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ANTIDEPRESSANT PHENYLOXYALKYLAMINES

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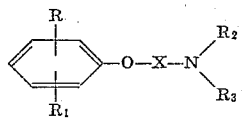
This invention relates to antidepressant compositions and methods of producing antidepressant activity. The compositions of this invention are unexpectedly useful in the treatment of a wide range of mild to severe depressive disorders.

The novel compositions of this invention have a pharmacological profile strikingly similar to that of imipramine, a known antidepressant, but comprise as the active ingredient a compound of unrelated chemical structure. A prominent pharmacological property of these compositions is their ability to prevent reserpine-induced ptosis in rats. This pharmacological procedure is especially useful to characterize the antidepressant activity of imipramine.

Unlike other antidepressants, the compositions of this invention do not inhibit monoamine oxidase activity in vivo. These compositions are further characterized by relative freedom from side effects, a rapid onset of action and effectiveness in both mild and severe depression.

More specifically the antidepressant compositions of this invention comprise in dosage unit form a nontoxic pharmaceutical carrier and a phenoxyalkylamine of the following formula:



(I)

in which:

R and R_1 represent hydrogen, chlorine, bromine, lower alkyl of one to four carbon atoms, lower alkoxy of one to four carbon atoms or trifluoromethyl;

X represents the divalent group

$-CH_2CH_2-$, $-CHCH_2-$ (with CH_3), $-CH_2CH-$ (with CH_3) or $CC_2CH_2CH_2-$

R_2 represents hydrogen or methyl; and

R_3 represents methyl or, when taken together with R_2, forms with the nitrogen to which they are attached a pyrrolidine or piperidine ring.

A preferred composition in accordance with this invention comprises the compound N,N-dimethyl-2-(2,6-dichlorophenoxy)propylamine.

The nontoxic pharmaceutically acceptable acid addition salts of the compounds of the above formula are also included within the scope of this invention since such salts are likewise effective for producing antidepressant activity. Both organic and inorganic acids can be employed to form pharmaceutically acceptable salts, illustrative acids being sulfuric, nitric, phosphoric hydrochloric, citric, acetic, lactic, tartaric, ethanedisulfonic, sulfamic, succinic, fumaric, maleic, benzoic and the like. These salts are prepared by methods known to the art.

The pharmaceutical compositions of this invention comprise a phenoxyalkylamine of Formula I in an amount sufficient to produce antidepressant activity. Preferably the compositions contain from about 10 mg. to about 500 mg. of medicament, advantageously from about 25 mg. to about 400 mg. per dosage unit.

The pharmaceutical carrier employed in the composition can be either a solid or liquid. Exemplary of solid carriers are lactose, magnesium stearate, terra alba, sucrose, talc, stearic acid, gelatin, agar pectin or acacia.

Exemplary of liquid carriers are peanut oil, olive oil, sesame oil and water. Similarly the carrier or diluent may include a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed and are prepared by methods well known to the art. Thus, if a solid carrier is used the composition can be tabletted, used as a pharmaceutical powder, placed in a hard gelatin capsule or in the form of a troch or lozenge. If a liquid carrier is used the composition can be in the form of a soft gelatin capsule or a liquid suspension. Parenteral dosage forms are obtained by dissolving a water-soluble salt of the active medicament in water or saline solution in a concentration such that 1 cc. of the solution contains from about 10 mg. to about 50 mg. of active medicament. The solution can then be filled into single or multiple dose ampules.

The method for using the compositions in accordance with this invention comprises administering internally to animals, including human beings, a phenoxyalkylamine of Formula I or a nontoxic organic or inorganic acid addition salt thereof, preferably with a nontoxic pharmaceutical carrier such as described above, in an amount sufficient to produce antidepressant activity. The compositions are administered to treat both mild and severe depression as exhibited by mildly depressed outpatients and more severely disturbed and hospitalized depressed patients, respectively. The active medicament in dosage units as described above is administered orally or parenterally in repeated doses in a range of from about 10 mg. to about 1500 mg. daily. In mild depression, the daily dosage is from about 10 mg. to about 250 mg. of active medicament, advantageously from about 25 mg. to about 250 mg. In severe depression, the daily dosage is from about 250 mg. to about 1500 mg. of active medicament, advantageously from about 250 mg. to about 1200 mg. When the methods described above are carried out, antidepressant activity is produced.

