCH_2CO), 4.19 (q, 2, J = 7.2 Hz, CH_2CH_3)
5	H	H				$C_{14}H_{21}NO_2$	($CDCl_3$) 1.38 (t, 3, J = 7.0 Hz, CH_2CH_3), 3.85 (d, 2, J = 5.6 Hz, OCH_2CH), 4.08 (q, 2, J = 7.0 Hz, CH_2CH_3)
5·HCl	H	H	132–134	EtOH/Et_2O	57	$C_{14}H_{22}ClNO_2$	(D_2O) 1.39 (t, 3, J = 7.0 Hz, CH_2CH_3), 4.03 (m, 2, OCH_2CH), 4.15 (q, 2, J = 7.0 Hz, CH_2CH_3)
8	OH	Bz	190–192 (0.02)		68	$C_{21}H_{27}NO_3$	($CDCl_3$) 1.25 (t, 3, J = 7.0 Hz, CH_2CH_3), 3.55 (s, 2, CH_2Ph), 3.97 (s, 2, OCH_2COH), 4.00 (q, 2, J = 7.0 Hz, CH_2CH_3)
14	H	Bz				$C_{21}H_{27}NO_2$	($CDCl_3$) 1.33 (t, 3, J = 6.8 Hz, CH_2CH_3), 3.48 (s, 2, CH_2Ph), 3.80 (d, 2, J = 5.6 Hz, OCH_2CH), 3.94 (q, 2, J = 6.8 Hz, CH_2CH_3)
14·$H_2C_2O_4$	H	Bz	173–175	MeOH	21	$C_{23}H_{29}NO_6$	(D_2O) 1.30 (t, 3, J = 7.0 Hz, CH_2CH_3), 3.95 (d, 2, J = 6.9 Hz, OCH_2CH), 4.04 (q, 2, J = 7.0 Hz, CH_2CH_3), 4.32 (d, 2, J = 3.6 Hz, CH_2Ph)

[a] No efforts were made to optimize yields. [b] Anal. C, H, N. [c] PE = petroleum ether (bp 80–100 °C). [d] Overall yield from 3.

seem to indicate that the alcoholic group of 3 does not play a fundamental role in determining the antidepressant activity of this compound. On the contrary, the results obtained with the 3-methoxy analogue 4 show that the substitution of the alcoholic proton of 3 with a methyl group leads to the reduction or to the complete abolition of the biological activities investigated, in vitro or in vivo, respectively.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra for comparison of compounds were taken on paraffin oil mulls or as liquid film, on a Perkin-Elmer Model 1310 instrument. ^{1}H NMR spectra were obtained in ca. 10% $CDCl_3$ [for the free bases (Me_4Si)] and D_2O [for the salts ($Me_3SiCD_2CD_2CO_2Na$)] solutions with a Varian EM360A spectrometer. The proton magnetic resonance assignments were established on the basis of the expected chemical shifts and the multiplicity of the signals. Evaporation was made in vacuo (rotating evaporator). $MgSO_4$ was always used as the drying agent. Me_2SO was distilled over CaH_2. Elemental analyses were performed by our analytical laboratory and agreed with theoretical values to within ±0.4%.

5-Benzyl-1-oxa-5-azaspiro[2.5]octane (7). A solution of compound 6[9] (24.0 g, 0.127 mol) in anhydrous Me_2SO (100 mL) was added dropwise with stirring to a solution of dimethyloxosulfonium methylide,[10] prepared under nitrogen from NaH (3.38 g, 0.141 mol) and trimethyloxosulfonium iodide[10] (31.0 g, 0.141 mol) in anhydrous Me_2SO (240 mL). The resulting mixture was stirred at room temperature for 6 h and then at 50 °C for 40 min. After the mixture was cooled and H_2O (70 mL) was added, the mixture was extracted with ether, and the combined extracts were washed with H_2O, dried, and evaporated to dryness. The crude residue (19.5 g) was distilled to give pure 7 (17.2 g, 67%): bp 104–105 °C (0.25 mm); ^{1}H NMR δ 2.45 (s, 2, CH_2O), 2.65 (s, 2, $OCCH_2N$), 3.59 (s, 2, $PhCH_2$). Anal. ($C_{13}H_{17}NO$) C, H, N.

