

PATENT SPECIFICATION

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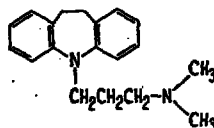


(54) PHENYL-PYRIDYLALLYLAMINES, AND A PROCESS FOR THEIR PREPARATION

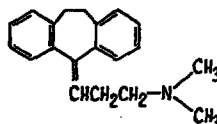
(71) We, AB HASSLE, a Swedish Body Corporate, of Fack S—402, 20 Göteborg, 5, Sweden, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

5 The present invention relates to new compounds having therapeutic activity, to their preparation and to pharmaceutical preparations containing them. 5

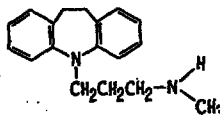
The antidepressive agents having the most widespread clinical use are the tricyclic tertiary amines imipramine having the structural formula:



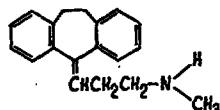
10 and amitriptyline having the structural formula: 10



Secondary amines such as desipramine having the structural formula:



and nortriptyline having the structural formula

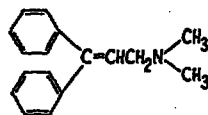


are used to a somewhat less extent. All these substances have, however, side effects which are not desired at therapeutic use such as orthostatism, anticholinergic effects and, in particular, an arrhythmogen-heart arrhythmic developing-effect when administered in large doses to old patients. The secondary amines, such as desipramine and nortriptyline, have also the known effect of developing anxiety in many depressed patients. Moreover, all the substances mentioned above have the drawback that the antidepressive effect first appears after some weeks of treatment. This delay in having an effect must be

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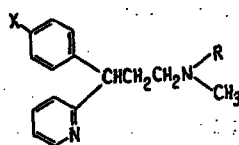
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ascribed to the fact that all the substances have a low antidepressive activity. Further, it is known from the literature that certain 1,1-diphenyl-3-aminoprop-1-enes, such as the compound having the formula:



V

have an antidepressive effect, cf J. Med. Chem. 14, 161—4 (1971). From the literature, compounds having the formula:

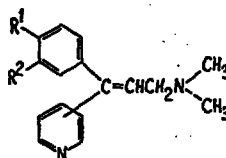


VI

wherein X is chlorine or bromine and R is hydrogen or methyl, are described as having both an antihistaminic effect and an antidepressive effect, cf U.S. Patent No. 3,423,510. The compound of formula VI wherein X is bromine and R is methyl is called brompheniramine in Table 1 below. However, the compounds of formula V and formula VI illustrated above both have the serious side-effects of developing anxiety and also developing orthostatism in the patient.

Accordingly, the present invention relates to new compounds having a good antidepressive effect but which do not produce orthostatism, anticholinergic effects or arrhythmogenic effects and to a process for their preparation.

Accordingly, the present invention provides a substituted allylamine compound having the structural formula:

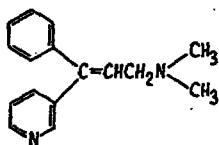


VII

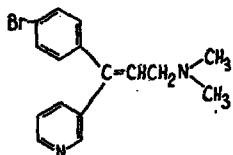
and therapeutically acceptable acid addition salts thereof, wherein the bond to the pyridine nucleus is in the *meta* or *para*-position, R¹ and R², which may be the same or different, are each H, Cl or Br, provided that R¹ is H or Br when R² is Br and that R¹ is H or Cl when R² is Cl, and when the bond to the pyridine nucleus is in the *ortho*-position, R¹ and R² are each Br, or R¹ is H or Br when R² is Br or H respectively. The compounds of the present invention together with the clinically most used tricyclic agents such as imipramine, desipramine, amitriptyline and nortriptyline, and those compounds known from the literature, such as those of formulae V and VI, are potently active antidepressive, depression solving agents, but the compounds of this invention do not give the most troublesome side effects such as anxiety orthostatism, and heartarrhythmics. Illustrative examples of the compounds of the invention are:

Structure formula

Code number



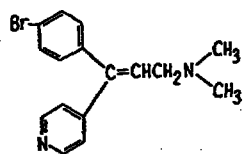
H 102/01



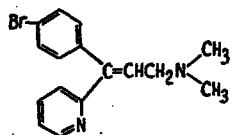
H 102/09

Structure formula

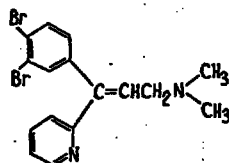
Code number



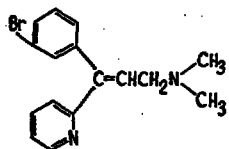
H 102/10



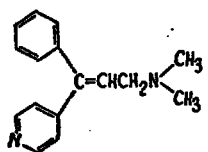
H 100/04



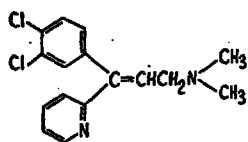
H 99/88



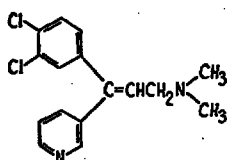
H 102/30



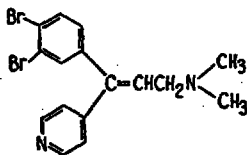
H 102/04



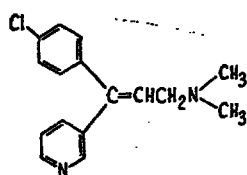
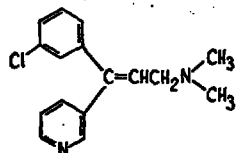
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The preferred compounds of the invention are the compounds having code numbers H 102/09, H 102/10, and H 100/04.

The present invention also provides a process for preparing a compound of formula VII which comprises dehydrating a compound of the formula:



10 The dehydration of the compound of formula IX may for example be done by means of concentrated sulphuric acid and heating the reaction mixture to a high temperature, about 165 to 175°C. The dehydration of the compound of formula IX may also be done by means of other types of acid-catalysis, such as, for example, by means of hydrochloric acid, HCl, phosphoric acid, H₃PO₄, potassium hydrogen sulphate, KHSO₄, or oxalic acid (COOH)₂, other methods for the dehydration of the compound of formula VII to the formation of a compound of the formula X are dehydration using phosphorus oxychloride POCl₃ in pyridine, and dehydration with thionyl chloride, SOCl₂, in pyridine. Also a catalytic dehydration of the compound of the formula VII may be used. The dehydration is in this case carried out at a temperature of about 300 to 500°C using a catalyst such as kaolin, aluminium or aluminium oxide, Al₂O₃, as a catalyst.

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Starting materials of the formula VII may be prepared in any way freely chosen, such as by reacting a compound of the formula:



with a pyridyllithium compound of the formula



XII

in which formulae R¹ and R² have the meanings indicated above and the lithium atom is bound in *ortho*-, *meta*-, or *para*-position to the pyridine nucleus.

25 The compounds of formula VII according to the invention may exist in the E- or Z-configuration according to the IUPAC-nomenclature. The E-Z nomenclature is explained in IUPAC Tentative Rules for the Nomenclature of Organic Chemistry: Section E Fundamental Stereochemistry, J. Org. Chem, 35 2849-2867, September 1970. The therapeutic effect cannot be significantly ascribed to only one of these forms but can to a greater or lesser extent be ascribed to one of or both the E- or Z-configuration.

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In clinical practice, the compounds of the present invention will normally be administered orally, rectally or by injection, in the form of pharmaceutical preparations comprising the active ingredient either as a free base or as a pharmaceutically acceptable acid addition salt, e.g., the hydrochloride, lactate, acetate or oxalate, in association with a pharmaceutically acceptable carrier which may be a solid, semi-solid or liquid diluent or an edible capsule.

