

# PATENT SPECIFICATION

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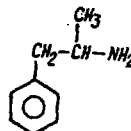


## (54) AMPHETAMINE DERIVATIVES

(71) We, ASTRA LAKEMEDEL AKTIEBOLAG, a Swedish Body Corporate of Kvarnbergagatan 16, S-151 85 Sodertalje, Sweden, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 4-aminoamphetamine derivatives, to methods for their preparation, to pharmaceutical compositions containing them and to their use.

Varying degrees of success have been obtained in the treatment of depressive disorders using chemical substances. Many types of chemical substances have been used, including the compound, known as amphetamine, of the structure

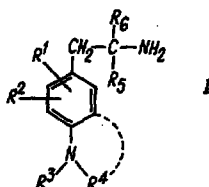


However, the euphoric effect and the risk of dependence of amphetamine have restricted its use to a great extent.

Nowadays amphetamine is mainly used for the treatment of narcolepsy and to treat asthenia in old people.

It has now been found that by incorporating certain substituents in amphetamine, the euphoric or central stimulant effect of amphetamine is lowered or completely removed.

Accordingly the invention provides compounds of the formula

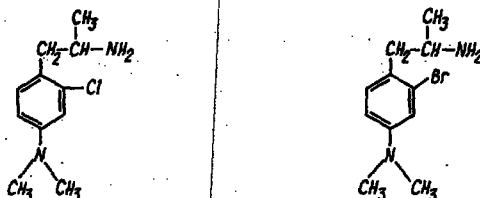


wherein each of R<sup>1</sup> and R<sup>2</sup>, which may be the same or different, is a hydrogen or halogen atom, or a lower alkyl group, R<sup>3</sup> is a lower alkyl group or a benzyl group, R<sup>4</sup> is a hydrogen atom, a lower alkyl group, a benzyl group or a —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>— bridge attached to the phenyl ring at the ortho-position relative to the N-substituent on the phenyl ring, R<sup>5</sup> is a hydrogen atom or a methyl group and R<sup>6</sup> is a lower alkyl group, with the proviso that when each of R<sup>3</sup> and R<sup>4</sup> is a methyl group and R<sup>5</sup> is a hydrogen atom, R<sup>1</sup> and/or R<sup>2</sup> is a lower alkyl group or a halogen atom; or a pharmaceutically acceptable acid addition salt thereof.

Preferably, R<sup>3</sup> is a lower alkyl group, R<sup>4</sup> is a lower alkyl group, R<sup>5</sup> is a hydrogen atom and R<sup>6</sup> is a methyl group.

Illustrative examples of the lower alkyl group are methyl, ethyl, n-propyl and isopropyl and of the halogen atom are chlorine, bromine, iodine and fluorine. The expression "lower alkyl group" used throughout this Specification means an alkyl group with 1 to 5 carbon atoms.

The preferred compounds of the invention are



These compounds are preferably prepared and used in the form of their dihydrochloride salts.

Racemic mixtures of the compounds of this invention ((+)- and (-)-forms), obtained by synthesis, may be used in therapy as well as the corresponding optically active isomers obtained by resolution of the racemic mixtures. The compounds of this invention may be administered as the free bases or as acid addition salts thereof with non-toxic acids. Some typical examples of these salts are the hydrobromide, hydrochloride, phosphate, sulphate, citrate and tartrate.

Pharmacological tests performed on the compounds of the invention indicate that they are potentially useful as anti-depressants and as anxiolytic agents.

In clinical practice the compounds of the present invention will normally be administered orally, rectally or by injection, in the form of pharmaceutical compositions comprising the active ingredient either as a free base or as a pharmaceutically acceptable non-toxic, acid addition salt, e.g. the hydrochloride, hydrobromide, lactate, acetate, sulphate or sulphamate in association with a pharmaceutically acceptable carrier. Accordingly, any reference in the Specification to the compounds of the invention, whether generic or specific, includes both the free amine base and the said acid addition salts of the free base, unless the context in which such a reference is made, e.g. in the Examples, is inconsistent with this definition. The carrier may be a solid, semi-solid or liquid diluent or capsule. These pharmaceutical compositions constitute a further aspect of this invention. Usually the active substance will constitute between 0.1 and 95% by weight of the preparation, more specifically between 0.5 and 20% by weight for a preparation intended for injection, and between 2 and 50% by weight for preparations suitable for oral administration.

To produce a pharmaceutical composition containing a compound of the invention in a form suitable for oral administration, the selected compound may be mixed with a solid pulverulent carrier, e.g. lactose, sucrose, sorbitol, mannitol, a starch such as potato starch, corn starch or amylopectin, a cellulose derivative, or gelatine, and a lubricant such as magnesium stearate, calcium stearate or a polyethylene glycol wax and then compressed to form tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, e.g. gum arabic, gelatine, talcum or titanium dioxide. Alternatively, the tablet can be coated with a lacquer dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to distinguish readily tablets containing different active substances and/or different amounts of the active compound.

For the preparation of soft gelatine capsules (pearl-shaped closed capsules) consisting of gelatine and for example, glycerol or similar closed capsules, the active substance may be admixed with a vegetable oil. Hard gelatine capsules may contain granulates of the active substance in combination with solid, pulverulent carriers such as lactose, sucrose, sorbitol, mannitol, starch (e.g. potato starch, corn starch or amylopectin), a cellulose derivative or gelatine.

Suppositories for rectal administration usually comprise a mixture of the active substance and a neutral fatty base. Gelatine rectal capsules, comprising a mixture of the active substance and vegetable or paraffin oil, can also be used for rectal administration of the active substance.

Liquid preparations for oral administration may be in the form of syrups or suspensions, for example, solutions containing from about 0.2% to about 20% by weight of the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol, and propyleneglycol. Optionally such liquid preparations may

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contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent.

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Solutions for parenteral applications by injection are usually aqueous solutions of a water-soluble pharmaceutically acceptable acid addition salt of a compound of the invention, the concentration of the salt preferably being from about 0.5% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

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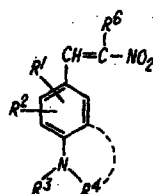
Suitable peroral doses of the compounds of the invention are 2—20 mg, preferably 5—15 mg given 1 to 3 times a day, preferably twice a day.

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The compounds of the invention can be prepared by the following methods:

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A. Reduction of a substituted  $\beta$ -nitrostyrene of the formula



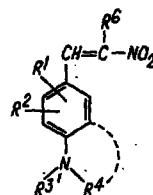
wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^6$  are as defined above, to a compound of the formula I wherein  $R^5$  is a hydrogen atom.

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The reduction can be effected by means of an appropriate reducing agent such as lithium aluminium hydride or by catalytic reduction, or by other known reducing agents.