1-Benzyl-3-[(2-ethoxyphenoxy)methyl]-3-piperidinol (8). A solution of 7 (20.0 g, 0.098 mol) in dioxane (40 mL) was added dropwise at 105–110 °C to a stirred mixture of NaOH (4.0 g, 0.10 mol) and o-ethoxyphenol (40.8 g, 0.295 mol) in dioxane (60 mL). After the mixture was stirred at 110 °C for 6 h and for 12 h at room temperature, it was treated with 10% aqueous NaOH (300 mL) and extracted with ether. Evaporation of the organic extracts, washed in succession with H_2O, 10% aqueous NaOH, and H_2O, yielded an oily residue (38.5 g), which was distilled to give pure 8 (see Table III).

3-[(2-Ethoxyphenoxy)methyl]-3-piperidinol (3). A solution of 8 (9.0 g, 0.026 mol) in EtOH (150 mL) was shaken under hydrogen at 50 °C and atmospheric pressure in the presence of 10% Pd on charcoal (2.75 g). When the absorption of hydrogen stopped, the catalyst was filtered off, and the solution was evaporated to give a solid residue (7.1 g), which was crystallized to yield pure 3 (see Table III).

3-[(2-Ethoxyphenoxy)methyl]-3-methoxypiperidine (4). Anhydrous pyridine (10.4 g, 0.130 mol) and Ac_2O (22.3 g, 0.12 mol) were added to a solution of 3 (6.0 g, 0.024 mol) in anhydrous toluene (85 mL). The mixture was refluxed for 5 h and evaporated. The residue was extracted with $CHCl_3$ and the organic extract washed (10% HCl, saturated aqueous $NaHCO_3$, and H_2O) and evaporated to give an oily residue (6.2 g) consisting essentially of **1-acetyl-3-[(2-ethoxyphenoxy)methyl]-3-piperidinol (9)** [IR 1636 cm^{-1} (amide C=O); ^{1}H NMR δ 1.32 (t, 3, J = 7.0 Hz, CH_2CH_3), 2.17 (s, 3, $COCH_3$), 3.97 (s, 2, OCH_2COH), 4.10 (q, 2, J = 7.0 Hz, OCH_2CH_3)], which was directly used in the following transformation.

A solution of 9 (4.5 g, 0.016 mol) in anhydrous toluene (50 mL) was added dropwise to a stirred suspension of NaH (6.0 g, 0.25 mol) in anhydrous toluene (70 mL). The resulting mixture was refluxed for 3 h and then treated at room temperature with MeI (50 g, 0.35 mol) and refluxed for 2 h. The cooled mixture was treated with an additional portion of MeI (14 g, 0.10 mol) and stirred for 12 h at 20 °C and then for 3 h at refluxing temperature. Evaporation of the washed (H_2O, 10% aqueous HCl, and H_2O) organic layer yielded an oily residue (2.7 g) consisting almost exclusively of **1-acetyl-3-[(2-ethoxyphenoxy)methyl]-3-methoxypiperidine (10)** [IR 1640 cm^{-1} (amide C=O); ^{1}H NMR δ 1.40 (t, 3, J = 7.0 Hz, CH_2CH_3), 2.14 (s, 3, $COCH_3$), 3.30 (s, 3, OCH_3), 3.97 (s, 2, OCH_2COCH_3), 4.02 (q, 2, J = 7.0 Hz, CH_2CH_3)], which was directly used in the following transformation.

A solution of 10 (5.4 g, 0.017 mol) in aqueous 5% HCl (140 mL) was refluxed for 2 h, cooled, basified with concentrated aqueous

NH_3, and extracted with $CHCl_3$. Evaporation of the washed (H_2O) and filtered extracts yielded an oily residue (3.5 g), which was distilled to give pure **4** (see Table III).