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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 preparations intended for injection and between 0.1 and 50% by weight for preparations suitable for oral administration.

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To produce pharmaceutical preparations in the form of dosage unit for oral application containing a compound of the invention in the form of the free base, or a pharmaceutically acceptable salt thereof, the active ingredient may be mixed with a solid, pulverized carrier, for example lactose, saccharose, sorbitol or mannitol, a starch, such as potato starch, corn starch, maize starch or amylopectin, a cellulose derivative or gelatin, and also may include lubricants such as magnesium or calcium stearate or a Carbowax (Carbowax is a Registered Trade Mark) or other polyethylene glycol waxes and com-

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pressed to form tablets or centres for dragées. If dragées are required, the centres may be coated, for example with concentrated sugar solutions which may contain gum arabic, talc and/or titanium dioxide, or alternatively with a lacquer dissolved in easily volatile organic solvents or mixtures of organic solvents. Dyestuffs can be added to these coatings. For the preparation of soft gelatin capsules (pearl shaped closed capsules) consisting of gelatin and, for example, glycerol, or similar closed capsules, the active substance may be admixed with a Carbowax. Hard gelatin capsules may contain granulates of the active substance with solid, pulverized carriers such as lactose, saccharose, sorbitol or mannitol, starches, for example potato starch, corn starch or amylopectin, cellulose derivatives or gelatin, and may also include magnesium stearate or stearic acid. Dosage units for rectal application may be in the form of suppositories comprising the active substance in admixture with a neutral fatty base, or gelatin rectal capsules comprising the active substance in admixture with a Carbowax or other polyethylene glycol waxes.

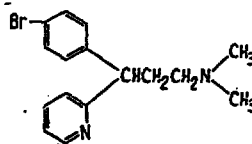
Liquid preparations for oral application may be in the form of syrups, suspensions or emulsions, for example containing from about 0.1% to 20% by weight of active substance, sugar and a mixture of ethanol, water, glycerine, propylene glycol and any flavouring agent, saccharine and/or carboxy methyl cellulose as a dispersing agent.

For parenteral application by injection the preparations may contain an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance preferably in a concentration of 0.5 to 10%, optionally a stabilizing agent and/or buffer substance in an aqueous solution. Dosage units of the solution may advantageously be enclosed in ampoules.

Suitable daily doses of the compounds of the invention for therapeutic treatment is 5 to 500 mg for peroral administration, preferably 50 to 250 mg and 1 to 100 for parenteral administration, preferably 10 to 50 mg.

Biological effect.

It is impossible to produce depressions in test animals in an experimental way. In order to obtain a possibly anti-depressive effect of new substances, biochemical-pharmacological test methods have to be carried out. Such a test method which seems to give such indications of the antidepressive effect of a compound, which effect corresponds quite well to the clinically described effect, has been worked out and is described in European Journal of Pharmacology, 5, 367—373, (1969) and European Journal of Pharmacology, 5, 357—366, (1969). This test method means that the ability of a compound to block the liberation of noradrenaline in the brain and heart which is induced by an injection of 4- α -dimethyl-*m*-tyramine, and the ability of the compound to block the liberation of 5-hydroxy-tryptamine in the brain, which is induced by an injection of 4-methyl- α -ethyl-*m*-tyramine is tested. Substances which block the liberation of noradrenaline in the brain and heart are especially secondary amines of the type desipramine and nortriptyline, but such secondary amines have the serious side-effect of inducing anxiety. The blocking of the liberation of noradrenaline in the brain and heart, by these compounds also probably induces the ortho-statism. It appears that the effect of a substance to reduce depression seems to be related to the blocking of the liberation of 5-hydroxytryptamine. As shown below it has surprisingly been found that the compounds of the invention have a strong blocking effect on the liberation of 5-hydroxytryptamine, which is induced by 4-methyl- α -ethyl-*m*-tyramine, while the ability of the compounds to block the liberation of noradrenaline, which is induced by 4- α -dimethyl-*m*-tyramine is either lacking completely or is very weak. Further, the compounds of the invention differ from all tricyclic antidepressive agents hitherto used in that they have a much lower heart arrhythmia inducing effect. Compounds of the type described in Journal of Medicinal Chemistry 14, 161—164, (1971) have certainly an anti-depressive effect, but this antidepressive effect is low compared to the effect of the compounds of this invention, and these known compounds, which are illustrated by compound V above, are also able to substantially block the liberation of noradrenaline in the brain and heart induced by 4- α -dimethyl-*m*-tyramine, which in man leads to unwanted side-effects of anxiety and probably also orthostatism. The compounds described in the US Patent Specification No. 3,423,510 and illustrated by compound VI above, are described as antihistaminic and antidepressive agents. The compound bromopheniramine having the formula:



XIII

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seems, indeed, to have a strongly blocking effect on the liberation of 5-hydroxy-tryptamine but this compound also blocks the liberation of noradrenaline induced by 4- α -dimethyl-*m*-tyramine to a high extent, which in man leads to unwanted side-effects such as anxiety and orthostatism.

A pharmacological comparison between the compounds of the invention and previously used tricyclic antidepressive agents and compounds described in the literature is given below.

1. Blocking effect on the liberation of 5-hydroxy-tryptamine induced by 4-methyl- α -ethyl-*m*-tyramine

1.1 Rats

The substance to be tested is injected intraperitoneally into a rat. 30 minutes later 50 mg/kg of 4-methyl- α -ethyl-*m*-tyramine is injected intraperitoneally. Two hours later the animal is killed and the amount of 5-hydroxy-tryptamine in the brain is determined. Animals which are treated with the test substance only, with 4-methyl- α -ethyl-*m*-tyramine only respectively and untreated animals serve as controls. The percentage inhibition of the liberation of 5-hydroxy-tryptamine is determined according to the following formula.

$$\% \text{ inhibition} = \frac{A - B}{C - B} \cdot 100$$

A = the amount of 5-hydroxy-tryptamine (ng/g) in the brain after the administration of the test substance and 4-methyl- α -ethyl-*m*-tyramine,

B = the amount of 5-hydroxy-tryptamine (ng/g) in the brain after the administration of 4-methyl- α -ethyl-*m*-tyramine,

C = the amount of 5-hydroxy-tryptamine (ng/g) in the brain after the administration of the test substance.

The effective dose which inhibits the liberation of 5-hydroxy-tryptamine to 50% (ED₅₀) is calculated by a regression analysis. The test results are given in Table 1 below.

1.2 Mice

The substance to be tested is injected intraperitoneally in mice. 30 minutes later 100 mg/kg of 4-methyl- α -ethyl-*m*-tyramine is injected intraperitoneally. 90 minutes later the test substance is administered again now in an amount corresponding to half the original dose and 30 minutes later 4-methyl- α -ethyl-*m*-tyramine (100 mg/kg) is administered. Additional 2 hours later the animals are killed and the amount of 5-hydroxy-tryptamine in the brain is determined.

The percentage inhibition of the liberation of 5-hydroxy-tryptamine and the ED₅₀ is determined in the same way as under 1.1. A detailed description of the method is given in European Journal of Pharmacology 5, 357-366, (1969). The test result is given in Table 1 below.

2. The blocking effect of the liberation of noradrenaline induced by 4, α -dimethyl-*m*-tyramine.

The substance to be tested is injected intraperitoneally in mice (10 mg/kg). 30 minutes later 4, α -dimethyl-*m*-tyramine is administered (12.5 mg/kg). 90 minutes later half the original dose of test substance (5 mg/kg) is administered to the animals and 30 minutes later 4, α -dimethyl-*m*-tyramine (12.5 mg/kg) is administered. Additional 2 hours later the animals are killed and the amount of noradrenaline in the brain and the heart is determined. Animals treated with the test substance only and with 4, α -dimethyl-*m*-tyramine only respectively and untreated animals are used as controls.