The compounds of Formula I above which form the active medicament in the pharmaceutical compositions and are useful in the method of this invention are prepared by the following general procedure. The appropriate phenol (as the sodium salt) is condensed with the aminoalkyl halide to give the product directly or alternatively condensed with an α-haloaminoalkylamide and the resultant phenoxyamide reduced with for example lithium aluminum hydride to the alkylamine.

The following examples are not limiting but set forth in more detail the preparative procedures for the compounds of Formula I and illustrate specific pharmaceutical compositions of this invention.

Example 1

To a suspension of 1.9 g. of sodium hydride in 50 ml. of dry toluene is rapidly added a solution of 8.8 g. of 2,6-dimethylphenol in 60 ml. of dry toluene. The mixture is stirred at reflux for one hour, then cooled in an ice bath while a solution of 15 g. of N,N-dimethyl-α-bromopropionamide (prepared from the reaction of α-bromopropionyl bromide and dimethylamine) is added. The mixture is stirred at reflux for 12 hours and then filtered. The filtrate is washed with 10 percent sodium hydroxide solution and then with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is distilled at 110–123° C./0.6–0.8 mm. to give N,N-dimethyl-α-(2,6-dimethylphenoxy)propionamide.

To a stirred suspension of 11.7 g. of lithium aluminum hydride in 250 ml. of dry ether is added a solution of 25.3 g. of N,N-dimethyl-α-(2,6-dimethylphenoxy)propionamide in 250 ml. of dry ether. During the addition the exothermic reaction warms the mixture to reflux and an additional 300 ml. of ether is added. The mixture is

stirred at reflux for two and one-half hours and then at room temperature for 61 hours. A solution of 24.3 ml. of ethyl acetate in 50 ml. of ether is added during 15 minutes, followed by 22.5 ml. of water during 20 minutes.

The mixture is stirred at room temperature for one hour and filtered. The filtrate is dried over sodium sulfate and concentrated. The residue is distilled at 70–74° C./0.3 mm. to give N,N-dimethyl-2-(2,6-dimethylphenoxy)propylamine.

To a sample of the amine in ether is added ethereal hydrochloric acid to form the hydrochloride salt. Recrystallization from absolute ethanol-ether and then from isopropanol-ether yields the N,N-dimethyl-2-(2,6-dimethylphenoxy)propylamine hydrochloride, M.P. 161.5–162.5° C.

Example 2

Using the same procedure as in Example 1, 2.6 g. of sodium hydride, 16.3 g. of 2,6-dichlorophenol and 21.1 g. of N,N-dimethyl-α-bromopropionamide are reacted to yield N,N-dimethyl-α-(2,6-dichlorophenoxy)propionamide.

Similarly, 6.25 g. of lithium aluminum hydride and 17.6 g. of N,N-dimethyl-α-(2,6-dichlorophenoxy)propionamide are refluxed together for 22 hours to yield N,N-dimethyl-2-(2,6-dichlorophenoxy)propylamine.

Ethereal hydrochloric acid is added to a solution of a sample of this amine in ether to form the hydrochloride salt. Recrystallization from isopropanol-ether yields N,N-dimethyl-2-(2,6-dichlorophenoxy)propylamine hydrochloride, M.P. 175.5–177.5° C.

Example 3

A solution of 22.5 g. of anhydrous dimethylamine in 26.3 g. of formic acid and 50 g. of 2,6-dichlorophenoxyacetone (prepared from the reaction of 2,6-dichlorophenol and chloroacetone) is heated at a reaction temperature of 120–125° C. until the evolution of carbon dioxide almost ceases. The mixture is cooled to room temperature and made acidic with dilute hydrochloric acid. The aqueous layer is separated, washed with ether, made alkaline with 40% sodium hydroxide and the amine taken up with ether. After drying over potassium carbonate the ether is removed by evaporation and the oily residue is distilled at 90–91° C./0.25 mm. to give a yelow oil, 2-(2,6-dichlorophenoxy)-N,N-1-trimethylethylamine.

A sample of this amine in ether is treated with anhydrous hydrochloric acid, and the colorless hydrochloride salt is collected and recrystallized from alcohol-ether, then isopropanol, to give white crystals, M.P. 196–197° C.

