1 561 286

# PATENT SPECIFICATION

(11) 1 561 286

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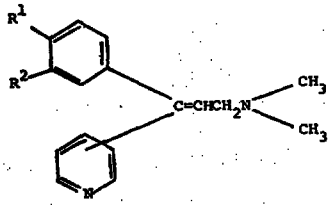
## (54) N,N-DIMETHYL-3-(4-BROMOPHENYL)-3-(3-PYRIDYL)-ALLYLAMINE DIHYDROCHLORIDE MONOHYDRATE

(71) We, ASTRA PHARMACEUTICALS AB, a Swedish Body Corporate of Fack 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:—

The present invention relates to a therapeutically active compound.

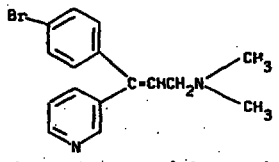
The object of the invention is to obtain a compound which has improved storage properties and which may be produced in an advantageous manner as compared to a similar, previously known compounds.

From Belgian Patent No. 781,105 and British patent specification No. 1,366,241 compounds of the general formula



I

are known, wherein $R^1$ and $R^2$ are each H, Cl and Br, and wherein the pyridyl group is bound in the 2, 3 or 4 position. Specifically mentioned is, among other compounds, the anhydrous di-hydrochloride of the compound



II

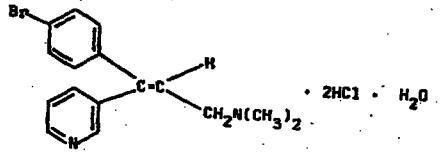
having a therapeutical value in the treatment of depressive conditions.

According to the reference mentioned, the anhydrous compound is obtained from the corresponding base in ether solution, by introduction of dry HCl. It has turned out that, in working up the compound by separation and drying, a considerable amount of the anhydrous compound is most unsuitable for preparation of pharmaceutical compositions. For similar compounds, crystallisation of the dihydrochloride from ethanol is taught by the reference. By this procedure the ethanolate is obtained. It has however turned out that, on working up said compound by separation and drying, a considerable amount of solvent is retained. To remove said solvent, drying for about 1 to 2 days at a temperature of around 90 to 100°C is required. These conditions, being inconvenient *per se*, may further cause discolouration and decomposition of the product. The anhydrous compound is not suitable for preparation of pharmaceutical preparations such as tablets, due to its hygroscopic properties. On storage the anhydrous compound absorbs moisture to form hard cakes, which must be broken up before further processing.

The drawbacks of the previously known compound are overcome by the present invention which provides, as a new compound, the dihydrochloride monohydrate of the compound of formula II above, i.e. N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride monohydrate.

The compound of the invention exists in two stereoisomeric forms, i.e. in an E-form and a Z-form. The therapeutical properties of the compound reside mainly

in one of said isomers, namely the Z-isomer. The preferred embodiment of the present invention is thus Z-N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride monohydrate having the formula III.



III

Pharmaceutical preparations of the new compound constitute a further advantageous aspect of the invention. The compound may thus be incorporated together with a solid, pharmaceutically acceptable carrier, in different forms of solid pharmaceutical preparations such as tablets or granules. Suitably the compound is included in pharmaceutical preparations for oral application. Usually the active substance will constitute from 0.1 to 95% by weight of the preparation, more specifically from 2 to 50% by weight for preparations suitable for oral administration.

To produce pharmaceutical preparations containing a compound of the invention in the form of dosage units for oral application, the selected compound may be mixed with a solid pulverulent carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, or gelatine, and a lubricant such as magnesium stearate or polyethylene glycol waxes, 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 distanguish readily between tablets containing different active substances or different amounts of the active compound.

Dosage units for rectal application can be prepared in the form of suppositories comprising the active substance in admixture with a neutral fatty base, or gelatine rectal capsules comprising the active substance in admixture with vegetable oil or paraffin oil.

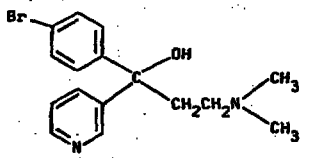
The compound of the invention may, for example, be prepared in the following manner:

a) Reaction of the base of formula II, N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine, in solution with hydrous hydrogen chloride, followed, if desired, by collection of the precipitated dihydrochloride monohydrate. The reaction is suitably carried out in an organic solvent with cooling, preferably at about 0°C. Suitable organic solvents are polar solvents such as acetone. The hydrous hydrogen chloride is suitably concentrated hydrochloric acid. Alternatively $H_2O$ may be added to a solution of the base whereafter anhydrous HCl is added.

b) Hydration of the anhydrous dihydrochloride of the compound of formula II.

The starting material for the reaction a) above may be obtained

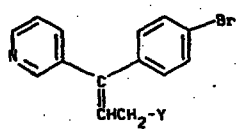
aa) by dehydration of a compound of the formula



V

The dehydration may be effected by means of treatment with sulphuric acid and heating of the reaction mixture, by means of other types of acid catalysis or by catalysis with a solid dehydration catalyst at a temperature of 300 to 500°C.

