OPTICALLY ACTIVE
5H-PYRROLO[3,4-B]PYRAZINE
DERIVATIVE, ITS PREPARATION AND
PHARMACEUTICAL COMPOSITIONS
CONTAINING SAME

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This patent is subject to a terminal disclaimer.

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Jul. 23, 2002, now Pat. No. 6,864,257, which is a
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23, 1995, now abandoned, which is a continuation of application No. 08/342,794, filed on Nov. 21, 1994,
now abandoned, which is a continuation of application No. 08/232,313, filed on Apr. 25, 1994, now abandoned, which is a continuation of application No. 08/109,863, filed on Aug. 20, 1993, now abandoned, which is a continuation of application No. 08/034,199, filed on Mar. 19, 1993, now abandoned, which is a continuation of application No. 07/821,662, filed on Jan. 16, 1992, now abandoned.

Foreign Application Priority Data
Jan. 17, 1991 (FR) .......................... 91 00490

(Continued)

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ABSTRACT
Dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazine)carboxyl]oxy]-7-oxo-6,7-dihydro-5H-
pyrrolo[3,4-b]pyrazidine, its preparation and pharmaceutical
compositions containing it which are usable as tranquillisers and hypnotics.

5 Claims, No Drawings
OTHER PUBLICATIONS


G.W. Snedecor et al., Statistical Methods, 7th ed., 149.


The best Cited references for this document are:


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This application is a continuation of application Ser. No. 10/951,844, filed Sep. 28, 2004, now U.S. Pat. No. 7,125,874, which is a continuation of application Ser. No. 10/200,510, filed Jul. 23, 2002, now U.S. Pat. No. 6,864,257, which is a divisional of application Ser. No. 09/722,438, filed Nov. 28, 2000, now U.S. Pat. No. 6,444,673, which is a continuation of application Ser. No. 09/124,651, filed Jul. 29, 1998, now U.S. Pat. No. 6,319,926, which is a continuation of application Ser. No. 08/342,794, filed Nov. 21, 1994 (abandoned), which is a continuation of application Ser. No. 08/232,313, filed Apr. 25, 1994 (abandoned), which is a continuation of application Ser. No. 08/109,863, filed Aug. 20, 1993 (abandoned), which is a continuation of application Ser. No. 08/034,199, filed Mar. 19, 1993 (abandoned), which is a continuation of application Ser. No. 07/821,662, filed Jan. 16, 1992 (abandoned). U.S. Ser. No. 07/821,662 claimed the priority of French application 91 00490, filed Jan. 17, 1991. The entire contents of each of the prior applications are incorporated herein by reference.

In French Patent FR 72/00,505, published under number 2,166,314, a description was given, in particular, of 6-(5-chloro-2-pyridyl)-5-[[4-(methyl-1-piperazinyl)carbonyl]oxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, also known by the name of zopiclone, which is a noteworthy hypnotic product.

As a result of the presence of an asymmetric carbon atom at the 5-position of the 5H-pyrrolo[3,4-b]pyrazine ring-system, zopiclone must be considered, in racemic form, to consist of a strictly equimolecular mixture of the laevorotatory and dextrorotatory forms.

It has now been found, and this forms the subject of the present invention, that the dextrorotatory isomer of zopiclone possesses properties which are not obvious in the light of those of racemic zopiclone.

The subject of the present invention is hence the dextrorotatory isomer of zopiclone, its preparation and pharmaceutical compositions containing it. In a racemic product, it is known that, often, one of the two enantiomers is active and that an enhancement of the toxicity may be linked to this activity, the other enantiomer being thereby markedly less active or inactive and less toxic. For such products, the gain in activity does not compensate for the drawbacks due to an enhanced toxicity.

In the case of zopiclone, it was found, surprisingly and unexpectedly, not only that the dextrorotatory isomer is approximately twice as active as the racemate while having a lower toxicity than that of the racemate, but that the laevorotatory isomer is both almost inactive and more toxic than the racemate.