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B. Reduction of a compound of the formula



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wherein  $R^1$ ,  $R^2$ ,  $R^4$  and  $R^6$  are as defined above and  $R^{3'}$  is a lower aliphatic acyl group or a benzoyl group to a compound of the formula I wherein  $R^5$  is a hydrogen atom.

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In this Specification the term "lower aliphatic acyl group" means an aliphatic acyl group

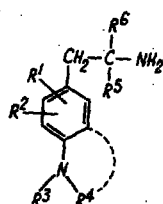


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wherein R is a hydrogen atom or  $C_{1-4}$  alkyl group. Illustrative examples of lower aliphatic acyl groups are formyl, acetyl, propionyl, butyryl, isobutyryl and valeryl.

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C. Direct halogenation of a compound of the formula



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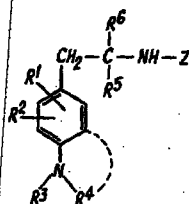
wherein  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are as defined above and either  $R^1$  or  $R^2$  or both are hydrogen, to form a compound of the formula I wherein  $R^1$  or  $R^2$  or both are a halogen atom.

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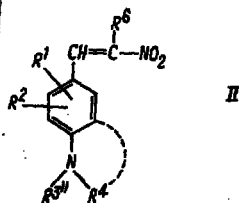
## D. Hydrolysing a compound of the formula



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are as defined above and  $Z$  is a lower aliphatic acyl group, to form a compound of formula 1.

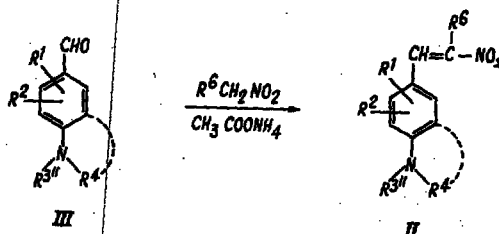
The hydrolysis is performed with a strong mineral acid.

A useful starting material for the preparation of the compounds of the formula I wherein  $R^5$  is a hydrogen atom is a compound of the formula



wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as defined above and  $R^{3''}$  is a lower alkyl group, a benzyl group, a lower aliphatic acyl group or a benzoyl group with the proviso that when each of  $R^{3''}$  and  $R^4$  are a methyl or an ethyl group or when  $R^{3''}$  is an acetyl group and  $R^4$  is a hydrogen atom,  $R^1$  and/or  $R^2$  is a lower alkyl group or a halogen atom; or a salt thereof.

The compounds of the formula II are prepared as outlined below



using a process comprising condensation of an aldehyde of formula III with excess nitroalkane, preferably in a suitable solvent, for instance n-propyl alcohol, ethanol or acetic acid in the presence of a base e.g. ammonium acetate.

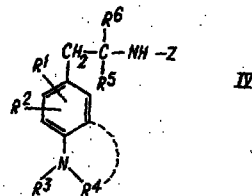
Aldehydes of formula III wherein  $R^3$  is a lower alkyl group or a benzoyl group, i.e.  $R^{3''}=R^3$ , and  $R^4$  is as defined above are prepared by formylation of a substituted aniline according to the Vilsmeier-Haack reaction:



The formylation is effected by using a mixture of dimethylformamide and phosphorus oxychloride. Alternatively the preparation is achieved by using a mixture of phosphorus tribromide and dimethylformamide (Acta. Pharm. Suecica 7, 87, 1970).

Compounds other than dimethylformamide which may serve as the formylating agent are for instance N-methylformanilide or formamide. Other suitable catalysts are thionyl chloride, phosgene or aluminium chloride.

Another valuable starting material for the preparation of the compounds of the formula I is a compound of the formula

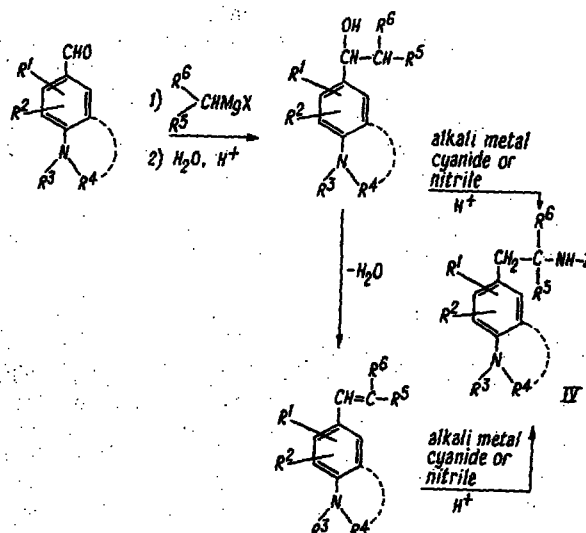


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wherein  $R^1$ ,  $R^2$ ,  $R^4$  and  $R^6$  are as defined above,  $R^3$  is a lower alkyl group or a benzyl group,  $R^5$  is a hydrogen atom or a methyl group with the proviso that when each of  $R^3$  and  $R^4$  is a methyl group and  $R^5$  represents a hydrogen atom,  $R^1$  and/or  $R^2$  is a lower alkyl group or a halogen atom; or a salt thereof.

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The compounds of the formula IV can be prepared according to the reaction sequence



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wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and  $Z$  are as defined above and  $X$  is a bromide, chloride or iodide ion.

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The aldehyde (prepared as described above) is treated with the Grignard reagent and the obtained alcohol is either directly converted to the amide IV by reaction with an alkali metal cyanide or a nitrile in the presence of a strong acid, e.g. sulphuric acid or via the dimethylvinyl compound which is reacted with an alkali metal cyanide or a nitrile in the presence of a strong acid, e.g. sulphuric acid to form the amide compound.

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The following Examples illustrate the present invention. The Preparations describe the preparation of intermediates. Temperatures are in degrees C.

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#### Preparation 1.

##### *N,N*-Dimethyl-3-methyl-4-(2-nitropropenyl)aniline

##### (a) 4-Dimethylamino-2-methylbenzaldehyde

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45 ml of phosphorus oxychloride is added dropwise while stirring and cooling in an ice bath to 145 ml of dimethylformamide. To this cooled solution is added by portions 67.5 g of *N,N*-dimethyl-*m*-toluidine. After the addition the mixture is heated on a steam bath for 2 hours. The dark liquid is cooled and is cooled and poured into 1.5 l of crushed ice. The solution is made alkaline with sodium hydroxide. The crude, semi-solid aldehyde (59.6 g) which separates is collected and purified by recrystallization from isopropyl ether.

