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PATENT SPECIFICATION

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NO DRAWINGS

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 762 790 79Y LK



(54) A BENZODIAZEPINE DERIVATIVE

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzachstrasse, Basle, Switzerland, 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 is concerned with a benzodiazepine derivative.

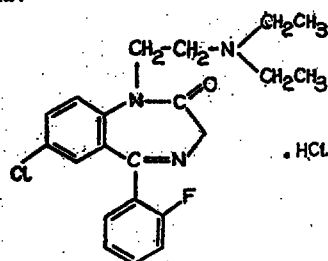
As a consequence of its outstanding therapeutic properties, the compound 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one has attained a leading position in the treatment of all sleep disturbances, especially in those cases which are characterised by disturbances in going to sleep, frequent waking up at night or premature waking up in the morning. Moreover, the compound has proved to be useful for the regulation of the disturbed sleeping-waking rhythm and for the elimination of sleep disturbances which occur as a consequence of a chronic illness. The compound has hitherto been employed in practice as the dihydrochloride, although this dihydrochloride causes great difficulties in the processing into satisfactory and stable dosage forms. Thus, for example, the dihydrochloride is very strongly moisture-sensitive and yields strongly acidic solutions. It is therefore only suitable for the manufacture of capsules and even with this pharmaceutical dosage form a sufficient stability can only be achieved with strict observation of certain technical-operational limitations such as anhydrous granulation in rooms with less than 20% relative humidity, use of only very difficultly obtainable anhydrous lactose, storage of the capsules over silica gel and the like.

In spite of the foregoing disadvantages, the dihydrochloride is, as mentioned earlier, used exclusively. Accordingly, it has hitherto evidently been the view that the dihydrochloride

represents practically the only utilisable salt of the said benzodiazepine.

It has now been surprisingly found in accordance with the present invention that the corresponding monohydrochloride can be easily manufactured and that the therapeutic properties of the monohydrochloride conform to those of the dihydrochloride. Further, it has been surprisingly found that the monohydrochloride does not possess the aforementioned disadvantages of the dihydrochloride. Thus, the monohydrochloride can be galenically processed without the need for special precautions and is also practically unlimitedly stable in the form of tablets and dry ampoules. Moreover, the monohydrochloride has the further advantage that it yields substantially less acidic solutions than the corresponding dihydrochloride.

The present invention is accordingly concerned with 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride which has the following formula:



The invention is also concerned with a process for the manufacture of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride, which process comprises reacting 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one with not more than the equimolar amount of hydrochloric acid or reacting the corresponding dihydrochloride with the equimolar amount of base or with

water and isolating the 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride formed.

- 5 The reaction of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one with not more than the equimolar amount of hydrochloric acid is expediently carried out in an organic solvent such as methanol, ethanol, isopropanol, acetone and the like. The reaction is preferably carried out using alcoholic hydrochloric acid, for example ethanolic hydrochloric acid, in which case the monohydrochloride can be precipitated by the addition of ether. In the case of large batches, the monohydrochloride aforesaid can also be manufactured by introducing an equimolar amount of hydrogen chloride gas into a solution of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

- 10 The reaction of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one dihydrochloride with the equimolar amount of base is likewise expediently carried out in an organic solvent such as methanol, ethanol, acetone, chloroform and the like or mixtures thereof. Suitable bases which can be used include alkali metal hydroxides such as sodium hydroxide and potassium hydroxide, alkaline earth metal hydroxides such as barium hydroxide, amines such as triethylamine and the like. It is preferable to use a base which forms a salt with hydrochloric acid which is soluble in the solvent or solvent mixture used. In another specially preferred embodiment, 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one is used as the base. In a further preferred embodiment, the dihydrochloride is dissolved in water and the 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride formed is extracted with a suitable solvent, preferably methylene chloride.

- 50 The invention is further concerned with pharmaceutical preparations, said preparations comprising 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride in association with a compatible pharmaceutical carrier material.