The percentage inhibition of the liberation of noradrenaline is determined according to the following formula:

$$\% \text{ inhibition} = \frac{A - B}{C - B} \cdot 100$$

A = the amount of noradrenaline (ng/g) in the brain and heart, respectively, after administration of test substance and 4, α -dimethyl-*m*-tyramine.

B = the amount of noradrenaline (ng/g) in the brain and heart, respectively, after the administration of 4, α -dimethyl-*m*-tyramine.

C = The amount of noradrenaline (ng/g) in the brain and heart, respectively, after the administration of the test substance.

The test result is given in Table 1 below.

3. The heart arrhythmia inducing effect

A solution of the test substance is constantly and slowly infused to nembutal anaesthetized rats and the electrocardiograms of the animals are observed. After a certain time an irregular heart rhythm occurs, which becomes more serious and finally leads to a ventricular fibrillation, whereby the animals die. The accumulated dose which is necessary to induce ventricular fibrillation is given in Table 1 below.

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TABLE 1

Blocking effect on the liberation of 5-hydroxy-tryptamine induced by 4-methyl- α -ethyl-*m*-+ tyramine;Blocking effect on the liberation of noradrenaline induced by 4, α -dimethyl-*m*-tyramine and arrhythmia inducing effect.

Compound tested	Blocking of the liberation of 5-hydroxy-tryptamine induced by 4-methyl- α -ethyl- <i>m</i> -tyramine ED ₅₀ mg/kg		Blocking of the liberation of noradrenaline in mice induced by 4, α -dimethyl- <i>m</i> -tyramine		Dose (mg/kg bodyweight i.p.) which induces ventricular fibrillation at constant infusion
	mice	rats	brain	heart	
imipramine	25	not tested	11	14	9
amitriptyline	14	not tested	11	45	10
chloroimipramine	7.5	10	0	30	11
bromoemiramine	7.2	14	21	61	40
1-p-bromophenyl-1-phenyl-3-dimethylamino-propene (-l)	15	20	19	52	20
1,1-diphenyl-3-dimethylaminopropene (-l)	20	25	15	41	20
1-p-chlorophenyl-1-phenyl-3-methylamino-propene	>>25	>>25	50	70	34
H 100/04	4	10	6	26	74
H 102/09	3.5	5	6	9	64
H 102/10	5	9	17	24	not tested
H 99/88	4	5	8	15	not tested
H 102/01	8	5	10	15	not tested
H 99/68	10	10	10	10	not tested

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8 10 10

5 5 10

4 8 10

H 99/88
H 102/01
H 99/68

is recrystallized from petroleum ether 40—60°C. Yield 98 g of 1-(4'-bromophenyl)-3-(N,N-dimethylamino)-1-(2''-pyridyl)-propanol. Mp 85°C.

Example 2. The preparation of 3-(4'-bromophenyl)-3-(3''-pyridyl)-dimethylallylamine dihydrochloride.

3.6 g of 1-(4'-bromophenyl)-3-(N,N-dimethylamino)-1-(3''-pyridyl)-propanol are dissolved in 15 ml of 85% H_2SO_4 and heated at 170°C for 10 minutes. The reaction mixture is poured into 60 ml of water, which then is made alkaline with 10 N NaOH, and is extracted with 2×25 ml of ether. The ether is dried with Na_2SO_4 , treated with active carbon and evaporated. The residue is dissolved in 25 ml of acetone and an equivalent amount of oxalic acid dissolved in 25 ml of acetone is added. The precipitate obtained is filtered off, is dissolved in 50 ml of water, which is made alkaline with 10 N NaOH and is extracted with 2×25 ml of ether. The ether solution is dried with Na_2SO_4 , is filtered, whereupon dry HCl is introduced. The precipitate obtained is filtered off. Yield 1.2 g of 3-(4'-bromophenyl)-3-(3''-pyridyl)-dimethylallylamine dihydrochloride (H 102/09). Mp 193°C.