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Yield: 28.6 g, m.p. 65–66°. Equiv. weight 163 (calc. 163.22)

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The compound is also prepared as follows:

67.5 g of *N,N*-dimethyl-*m*-toluidine is dissolved in 250 ml of dimethyl formamide, and 35 ml of phosphorus tribromide is added dropwise with stirring and cooling

in water. The temperature is not allowed to rise over 50°. The mixture is heated for 1.5 hour on a steam bath and poured into approximately 1.5 l of an ice water mixture. The solution is made alkaline with sodium hydroxide and the crude product (46.9 g) which separates, is recrystallized from isopropyl ether.

Yield: 20.5 g, m.p. 63—65°. A second recrystallization from the same solvent gives 14.6 g of the pure aldehyde, melting at 65—66°.

(b) *N,N* - Dimethyl - 3 - methyl - 4 - (2 - nitropropenyl)aniline. A solution of 28.0 g of 4 - dimethylamino - 2 - methylbenzaldehyde, 20 ml of nitroethane and 15 g of ammonium acetate in 200 ml of 1-propanol is refluxed for 4 hours. The mixture is then poured into 1 l of ice water. The crude compound (30.2 g) is collected and purified by recrystallization from ethanol-petroleum ether.

Yield: 12.9 g, m.p. 75—76°.

Analysis.

Calculated for  $C_{12}H_{13}N_2O_2$ : C 65.44, H 7.32, N 12.72%.

Found: C 64.7, H 7.38, N 12.7%.

#### Preparation 2.

##### *N,N*-Dimethyl-3-chloro-4-(2-nitropropenyl)aniline

A solution of 36.8 g of 2-chloro-4-dimethylaminobenzaldehyde, 18 ml of nitroethane and 15 g of ammonium acetate in 150 ml of absolute ethanol is refluxed for 2 hours. The mixture is then poured into 1.5 l of water, whereupon the compound separates as a viscous red oil, which crystallizes on scratching. Recrystallization from ethanol yields 18.0 g of the compound, melting at 93—94°.

Analysis.

Calculated for  $C_{11}H_{13}ClN_2O_2$ : C 54.89, H 5.44, Cl 14.73, N 11.64%.

Found: C 54.2, H 5.48, Cl 14.9, N 11.5%.

#### Preparation 3.

##### *N,N*-Dimethyl-3,5-dichloro-4-(2-nitropropenyl)aniline

(a) *N,N*-Dimethyl-3,5-dichloroaniline. To a mixture of 40.5 g of 3,5-dichloroaniline and 62.0 g of sodium bicarbonate in 200 ml of 50% aqueous dioxane is added dropwise over 2 hours with stirring and cooling in ice 60 ml of dimethyl sulphate. 100 ml of 30% sodium hydroxide solution is then added and the mixture is refluxed for 1 hour. After filtration the solution is extracted with ether. The extracts are dried over anhydrous sodium sulphate and the solvent is evaporated. The residue is recrystallized from methanol.

Yield: 16.5 g, m.p. 53—54°. Equiv. weight 193.5 (calc. 190.08).

(b) 2,6 - Dichloro - 4 - dimethylaminobenzaldehyde. 9 ml of phosphorus oxychloride is added dropwise while stirring and cooling in ice to a solution of 19.0 g of *N,N* - dimethyl - 3,5 - dichloroaniline in 29 ml of dimethylformamide. The mixture is heated for 1 hour on a steam bath and poured into ice. The solution is made alkaline with sodium hydroxide and the crude product is filtered off.

Yield: 18.5 g, m.p. 152—157°. The compound is purified by recrystallization from ethanol-dioxane.

Yield: 13.9 g, m.p. 167—168°.

Analysis.

Calculated for  $C_{12}H_9Cl_2NO$ : C 49.56, H 4.16, Cl 32.51, N 6.42, O 7.34%.

Found: C 49.2, H 4.25, Cl 32.6, N 6.27, O 7.46%.

(c) *N,N* - Dimethyl - 3,5 - dichloro - 4 - (2 - nitropropenyl)aniline. A solution of 13.8 g of 2,6 - dichloro - 4 - dimethylaminobenzaldehyde, 7 ml of nitroethane and 10.0 g of ammonium acetate in 100 ml of 1-propanol is refluxed for 24 hours. The mixture is then poured into 1 l of ice water. The precipitate is filtered off and washed with water. Yield: 16.8, m.p. 105—110°. Recrystallization from aqueous ethanol gives 14.4 g of analytically pure product, melting at 113—114°.

Analysis.

Calculated for  $C_{11}H_{12}Cl_2N_2O_2$ : C 48.02, H 4.40, Cl 25.77, N 10.18, O 11.63%.

Found: C 47.8, H 4.43, Cl 26.1, N 9.95, O 11.6%.

## Preparation 4.

## N-Methyl-6-(2-nitropropenyl)-1,2,3,4-tetrahydroquinoline

(a) *N* - Methyl - 1,2,3,4 - tetrahydroquinoline. To a mixture of 100 g of 1, 2, 3, 4-tetrahydroquinoline and 100 g of sodium bicarbonate in 600 ml of 50% aqueous dioxane is added dropwise over 2 hours with stirring and cooling in ice 100 ml of dimethyl sulphate. After the addition the mixture is stirred over night at room temperature. 200 ml of 30% sodium hydroxide solution is then added and the mixture is refluxed for 1 hour. After filtration the solution is extracted with ether. The extracts are dried over anhydrous sodium sulphate and the solvent is evaporated. The residual oil (63.2 g) is distilled.

Yield: 50.4 g, b.p. 108—110°/10 mm. Equiv. weight 148 (calc. 147.22).

(b) 6 - Formyl - 1 - methyl - 1,2,3,4 - tetrahydroquinoline. 31 ml of phosphorus oxychloride is added dropwise while stirring and cooling in ice in 100 ml of dimethylformamide. To the stirred and cooled solution is added by portions 50.0 g of *N* - methyl - 1,2,3,4 - tetrahydroquinoline. After the addition the mixture is heated on a steam bath for 1 hour. The liquid is cooled and poured into 1 l of crushed ice. The solution is made alkaline with sodium hydroxide and extracted with ether. The extract is dried over anhydrous sodium sulphate and the solvent evaporated. The residual oil is distilled.

Yield: 47.4 g, b.p. 175—178°/6 mm. Equiv. weight 178 (calc. 175.23).

(c) *N* - Methyl - 6 - (2 - nitropropenyl) - 1,2,3,4 - tetrahydroquinoline. A solution of 47.1 g of 6 - formyl - 1 - methyl - 1,2,3,4 - tetrahydroquinoline, 24 ml of nitroethane and 20 g of ammonium acetate in 200 ml of 1-propanol is refluxed for 5 hours. The mixture is then poured into 1 l of ice water. The precipitated oil is extracted with ether and dried with anhydrous sodium sulphate. Evaporation of the solvent gives 54.8 g of a dark yellow oil, which, however, could not be recrystallized. The product is used directly, without further purification.