Example 4

A dry toluene solution of β-dimethylaminoethyl chloride is prepared by trituration of 144.1 g. of the amine hydrochloride in toluene with large excess of potassium hydroxide pellets.

2,6-dichlorophenol (81.5 g.) in 300 ml. of dry toluene is added slowly to a stirred suspension of 12.5 g. of sodium hydride in 200 ml. of toluene over a period of 20 minutes. The mixture is stirred at reflux for one hour and cooled. The toluene solution of β-dimethylaminoethyl chloride is added dropwise over a period of one hour and the well-stirred mixture is refluxed for eight hours. After cooling to room temperature the mixture is treated with 150 ml. of water followed by 250 ml. of 3 M hydrochloric acid. The toluene layer is separated and extracted with 250 ml. of 3 M hydrochloric acid. The combined aqueous acid solution is extracted with ether and then made basic with 40% sodium hydroxide. The amine is taken up with ether and the aqueous layer is extracted several times with ether. The combined ether solution is extracted once with water, dried over potassium carbonate, and evaporated. The amber residue is

distilled at 90–92° C./0.8–0.9 mm. to give N,N-dimethyl-2-(2,6-dichlorophenoxy)ethylamine.

A sample of N,N-dimethyl-2-(2,6-dichlorophenoxy)ethylamine in 50 ml. of absolute ether is treated with anhydrous hydrochloric acid until the mixture is acidic. The solid is collected by filtration and is recrystallized from absolute ethanol-ether to give the hydrochloride salt, M.P. 172–174° C.

Example 5

To a stirred suspension of 2.9 g. of sodium hydride in 75 ml. of sodium-dried toluene is added a solution of 13.6 g. of 2,6-dimethylphenol in 100 ml. of dry toluene over a 20 minute period. The mixture is stirred at reflux for one hour and cooled. A toluene solution of 3-dimethylaminopropylchloride, which is prepared by triturating 35.4 g. of 3-dimethylaminopropylchloride hydrochloride with an excess of potassium hydroxide pellets under toluene, is added over a one hour period. Reflux is resumed and continued for eight hours. After the mixture is cooled, 50 ml. of water and 75 ml. of 3 N hydrochloric acid are added. The toluene layer is separated and extracted with 75 ml. of 3 N hydrochloric acid. The combined aqueous extract is washed with ether, made basic with 40% sodium hydroxide and extracted with ether. The ether solution is washed with water, dried over potassium carbonate and concentrated. The residue is distilled to give a colorless oil, N,N-dimethyl-3-(2,6-dimethylphenoxy)propylamine, B.P. 104–107° C./0.5–0.75 mm.

Anhydrous hydrogen chloride is bubbled into an ether solution of a sample of this amine. The white precipitate which forms is recrystallized from ethanol-ether to yield the hydrochloride salt, M.P. 170–172° C.

Example 6

To a stirred suspension of 4.7 g. of sodium hydride in 110 ml. of sodium-dried toluene is added a solution of 25.1 g. of 2,4-dichlorophenol in 180 ml. of dry toluene over a 15 minute period. The mixture is stirred at reflux for 55 minutes, then cooled in an ice bath during the 15 minute addition of a toluene solution of β-dimethylaminoethyl chloride, prepared by triturating 46 g. of β-dimethylaminoethyl chloride hydrochloride with potassium hydroxide pellets under toluene. After an eight hour period of stirring at reflux the mixture is cooled and 50 ml. of water and 80 ml. of 3N hydrochloric acid are added. The toluene layer is separated and washed with 3N hydrochloric acid. The combined acid extract is washed with ether, made basic with 40 percent sodium hydroxide solution and extracted with ether. The ether extract is washed with distilled water, dried over sodium sulfate and concentrated. Fractional distillation of the residue yields a light yellow oil, N,N-dimethyl-2-(2,4-dichlorophenoxy)ethylamine, B.P. 94–107° C./.35 mm.

Ethereal hydrochloric acid is added to a solution of a sample of this amine in ether. The resulting solid is recrystallized from isopropanol-ether to yield the hydrochloride salt, M.P. 125.5–127.5° C.

