

5-(AMINOALKYL)-11-PHENYL-5H-DIBENZO
[b,e][1,4] DIAZEPINES
IN THE TREATMENT OF DEPRESSION

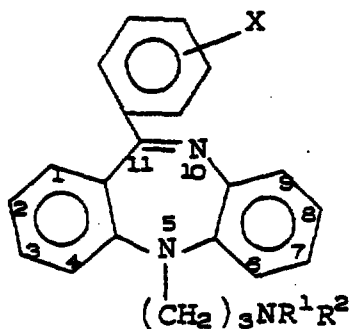
The present invention relates to certain 5-(aminoalkyl)-11-phenyl-5H-dibenzo[b,e][1,4] diazepines for use in treating depression in humans, and to certain of the compounds which are novel.

5. Wander, A. in British Patent 907,646 discloses preparation of certain of the dibenzodiazepines utilized in the method of this invention; e.g., the active ingredient of the compound of example 1 below in the form of the maleate salt.
10. Wander, A. in British Patent 959,994 discloses utility of reduced forms; e.g., 5-(aminoalkyl)-11-phenyl-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepines as parasympathologics, antihistamines, spasmolytics, tranquilizers and psychic energizers.
15. Greig, M. E., et al, in J. Med. Chem. 14, No. 2 page 153 (1971) discloses anaphylaxis activity of certain dibenzodiazepine homologs in mice particularly 2-chloro-5-(dimethylaminoethyl)-11-phenyl-5H-dibenzo[b,e][1,4]diazepine.
- According to the present invention there are
20. provided compounds having the formula:

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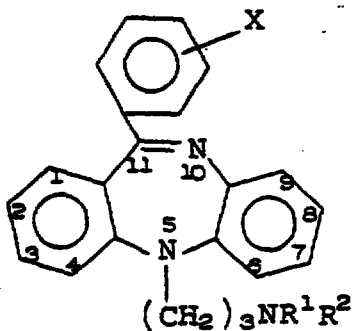
Formula I

wherein R^1 and R^2 each represent a hydrogen or a methyl group, and may be the same or different, and

X represents a hydrogen, chlorine, bromine or fluorine atom,

and the pharmaceutically acceptable acid addition salts thereof, for use in treating depression.

The invention also extends to compounds having the formula



Formula I

wherein R^1 and R^2 both represent a hydrogen atom or one represents a methyl group and the other represents a hydrogen atom.

3.

5.

- Pharmaceutically acceptable acid addition salts are
10. those salts which are physiologically compatible, such salts being formed either by strong or weak acids. Representative of strong acids are hydrochloric, sulfuric and phosphoric acids. Representative of weak acids are fumaric, maleic, succinic, oxalic and cyclohexamic acids.
15. For the purpose of demonstrating antidepressant utility for the compounds of Formula I, the procedure given by Englehardt, E. L., et al., J. Med. Chem. 11(2): 325 (1968) which has been indicative in the past of usefulness of compounds for treating human depression was used as
20. follows: 20 mg/kg of the compound to be tested was administered to five adult female mice (ICR-DUB strain), intraperitoneally, 30 minutes prior to the administration of a ptotic dose (32 mg/kg, I.P.) of tetrabenazine (as the methane sulphonate salt). Thirty minutes later, the presence
25. or absence of complete eyelid closure (ptosis) was assessed in each animal. An ED₅₀ (Median Effective Dose) may be established for each tested compound in blocking tetrabenazine induced depression in mice, following the procedure given by Litchfield et al., J. Pharmacol. Exp. Therap. 96:

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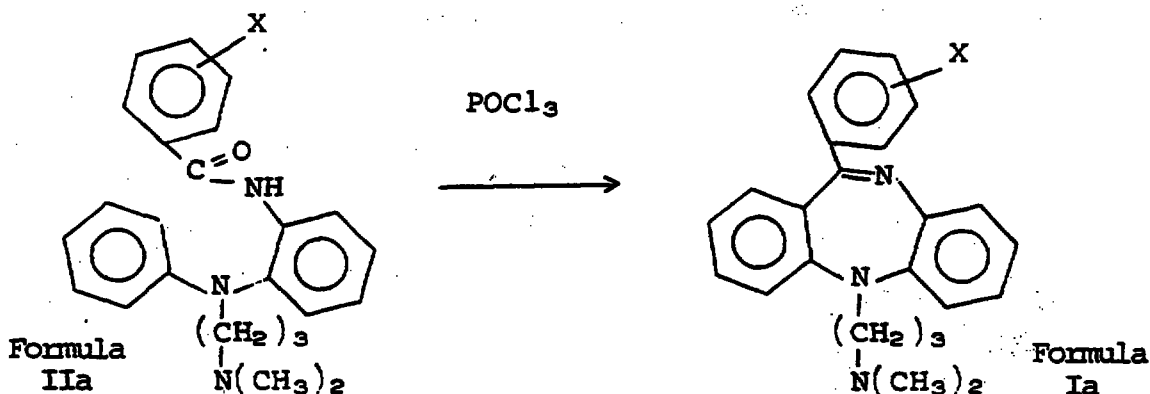
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99-113 (1949). The preferred dibenzodiazepine useful in the method of this invention is the active agent of Example 1; namely, 5-(3-dimethylaminopropyl)-11-phenyl-5H-dibenzo[b,e][1,4]diazepine.

It is therefore an object to provide compounds and pharmaceutical compositions useful in the treatment of depression.