## Preparation 5.

## N,N - Dimethyl - 3 - bromo - 4 - (2 - nitropropenyl)aniline

(a) 2 - Bromo - 4 - dimethylaminobenzaldehyde. 14.5 ml of phosphorus oxychloride is added dropwise while stirring and cooling to a solution of 31.6 g of N,N-dimethyl - 3 - bromoaniline in 46 ml of dimethylformamide. The mixture is heated with sodium hydroxide. The precipitate is filtered off and recrystallized from aqueous ethanol.

Yield: 19.6 g, m.p. 81—82°.

## Analysis.

Calculated for  $C_{10}H_{10}BrNO$ : C 47.39, H 4.42, Br 35.04, N 6.14, O 7.01%.

Found: C 47.1, H 4.38, Br 35.0, N 6.11, O 7.40%.

(b) N,N - Dimethyl - 3 - bromo - 4 - (2 - nitropropenyl)aniline. A solution of 19.0 g of 2 - bromo - 4 - dimethylaminobenzaldehyde, 10 ml of nitroethane and 15 g of ammonium acetate in 100 ml of 1-propanol is refluxed for 7 hours. The mixture is then poured into 1 l of ice water. The precipitate is filtered off and purified by recrystallization from aqueous ethanol.

Yield: 10.2 g, m.p. 102—103°.

## Analysis.

Calculated for  $C_{11}H_{13}BrN_2O_2$ : C 46.33, H 4.59, Br 28.03, N 9.82, O 11.22%.

Found: C 45.9, H 4.57, Br 28.0, N 9.63, O 11.3%.

## Preparation 6.

N-[ $\alpha,\alpha$ -dimethyl- $\beta$ -(4-dimethylaminophenyl)ethyl]acetamide

9.2 ml of acetonitrile is added dropwise at room temperature to a stirred solution of 18.5 ml of concentrated sulphuric acid in 140 ml of acetic acid. 30.6 g of N,N-dimethyl - p - 2',2' - dimethylvinylaniline is then added and the mixture is heated and stirred for 1 hour at 70°. The liquid is poured into crushed ice and the mixture is neutralized with sodium hydroxide (pH 6). The crude compound (29.8 g) is filtered off and purified by recrystallization from ethanol/ligroin.

Yield: 17.0 g, m.p. 156—157°.

## Analysis.

Calculated for  $C_{24}H_{28}N_2O$ : C 71.75, H 9.46, N 11.96, O 6.83%.

Found: C 71.4, H 9.4, N 12.0, O 6.9%.

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#### Preparation 7.

##### N,N-Dimethyl-3-chloro-4-(2-nitro-1-butenyl)aniline

A solution of 36.8 g of 2-chloro-4-dimethylaminobenzaldehyde, 25 ml of 1-nitropropane and 20 g of ammonium acetate in 150 ml of 1-propanol is refluxed for 15 hours. The mixture is then poured into 1.5 l of water whereupon the compound separates as a viscous red oil. Recrystallization twice from aqueous acetic acid yields 5.0 g of the compound, melting at 90—91°.

##### Analysis.

Calculated for  $C_{12}H_{14}ClN_2O_2$ : C 56.58, H 5.94, U 13.92, N 11.00, O 12.56%.

Found: C 56.8, H 5.6, Cl 14.0, N 10.9%.

#### Example 1.

##### $\beta$ -(2-methyl-4-dimethylaminophenyl)- $\alpha$ -methylethylamine dihydrochloride (Method A)

12.5 g of N,N - dimethyl - 3 - methyl - 4 - (2 - nitropropenyl)aniline in 150 ml of dry ether is added to a stirred mixture of 9.1 g of lithium aluminium hydride in 200 ml of dry ether at such a rate that the solvent refluxes gently without external heating. The mixture is stirred and refluxed for 5 hours. 50 ml of saturated sodium sulphate solution is added dropwise with vigorous stirring and cooling in ice water. The mixture is filtered and the ethereal solution dried over anhydrous sodium sulphate. The dihydrochloride is precipitated from the solution by the addition of ether saturated with hydrogen chloride. The crude salt is purified by recrystallization from ethanol-isopropyl ether.

Yield: 12.6 g, m.p. 205—207°.

A second recrystallization from the same solvent gives 11.0 g of the compound, melting at 208—209°.

#### Example 2.

##### $\beta$ -(4-ethylaminophenyl)- $\alpha$ -methylethylamine dihydrochloride (Method B)

11.0 g of 4 - (2 - nitropropenyl)acetanilide dissolved in 150 ml of dry tetrahydrofuran is added dropwise to a stirred mixture of 11.0 g of lithium aluminium hydride in 200 ml of dry ether. After the addition the reaction mixture is stirred and refluxed for 4 hours. 60 ml of saturated sodium sulphate solution is added carefully with stirring and cooling. The mixture is filtered and the ethereal solution is evaporated. The residue is dissolved in dilute hydrochloric acid and the solution is shaken with ether. The acidic layer is made alkaline with sodium hydroxide and the solution is extracted with ether. After drying over solid sodium hydroxide the extract is evaporated. The residue is distilled to obtain 4.7 g of the free base boiling at 97—100°/0.03 mm. The free base is converted to the dihydrochloride by dissolving the base in ether and treating the solution with an excess of dry hydrogen chloride. Recrystallization of the resultant precipitate yields 4.8 g of the pure salt, melting at 184—185°.

#### Example 3.

##### $\beta$ -(2-chloro-4-dimethylaminophenyl)- $\alpha$ -methylethylamine dihydrochloride (Method A)

A solution of 12.0 g of N,N - dimethyl - 3 - chloro - 4 - (2 - nitropropenyl)aniline in 150 ml of dry tetrahydrofuran is added dropwise with stirring to 8.0 g of lithium aluminium hydride in 200 ml of dry ether. After the addition the reaction mixture is refluxed for 5 hours. 40 ml of saturated sodium sulphate solution is added by portions and the mixture is filtered. The filtrate is dried with anhydrous sodium sulphate and acidified with hydrogen chloride in ether. The precipitate is removed by filtration and recrystallized from ethanol-isopropyl ether.

Yield: 9.3 g, m.p. 187—191°.

A second recrystallization from the same solvent yields 8.1 g of the pure compound, melting at 193—195°.

#### Example 4.

##### $\beta$ -(2,6-dichloro-4-dimethylaminophenyl)- $\alpha$ -methylethylamine dihydrochloride (Method A)

A solution of 13.7 g of N,N - dimethyl - 3,5 - dichloro - 4 - (2 - nitropropenyl)aniline in 150 ml of dry tetrahydrofuran is added dropwise with stirring to 8.0 g lithium aluminium hydride in 200 ml of dry ether. The mixture is then refluxed for 4 hours. 40 ml of saturated sodium sulphate solution is added dropwise and the

mixture is filtered. The filtrate is dried over anhydrous sodium sulphate and acidified with hydrogen chloride. The precipitated salt is filtered off and washed with ether.