The starting material, 1-(4'-bromophenyl)-3-(N,N-dimethylamino)-1-(3''-pyridyl)-propanol is prepared in the following way.

To 9 g of *n*-butyllithium in 200 ml of dry ether 20 g of 3-bromopyridine is added as quickly as possible at -40°C without rising the temperature. When the addition is finished the mixture is stirred for another 30 minutes. Thereafter 32.5 g of ω -dimethylamino-4'-bromopropiophenone is added in such a way that the temperature does not exceed -40°C. The cooling is discontinued and the mixture is stirred over night whereupon the reaction mixture is poured onto ice and diluted HCl, washed with ether and extracted with 20 ml of methylene dichloride. The methylene dichloride is dried and evaporated. The crystals are dissolved in water, which then is made alkaline with a solution of Na_2CO_3 , is extracted with ether, dried and evaporated and recrystallized from isopropyl ether:petroleum ether 1:1. Yield 4 g of 1-(4'-bromophenyl)-3-(N,N-dimethylamino)-1-(3''-pyridyl)-propanol. Mp. 67°C.

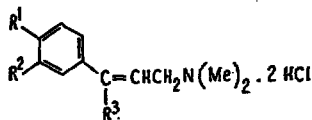
Example 3. The preparation of 3-(4'-bromophenyl)-3-(4''-pyridyl)-dimethylallylamine dihydrochloride.

3 g of 1-(4'-bromophenyl)-3-(N,N-dimethylamino)-1-(4''-pyridyl)-propanol are dissolved in 10 ml of 85% H_2SO_4 and is heated at 170°C for 15 min. The reaction mixture is then poured into ice water, which is made alkaline with 10 N NaOH and is extracted with ether. The ether phase is dried and dry HCl is introduced. The precipitate obtained is filtered off and recrystallized by dissolving it in ethanol and then precipitating it by adding acetone. Yield 1.4 g of 3-(4'-bromophenyl)-3-(4''-pyridyl)-dimethylallylamine dihydrochloride. Mp 190°C (H 102/10).

The starting material, 1-(4'-bromophenyl)-3-(N,N-dimethylamino)-1-(4''-pyridyl)-propanol is prepared in the following way.

To 10 g of *n*-butyllithium in 250 ml of dry ether 17.7 g of 4-bromopyridine is added at -40°C as quickly as possible without rising the temperature, whereupon the mixture is stirred for another 30 minutes. 28.7 g of ω -dimethylamino-4'-bromopropiophenone is added in such a way that the temperature does not exceed -40°C. The cooling is discontinued and the mixture is stirred overnight whereupon the reaction mixture is poured onto ice and diluted HCl. The aqueous phase is washed with methylene dichloride whereupon it is made alkaline with 10 N NaOH and is extracted with ether. The ether phase is dried with Na_2SO_4 , carbonised and evaporated. The residue is recrystallized from diisopropylether. Yield 3 g of 1-(4'-bromophenyl)-3-(N,N-dimethylamino)-1-(4''-pyridyl)-propanol. Mp 120°C.

The following compounds were prepared in a manner analogously with the process of Examples 1 to 3.



Example	Compound (code number)	R ³	R ¹	R ²	Melting point °C
4	H 102/30	2-pyridyl-	H	Br	154
1	H 100/04	„-	Br	H	195
1	H 100/03	„-	Br	H	160
5	H 99/88	„-	Br	Br	136
6	H 102/01	3-pyridyl	H	H	140 (oxalate)
2	H 102/09	„-	Br	H	193
7	H 102/04	4-pyridyl	H	H	204
3	H 102/10	„-	Br	H	190

Following examples illustrate how the compound of the present invention may be included into pharmaceutical preparations.