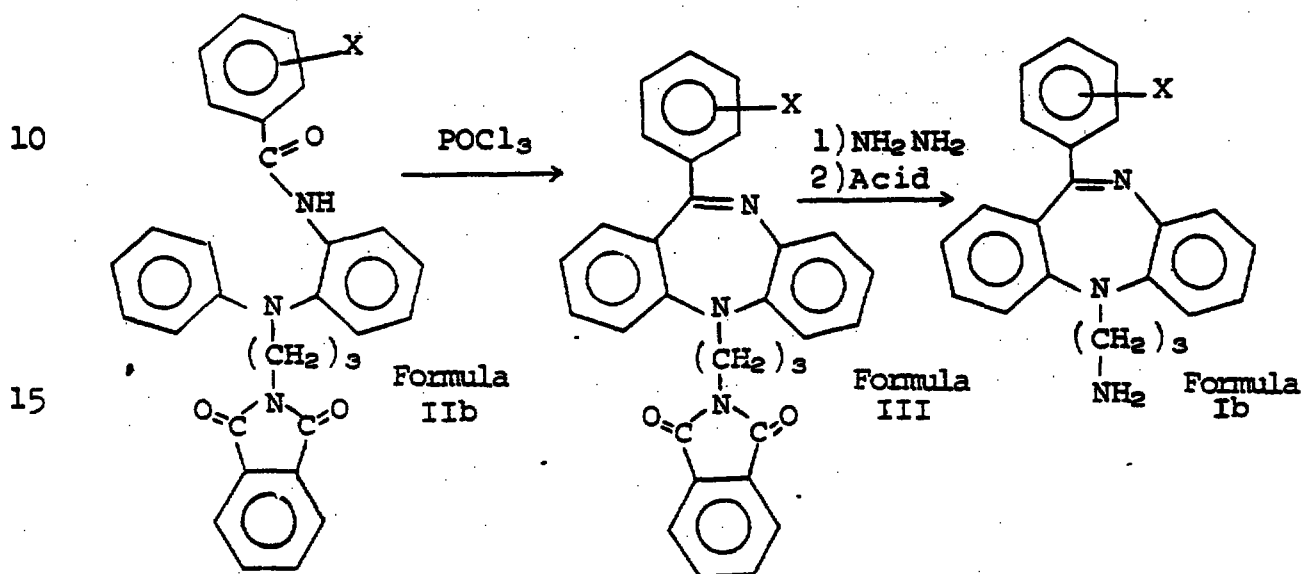
Generally, the usual dosage forms are employed. They comprise active substance (the active ingredient of Formula I) with a suitable pharmaceutical carrier to provide pharmaceutical compositions such as solutions, syrups, elixirs, tablets, capsules, suppositories or powders.

The compounds of Formula I wherein the 5-position is substituted by the 3-dimethylaminopropyl radical are prepared by cyclodehydration of the N-(3-dimethylaminopropyl)-o-benzamido-diphenylamines as in British Patent 907,646 using a dehydrating-condensation catalyst; for example, phosphorus pentoxide or oxyhalogenides of phosphorus, preferably the latter, in a suitable solvent; e.g., 1,1,2,2-tetrachloroethane. The equation is:



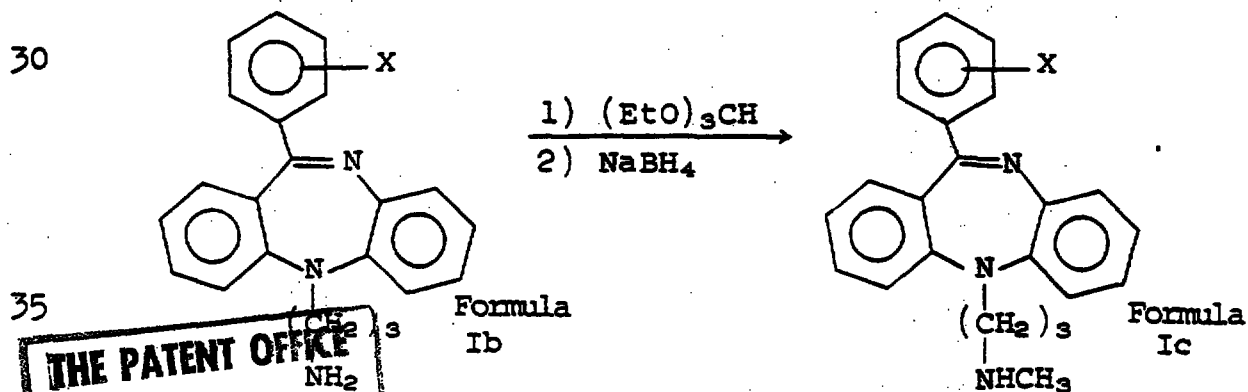
wherein X has the values assigned under Formula I above.

The novel compounds of Formula I wherein the 5-position is substituted by the 3-aminopropyl radical are prepared by cyclodehydration of novel N-[3-(1-phthalimido)propyl]-o-benzamido-diphenylamines (IIb) and thereafter converting the phthalimido moiety to amino (NH_2) with hydrazine and acid. The equation is:



20 wherein X has the values assigned under Formula I. Compounds of Formula III are also novel.