Yield: 15.2 g, m.p. 195—197°.

The product is recrystallized from aqueous ethanol-isopropyl ether.

Yield: 11.9 g, m.p. 199—200°.

#### Example 5.

##### $\beta$ -(3-bromo-4-dimethylaminophenyl)- $\alpha$ -methylethylamine dihydrochloride (Method C)

To a mixture of 2.51 g of  $\beta$ -(4-dimethylaminophenyl)- $\alpha$ -methylethylamine dihydrochloride and 5.0 g of anhydrous sodium acetate in 50 ml of acetic acid is added dropwise with stirring a solution of 0.51 ml of bromine in 50 ml of acetic acid. The mixture is stirred at room temperature for 2 hours. The solvent is evaporated and the residue dissolved in 200 ml of water. The solution is made alkaline with sodium hydroxide and extracted with ether. The ether extract is dried over anhydrous sodium sulphate and acidified with hydrogen chloride in ether. The precipitate is filtered off and recrystallized from ethanol-ethyl acetate.

Yield: 2.3 g, m.p. 190—191°.

#### Example 6.

##### 6-(2-aminopropyl)-1-methyl-1,2,3,4-tetrahydroquinoline dihydrochloride (Method A)

A solution of 11.6 g of crude N-methyl-6-(2-nitropropenyl)-1,2,3,4-tetrahydroquinoline in 150 ml of dry ether is added dropwise with stirring to 8.0 g of lithium aluminium hydride in 150 ml of ether. The reaction mixture is refluxed for 4 hours. 40 ml of saturated sodium sulphate solution is added dropwise and the mixture is filtered. The filtrate is acidified with hydrogen chloride in ether. The precipitated syrupy product is dissolved in 250 ml of water and made alkaline with sodium hydroxide. The solution is extracted with ether and the extract is dried over anhydrous sodium sulphate. The solvent is evaporated and the residual oil is distilled.

Yield: 3.3 g, b.p. 135—137°/0.07 mm. The base is dissolved in ether and the dihydrochloride is precipitated from the solution by the addition of an excess hydrogen chloride in ether. The precipitated salt is recrystallized from ethanol-isopropyl ether.

Yield: 3.3 g, m.p. 221—222°.

#### Example 7.

##### $\beta$ -(2-bromo-4-dimethylaminophenyl)- $\alpha$ -methylethylamine dihydrochloride (Method A)

A solution of 10.0 g of N,N-dimethyl-3-bromo-4-(2-nitropropenyl)-aniline in 100 ml of dry tetrahydrofuran is added dropwise with stirring to 8.0 g of lithium aluminium hydride in 200 ml of dry ether. After the addition the reaction mixture is refluxed for 4 hours. 40 ml of saturated sodium sulphate solution is then added by portions and the mixture is filtered. The filtrate is acidified with hydrogen chloride in ether. The precipitated syrupy product is dissolved in water. The solution is washed with ether and made alkaline with sodium hydroxide. The separated oil is extracted with ether and the ether extract is dried over anhydrous sodium sulphate. The solution is acidified with hydrogen chloride in ether and the semi-solid precipitate is filtered off and recrystallized from ethanol-isopropyl ether.

Yield: 8.2 g, m.p. 195—196°.

#### Example 8.

##### $\beta$ -(4-dimethylaminophenyl)- $\alpha,\alpha$ -dimethylethylamine dihydrochloride (Method D)

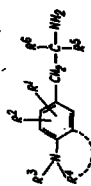
A solution of 3.5 g of N-[ $\alpha,\alpha$ -dimethyl- $\beta$ -(4-dimethylaminophenyl)-ethyl]acetamide in a mixture of 25 ml of water and 25 ml of concentrated hydrochloric acid is refluxed for 16 hours. The solution is then evaporated under reduced pressure and the residue is recrystallized twice from methanol isopropyl ether.

Yield: 1.1 g, m.p. 239.5—240.5°.

Physical data for some compounds of the invention, including those described in Examples 1—8, are given in Table 1.

Physical data for some intermediates including those described in Preparations 1—7 are given in Table 2. Those intermediates not exemplified above are prepared using methods analogous to those described above. The intermediates which are oils are used directly without further purification.