Example 7

To a stirred suspension of 7.5 g. of sodium hydride in 350 ml. of sodium-dried toluene is added a solution of 50 g. of 2,6-diisopropylphenol in 200 ml. of dried toluene over a 30 minute period. The mixture is stirred for one hour at 25° C. and for 70 minutes at reflux temperature. To the cooled mixture is added a toluene solution of β-dimethylaminoethyl chloride (prepared by triturating 140 g. of β-dimethylaminoethyl chloride hydrochloride with excess potassium hydroxide pellets under toluene) during a 20 minute period. Reflux is resumed and continued for 12 hours. To the cooled, stirred mixture is added 100 ml. of water and 160 ml. of 3 N hydrochloric acid. The toluene layer is separated and washed with 3 N hydrochloric acid. This acidic aqueous solution is washed with ether, made basic with excess 40% sodium hydroxide so-

lution and extracted with ether. The ether extract is washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated. Vacuum distillation of the residue gives a colorless oil, N,N-dimethyl-2-(2,6-diisopropylphenoxy)ethylamine, B.P. 84–88° C./.3 mm.

Anhydrous hydrogen chloride is bubbled into an ethereal solution of a sample of this amine until the mixture is acidic. The hydrochloride salt formed is recrystallized from isopropanol-ether, M.P. 207–210.5° C.

Example 8

To a stirred suspension of 2.9 g. of sodium hydride in 70 ml. of sodium-dried toluene is added a solution of 25.2 g. of 2,6-dibromophenol in 70 ml. of dry toluene over a 10 minute period. The mixture is stirred at reflux temperature for 55 minutes, then cooled in an ice bath while a toluene solution of β-dimethylaminoethyl chloride, which had been prepared by triturating 28.8 g. of β-dimethylaminoethyl chloride hydrochloride with potassium hydroxide pellets under toluene, is added over a 15 minute period. This mixture is stirred at reflux for eight hours, then cooled to room temperature. After addition of 30 ml. of distilled water and 50 ml. of 3 N hydrochloric acid, the toluene layer is separated and washed with 50 and 20 ml. portions of 3 N hydrochloric acid. The combined acid solution is washed with ether, made basic with 40 percent sodium hydroxide solution and extracted with ether. The ether extract is washed with distilled water, dried over potassium carbonate and concentrated. Fractional distillation of the residue yields a light yellow oil, N,N-dimethyl-2-(2,6-dibromophenoxy)ethylamine, B.P. 106–116° C./.35–.60 mm.

Ethereal hydrochloric acid is added to an ethereal solution of a sample of this oil. The hydrochloride salt is recrystallized from isopropanol-ether to give white crystals, M.P. 201–203.5° C.

Example 9

Following the general procedure of Example 4, the sodium 2,6-dichlorophenoxide (18.5 g.) prepared from sodium hydride and 2,6-dichlorophenol is reacted with 20.4 g. of N-(β-chloroethyl)pyrrolidine freshly liberated in toluene to give upon workup an oily residue which is distilled to give N-[2-(2,6-dichlorophenoxy)ethyl]pyrrolidine, B.P. 118–122° C./0.15 mm.; hydrochloride salt, M.P. 181.5–182.5° C.

Example 10

Similarly following the general procedure of Example 4, the sodium 2,6-dichlorophenoxide (18.5 g.) prepared from sodium hydride and 2,6-dichlorophenol is reacted with 22.3 g. of N-(β-chloroethyl)piperidine freshly liberated in toluene to give upon workup an oily residue which is distilled to give N-[2-(2,6-dichlorophenoxy)ethyl]piperidine, B.P. 121–124° C./0.15 mm.; hydrochloride salt, M.P. 185–186° C.

Example 11

A solution of 18.9 g. of N,N-dimethyl-2-(2,6-dichlorophenoxy)propylamine (prepared as in Example 2) in 75 ml. of benzene is added over a two hour period to a solution of 12.1 g. of cyanogen bromide in 100 ml. of benzene, at 50–55° C. The reaction mixture is heated at this temperature for two hours and then allowed to stand for 18 hours. The solution is extracted with dilute hydrochloric acid and then washed with water. The benzene is removed in vacuo and the residue is hydrolyzed for 24 hours with 14.6 g. of sodium hydroxide and 175 ml. of 65% ethanol. The solvents are removed in vacuo, toluene is added and then extracted with dilute hydrochloric acid. The acid extract is basified, extracted with ether and the dried ether extract is subsequently evaporated. The residue is distilled to give N-monomethyl-2-(2,6-dichlorophenoxy)propylamine, B.P. 96–116° C./.15 mm. The hydrochloride salt after recrystallization from ethanol/ether melted at 156–157° C.