The novel compounds of Formula I wherein the 5-position is substituted by 3-monomethylpropyl amine are prepared by further reaction of the 3-aminopropyl compound with triethylorthoformate followed by reaction with sodium borohydride (procedure of Crockett & Blanton, 1974(1): 55-6 Synthesis). The equation is as follows:

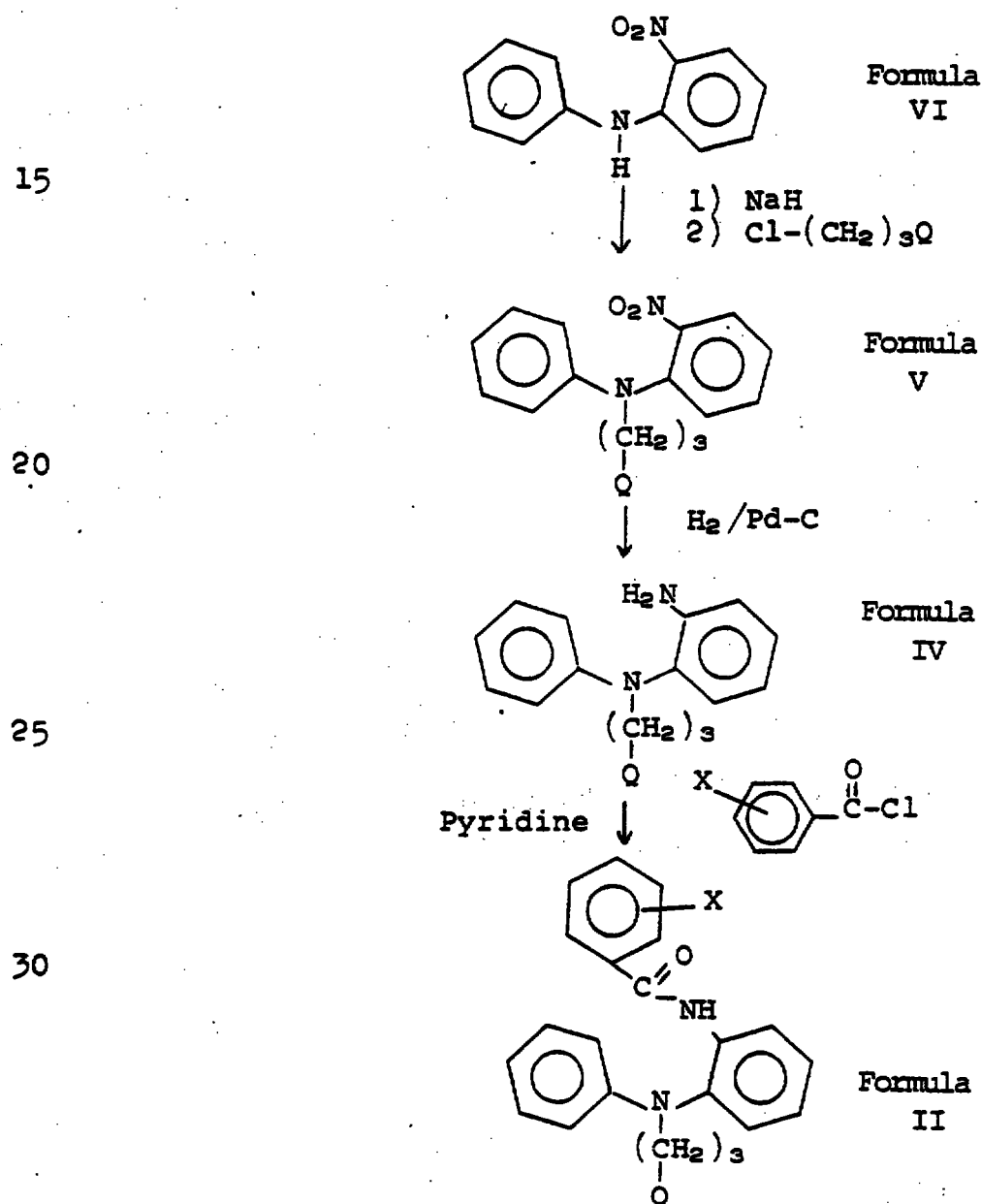


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The starting benzamido compounds of Formula II (IIa and IIb) are prepared by a modification of the procedure of British Patent 907,646. Ortho-nitro-diphenylamine is first reductively alkylated with a solution of β -chloropropyl dimethylamine or 3-(1-phthalimido)-1-chloropropane and following this the nitro moiety is reduced with hydrogen over palladium on carbon to give the corresponding ortho amino compound. The amino radical in the ortho position is then reacted with benzoyl halide or a substituted benzoyl halide. The equation is as follows:



The invention may be put into practice in various ways and a number of specific embodiments will be described to illustrate the invention with reference to the accompanying Examples in which Examples 1 to 5 are examples of preparation of starting materials and Examples 6 to 12 are examples of compounds of Formula I, Examples 13 to 15 are examples of pharmaceutical compositions in accordance with the invention.

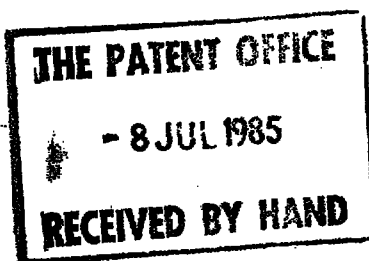
Example 1

10. N-(3-Dimethylaminopropyl)-o-aminodiphenylamine.

A mixture of 32.0 g (0.107 mole) of N-(3-dimethylaminopropyl)-o-nitrodiphenylamine (b.p. 155° at 0.4 mm Hg pressure to 174°C at 0.33 mm Hg pressure), 100 ml of 200 proof ethyl alcohol and 1.5 g of 10% palladium-on-carbon catalyst was shaken under a hydrogen atmosphere at room temperature for 1 hr. After approximately the theoretical amount of hydrogen was absorbed the catalyst was filtered off through a ^(Registered Trade Mark) Celite filter cake and solvent removed under reduced pressure. The residue was distilled under high vacuum as follows:

		<u>b.p., °C.</u>	<u>Amt., g</u>
20.	Fraction 1	80-130° at 0.2 mm Hg pressure	4.0
	2	130-137° at 0.2 mm Hg pressure	7.0
	3	137-142° at 0.2 mm Hg pressure	15.5

Thin layer chromatography using 20% methyl alcohol - 80% benzene on silica gel, showed Fraction 3 to be quite pure.