TABLE 1

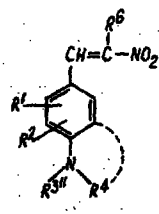


| Described<br>Preparation<br>No. | M.P. HCl-salt °C  |                |                                               |                                               |                 |                               | Yield %<br>HCl-salt |                                     | HCl-salt, analysis: Calculated %<br>Found % |              |               |               |  |  |
|---------------------------------|-------------------|----------------|-----------------------------------------------|-----------------------------------------------|-----------------|-------------------------------|---------------------|-------------------------------------|---------------------------------------------|--------------|---------------|---------------|--|--|
|                                 | R <sup>1</sup>    | R <sup>2</sup> | R <sup>3</sup>                                | R <sup>4</sup>                                | R <sup>5</sup>  | R <sup>6</sup>                | Base                | Recrystallization<br>from           | C                                           | H            | Cl            | N             |  |  |
| 1                               | 2-CH <sub>3</sub> | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | H               | CH <sub>3</sub>               | 83                  | ethanol/iso-<br>propyl ether        | 54.34<br>54.4                               | 8.36<br>8.37 | 26.73<br>26.6 | 10.56<br>10.5 |  |  |
| -                               | 3-CH <sub>3</sub> | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | H               | CH <sub>3</sub>               | 43                  | ethanol/ethyl<br>acetate            | 54.34<br>54.2                               | 8.36<br>8.34 | 26.73<br>26.4 | 10.56<br>10.5 |  |  |
| 2                               | H                 | H              | H                                             | C <sub>2</sub> H <sub>5</sub>                 | H               | CH <sub>3</sub>               | -                   | ethanol/iso-<br>propyl ether        | 52.59<br>52.6                               | 8.03<br>8.06 | 28.23<br>28.0 | 11.15<br>11.2 |  |  |
| -                               | H                 | H              | CH <sub>3</sub>                               | C <sub>2</sub> H <sub>5</sub>                 | H               | CH <sub>3</sub>               | 61                  | ethanol/iso-<br>propyl ether        | 54.34<br>54.1                               | 8.36<br>8.43 | 26.73<br>26.4 | 10.56<br>10.5 |  |  |
| -                               | H                 | H              | C <sub>2</sub> H <sub>5</sub>                 | C <sub>2</sub> H <sub>5</sub>                 | H               | CH <sub>3</sub>               | -                   | ethanol/iso-<br>propyl ether        | 55.91<br>55.6                               | 8.66<br>8.62 | 25.41<br>25.4 | 10.03<br>9.94 |  |  |
| -                               | H                 | H              | C <sub>2</sub> H <sub>5</sub> CH <sub>2</sub> | C <sub>2</sub> H <sub>5</sub> CH <sub>2</sub> | H               | CH <sub>3</sub>               | 50                  | ethanol/ethyl<br>acetate            | 68.48<br>67.8                               | 7.00<br>7.01 | 17.58<br>17.1 | 6.95<br>6.91  |  |  |
| 3                               | 2-Cl              | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | H               | CH <sub>3</sub>               | 65                  | ethanol/iso-<br>propyl ether        | 46.25<br>46.1                               | 6.70<br>6.89 | 37.24<br>37.5 | 9.81<br>9.73  |  |  |
| 4                               | 2-Cl              | 6-Cl           | CH <sub>3</sub>                               | CH <sub>3</sub>                               | H               | CH <sub>3</sub>               | 95                  | aqueous ethanol/<br>isopropyl ether | 41.27<br>41.7                               | 5.67<br>5.84 | 44.31<br>44.1 | 8.75<br>8.60  |  |  |
| 5                               | 3-Br              | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | H               | CH <sub>3</sub>               | 70a                 | ethanol/ethyl<br>acetate            | 40.02<br>39.7                               | 5.80<br>5.81 | 21.48<br>21.4 | 8.49<br>8.42  |  |  |
| 7                               | 2-Br              | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | H               | CH <sub>3</sub>               | 70                  | ethanol/iso-<br>propyl ether        | 40.02<br>40.6                               | 5.80<br>5.95 | 21.48<br>21.5 | 8.49<br>8.55  |  |  |
| 8                               | H                 | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | CH <sub>3</sub> | CH <sub>3</sub>               | 28                  | methanol/iso-<br>propyl ether       | 54.34<br>53.5                               | 8.36<br>8.40 | 26.73<br>26.3 | 10.56<br>10.4 |  |  |
| -                               | 2-Cl              | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | H               | C <sub>2</sub> H <sub>5</sub> | 85                  | ethanol/iso-<br>propyl ether        | 48.09<br>47.8                               | 7.06<br>7.13 | b             | 9.35<br>9.23  |  |  |
| 6                               |                   |                |                                               |                                               |                 |                               | -                   | ethanol/iso-<br>propyl ether        | 56.32<br>55.7                               | 8.0<br>8.15  | 25.58<br>25.3 | 10.11<br>9.91 |  |  |

a Cl+Br: Calc. 45.69; found 45.2

b Cl: Calc. 23.66; found 23.2

TABLE 2



| R <sup>1</sup>    | R <sup>2</sup> | R <sup>3</sup>                                | R <sup>4</sup>                                | R <sup>6</sup>                | M.p.<br>°C | Described<br>in<br>Prepara-<br>tion<br>No. |
|-------------------|----------------|-----------------------------------------------|-----------------------------------------------|-------------------------------|------------|--------------------------------------------|
| 3-CH <sub>3</sub> | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | CH <sub>3</sub>               | 75-76      | 1 (b)                                      |
| 2-CH <sub>3</sub> | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | CH <sub>3</sub>               | Oil        | —                                          |
| H                 | H              | CH <sub>3</sub>                               | C <sub>2</sub> H <sub>5</sub>                 | CH <sub>3</sub>               | Oil        | —                                          |
| H                 | H              | C <sub>2</sub> H <sub>5</sub> CH <sub>2</sub> | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> | CH <sub>3</sub>               | Oil        | —                                          |
| 3-Cl              | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | CH <sub>3</sub>               | 93-94      | 2                                          |
| 3-Cl              | 5-Cl           | CH <sub>3</sub>                               | CH <sub>3</sub>                               | CH <sub>3</sub>               | 113-114    | 3 (c)                                      |
| 3-Br              | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | CH <sub>3</sub>               | 102-103    | 5 (b)                                      |
| 3-Cl              | H              | CH <sub>3</sub>                               | CH <sub>3</sub>                               | C <sub>2</sub> H <sub>5</sub> | 90-91      | 7                                          |
|                   |                |                                               |                                               |                               | Oil        | 4 (c)                                      |

- 5

It is not possible by experimental means to induce depression in laboratory animals. In order to evaluate a possible anti-depressive-effect on new substances biochemical pharmacological test methods must be used. One such method, which seems to give a good indication of the potential anti-depressive effects of the test substances, is described in Europ. J. Pharmacol. 17, 107, 1972. This method involves the measurement of the potentiation of the syndromes produced by 5-hydroxytryptophan (5-HTP) in a laboratory animal.

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The lack of euphoric effect, that is lack of central stimulatory activity, is tested by measuring the motor activity in mice after administration of the test substance.

Potential anxiolytic activity is tested by measuring the antiaggressiveness in isolated mice after administration of the test substance. In this test not amphetamine but Valium — a wellknown anxiolytic substance — is used as a reference. (Valium is a Registered Trade Mark).

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**5-HTP response potentiation test**

Inhibition of the uptake of 5-HTP potentiates the effects of administered 5-hydroxytryptophan (5-HTP) probably by increasing the amount of 5-HT at the receptor. Three mice are given the test drugs one hour (or 4, 24 hours) before dl-5-HTP, 90 mg/kg i.v. 5-HTP alone gives only a weak behavioural syndrome but in

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pretreated mice there is seen a characteristic behavioural syndrome, which comes within five minutes: tremor, lordosis, abduction of the hindlegs, head-twitches.

5 The absence or presence of respective syndrome is scored in groups of ten mice. The compound was administered in at least five doses and the quantal responses were analysed by probit analysis and  $ED_{50}$  determined according to the method of Litchfield and Wilcoxon. The results are shown in Table 3.

#### *Motor activity in mice*

10 The exploratory activity of mice was recorded in a locomotion cage in which the movements were counted each time the animal cross-circuits an electrical current in the bottom plate. The activity was recorded for ten minutes one hour after the administration of the drug. The animals were tested individually. Groups of six mice were used and the mice were only used once. The activity was expressed in per cent of the activity of control groups run simultaneously. The compounds were administered in at least four doses. The increase (+) or decrease (-) of the activity compared to control groups was determined from log dose response curves. The results are shown in Table 3.