For example, when administered orally to mice, zopiclone possesses a toxicity (LD$_0$) in the region of 850 mg/kg, whereas the dextrorotatory isomer has a toxicity in the region of 1.5 g/kg and the laevorotatory isomer possesses an LD$_0$ of between 500 and 900 mg/kg.
3 starch. These compositions can also comprise substances other than diluents, e.g. a lubricant such as magnesium stearate.

As liquid compositions for oral administration, solutions, suspensions, syrups, elixirs and pharmaceutically acceptable emulsions, containing inert diluents such as water or liquid paraffin, may be used. These compositions can also comprise substances other than diluents, e.g. wetting, sweetening or flavouring products.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilisation may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilising agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

The compositions for rectal administration are suppositories which can contain, apart from the active product, excipients such as cocoa butter.

In human therapy, the doses depend on the effect sought and the treatment period; taken orally, they are generally between 2.5 and 15 mg per day for an adult.

The examples which follow, given without implied limitation, illustrate the present invention.

**EXAMPLE 1**

A solution of zopiclone (23.28 g; 0.06 mol) in dichloromethane (300 cc) is added to a solution of D(++)-O,O'-dibenzoyletaric acid in the form of a monohydrate (22.56 g; 0.06 mol) in dichloromethane (300 cc). The reaction mixture is concentrated to dryness under reduced pressure. The crude salt obtained is recrystallised in acetonitrile (2000 cc) to give, in a 46% yield, a crystallised product (21.3 g), m.p. 160-165°C. (with decomposition), the optical rotation of which is $\alpha_D^{20}=+83^\circ$ (c=0.5; acetone).

The product obtained is dissolved in dichloromethane (180 cc) under reflux. Acetonitrile (200 cc) is added and the mixture is left standing for 1 hour at a temperature of 5°C. The crystallised product obtained is recrystallised again under the same conditions. A crystallised salt (16.5 g), m.p. 160-165°C. (with decomposition), the optical rotation of which is $\alpha_D^{20}=102^\circ$ (c=0.5; acetone), is thereby obtained in a 36% yield.

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration, evaporation of the solvent and recrystallisation of the product obtained in acetonitrile (80 cc), the dextrorotatory isomer (5.4 g) of zopiclone, m.p. 206.5°C, the optical rotation of which is $\alpha_D^{20}=155^\circ+3^\circ$ (c=1.0; acetone), is obtained in a 23% yield.

The mother liquors of crystallisation of the salt of zopiclone with D(++)-O,O'-dibenzyoltaric acid are concentrated to dryness under reduced pressure to give a salt (22.05 g) the optical rotation of which is $\alpha_D^{20}=+21^\circ$ (c=0.2; acetone).

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration, evaporation of the solvent and recrystallisation of the

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**EXAMPLE 2**

Tablets containing 3 mg of active product and having the following composition are prepared according to the usual technique:

<table>
<thead>
<tr>
<th>Composition</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>dextrorotatory isomer</td>
<td>0.003 g</td>
</tr>
<tr>
<td>of zopiclone</td>
<td></td>
</tr>
<tr>
<td>starch</td>
<td>0.100 g</td>
</tr>
<tr>
<td>precipitated silica</td>
<td>0.035 g</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>0.005 g</td>
</tr>
</tbody>
</table>

The invention claimed is:

1. A mixture of isomers of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyl-oxyl]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, wherein the mixture has an optical rotation $\alpha_D^{20}$ of 135°±3° when measured at 1.0 g/100 ml in acetone.

2. A pharmaceutical composition comprising the mixture of claim 1 and one or more pharmaceutically acceptable diluents, coatings, lubricants, wetting products, sweetening products, flavouring products, solvents, vehicles or adjuvants.

3. The pharmaceutical composition of claim 2 that is in the form of a tablet, pill, powder or granule.

4. The pharmaceutical composition of claim 2 that is in the form of a tablet.

5. A method of inducing an effect selected from the group consisting of a hypnotic effect, a sedative effect and a tranquillising effect, comprising administering to a human in need thereof an effective amount of the mixture of claim 1.

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