Example 2AN-(3-Dimethylaminopropyl)-o-benzamidodiphenylamine.

- To a solution of 15.5 g (0.0575 mole) of N-(3-dimethylaminopropyl)-o-aminodiphenylamine in 100 ml of pyridine
5. cooled to about 5°C. under a nitrogen atmosphere was added 17.8 g (0.063 mole) of benzoyl chloride. A small amount of benzene was used to wash the remaining benzoyl chloride into the reaction vessel. The mixture was stirred for 1 hr and the vessel stoppered and placed in a refrigerator over
 10. the weekend. The solvent was then evaporated under reduced pressure. The residual oil was dissolved in 100 ml of methylene chloride and the solution washed once with 150 ml of 3 N sodium hydroxide and three times with 250 ml of water. The methylene chloride layer was dried over magnesium
 15. sulphate and evaporated under reduced pressure. Residual pyridine was then removed under high vacuum (0.2 mm Hg) over night. The weight of the residual oil, the free base, was 24.9 g.

Example 2B. Preparation of the Oxalate Salt of 2A. - To a hot solution of 4.0 g of the free base of Example 2A in isopropyl alcohol was added 1.35 g (0.0107 mole) of oxalic acid dihydrate. The precipitated oxalate salt of the title compound weighed 3.5 g and melted at 162-5°C. The salt after drying 1 hr at 97-98°C (refluxing propyl alcohol) and overnight at room temperature all at 0.1 mm Hg pressure, analyzed as follows:

Analysis: Calculated for $C_{28}H_{29}N_3O_5$: C, 67.37; H, 6.31; N, 9.06
Found : C, 67.42; H, 6.35; N, 9.01

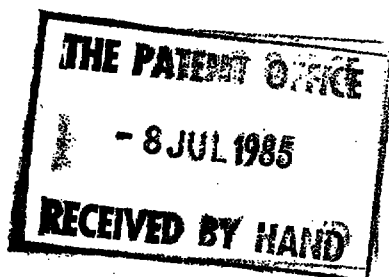
Examples 3a to 3g

Following the procedure of Example 2A and substituting the following for benzoyl chloride:

- 2-chloro-benzoyl chloride,
- 3-chloro-benzoyl chloride,
- 2-fluoro-benzoyl chloride,
- 3-fluoro-benzoyl chloride,
- 2-bromo-benzoyl chloride,
- 3-bromo-benzoyl chloride, and
- 4-chloro-benzoyl chloride,

there were obtained:

- a) N-(3-dimethylaminopropyl)-o-(2-chlorobenzamido) diphenylamine,
- b) N-(3-dimethylaminopropyl)-o-(3-chlorobenzamido) diphenylamine,
- c) N-(3-dimethylaminopropyl)-o-(2-fluorobenzamido) diphenylamine,
- d) N-(3-dimethylaminopropyl)-o-(3-fluorobenzamido) diphenylamine,
- e) N-(3-dimethylaminopropyl)-o-(2-bromobenzamido) diphenylamine,
- f) N-(3-dimethylaminopropyl)-o-(3-bromobenzamido) diphenylamine, and
- g) N-(3-dimethylaminopropyl)-o-(4-chlorobenzamido) diphenylamine.



Example 4N-3-(1-Phthalimido)propyl-o-aminodiphenylamine.

o-Nitrodiphenylamine was reacted with sodium hydride and 3-(1-phthalimido)-1-chloropropane to give N-3-(1-phthalimido)propyl-o-nitrodiphenylamine which was then
5 reduced with hydrogen over palladium-on-carbon in ethanol to give the title compound.

Examples 5a to 5g

When in the procedure of Example 2A, N-3-(1-phthalimido)propyl-o-aminodiphenylamine is reacted with
10 each of the following acyl chlorides in excess in the manner of Example 2A:

2-chloro-benzoyl chloride,
3-chloro-benzoyl chloride,
2-fluoro-benzoyl chloride,
15 3-fluoro-benzoyl chloride,
2-bromo-benzoyl chloride,
3-bromo-benzoyl chloride, and
4-chloro-benzoyl chloride,

there were obtained:

- 20 a) N-3-(1-phthalimido)propyl-o-(2-chlorobenzamido) diphenylamine,
b) N-3-(1-phthalimido)propyl-o-(3-chlorobenzamido) diphenylamine,
c) N-3-(1-phthalimido)propyl-o-(2-fluorobenzamido)
25 diphenylamine,
d) N-3-(1-phthalimido)propyl-o-(3-fluorobenzamido) diphenylamine,
e) N-3-(1-phthalimido)propyl-o-(2-bromobenzamido) diphenylamine,
30 f) N-3-(1-phthalimido)propyl-o-(3-bromobenzamido) diphenylamine, and
g) N-3-(1-phthalimido)propyl-o-(4-chlorobenzamido) diphenylamine.

Example 6

5-(3-Dimethylaminopropyl)-11-phenyl-5H-dibenzo
[b,e][1,4]diazepine, fumarate [1:1].