#### *Aggressive behaviour in mice*

20 Male mice kept isolated for 3 weeks or longer develop an aggressive behaviour when caged together. The method used follows that of Valzelli *et al.* (Europ. J. Pharmacol. 2, 144, 1967), with the exception that 2 mice were tested on each other. The aggressiveness was scored during a 5 min test according to the following rating:

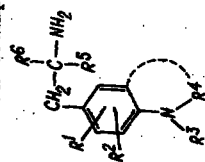
25 0 the animals show no interest in each other except occasional nosing  
25 frequent vigorous nosing and tail rattling, the animals assume a fighting position and occasionally attack each other — no more than 3—4 times in the 5 min period  
50 rattling, powerful attacks — no more than 10 times in the test period  
75 the animals follow their partners, attacking and biting for most of the time  
100 attacks over the entire period.

30 Controls administered with the solvent were tested, the repeated testing did not influence on the aggressiveness. The animals were used for several experiments but with intervals of at least one week. Groups of 10 mice were used.

$ED_{50}$  in the dose which reduces the aggressiveness score by 50%.  
Results are shown in Table 3.

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TABLE 3  
Pharmacological effects of 4-aminoamphetamine derivatives



| Compound            |                   | R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup>                | R <sup>4</sup>                   | R <sup>5</sup>  | R <sup>6</sup>                | Potential of 5-HTP<br>ED <sub>50</sub> mg/kg<br>i.p. | Motor Activity<br>+ = increase<br>- = decrease<br>0 = no effect | Anti-aggressive<br>behaviour<br>in mice<br>ED <sub>50</sub> mg/kg<br>i.p. |
|---------------------|-------------------|----------------|----------------|-------------------------------|----------------------------------|-----------------|-------------------------------|------------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------|
| Valium              |                   |                |                |                               |                                  |                 |                               | >5                                                   | +++                                                             | 2.5                                                                       |
| Amphetamine         |                   |                |                |                               |                                  |                 |                               | 11.5                                                 |                                                                 | *                                                                         |
| p-Aminoamphetamine  |                   |                |                |                               |                                  |                 |                               | 0.8                                                  | ++                                                              | 0.3                                                                       |
| p-Chloroamphetamine |                   |                |                |                               |                                  |                 |                               | 2                                                    | -                                                               | 5-10                                                                      |
| H                   | H                 |                |                | C <sub>2</sub> H <sub>5</sub> | C <sub>2</sub> H <sub>5</sub>    | H               | CH <sub>3</sub>               | 0.25                                                 | -                                                               | 2.5-5                                                                     |
| H                   | 2-Cl              |                |                | CH <sub>3</sub>               | CH <sub>3</sub>                  | H               | CH <sub>3</sub>               | 1                                                    | -                                                               | 1.25                                                                      |
| H                   | H                 |                |                | C <sub>2</sub> H <sub>5</sub> | H                                | H               | CH <sub>3</sub>               | 0.6                                                  | -                                                               | 2.5-5                                                                     |
| H                   | 2-CH <sub>3</sub> |                |                | CH <sub>3</sub>               | CH <sub>3</sub>                  | H               | CH <sub>3</sub>               | 0.7                                                  | -                                                               | <5                                                                        |
| H                   | H                 |                |                | C <sub>2</sub> H <sub>5</sub> | CH <sub>3</sub>                  | H               | CH <sub>3</sub>               | 1                                                    | -                                                               | >5                                                                        |
| H                   | 3-Br              |                |                | CH <sub>3</sub>               | CH <sub>3</sub>                  | H               | CH <sub>3</sub>               | 0.1                                                  | -                                                               | >5                                                                        |
| 2-Cl                | 6-Cl              |                |                | CH <sub>3</sub>               | CH <sub>3</sub>                  | H               | CH <sub>3</sub>               | 1.5                                                  |                                                                 | >5                                                                        |
| H                   | H                 |                |                | CH <sub>3</sub>               | -(CH <sub>2</sub> ) <sub>3</sub> | H               | CH <sub>3</sub>               | 0.1                                                  |                                                                 | >5                                                                        |
| H                   | 2-Br              |                |                | CH <sub>3</sub>               | CH <sub>3</sub>                  | H               | CH <sub>3</sub>               | 2.5                                                  | 0                                                               |                                                                           |
| H                   | H                 |                |                | CH <sub>3</sub>               | CH <sub>3</sub>                  | CH <sub>3</sub> | CH <sub>3</sub>               | 0.25                                                 | 0                                                               |                                                                           |
| H                   | 2-Cl              |                |                | CH <sub>3</sub>               | CH <sub>3</sub>                  | H               | C <sub>2</sub> H <sub>5</sub> |                                                      |                                                                 |                                                                           |

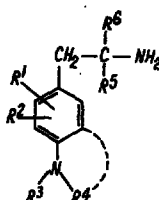
\* Not tested, due to interference with motor activity.

As can be seen from the results in Table 3 the tested substances differ considerably in activity from amphetamine both qualitatively and quantitatively. In contrast to amphetamine the tested compounds of the invention strongly potentiate the 5-HTP response. Furthermore the tested compounds lack the central stimulation which is pronounced after amphetamine and *p*-chloroamphetamine and instead give a weak solution. Thus, the potential anti-depressive activity as indicated by the potentiation of 5-HTP and the lack of central stimulatory activity indicates that the compounds of this invention are valuable potential antidepressive agents.

The tested compounds antagonize the aggressive behaviour of male mice which have been kept isolated for one month or more. Many of the compounds are at least as active as Valium in this test which indicates that these compounds may have therapeutic value as anxiolytic compounds.

#### WHAT WE CLAIM IS:—

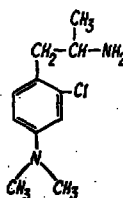
1. A compound of the formula



wherein each of  $R^1$  and  $R^2$ , which may be the same or different, is a hydrogen or halogen atom or a lower alkyl group,  $R^3$  is a lower alkyl group or a benzyl group,  $R^4$  is a hydrogen atom, a lower alkyl group, a benzyl group or a  $-\text{CH}_2\text{CH}_2\text{CH}_2-$  bridge attached to the phenyl ring at the ortho-position relative to the N-substituent on the phenyl ring,  $R^5$  is a hydrogen atom or a methyl group and  $R^6$  is a lower alkyl group, with the proviso that when each of  $R^3$  and  $R^4$  is a methyl group and  $R^5$  is a hydrogen atom,  $R^1$  and/or  $R^2$  is a lower alkyl group or a halogen atom; or a pharmaceutically acceptable acid addition salt thereof.

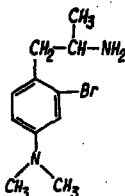
2. A compound according to claim 1, wherein  $R^3$  is a lower alkyl group,  $R^4$  is a lower alkyl group,  $R^5$  is a hydrogen atom and  $R^6$  is a methyl group.

3. A compound of the formula



or a pharmaceutically acceptable acid addition salt thereof.