Example 8. Preparation of soft gelatin capsules.

500 g of active substance were mixed with 500 g of corn oil, whereupon the mixture was filled in soft gelatin capsules, each capsule containing 100 mg of the mixture (i.e. 50 mg of active substance).

Example 9. Preparation of soft gelatin capsules.

500 g of active substance were mixed with 750 g of pea nut oil, whereupon the mixture was filled on soft gelatin capsules, each capsule containing 125 mg of the mixture (i.e. 50 mg of active substance).

Example 10. Preparation of tablets.

50 kg of active substance were mixed with 20 kg of silicic acid of the trade mark Aerosil. 45 kg of potato starch and 50 kg of lactose were mixed therewith and the mixture was moistened with a starch paste prepared from 5 kg of potato starch and distilled water, whereupon the mixture was granulated through a sieve. The granulate was dried and sieved, whereupon 2 kg of magnesium stearate was mixed into it. Finally the mixture was pressed into tablets each weighing 172 mg.

Example 11. Preparation of an emulsion.

100 g of active substance were dissolved in 2500 g of pea nut oil. From the solution thus obtained, 90 g of gum arabic, aroma and colouring agents (q.s.) and 2500 g of water an emulsion was prepared.

Example 12. Preparation of a syrup.

100 g of active substance were dissolved in 300 g of 95% ethanol, whereupon 300 g of glycerol, aroma and colouring agents (q.s.) and 1000 ml of water were mixed therein. A syrup was obtained.

Example 13. Preparation of a solution.

100 g of active substance were dissolved in 2000 g of polyoxyethylene sorbitane monooleate, whereupon flavouring agents and colouring agents (q.s.) and water to 5000 ml was mixed therein. A drop solution was obtained.

Example 14. Preparation of effervescing tablets.

100 g of active substance, 140 g of finely divided citric acid, 100 g of finely divided sodium hydrogen carbonate, 3.5 g of magnesium stearate and flavouring agents (q.s.) were mixed and the mixture was pressed into tablets each containing 100 mg of active substance.

Example 15. Preparation of a drop solution.

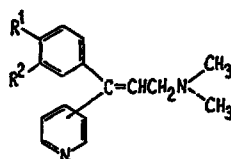
100 g of active substance were mixed with 300 g of ethanol, whereupon 300 g of glycerol, water to 1000 ml, aroma and flavouring agents (q.s.) and 0.1 N sodium hydroxide solution (to pH 4.5 to 5.5) was added while stirring. A drops solution was obtained.

Example 16. Preparation of a sustained release tablet.

200 g of active substance were melted together with 50 g of stearic acid and 50 g of carnauba wax. The mixture thus obtained was cooled and ground to a particle size of at most 1 mm in diameter. The mixture thus obtained was mixed with 5 g of magnesium stearate and pressed into tablets each weighing 305 mg. Each tablet thus contains 200 mg of active substance.

WHAT WE CLAIM IS:—

1. A substituted allylamine compound having the structural formula:



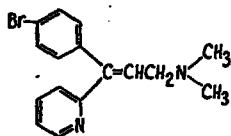
I

and therapeutically acceptable acid addition salts thereof, wherein the bond to the pyridine nucleus is in the *meta*- or *para*-position, R¹ and R², which may be the same or different, are each H, Cl, and Br, provided that R¹ is H or Br when R² is Br and that R¹ is H or Cl when R² is Cl, and when the bond to the pyridine nucleus is in the *ortho*-position, R¹ and R² are each Br, or R¹ is H or Br when R² is Br or H respectively.

2. A compound according to claim 1 in E-form.

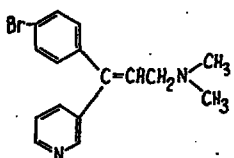
3. A compound according to claim 1 in Z-form.