A stirred mixture of 18.9 g (0.05 mole) of N-(3-dimethylaminopropyl)-o-benzamidodiphenylamine and 32.19 g
 5 (0.2 mole) of phosphorus oxychloride in 50 ml of 1,1,2,2-tetrachloroethane was heated at 150°C under nitrogen atmosphere for 1.5 hr. The mixture was cooled somewhat and poured over approximately 1000 ml of crushed ice and then diluted with enough water for a final volume of 1000
 10 ml. The aqueous suspension was extracted twice with methylene chloride and the methylene chloride layer discarded. The aqueous layer was made basic with 3 N sodium hydroxide and extracted with three - 250 ml portions of methylene chloride. These three methylene chloride washes
 15 were combined, dried over magnesium sulphate and evaporated under reduced pressure to give a residual oil weighing 13.8 g, the free base of the title compound. The oil was dissolved in hot isopropyl alcohol and reacted with 4.5 g (0.039 mole) of fumaric acid. The fumarate salt was
 20 collected by filtration, yielding 13 g when dried, m.p. 168-170°C.

Analysis: Calculated for $C_{28}H_{29}N_3O_4$: C, 71.32; H, 6.20;
 N, 8.91
 Found : C, 71.19; H 6.19;
 N, 8.89

Examples 7a to 7g

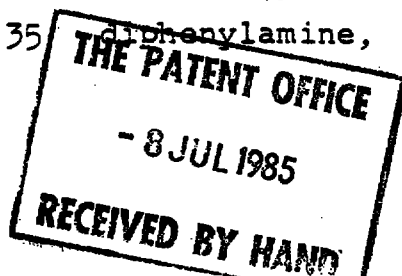
25 Following the procedure of Example 6 and substituting equal molar amounts of the following for N-(3-dimethylaminopropyl)-o-benzamidodiphenylamine:

N-(3-dimethylaminopropyl)-o-(2-chlorobenzamido)
 diphenylamine,

30 N-(3-dimethylaminopropyl)-o-(3-chlorobenzamido)
 diphenylamine,

N-(3-dimethylaminopropyl)-o-(2-fluorobenzamido)
 diphenylamine,

N-(3-dimethylaminopropyl)-o-(3-fluorobenzamido)
 35 diphenylamine,



N-(3-dimethylaminopropyl)-o-(2-bromobenzamido)
diphenylamine,

N-(3-dimethylaminopropyl)-o-(3-bromobenzamido)
diphenylamine, and

5 N-(3-dimethylaminopropyl)-o-(4-chlorobenzamido)
diphenylamine,
there were obtained:

- a) 11-(2-chlorophenyl)-5-(3-dimethylaminopropyl)-5H-
dibenzo[b,e][1,4]diazepine, fumarate,
- 10 b) 11-(3-chlorophenyl)-5-(3-dimethylaminopropyl)-5H-
dibenzo[b,e][1,4]diazepine, fumarate,
- c) 11-(2-fluorophenyl)-5-(3-dimethylaminopropyl)-5H-
dibenzo[b,e][1,4]diazepine, fumarate,
- d) 11-(3-fluorophenyl)-5-(3-dimethylaminopropyl)-5H-
15 dibenzo[b,e][1,4]diazepine, fumarate,
- e) 11-(2-bromophenyl)-5-(3-dimethylaminopropyl)-5H-
dibenzo[b,e][1,4]diazepine, fumarate,
- f) 11-(3-bromophenyl)-5-(3-dimethylaminopropyl)-5H-
dibenzo[b,e][1,4]diazepine, fumarate, and
- 20 g) 11-(4-chlorophenyl)-5-(3-dimethylaminopropyl)-5H-
dibenzo[b,e][1,4]diazepine, fumarate.

Examples 8a to 8h

When in the procedure of Example 6 prior to addition
of fumaric acid, the following were substituted for N-(3-
25 dimethylaminopropyl)-o-benzamidodiphenylamine:

- N-3-(1-phthalimido)propyl-o-benzamidodiphenylamine,
N-3-(1-phthalimido)propyl-o-(2-chlorobenzamido)
diphenylamine,
N-3-(1-phthalimido)propyl-o-(3-chlorobenzamido)
30 diphenylamine,
N-3-(1-phthalimido)propyl-o-(2-fluorobenzamido)
diphenylamine,
N-3-(1-phthalimido)propyl-o-(3-fluorobenzamido)
diphenylamine,
35 N-3-(1-phthalimido)propyl-o-(2-bromobenzamido)
diphenylamine,

N-3-(1-phthalimido)propyl-o-(3-bromobenzamido)
diphenylamine, and

N-3-(1-phthalimido)propyl-o-(4-chlorobenzamido)
diphenylamine,

5 there were obtained:

- a) 5-[3-(1-phthalimido)propyl]-11-phenyl-5H-dibenzo
[b,e][1,4]diazepine,
- b) 5-[3-(1-phthalimido)propyl]-11-(2-chlorophenyl)-5H-
dibenzo[b,e][1,4]diazepine,
- 10 c) 5-[3-(1-phthalimido)propyl]-11-(3-chlorophenyl)-5H-
dibenzo[b,e][1,4]diazepine,
- d) 5-[3-(1-phthalimido)propyl]-11-(2-fluorophenyl)-5H-
dibenzo[b,e][1,4]diazepine,
- e) 5-[3-(1-phthalimido)propyl]-11-(3-fluorophenyl)-5H-
15 dibenzo[b,e][1,4]diazepine,
- f) 5-[3-(1-phthalimido)propyl]-11-(2-bromophenyl)-5H-
dibenzo[b,e][1,4]diazepine,
- g) 5-[3-(1-phthalimido)propyl]-11-(3-bromophenyl)-5H-
dibenzo[b,e][1,4]diazepine,
- 20 h) 5-[3-(1-phthalimido)propyl]-11-(4-chlorophenyl)-5H-
dibenzo[b,e][1,4]diazepine.