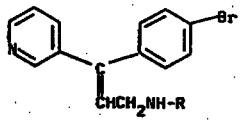
ab) by alkylation of dimethylamine with a compound of the formula



wherein Y is a leaving group, to form a compound of the formula II.

Illustrative examples of Y are halogen atoms such as Cl, Br and I or organic sulphonyloxy groups such as methanesulphonyloxy, toluenesulphonyloxy and benzenesulphonyloxy.

ac) by mono- or di-methylation of a compound of the formula



wherein R is $CH_3$ or H.

The starting material for the reaction b) above may be obtained by treating a compound obtained by any of the reactions aa), ab) or ac) with dry HCl.

A pure isomer product, e.g. the preferred Z-isomer of formula III, may be obtained by isomer separation or conversion of an isomer mixture of either the end product, a starting material or an intermediate of any reaction step, provided that the double bond of the end product is present in said starting material or intermediate, and that said double bond is not broken up in a subsequent reaction step.

The following Examples serve to illustrate the present invention.

## Example 1

90 g of N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine was dissolved in acetone (900 ml) and 2 equivalents of concentrated hydrochloric acid was added with cooling. After cooling at about 0°C for 1 hour the precipitate was filtered off and washed with acetone. Recrystallisation was effected from isopropanol (800 ml) and water (15 ml). (Z)-N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride monohydrate was obtained after washing with isopropanol and drying at about 50°C. M.p. 195—200°C (decomposition). Karl Fisher analysis showed a water content of 4.4% by weight.

An IR spectrum was obtained with the KBr pellet technique (1 mg in 250 mg KBr). Region: 4000—650 $cm^{-1}$. Instrument: Perkin-Elmer IR Spectrometer.

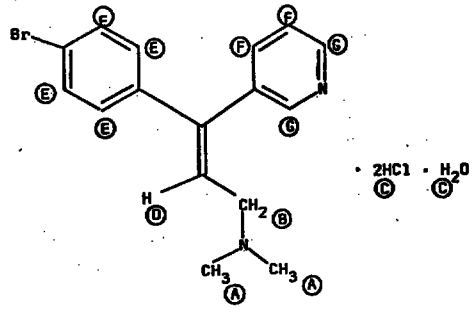
Marked absorption (in general less than 50% transmittance) was recorded at the wave numbers given below with their presumed corresponding structural elements.

| Wave number $cm^{-1}$ | Structural element |
|---|---|
| 3300 | $OH^-$ in water |
| 2600—2400 | Ammonium |
| 1650 | Carbon double band (transmittance ~60%) |
| 1490 and 1470 | Aromatic double bands |
| 820 | Disubstituted benzene |

An NMR spectrum was obtained from a solution of 100 mg of the compound in 0.5 ml deuterium oxide. Tetramethylsilane (TMS) was employed as an internal reference. Instrument: "Varian" (Registered Trade Mark) T 60 (60 $MH_2$).

The chemical shifts are given as follows.

| Proton | Chemical shift (ppm) |
|---|---|
| A | 3.12 |
| B | 4.12 |
| C | 4.88 |
| D | 6.73 |
| E | 7.23—7.84 |
| F | 8.24—8.87 |
| G | 8.90—9.30 |



Example 2

30.0 g of crude N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine was dissolved in 300 ml of ether and 95 ml of 2.6N HCl in ether was added. The crude anhydrous di-hydrochloride obtained was filtered off and vacuum dried. The anhydrous dihydrochloride was dissolved in 150 ml of isopropanol and 4 ml of water (5 equivalents) under heating and the product was allowed to crystallize. Yield 20 g of (Z)-N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride monohydrate. Karl Fisher analysis showed a water content of 4.5% by weight.

Example 3

Preparation of intermediates

Stage 1: 1-(4-bromophenyl)-3-dimethylamino-1-1-propane

This compound was prepared by reacting 4-bromoacetophenone with paraformaldehyde and dimethylhydrochloride in a conventional Mannich reaction.

Stage 2: 1-(4-bromophenyl)-1-(3-pyridyl)-3-dimethylamino-1-propanol

The intermediate 3-pyridyllithium, formed by treating 3-bromopyridine with butyllithium in ether at a low temperature, was treated with 1-(4-bromophenyl)-1-dimethylamino-1-propanone, dissolved in ether to yield 1-(4-bromophenyl)-1-(3-pyridyl)-3-dimethylamino-1-propanol.

The reaction mixture was hydrolyzed with ice and water, the aqueous layer was extracted with methylene chloride at pH 4, followed by an ether extraction at pH 10. The residue after evaporation was triturated with petroleum ether and ether. The crystalline product was recrystallized from isopropanol.

Stage 3: N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine

The product from stage 2 was dehydrated with acetic acid anhydride and sulphuric acid. The reaction mixture was poured onto ice and the aqueous phase extracted with ether at pH 10. Evaporation of the solvent yielded the base.