4. A compound having the structure:



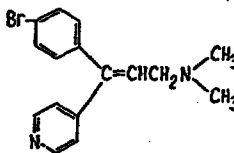
and therapeutically acceptable acid addition salts thereof.

5. A compound having the structure:



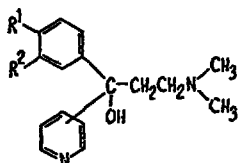
and therapeutically acceptable acid addition salts thereof.

6. A compound having the structure



and therapeutically acceptable acid addition salts thereof.

7. A process for the preparation of a substituted allylamine compound according to any one of the preceding claims wherein a compound of the formula:



is dehydrated.



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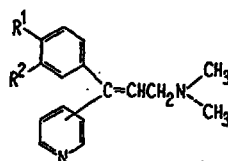
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Example 15. Preparation of a drop solution.
100 g of active substance were mixed with 300 g of ethanol, whereupon 300 g of glycerol, water to 1000 ml, aroma and flavouring agents (q.s.) and 0.1 N sodium hydroxide solution (to pH 4.5 to 5.5) was added while stirring. A drops solution was obtained.

Example 16. Preparation of a sustained release tablet.
200 g of active substance were melted together with 50 g of stearic acid and 50 g of carnauba wax. The mixture thus obtained was cooled and ground to a particle size of at most 1 mm in diameter. The mixture thus obtained was mixed with 5 g of magnesium stearate and pressed into tablets each weighing 305 mg. Each tablet thus contains 200 mg of active substance.

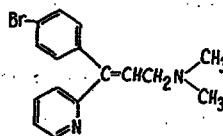
WHAT WE CLAIM IS:—

1. A substituted allylamine compound having the structural formula:

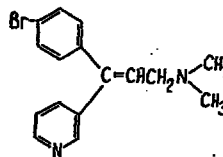


and therapeutically acceptable acid addition salts thereof, wherein the bond to the pyridine nucleus is in the *meta*- or *para*-position, R¹ and R², which may be the same or different, are each H, Cl, and Br, provided that R¹ is H or Br when R² is Br and that R¹ is H or Cl when R² is Cl, and when the bond to the pyridine nucleus is in the *ortho*-position, R¹ and R² are each Br, or R¹ is H or Br when R² is Br or H respectively.

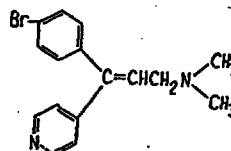
2. A compound according to claim 1 in E-form.
3. A compound according to claim 1 in Z-form.
4. A compound having the structure:



and therapeutically acceptable acid addition salts thereof.
5. A compound having the structure:

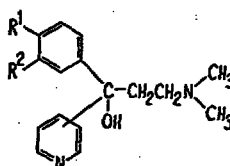


and therapeutically acceptable acid addition salts thereof.
6. A compound having the structure



and therapeutically acceptable acid addition salts thereof.

7. A process for the preparation of a substituted allylamine compound according to any one of the preceding claims wherein a compound of the formula:



is dehydrated.



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8. A process according to claim 7 wherein the dehydration is carried out using concentrated H_2SO_4 at an elevated temperature.

9. A process according to claim 7 or 8 wherein the E- and the Z-configurations of the allylamine are separated from one another

10. A process according to any one of claims 7 to 9 wherein the allylamine is converted into a therapeutically acceptable acid addition salt by reacting it with an acid.

11. A process according to claim 7 substantially as hereinbefore described.

12. A substituted allylamine obtained by a process according to any one of claims 7 to 11.

13. A pharmaceutical preparation containing as an active substance at least one compound or salt according to any one of claims 1 to 6 or 10 together with a pharmaceutically acceptable carrier.

14. A pharmaceutical preparation according to claim 13 in the form of dosage units suitable for oral, rectal or parenteral administration.

15. A pharmaceutical preparation according to claim 13 substantially as hereinbefore described.

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