Example 12

To the sodium alkoxide formed from 2.54 g. of sodium and 9.8 g. of N,N-dimethylaminoethanol in 60 ml. of N,N-dimethylaminoethanol is added 22.0 g. of o-trifluoromethylbromobenzene and the mixture is refluxed for about 20 hours. The reaction mixture is filtered and the excess aminoalcohol removed. Ether is added and then extracted with dilute hydrochloric acid. The acidic extract is made basic, saturated with potassium carbonate solution and extracted with ether which gives a residual oil, N,N-dimethyl-2-(2-trifluoromethylphenoxy)ethylamine, B.P. 122–124° C./22 mm. The styphnate salt melts at 188–188.5° C.

Example 13

Following the general procedure of Example 4, the sodium 3,5-bistrifluoromethylphenoxide prepared from 12.0 g. of 3,5-bis-trifluoromethylphenol and 2.6 g. of sodium hydride is reacted with 8.45 g. of N,N-dimethylaminoethyl chloride in 300 ml. of toluene. Working up the reaction mixture yields N,N-dimethyl-2-(3,5-bis-trifluoromethylphenoxy)ethylamine, B.P. 110° C./21 mm. The hydrochloride salt recrystallized from acetone melts at 193–193.5° C.

Example 14

To a stirred suspension of 8.4 g. of sodium hydride in 300 ml. of anhydrous toluene is added a solution of 50 g. of 2,6-dimethoxyphenol in 200 ml. of anhydrous toluene and the mixture is stirred and refluxed for two and one-half hours. The reaction mixture cooled in an ice-bath is treated slowly with N,N-dimethylaminoethyl chloride freshly liberated from 144 g. of its hydrochloride with potassium hydroxide pellets under toluene. Refluxing is resumed for 12 hours and then the reaction mixture is cooled in an ice-bath while 100 ml. of water and 85 ml. of 12 N hydrochloric acid are added. The separated toluene layer is acid washed and the combined acid extract is washed with ether, made basic with excess 40% sodium hydroxide solution and extracted with ether. The ether extract is washed with saturated sodium chloride solution, dried and concentrated. Fractional distillation of the residue yields N,N-dimethyl-2-(2,6-dimethoxyphenoxy)ethylamine, B.P. 107–115° C./0.7–0.85 mm. Hydrochloride salt, M.P. 186.5–187.5° C.

Example 15

To a mixture of 26.6 g. of lithium aluminum hydride in 700 ml. of ether is added over a period of one hour a solution of 80 g. of N,N-dimethyl-α-(2-chloro)phenoxypropionamide. The resulting mixture is stirred for two days at room temperature and the excess hydride then destroyed by careful addition of 25 ml. of water, 50 ml. of 10% sodium hydroxide solution and 25 ml. of water. The mixture is stirred for one hour and filtered. The dried ethereal filtrate is evaporated and the residue distilled in vacuo to give N,N-dimethyl-2-(2-chlorophenoxy)propylamine, B.P. 75° C./1.0 mm. Hydrochloride salt, M.P. 134.5–136° C.

Example 16

To a mixture of 19.7 g. of lithium aluminum hydride in 700 ml. of ether is added a solution of 50 g. of N,N-dimethyl-2-phenoxypropionamide in two liters of ether over a period of one hour. The resulting mixture is stirred at room temperature for three days and then treated cautiously with 25 ml. of water, 50 ml. of 10% sodium hydride solution and 25 ml. of water. This mixture is stirred for one hour, filtered and the dried filtrate evaporated. The residue is distilled in vacuo to give N,N-dimethyl-2-phenoxypropylamine, B.P. 54–59° C./0.5–0.6 mm. Hydrochloride salt, M.P. 146–147° C.