The following Examples illustrate the process provided by the present invention:

Example 1

- 60 38.8 g (0.1 mol) of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one are finely powdered, suspended in 115 ml of ethanol and treated dropwise with

stirring with 16.8 ml of 6-N ethanolic hydrochloric acid, the suspension gradually turning into a clear solution. After completion of the addition, the reaction solution is evaporated under reduced pressure and the residual light-yellow coloured oil dissolved in 28 ml of ethanol, treated with 250 ml of diethyl ether and allowed to stand overnight at 0°C, 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride being obtained; melting point 202°—203°C.

$C_{21}H_{23}N_2OClF \cdot HCl$

calc: C 59.44 H 5.70 N 9.90 Cl 16.71% (424.34)

found: C 59.56 H 5.84 N 9.80 Cl 16.98%

Example 2

15.54 kg (33.72 mol) of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one dihydrochloride are added in portions with good stirring at 25°C to a mixture of 56.20 kg of water, 10.60 kg of 28% caustic soda and 60.50 kg of toluene in a stirring kettle. After completion of the addition, the reaction mixture is stirred for a further 30 minutes and subsequently transferred into a conical kettle. The stirring kettle is washed with a further 36.5 kg of toluene. This toluene solution is combined with the reaction mixture. The aqueous phase is thereafter separated off, transferred into a second conical kettle and extracted with 48.5 kg of toluene. The two toluene extracts are thereafter washed twice with 40 kg and once with 25 kg of water, combined and transferred into a distillation kettle. The solvent is subsequently distilled off under reduced pressure at 35°—45°C. After dissolving the oily residue in 31.0 kg of absolute ethanol, 5.620 litres of a 6.0-N ethanolic hydrochloric acid are allowed to flow in for 30 minutes, the temperature being held between 25°C and 30°C by cooling. After completion of the addition, the mixture is stirred for a further 5 minutes. The solvent is thereafter distilled off under reduced pressure at 30°—35°C, the residue dissolved in 7.5 kg of absolute ethanol at 25°C, treated with 31.5 kg of diethyl ether and seeded. After filtration, the crystalline product is washed twice with 5.5 litres of a previously cooled diethyl ether/alcohol mixture (5.3:1) each time and subsequently dried at 60°C under reduced pressure, 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride being obtained; melting point 203.5°C.

Example 3

2.3 g (5.0 mmol) of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 -

one dihydrochloride and 2.1 g (5.4 mmol) of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one are dissolved together in 5 ml of ethanol and treated with 15 ml of diethyl ether. After seeding and allowing to stand overnight, 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride is obtained: melting point 203°C.

Example 4

2.3 g (5.0 mmol) of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one dihydrochloride are suspended in 2.5 ml of ethanol, treated with a solution of 0.33 g (5 mmol) of potassium hydroxide in 2.5 ml of ethanol and shaken for 30 minutes on a mechanical shaker. The precipitated potassium chloride is thereafter filtered off and the filtrate concentrated to 3 ml under reduced pressure. After the addition of 3 ml of diethyl ether, the weakly turbid solution is filtered, treated with a further 3 ml of diethyl ether and seeded; 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride being obtained; melting point 202°—203°C.

Example 5

1 g (2.17 mmol) of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one dihydrochloride is dissolved in 20 ml of water and extracted three times with 25 ml of methylene chloride each time. The methylene chloride extracts are dried over sodium sulphate and evaporated to dryness under reduced pressure. Crystallisation of the residue from ethanol/diethyl ether yields 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride of melting point 202°—203°C.

The following Examples illustrate pharmaceutical preparations containing the monohydrochloride provided by the present invention:

Example A

Capsules containing the following ingredients are manufactured:

	per capsule:	
7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride	16.4 mg	
mannitol	105.0 mg	
talc	8.1 mg	
magnesium stearate	0.5 mg	
total weight	130.0 mg	

The active ingredient, the magnesium stearate and the talc are mixed together little by little and then passed through a sieve. The mannitol is then admixed, the whole mixture passed through a sieve and subsequently mixed once more. The mixture is mechanically filled into hard gelatine capsules.