3-(Hydroxymethyl)piperidine (11). Compound **11** was prepared by a modification of the procedure of Sandborn and Marvel.[12] Treatment of ethyl nicotinate with Na and EtOH under the conditions previously described[12] yielded an oily residue that even after distillation appeared to be constituted by an ca. 60:40 mixture of partially reduced product and **11**, respectively (^1H NMR, GLC). A solution of this mixture (3.7 g) in EtOH (65 mL) was shaken for 6 h under hydrogen at room temperature and atmospheric pressure in the presence of 10% Pd on charcoal. The catalyst was filtered off, and the solution was evaporated to give an oily residue (3.6 g), which was distilled to yield pure **11** (2.3 g): bp 80–82 °C (0.3 mm); n^{20}_D 1.4959 [lit.[12] bp 106–107 °C (3.5 mm); n^{20}_D 1.4964]; ^1H NMR δ 3.43 (d, 2, J = 6.0 Hz, CH_2O).

1-Benzyl-3-(chloromethyl)piperidine (13). A solution of **11** (2.3 g, 0.02 mol) in anhydrous Me_2CO (20 mL) was treated with benzyl chloride (2.8 g, 0.022 mol) and solid anhydrous K_2CO_3 (3.0 g, 0.022 mol), and the mixture was stirred for 24 h at room temperature, filtered, and evaporated. The residue was dissolved in 10% aqueous HCl and extracted with Et_2O. The aqueous layer was made basic with solid KOH and extracted with Et_2O. The washed (H_2O) and dried extracts gave, after evaporation, practically pure **1-benzyl-3-(hydroxymethyl)piperidine (12)** (3.2 g) [^1H NMR δ 3.56 (s, 2, CH_2Ph), 7.46 (s, 5, Ph)], which was directly used in the following transformation.

A solution of **12** (3.2 g, 0.016 mol) in $CHCl_3$ (20 mL) was saturated with HCl and then treated dropwise at reflux temperature with $SOCl_2$ (10.0 g, 0.084 mol). The resulting mixture was refluxed for 1.5 h and evaporated to yield a residue (3.5 g), which was dissolved in H_2O, basified with solid KOH, and extracted with Et_2O. Evaporation of the washed (H_2O) and dried extracts gave an oily residue (1.8 g), which was distilled to yield **13** (1.4 g): bp 92–93 °C (0.04 mm); ^1H NMR δ 3.49 (d, 2, J = 6.0 Hz, CH_2Cl), 3.58 (s, 2, CH_2Ph), 7.42 (s, 5, Ph). Anal. ($C_{13}H_{18}ClN$) C, H, N.

1-Benzyl-3-[(2-ethoxyphenoxy)methyl]piperidine (14). A mixture of **13** (8.0 g, 0.036 mol), *o*-ethoxyphenol (5.0 g, 0.036 mol), and powdered NaOH (3.0 g, 0.075 mol) in anhydrous EtOH (10 mL) was heated at 100 °C in an autoclave for 30 h. Evaporation of the cooled mixture gave a residue, which was dissolved in CH_2Cl_2 (100 mL). The organic phase was washed with 10% aqueous NaOH, extracted twice with 40 mL of 10% aqueous HCl in order to remove the most water soluble salt of unreacted **13**, and then shaken with 20% aqueous NaOH (40 mL). Evaporation of the filtered CH_2Cl_2 extracts yielded an oily residue (3.7 g) consisting almost exclusively of **14**, which was dissolved in a 4:1 Et_2O/MeOH mixture and treated with a solution of oxalic acid in the same solvent mixture. The crude product was filtered and recrystallized to give the pure acid oxalate of **14** (see Table III).

