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PATENT SPECIFICATION (11) 1392475

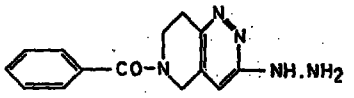
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(54) A HYDRAZINO-PYRIMIDO-PYRIDAZINE DERIVATIVE

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, 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:—

This invention relates to a compound of formula I,



I

which is

6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c] pyridazine.

The compound exhibits interesting pharmacological properties and therefore is indicated for use as a medicament. In particular the compound exhibits anti-hypertensive properties as indicated by, for example, tests in the hypertonic Grollmann rat [described in A. Grollmann, Proc. Soc. Exper. Biol. Med. *57*, 104 (1944)].

The compound is therefore indicated for use as an anti-hypertensive agent. For this use an indicated daily dose is from 5 to 700 mg, conveniently administered 2 to 4 times a day in unit dosage form in which the amount of compound is in the range from 1.2 to 350 mg, or in sustained release form.

The compound may be administered in pharmaceutically acceptable acid addition salt form. Such salt forms possess the same order of activity as the free base form and are readily prepared in conventional manner.

The invention also provides a pharmaceutical composition comprising 6 - benzoyl - 3 - hydrazino - 5,6,7, 8 - tetrahydro - pyrido-[4,3 - c]pyridazine in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

The compound may be prepared as in the following Example in which all temperatures are in degrees Centigrade.

EXAMPLE:

6 - Benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine.

a) A mixture of 342.6 g of 1 - carbethoxy - 4 - piperidone and 214.0 g of pyrrolidine in 1 litre of benzene is heated to the boil at reflux for 2 hours, and the resulting water is continuously removed azeotropically. The mixture is concentrated and the crude 1, - 2,3,6 - tetrahydro - 4 - pyrrolidinylpyridine - 1 - carboxylic acid ethyl ester is purified by distillation in a high vacuum. B.P. 144—150° at 0.03 mm of Hg.

b) A mixture of 1460 g of 1,2,3,6 - tetrahydro - 4 - pyrrolidinylpyridine - 1 - carboxylic acid ethyl ester and 1250 g of bromoacetic acid ethyl ester in 6 litres of benzene is heated at reflux while stirring for 20 hours. 2 litres of water are added to the mixture and this is again heated to the boil at reflux for 3 hours. After cooling to room temperature 400 cc of a 10% aqueous ammonia solution are added. The organic phase is separated, dried over sodium sulphate and concentrated in a vacuum. The crude 1 - carbethoxy - 4 - piperidone - 3 - acetic acid ethyl ester is purified by vacuum distillation. B.P. 145—170° at 0.05 mm of Hg.

c) 514 of 1 - carbethoxy - 4 - piperidone - 3 - acetic acid ethyl ester and 100 g of hydrazine hydrate are stirred at reflux in 1.5 litres of 95% ethanol and 200 cc of glacial acetic acid in a stream of nitrogen for 5 hours. The dark solution is completely concentrated in a vacuum and subsequently divided between chloroform and a 10% aqueous caustic soda solution. After concen-

trating in the organic phase in a vacuum, the resulting crystalline 2,3,4,4a,5,6,7,8 - octahydro - 3 - oxo - 6 - pyrido[4,3 - c]pyridazine carboxylic acid ethyl ester is recrystallized from 1 litre of 95% ethanol. M.P. 163—166° (decomp.).

d) 320 g of bromine in 500 cc of chloroform is added dropwise to a boiling solution of 450.5 g of 2,3,4,4a,5,6,7,8 - octahydro - 3 - oxo - 6 - pyrido[4,3 - c]pyridazinecarboxylic acid ethyl ester in 2 litres of chloroform within 2-1/2 hours and the mixture is stirred for a further hour at the same temperature. After cooling to room temperature 1 kg of ice/water is added to the mixture, the chloroform portion is separated and the acid aqueous phase is again extracted with 500 cc of chloroform. The semicrystalline crude 6 - carbethoxy - 5,6,7,8 - tetrahydro - 3(2H)pyrido[4,3 - c]pyridazinone obtained after concentrating the chloroform phase, is recrystallized with 250 cc of absolute ethanol. M.P. 165—168° (decomp.).