Example 9

5-(3-Aminopropyl)-11-phenyl-5H-dibenzo[b,e][1,4]
diazepine hydrochloride.

- 25 A mixture of 0.035 mole of 5-[3-(1-phthalimido)propyl]-
11-phenyl-5H-dibenzo[b,e][1,4]diazepine, 0.039 mole of
hydrazine hydrate and 175 ml of 190 proof ethyl alcohol was
refluxed for 2.5 hr and allowed to stand for several hours.
A solution of 10 ml concentrated hydrochloric acid in 50 ml
30 water was added to the mixture and the mixture was stirred
for several hours. The mixture was filtered and the filtrate
evaporated under reduced pressure. The hydrochloride salt
was isolated by recrystallization from a suitable solvent
and dried under reduced pressure.

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Examples 10a to 10g

Following the procedure of Example 9 and substituting equal molar amounts of the following for 5-[3-(1-phthalimido)propyl]-11-phenyl-5H-dibenzo[b,e][1,4]diazepine:

- 5 11-(2-chlorophenyl)-5-[3-(1-phthalimido)propyl]-5H-dibenzo[b,e][1,4]diazepine,
11-(3-chlorophenyl)-5-[3-(1-phthalimido)propyl]-5H-dibenzo[b,e][1,4]diazepine,
11-(2-fluorophenyl)-5-[3-(1-phthalimido)propyl]-5H-dibenzo[b,e][1,4]diazepine,
10 11-(3-fluorophenyl)-5-[3-(1-phthalimido)propyl]-5H-dibenzo[b,e][1,4]diazepine,
11-(2-bromophenyl)-5-[3-(1-phthalimido)propyl]-5H-dibenzo[b,e][1,4]diazepine,
11-(3-bromophenyl)-5-[3-(1-phthalimido)propyl]-5H-dibenzo[b,e][1,4]diazepine, and
15 11-(4-chlorophenyl)-5-[3-(1-phthalimido)propyl]-5H-dibenzo[b,e][1,4]diazepine,

there were obtained:

- a) 5-(3-aminopropyl)-11-(2-chlorophenyl)-5H-dibenzo
20 [b,e][1,4]diazepine hydrochloride,
b) 5-(3-aminopropyl)-11-(3-chlorophenyl)-5H-dibenzo
[b,e][1,4]diazepine hydrochloride,
c) 5-(3-aminopropyl)-11-(2-fluorophenyl)-5H-dibenzo
[b,e][1,4]diazepine hydrochloride,
25 d) 5-(3-aminopropyl)-11-(3-fluorophenyl)-5H-dibenzo
[b,e][1,4]diazepine hydrochloride,
e) 5-(3-aminopropyl)-11-(2-bromophenyl)-5H-dibenzo
[b,e][1,4]diazepine hydrochloride,
f) 5-(3-aminopropyl)-11-(3-bromophenyl)-5H-dibenzo
30 [b,e][1,4]diazepine hydrochloride,
g) 5-(3-aminopropyl)-11-(4-chlorophenyl)-5H-dibenzo
[b,e][1,4]diazepine hydrochloride.

Example 11

N-Methyl-11-phenyl-5H-dibenzo[b,e][1,4]diazepin-5-propanamine, hydrochloride.

The hydrochloride salt of 5-(3-aminopropyl)-11-phenyl-5H-dibenzo[b,e][1,4]diazepine was converted to the free base by partitioning between dilute sodium hydroxide and methylene chloride, drying and concentrating the methylene chloride layer to dryness, adding dry benzene and again concentrating to drive off the benzene. The resulting free base was dissolved in a large excess of freshly distilled triethyl-orthoformate with refluxing for several hours. The mixture was concentrated in vacuo, ethanol was added and the mixture concentrated again. The resulting imidate was dissolved in ethanol and sodium borohydride was added with stirring at 15-20°C until thin-layer chromatography indicated the substantial absence of starting material. The mixture was cooled and gradually flooded with water followed by extraction with ethylacetate. The ethylacetate layer washed to neutrality and salted, filtered and evaporated. Crude free base was isolated by column chromatography and reacted with ethereal hydrogen chloride and recrystallized to give the title compound.

Examples 12a to 12g

Following the procedure of Example 11 and substituting equal molar amounts of the following for 5-(3-aminopropyl)-11-phenyl-5H-dibenzo[b,e][1,4]diazepine:

- 5-(3-aminopropyl)-11-(2-chlorophenyl)-5H-dibenzo[b,e][1,4]diazepine hydrochloride,
- 5-(3-aminopropyl)-11-(3-chlorophenyl)-5H-dibenzo[b,e][1,4]diazepine hydrochloride,
- 5-(3-aminopropyl)-11-(2-fluorophenyl)-5H-dibenzo[b,e][1,4]diazepine hydrochloride,
- 5-(3-aminopropyl)-11-(3-fluorophenyl)-5H-dibenzo[b,e][1,4]diazepine hydrochloride,
- 5-(3-aminopropyl)-11-(2-bromophenyl)-5H-dibenzo[b,e][1,4]diazepine hydrochloride,

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5-(3-aminopropyl)-11-(3-bromophenyl)-5H-dibenzo-
[b,e][1,4]diazepine hydrochloride, and

5-(3-aminopropyl)-11-(4-chlorophenyl)-5H-dibenzo
[b,e][1,4]diazepine hydrochloride,

