Description

The invention relates to the new compound 3-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)-butyl]-5-hydroxy-indole methanesulfonate (I).

The underlying base (II) and the corresponding hydrochloride (III) are described in DE-OS 2,910,367.

It has been found that I has considerably more favourable pharmacokinetic properties than III. Thus, for example, 100 mg/kg of I administered orally to Cynomolgus monkeys already lead to a sedating reaction, whilst this effect can be achieved with III only with doses above 500 mg/kg. I also has a considerably better solubility in water (0.921 g in 100 ml) than III (0.035 g in 100 ml).

The invention accordingly relates to the new compound I and a process for its preparation, which comprises reacting the base II with methanesulfonic acid.

This reaction is advantageously carried out in an inert solvent, for example methanol or ethanol, at temperatures between 0 and 80°, preferably between 15 and 30°. Stoichiometric amounts of the starting substances are preferably used.

The compound I can be used to prepare pharmaceutical formulations, in particular by a non-chemical route. For this, it can be brought into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or auxiliary and if appropriate in combination with one or more other active compound(s).

The invention furthermore relates to pharmaceutical formulations containing the compound I. These formulations can be used as medicaments in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (for example oral) or parenteral administration or topical application and do not react with the new compound, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatine, carbohydroates, such as

lactose or starch, magnesium stearate, talc and vaseline. Tablets, coated tablets, capsules, syrups, elixirs, drops or suppositories are used, in particular, for enteral administration, solutions, preferably oily or aqueous solutions, and furthermore suspensions, emulsions or implants, are used for parenteral administration and ointments, creams or powders are used for topical application. The new compound can also be lyophilized and the resulting lyophilisates can be used, for example, to produce injection preparations. The formulations mentioned can be sterilized and/or contain auxiliaries, such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, dyestuffs, flavouring substances and/or aroma substances. If desired, they can also contain one or more other active compounds, for example one or more vitamins.

The compound I can be administered to humans or animals, in particular mammals, such as monkeys, dogs, cats, rats or mice, and can be used in the therapeutic treatment of the human or animal body and in combating diseases, in particular in the therapy of Parkinsonism, extrapyramidal disturbances in neuroleptic therapy, depression and/or psychoses and side effects in the treatment of hypertension (for example with α-methyldopa). The compound I can also be used in endocrinology and gynaecology, for example for the therapy of acromegaly, hypogonadism, secondary amenorrhoea, premenstrual syndrome, undesirable puerperal lactation and generally as a prolactin inhibitor, and furthermore for the therapy of cerebral disturbances (for example migraine), in particular in geriatrics in the same way as certain ergot alkaloids, and also for reducing blood pressure.

The compound I is as a rule thereby administered analogously to known commercially available preparations (for example bromocriptine and dihydroergocornine), preferably in dosages of between about 0.05 and 5 mg, in

particular between 0.2 and 2 mg per dosage unit. The daily dosage is preferably between about 0.001 and 0.1 mg/kg of body weight. However, the specific dose for each particular patient depends on the most diverse factors, for example on the age, body weight, general state of health, sex, diet, administration time and method, rate of excretion, drug combination and the severity of the particular disease to which the therapy applies. Oral administration is preferred.

Preparation Example

A solution of 7 g of methanesulfonic acid in 40 ml of ethanol is added to a suspension of 23 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyridyl)-butyl]-5-hydroxy-indole (II) in 340 ml of ethanol at 15°C, the mixture is warmed briefly to 30°C and cooled to 15°C and the resulting 3-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)-butyl]-5-hydroxyindole methanesulfonate (I) is filtered off. Melting point 176°C.

The following examples relate to pharmaceutical formulations containing the compound I:

Example A: Tablets

A mixture of 1 kg of I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed into tablets in the customary manner such that each tablet contains 1 mg of active compound.

Example B: Coated tablets

Tablets are pressed analogously to Example A and are then coated in the customary manner with a coating of sucrose, potato starch, talc, tragacanth and dyestuff.

Example C: Capsules

Hard gelatine capsules are filled with 10 kg of I in the customary manner such that each capsule contains 1 mg of active compound.

Example D: Ampoules

A solution of 1 kg of I in 30 l of doubly-distilled water is subjected to sterile filtration and ampoules are filled with the solution, lyophilized under

sterile conditions and subjected to sterile sealing. Each ampoule contains 0.5 mg of active compound.

Patent Claims

1. 3-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)-butyl]-5-hydroxyindole methanesulfonate (I).

2. Process for the preparation of the compound I according to Claim 1, characterized in that 3-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)-butyl]-5-hydroxy-indole is reacted with methanesulfonic acid.

3. Process for the preparation of pharmaceutical formulations, characterized in that the compound I according to Claim 1, is brought into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or auxiliary and if appropriate in combination with one or more other active compounds.

4. Pharmaceutical formulation, characterized in that it contains the compound I according to Claim 1.

5. Compound I according to Claim 1 for combating diseases.

6. Use of the compound I according to Claim 1 for the preparation of medicaments.

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Revendications (as printed)

1. Le méthane-sulfonate du 3 - [4 - (4 - phényl - 1,2,3,6 - tétrahydro - 1 - pyridyl) - butyl] - 5 - hydroxy indole (I).

2. Procédé de préparation du composé I de la revendication 1, caractérisé en ce que l'on fait réagir le 3 - [4 - (4 - phényl - 1,2,3,6 - tétrahydro - 1 - pyridyl) - butyl] - 5 - hydroxy - indole avec l'acide méthane-sulfonique.

3. Procédé de préparation de compositions pharmaceutique, caractérisé en ce que l'on met le composé I de la revendication 1, accompagné d'au moins un véhicule ou produit auxiliaire solide, liquide ou semiliquide et le cas échéant en combinaison avec une ou plusieurs autres substances actives, sous une forme de dosage appropriée.

4. Composition pharmaceutique caractérisé en ce qu'elle contient le composé I de la revendication 1.

5. Le composé I de la revendication 1, pour le traitement de maladies.

6. Utilization du composé I de la revendication 1, pour la préparation de médicaments.

Claims (as printed)

1. 3 - [4 - (4 - Phenyl - 1,2,3,6 - tetrahydro - 1 - pyridyl) - butyl] - 5 - hydroxy - indole methanesulfonate (I).

2. Process for the preparation of the compound I according to claim 1, characterized in that 3 - [4 - (4 - phenyl - 1,2,3,6 - tetrahydro - 1 - pyridyl) - butyl] - 5 - hydroxy - indole is reacted with methanesulfonic acid.

3. Process for the preparation of pharmaceutical formulations, characterized in that the compound I according to Claim 1, is brought into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or auxiliary and if appropriate in combination with one or more other active compounds.

4. Pharmaceutical formulation, characterized in that it contains the compound I according to Claim 1.

5. Compound I according to Claim 1 for combating diseases.

6. Use of the compound I according to Claim 1 for the preparation of medicaments.