Example B

Capsules containing the following ingredients are manufactured:

	per capsule:	
7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride	32.8 mg	
mannitol	88.1 mg	
talc	8.1 mg	
magnesium stearate	1.0 mg	
total weight	130.0 mg	

The active ingredient, the magnesium stearate and the talc are mixed together little by little and then passed through a sieve. The mannitol is then admixed, the whole mixture passed through a sieve and subsequently mixed once more. The mixture is mechanically filled into hard gelatine capsules.

Example C

Tablets containing the following ingredients are manufactured:

	per tablet:	
7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride	16.41 mg	
mannitol	74.59 mg	
maize starch	50.00 mg	
polyvinylpyrrolidone	6.00 mg	
talc	2.70 mg	
magnesium stearate	0.30 mg	
total weight	150.00 mg	

The active ingredient, the mannitol and a portion of the maize starch are well mixed in a suitable mixing apparatus and subsequently moistened with a polyvinylpyrrolidone solution in ethanol or a chlorinated hydrocarbon, granulated and dried. The talc, the magnesium stearate and the remaining maize starch are thereafter added. The mixture is mixed and compressed.

Example D

Tablets containing the following ingredients are manufactured:

	per tablet:
5 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride	11.00 mg
10 mannitol	80.00 mg
maize starch	50.00 mg
polyvinylpyrrolidone	6.0 mg
talc	2.70 mg
15 magnesium stearate	0.30 mg
total weight	150.00 mg

The active ingredient, the mannitol and a portion of the maize starch are well mixed in a suitable mixing apparatus and subsequently moistened with a polyvinylpyrrolidone solution in ethanol or a chlorinated hydrocarbon, granulated and dried. The talc, the magnesium stearate and the remaining maize starch are thereafter added. The mixture is mixed and compressed.

WHAT WE CLAIM IS:—

- 1) 7 - Chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride.
- 2) Crystalline, isolated 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride.
- 3) A process for the manufacture of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 -

benzodiazepin - 2 - one monohydrochloride, which process comprises reacting 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one with not more than the equimolar amount of hydrochloric acid or reacting the corresponding dihydrochloride with the equimolar amount of base or with water and isolating the 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride formed.

4) A process for the manufacture of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride, substantially as hereinbefore described with reference to Examples 1 to 5.

5) 7 - Chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride, when manufactured by the process claimed in claim 3 or claim 4.

6) A pharmaceutical preparation comprising 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride in association with a compatible pharmaceutical carrier material.

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Reference has been directed in pursuance of section 9, subsection (1) of the Patents Act 1949, to patent No. 1,040,548.

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Example D

Tablets containing the following ingredients are manufactured:

		per tablet:
5	7 - chloro - 1 - (2 - diethyl- aminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - ben- zodiazepin - 2 - one mono-	
10	hydrochloride	11.00 mg
	mannitol	80.00 mg
	maize starch	50.00 mg
	polyvinylpyrrolidone	6.0 mg
	talc	2.70 mg
15	magnesium stearate	0.30 mg
	total weight	150.00 mg

The active ingredient, the mannitol and a portion of the maize starch are well mixed in a suitable mixing apparatus and subsequently moistened with a polyvinylpyrrolidone solution in ethanol or a chlorinated hydrocarbon, granulated and dried. The talc, the magnesium stearate and the remaining maize starch are thereafter added. The mixture is mixed and compressed.

WHAT WE CLAIM IS:—

- 1) 7 - Chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride.
- 2) Crystalline, isolated 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride.
- 3) A process for the manufacture of 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 -

benzodiazepin - 2 - one monohydrochloride, which process comprises reacting 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one with not more than the equimolar amount of hydrochloric acid or reacting the corresponding dihydrochloride with the equimolar amount of base or with water and isolating the 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride formed.

4) A process for the manufacture of 7-chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride, substantially as hereinbefore described with reference to Examples 1 to 5.

5) 7 - Chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride, when manufactured by the process claimed in claim 3 or claim 4.

6) A pharmaceutical preparation comprising 7 - chloro - 1 - (2 - diethylaminoethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one monohydrochloride in association with a compatible pharmaceutical carrier material.

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Reference has been directed in pursuance of section 9, subsection (1) of the Patents Act 1949, to patent No. 1,040,548.