5 there were obtained:

a) 11-(2-chlorophenyl)-N-methyl-5H-dibenzo[b,e][1,4]
diazepin-5-propanamine hydrochloride,

b) 11-(3-chlorophenyl)-N-methyl-5H-dibenzo[b,e][1,4]
diazepin-5-propanamine hydrochloride,

10 c) 11-(2-fluorophenyl)-N-methyl-5H-dibenzo[b,e][1,4]
diazepin-5-propanamine hydrochloride,

d) 11-(3-fluorophenyl)-N-methyl-5H-dibenzo[b,e][1,4]
diazepin-5-propanamine hydrochloride,

e) 11-(2-bromophenyl)-N-methyl-5H-dibenzo[b,e][1,4]
15 diazepin-5-propanamine hydrochloride,

f) 11-(3-bromophenyl)-N-methyl-5H-dibenzo[b,e][1,4]
diazepin-5-propanamine hydrochloride, and

g) 11-(4-chlorophenyl)-N-methyl-5H-dibenzo[b,e][1,4]
diazepin-5-propanamine hydrochloride.

Formulation and Administration

Effective quantities of the foregoing pharmacologically active compounds of Formula I may be administered to humans for therapeutic purposes according to usual modes of administration and in usual forms, such as orally in solutions, emulsions, suspensions, pills, tablets and capsules, in pharmaceutically acceptable carriers and parenterally in the form of sterile solutions.

Exemplary of solid carriers for oral administration are such as lactose, magnesium stearate, terra alba, sucrose, talc, stearic acid, gelatin, agar, pectin or acacia.

Exemplary of liquid carriers for oral administration are vegetable oils and water.

For intramuscular administration the carrier or excipient may be a sterile, parenterally acceptable liquid; e.g., water or a parenterally acceptable oil; e.g., arachis oil contained in ampoules.

Although very small quantities of the active materials of the present invention are effective when minor therapy is involved or in cases of administration to subjects having a relatively low body weight, unit dosages are usually from five milligrams or above and preferably 10, 25, 50, or 100 milligrams or even higher, preferably administered three or four times per day, depending, of course, upon the emergency of the situation, the compound used, and the particular result desired. Twenty-five to 200 milligrams appears optimum per unit dose or usual broader ranges appear to be about 10 to 500 milligrams per unit dose. Daily dosages usually required should range from about 0.5 to about 20 mg/kg/day, preferably 0.5 to 10 mg/kg. The active ingredients of the invention may be combined with other pharmacologically active agents as stated above. It is only necessary that the active ingredient constitute an effective amount; i.e., such that a suitable effective dosage will be obtained consistent with the dosage form employed. Obviously, several unit dosage forms may be administered at about the same time. The exact individual dosages as well as daily dosages will, of course, be demonstrated according to

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be determined according to standard medical principles under the direction of a physician.

The following formulations are representative for the pharmacologically active compounds of this invention.

FORMULATIONS

Examples 13a to 13e

Capsules of 10 mg and 50 mg of active ingredient per capsule are prepared. With the higher amounts of active ingredient, reduction may be made in the amount of lactose.

Example	13a	13b
	10 mg Per Capsule	50 mg Per Capsule
15. <u>Typical blend for encapsulation</u>		
Active ingredient, as salt	10	50
Lactose	259	219
Starch	126	126
Magnesium stearate	4	4
20. Total	399	399

Additional capsule formulations preferably contain a higher dosage of active ingredient and are as follows:

Example	13c	13d	13e
	100 mg. per Capsule	250 mg. per Capsule	500 mg. per Capsule
25. <u>Ingredients</u>			
Active ingredient, as salt	100	250	500
Lactose	214	163	95
30. Starch	87	81	47
Magnesium stearate	4	6	8
Total	299	500	650

In each case, the selected active ingredient was uniformly blended with the lactose, starch, and magnesium stearate and the blend then encapsulated.

EXAMPLE 14

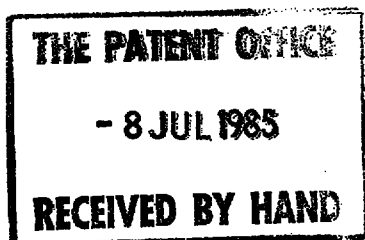
5. A typical formulation for a tablet containing 5.0 mg of active ingredient per tablet follows. The formulation may be used for other strengths of active ingredient by adjustment of the weight of dicalcium phosphate.

		<u>Per Tablet, mg.</u>
10.	1. Active ingredient	10.0
	2. Corn starch	15.0
	3. Corn starch (paste)	12.0
	4. Lactose	35.0
15.	5. Dicalcium phosphate	132.0
	6. Calcium stearate	<u>2.0</u>
	Total	202.0

- Ingredients 1, 2, 4 and 5 were first uniformly blended. Ingredient 3 was prepared as a 10% paste in water. The blend was granulated with the starch paste and the wet mass passed through an 8 mesh (U.S. sieve series) screen. The wet granulation was dried and sized through a 12 mesh (U.S. sieve series) screen. The dried granules were blended with the calcium stearate and compressed. 8 mesh has openings of 2.38 mm; 12 mesh of 1.68 mm.

EXAMPLE 15

An injectable sterile 2% solution was made up as follows:



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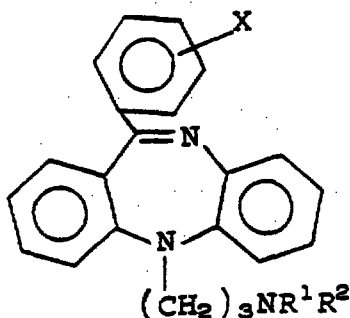
		<u>Per cc</u>
Active ingredient	mg.	20
Preservative, e.g.		
chlorobutanol, w/vol. percent		0.5
Water for injection q.s.		