e) A solution of 223.2 g of 6 - carbethoxy - 5,6,7,8 - tetrahydro - 3(2H)pyrido[4,3 - c]-pyridazinone in 1 litre of concentrated hydrochloric acid is heated to the boil at reflux for 22 hours while stirring. The mixture is concentrated in a vacuum, and the resulting crude crystalline hydrochloride of 5,6,7,8 - tetrahydro - 3(2H)pyrido[4,3-c]pyridazinone, having an M.P. of 307—310° (decomp., from methanol), is suspended in 0.75 litres of methanol, and 0.4 litres of triethylamine are slowly added to the suspension. After stirring for 15 minutes and cooling the violet suspension, the crude base is obtained. 25 g of the crude base are recrystallized from 300 cc of methanol, mixed with 10 cc of concentrated ammonia and 40 cc of water with the addition of a small amount of charcoal, 5,6,7,8-tetrahydro - 3(2H)pyrido[4,3 - c]pyridazinone has an M.P. of 223—225° (decomp.).

f) 30.3 g of 5,6,7,8 - tetrahydro - 3(2H)-pyrido[4,3 - c]pyridazinone and 250 cc of phosphorus oxychloride is heated to the boil while stirring for 2 hours, and the resulting reaction mixture concentrated to an oil in a vacuum. 500 g of ice/water are added to the residue as well as 250 cc of concentrated ammonia solution and the mixture is extracted several times with a total of 1.5 litres of chloroform. The chloroform phase is concentrated and the crude unstable base is converted into the maleate for working up. This is effected by boiling 24.8 g of the base in 150 cc of methanol with 17.5 g of maleic acid. Upon cooling the solution, the crude maleate is obtained, which is recrystallized from methanol with the addition of a small amount of charcoal. 3 - chloro - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine maleate has an M.P. of 162—164° (decomp).

g) A mixture of 12.6 g of benzoyl chloride in 100 cc of ethylene chloride is added dropwise to a suspension of 25.6 g of 3 - chloro - 5,6,7,8 - tetrahydropyrido[4,3 - c]-pyridazine maleate in 250 cc of ethylene chloride and 21.8 g of triethylamine within 18 minutes at room temperature while stirring. The mixture is stirred at room temperature for a further 14 hours, 200 cc of water are added, the organic phase is separated and concentrated to an oil in a vacuum. Upon adding ether/dimethoxyethane to this oil, crude 6 - benzoyl - 3 - chloro - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine is obtained. After recrystallization from absolute ethanol with the addition of a small amount of coal, the compound has an M.P. of 125—127° (decomp.).

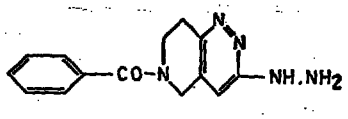
h) A suspension of 21.6 g of 6 - benzoyl - 3 - chloro - 5,6,7,8 - tetrahydropyrido[4,3-c]-pyridazine in 80 cc of hydrazine hydrate is boiled at reflux at an oil bath temperature of 110° for 1 hour. After a reaction time of approximately 15 minutes the material dissolves completely. The crude title compound resulting after cooling the mixture, is washed with a small amount of absolute ethanol and dissolved in 60 cc of dimethylformamide. 60 cc of absolute ethanol are added to the solution, whereupon the title compound crystallizes. M.P. 220—223° (decomp.).

The free base form of the compound of formula I may be converted into acid addition salt forms in conventional manner and *vice versa*. Suitable acids include fumaric acid, tartaric acid, benzene and methane sulphonic acids and hydrochloric, hydrobromic and sulphuric acids. The compound of formula I may also be used as an intermediate in the preparation of corresponding alkylidene hydrazones as described and claimed in our copending Application No. 21060/72 (Serial No. 1392474).

WHAT WE CLAIM IS:—

1. A compound of formula I,

I



which is

6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine.

or an acid addition salt form thereof.

2. A compound of Claim 1, in free base form.

3. A compound of Claim 1, in acid addition salt form.

4. A pharmaceutical composition compris-

trating in the organic phase in a vacuum, the resulting crystalline 2,3,4,4a,5,6,7,8 - octahydro - 3 - oxo - 6 - pyrido[4,3 - c]pyridazine carboxylic acid ethyl ester is recrystallized from 1 litre of 95% ethanol. M.P. 163—166° (decomp.).

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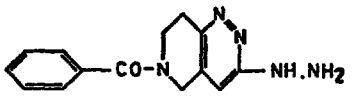
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ing 6 - benzyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

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