Example 17

Various strength capsules are prepared containing N,N-dimethyl-2-(2,6-dichlorophenoxy)propylamine either as the free base or an equivalent amount of a nontoxic

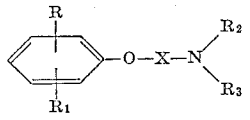
pharmaceutically acceptable acid addition salt thereof from the following ingredients:

Medicament, mg.	Lactose, mg.	Magnesium Stearate, mg.
10	330	2.0
25	310	2.0
50	255	3.0
100	115	3.0

The above ingredients are screened, mixed and filled into #2 hard gelatin capsules.

What is claimed is:

1. A method of producing antidepressant activity in animals and humans which comprises internally administering to said animals and humans a non-toxic but effective amount of a compound selected from the group consisting of a phenoxyalkylamine and a nontoxic pharmaceutically acceptable acid addition salt thereof, said phenoxyalkylamine having the following formula:



in which:

R and R_1 are members selected from the group consisting of hydrogen, chlorine, bromine, lower alkyl of from one to four carbon atoms, lower alkoxy of from one to four carbon atoms and trifluoromethyl;

X is an alkylene group selected from the group consisting of

$-CH_2CH_2-$, $-CHCH_2-$ (CH$_3$), $-CH_2CH-$ (CH$_3$) and $-CH_2CH_2CH_2-$

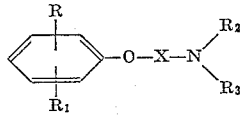
R_2 is a member selected from the group consisting of hydrogen and methyl; and

R_3 is a member selected from the group consisting of methyl and, when taken together with R_2 and the nitrogen to which they are attached, a pyrrolidine and a piperidine ring.

2. The method in accordance with claim 1 in which N,N-dimethyl-2-(2,6-dichlorophenoxy)propylamine is administered.

3. The method in accordance with claim 1 in which N,N-dimethyl-2-(2,6-dichlorophenoxy)propylamine hydrochloride is administered.

4. A method of producing antidepressant activity in animals and humans which comprises internally administering to said animals and humans a daily dosage of from about 10 mg. to about 250 mg. of an antidepressant selected from the group consisting of a phenoxyalkylamine and a nontoxic pharmaceutically acceptable acid addition salt thereof, said phenoxyalkylamine having the following formula:



in which:

R and R_1 are members selected from the group consisting of hydrogen, chlorine, bromine, lower alkyl of from one to four carbon atoms, lower alkoxy of from one to four carbon atoms and trifluoromethyl;

X is an alkylene group selected from the group consisting of

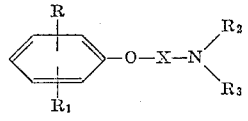
$-CH_2CH_2-$, $-CHCH_2-$ (CH$_3$), $-CH_2CH-$ (CH$_3$) and $-CH_2CH_2CH_2-$

R_2 is a member selected from the group consisting of hydrogen and methyl; and

R_3 is a member selected from the group consisting of methyl and, when taken together with R_2 and the nitrogen to which they are attached, a pyrrolidine and a piperidine ring.

5. The method in accordance with claim 4 in which a daily dosage of from about 10 mg. to about 250 mg. of N,N-dimethyl-2-(2,6-dichlorophenoxy)propylamine is administered.

6. A method of producing antidepressant activity in animals and humans which comprises internally administering to said animals and humans a daily dosage of from about 250 mg. to about 1500 mg. of an antidepressant selected from the group consisting of a phenoxyalkylamine and a nontoxic pharmaceutically acceptable acid addition salt thereof, said phenoxyalkylamine having the following formula:



in which:

R and R_1 are members selected from the group consisting of hydrogen, chlorine, bromine, lower alkyl of from one to four carbon atoms, lower alkoxy of from one to four carbon atoms and trifluoromethyl;

X is an alkylene group selected from the group consisting of

$-CH_2CH_2-$, $-CHCH_2-$ (CH$_3$), $-CH_2CH-$ (CH$_3$) and $-CH_2CH_2CH_2-$

R_2 is a member selected from the group consisting of hydrogen and methyl; and

R_3 is a member selected from the group consisting of methyl and, when taken together with R_2 and the nitrogen to which they are attached, a pyrrolidine and a piperidine ring.

7. The method in accordance with claim 6 in which a daily dosage of from about 250 mg. to about 1500 mg. of N,N-dimethyl-2-(2,6-dichlorophenoxy)propylamine is administered.

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