5. The solution was prepared, clarified by filtration, filled into vials, sealed and autoclaved.



CLAIMS

1. A compound having the formula:



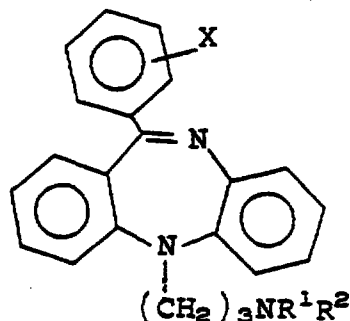
wherein R^1 and R^2 each represent a hydrogen atom or a methyl group,

X represents a hydrogen, chlorine, bromine or fluorine atom, and the pharmaceutically acceptable acid addition salts thereof, for use in treating depression.

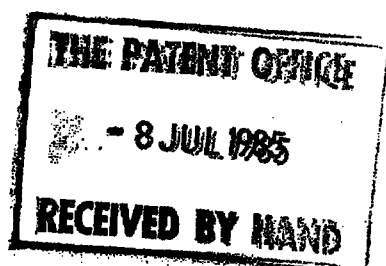
2. A compound as claimed in Claim 1 which is 5-(3-dimethylaminopropyl)-11-phenyl-5H-dibenzo[b,e][1,4]diazepine.

3. A compound as claimed in Claim 1 which is 5-(3-dimethylaminopropyl)-11-phenyl-5H-dibenzo[b,e][1,4]diazepine, fumarate [1:1].

4. A compound having the formula:



wherein X represents a hydrogen, chlorine, bromine or

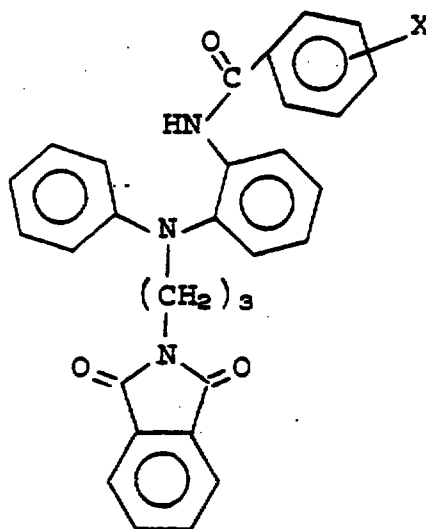




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fluorine atom, and R^1 and R^2 both represent a hydrogen atom or R^1 represents a hydrogen atom when R^2 represents a methyl group, and the pharmaceutically acceptable acid addition salts thereof.

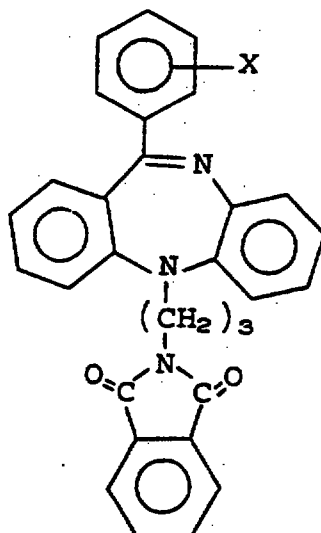
5. A compound having the formula:



wherein X represents a hydrogen, chlorine, bromine or fluorine atom.



6. A compound having the formula:



wherein X represents a hydrogen, chlorine, bromine or fluorine atom.

7. A compound as claimed in Claim 4 substantially as specifically described herein with reference to any one of Examples 6 to 12.

8. A compound as claimed in Claim 5 or Claim 6 substantially as specifically described herein with reference to any one of Examples 1 to 5.

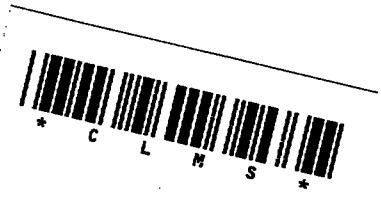
9. A pharmaceutical composition for treating depression in unit dosage form comprising (a) an effective amount of a compound as defined in any one of Claims 1 to 4, and (b) a pharmaceutical carrier therefor.

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10. A pharmaceutical composition as claimed in Claim 9 in which the compound is 5-(3-dimethylamino-propyl)-11-phenyl-5H-dibenzo[b,e][1,4] diazepine.

11. A pharmaceutical composition as claimed in Claim 9 in which the compound is 5-(3-dimethylamino-propyl)-11-phenyl-5H-dibenzo[b,e][1,4] diazepine fumarate.

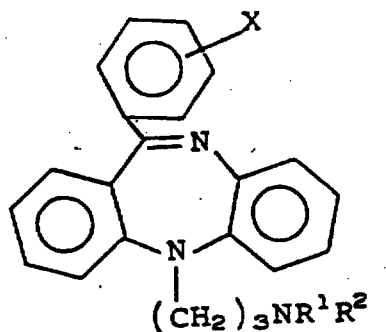
12. A pharmaceutical composition as claimed in any one of Claims 9 to 11 substantially as specifically described herein with reference to any one of Examples 13, 14 or 15.

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13. A pharmaceutical composition in unit dosage form comprising at least 5mg per unit dosage of a compound having the formula:



wherein R^1 and R^2 each represent a hydrogen atom or a methyl group,

X represents a hydrogen, chlorine, bromine or fluorine atom, or a pharmaceutically acceptable acid addition salt thereof.

14. A pharmaceutical composition as claimed in Claim 13, which composition comprises 5-(3-dimethylamino-propyl)-11-phenyl-5H-dibenzo[b,e][1,4]diazepine.