4. A compound of the formula



or a pharmaceutically acceptable acid addition salt thereof.

5.  $\beta$  - (2 - chloro - 4 - dimethylaminophenyl) -  $\alpha$  - methylethylamine dihydrochloride.

6.  $\beta$  - 2 - bromo - 4 - dimethylaminophenyl) -  $\alpha$  - methylethylamine dihydrochloride.

7.  $\beta$  - (2 - methyl - 4 - dimethylaminophenyl) -  $\alpha$  - methylethylamine or its dihydrochloride.

8.  $\beta$  - (4 - ethylaminophenyl) -  $\alpha$  - methylethylamine or its dihydrochloride.

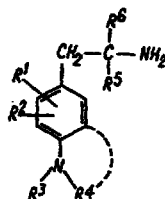
9.  $\beta$  - (2,6 - dichloro - 4 - dimethylaminophenyl) -  $\alpha$  - methylethylamine or its dihydrochloride.

As can be seen from the results in Table 3 the tested substances differ considerably in activity from amphetamine both qualitatively and quantitatively. In contrast to amphetamine the tested compounds of the invention strongly potentiate the 5-HTP response. Furthermore the tested compounds lack the central stimulation which is pronounced after amphetamine and *p*-chloroamphetamine and instead give a weak solution. Thus, the potential anti-depressive activity as indicated by the potentiation of 5-HTP and the lack of central stimulatory activity indicates that the compounds of this invention are valuable potential antidepressive agents.

The tested compounds antagonize the aggressive behaviour of male mice which have been kept isolated for one month or more. Many of the compounds are at least as active as Valium in this test which indicates that these compounds may have therapeutic value as anxiolytic compounds.

#### WHAT WE CLAIM IS:—

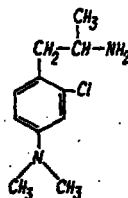
1. A compound of the formula



wherein each of  $R^1$  and  $R^2$ , which may be the same or different, is a hydrogen or halogen atom or a lower alkyl group,  $R^3$  is a lower alkyl group or a benzyl group,  $R^4$  is a hydrogen atom, a lower alkyl group, a benzyl group or a  $-\text{CH}_2\text{CH}_2\text{CH}_2-$  bridge attached to the phenyl ring at the ortho-position relative to the N-substituent on the phenyl ring,  $R^5$  is a hydrogen atom or a methyl group and  $R^6$  is a lower alkyl group, with the proviso that when each of  $R^3$  and  $R^4$  is a methyl group and  $R^5$  is a hydrogen atom,  $R^1$  and/or  $R^2$  is a lower alkyl group or a halogen atom; or a pharmaceutically acceptable acid addition salt thereof.

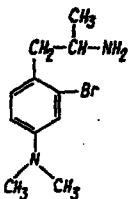
2. A compound according to claim 1, wherein  $R^3$  is a lower alkyl group,  $R^4$  is a lower alkyl group,  $R^5$  is a hydrogen atom and  $R^6$  is a methyl group.

3. A compound of the formula



or a pharmaceutically acceptable acid addition salt thereof.

4. A compound of the formula



or a pharmaceutically acceptable acid addition salt thereof.

5.  $\beta$  - (2 - chloro - 4 - dimethylaminophenyl) -  $\alpha$  - methylethylamine dihydrochloride.

6.  $\beta$  - 2 - bromo - 4 - dimethylaminophenyl) -  $\alpha$  - methylethylamine dihydrochloride.

7.  $\beta$  - (2 - methyl - 4 - dimethylaminophenyl) -  $\alpha$  - methylethylamine or its dihydrochloride.

8.  $\beta$  - (4 - ethylaminophenyl) -  $\alpha$  - methylethylamine or its dihydrochloride.

9.  $\beta$  - (2,6 - dichloro - 4 - dimethylaminophenyl) -  $\alpha$  - methylethylamine or its dihydrochloride.



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10.  $\beta$  - (3 - bromo - 4 - dimethylaminophenyl) -  $\alpha$  - methylethylamine or its dihydrochloride.

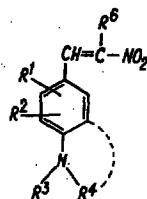
11.  $\beta$  - (4 - dimethylaminophenyl) -  $\alpha, \alpha$  - dimethylethylamine or its dihydrochloride.

12. 6 - (2 - Aminopropyl) - 1 - methyl - 1,2,3,4 - tetrahydroquinoline or its hydrochloride.

13. A compound according to any of claims 1 to 12, in the form of a substantially pure stereoisomer.

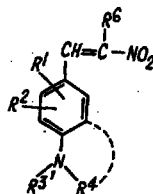
14. A process for the preparation of a compound of formula I as defined in claim 1, which process comprises

a) reducing a compound of the formula



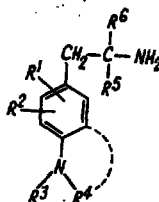
wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^6$  are as defined in claim 1, to a compound of formula I wherein  $R^5$  is a hydrogen atom; or

b) reducing a compound of the formula



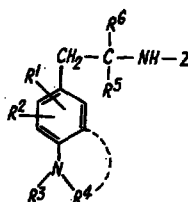
wherein  $R^1$ ,  $R^2$ ,  $R^4$  and  $R^6$  are as defined in claim 1 and  $R^{3'}$  is a lower aliphatic acyl group or a benzoyl group, to a compound of formula I wherein  $R^5$  is a hydrogen atom; or

c) halogenating a compound of the formula



wherein  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are as defined in claim 1 and either  $R^1$  or  $R^2$  or both are hydrogen, to give a compound of the formula I wherein  $R^1$  or  $R^2$  or both are a halogen atom, or

d) hydrolysing a compound of the formula



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wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are as defined in claim 1, and Z is a lower aliphatic acyl group, to give a compound of formula I; and then, if desired, converting the compound obtained in any of the methods a) to d) into a pharmaceutically acceptable acid addition salt thereof and/or resolving the same to give a substantially pure stereoisomer thereof.

15. A process according to claim 14, substantially as described in any one of the foregoing Examples 8 to 15.

16. A compound according to claim 1, when prepared by a process as claimed in claim 14 or 15.

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12 or 16 together with a pharmaceutically acceptable carrier or diluent.

18. A pharmaceutical composition according to claim 17 substantially as hereinbefore described.

19. A method for the treatment of depression in mammals excluding humans which comprises administering to the mammal an effective amount of a compound as claimed in any one of claims 1 to 12 or 16 or a composition as claimed in claim 17 or 18.

20. A method for the alleviation of anxiety in mammals excluding humans which comprises administering to the mammal an effective amount of a compound as claimed in any one of claims 1 to 12 or 16 or a composition as claimed in claim 17 or 18.

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