Example 4

Preparation of pharmaceutical preparations

Tablets of the following compositions were prepared

| | A | B |
|---|---|---|
| (Z)-N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride monohydrate | 25 mg | 50 mg |
| Lactose | 192 mg | 140 mg |
| Starch | 30 mg | 50 mg |
| Polyvinylpyrrolidone | 3 mg | 5 mg |
| Microcrystalline cellulose "Avicel" ["Avicel" is a Registered Trade Mark] | 18 mg | 23 mg |
| Magnesium stearate | 2 mg | 2 mg |

A granulate of the active substance, lactose and starch was made with polyvinylpyrrolidone dissolved in ethanol. The granulate was dried and screened, and microcrystalline cellulose "Avicel" and magnesium stearate were admixed. Tablets were compressed in a known manner.

Film-coated tablets were obtained by applying methyl cellulose and ethyl cellulose to the tablets in an organic solvent.

Comparative tests

Stability at constant humidity and room temperature

The compound of the invention was compared with the corresponding anhydrous dihydrochloride and dihydrochloride containing 1 equivalent of ethanol.

TABLE 1

Weight after storage at different relative humidity

| Relative humidity | Monohydrate | Anhydrous | Ethanolate |
|---|---|---|---|
| 40% | Unchanged (1 week) | Increased 4,6% (1 day) | Decreased 5% (4 days) |
| 60% | Unchanged (1 week) | Increased 4,6% (1 day) | Decreased 4% (5 days) |
| 90% | Increased 12% (1 week) | Increased 50% (6 days) Liquefied | Unchanged (8 h) Increased 11% (4 days) |

The results show that the monohydrate is stable at 40 and 60% relative humidity and room temperature, under which conditions the anhydrous compound and the ethanolate are not stable.

Stability on vacuum drying

Ethanolate: Drying at 110°C for about 24 h was required to decrease the amount of ethanol to the acceptable level of less than 0.5%. After drying decomposition is indicated by increased turbidity, colour ($A_{405nm}$ (i.e. proportion of light of wavelength 405nm which is absorbed) =0.165) and extra spots on TLC.

Monohydrate: Drying at 40°C for about 2 to 4 hours was required to obtain a product suitable for preparing a solid pharmaceutical preparation. Decomposition could not be detected by observing turbidity, colour or TLC. After storage at 45°C for 6 days $A_{405nm}$ was 0.05.

WHAT WE CLAIM IS:—

1. N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)allylamine dihydrochloride monohydrate.
2. N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride monohydrate in the form of its Z-isomer.
3. A process for preparing N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl-allylamine dihydrochloride monohydrate wherein a solution of N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allyl-amine is reacted with hydrous hydrogen chloride.
4. A process according to claim 3 wherein the solvent is a polar organic solvent.
5. A process according to claim 4 wherein the solvent is acetone.
6. A process according to any one of claims 3 to 5 wherein the reaction mixture is cooled during the reaction.
7. A process according to any one of claims 3 to 6 wherein the hydrous hydrogen chloride is concentrated hydrochloric acid.
8. A process for preparing N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)allylamine dihydrochloride monohydrate, wherein anhydrous N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride is hydrated.
9. A process according to any one of claims 3—8 wherein the Z-isomer is isolated.
10. A process for the preparation of N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride monohydrate, substantially as hereinbefore described with reference to Example 1 or 2.
11. N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride monohydrate obtained by a process according to any one of claims 3—10.
12. A pharmaceutical preparation in solid form comprising as active substance, a compound according to claim 1, 2 or 11 together with a solid pharmaceutically acceptable carrier.
13. A pharmaceutical preparation according to claim 12 in dosage unit form.
14. A pharmaceutical preparation according to claim 12 or 13 for oral application.
15. A pharmaceutical preparation according to claim 12 substantially as hereinbefore described with reference to Example 4.

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Reference has been directed in pursuance of section 9, subsection (1) of the Patents Act 1949, to patent No. 1,366,241.

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3. A process for preparing N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl-allylamine dihydrochloride monohydrate wherein a solution of N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allyl-amine is reacted with hydrous hydrogen chloride.
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7. A process according to any one of claims 3 to 6 wherein the hydrous hydrogen chloride is concentrated hydrochloric acid.
8. A process for preparing N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)allylamine dihydrochloride monohydrate, wherein anhydrous N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride is hydrated.
9. A process according to any one of claims 3—8 wherein the Z-isomer is isolated.
10. A process for the preparation of N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride monohydrate, substantially as hereinbefore described with reference to Example 1 or 2.
11. N,N-dimethyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine dihydrochloride monohydrate obtained by a process according to any one of claims 3—10.
12. A pharmaceutical preparation in solid form comprising as active substance, a compound according to claim 1, 2 or 11 together with a solid pharmaceutically acceptable carrier.
13. A pharmaceutical preparation according to claim 12 in dosage unit form.
14. A pharmaceutical preparation according to claim 12 or 13 for oral application.
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