3-[(2-Ethoxyphenoxy)methyl]piperidine (5). A solution of **14** (1.5 g, 4.6 mmol) in EtOH (12 mL) was shaken under hydrogen at 50 °C and atmospheric pressure for 5 h in the presence of 10% Pd on charcoal (0.30 g). The catalyst was separated by filtration, and the solution was evaporated to give an oily residue (0.7 g), which was dissolved in Et_2O and treated with a slightly excessive quantity of Et_2O·HCl. The crude precipitate (0.71 g) was filtered off and crystallized to yield pure **5**·HCl (see Table III).

Pharmacology. All in vivo tests were conducted on male ICEM:CET (SPF Caw) mice weighing 18–22 g. Four to 10 animals were used at each dose level. All the compounds were administered orally by gavage, dissolved in 0.5% Methocel in a volume of 0.1 mL/10 g of body weight.

The in vitro tests were carried out on synaptosomal preparations from pig brain.

Reserpine Antagonism, Pentylenetetrazole Antagonism, and Approximate Acute Toxicity. These tests were performed as described elsewhere.[13]

Amphetamine Antagonism. The hyperthermal effect of amphetamine was the main activity taken into consideration. *d*-Amphetamine sulfate was administered intraperitoneally at a dose of 10 mg/kg to groups of 10 male mice. All the compounds were administered at the screening dose of 50 mg/kg, 30 min before amphetamine, and the active ones were subsequently tested at lower doses, in order to obtain an ED_{50} by "eye-fit" linear plots on semilogarithmic paper. In each test, the initial temperature was taken, and then the temperature was taken twice more: once 5 min before injection of amphetamine to check the hypothermal effect of the drugs under consideration, and the second time 30 min after the amphetamine injection. Tests were conducted in a soundproof room at constant temperature (23 ± 1 °C) and humidity levels (55% ± 5% relative humidity).

Uptake of *dl*-[^{3}H]Norepinephrine, [^{3}H]Serotonin, and [^{3}H]Dopamine. Pig brains were obtained from a local slaughterhouse and rapidly dissected to remove the occipital and frontal cortex and the corpus striatum; synaptosomal fractions were then prepared as previously described.[14] The uptake of [^{3}H]NE (15 nM), [^{3}H]-5-HT (4 nM), and [^{3}H]DA (2 nM) into occipital cortex, frontal cortex, and corpus striatum synaptosomes, respectively, was measured as previously described,[14] in the presence of various concentrations of the tested compounds. Nonspecific transport was determined by measuring the amount of uptake in the presence of desipramine (10 μM), chlorimipramine (10 μM), or benztropine (100 μM), for NE, 5-HT, and DA transport, respectively. This nonspecific transport was also evaluated by measuring the radioactivity of the synaptosomal preparations in the absence of drugs when the temperature of the incubation mixtures was between 0 °C and 4 °C. The concentrations of the compounds that inhibit specific monoamine uptake by 50% (IC_{50}) were determined by log-probit analysis with four concentrations of the displacers, each performed in triplicate.

The following labeled compounds were used: *dl*-[7-^{3}H(N)]-norepinephrine (11.8 Ci/mmol) hydrochloride, [7-^{3}H(N)]dopamine (28 Ci/mmol) free base, and [1,2-^{3}H(N)]serotonin (26.2 Ci/mmol) bioxalate.

Acknowledgment. This work has been supported in part by a grant from the Consiglio Nazionale delle Ricerche and the Ministero della Pubblica Istruzione.

Registry No. **3**, 104778-52-1; **3**·HCl, 104778-60-1; **4**, 104778-53-2; **4**·$H_2C_2O_4$, 104778-61-2; **5**, 104778-54-3; **5**·HCl, 28569-12-2; **6**, 40114-49-6; **7**, 97267-35-1; **8**, 104778-55-4; **19**, 104778-56-5; **10**, 104778-57-6; **11**, 4606-65-9; **12**, 85387-44-6; **13**, 104778-58-7; **14**, 104778-59-8; **14**·$H_2C_2O_4$, 104778-62-3; 2-$EtOC_6H_4OH$, 94-71-3; BzCl, 100-44-7; ethyl nicotinate, 614-18-6.

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