

PATENT SPECIFICATION

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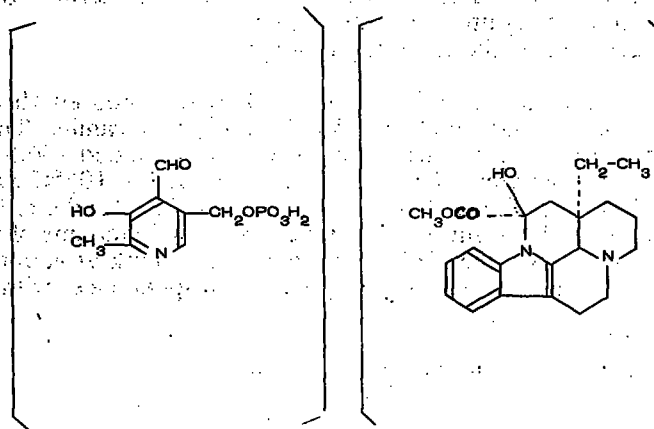
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 C2V 5
 (72) Inventor: André Esanu



(54) VINCAMINE SALT OF PYRIDOXAL PHOSPHATE

(71) We, Société d'Etudes de Produits Chimiques, a French body corporate of 4, Rue Theodule Ribot 75017 Paris, France, 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 invention relates to a new vincamine salt of therapeutic interest, to its preparation and to therapeutic compositions containing it. The new vincamine salt is vincamine pyridoxal phosphate which has the formula:



The new salt is yellow powder, fairly soluble in water and giving a colourless solution. The compound is sparingly soluble in ethanol, insoluble in chloroform and soluble in dimethyl sulphoxide at room temperature. It has a molecular weight of 601.58 with a percentage of vincamine of 58.92% by weight. The new salt is particularly interesting in that it has in general a better solubility than vincamine and also has a stronger therapeutic effect than vincamine. Tests have shown it to be from 4 to 10 times more active than vincamine. Moreover the new compound also presents some anti-depressive action which is specially interesting for patients receiving vincamine treatment who suffer from depressive syndromes.

The toxicity of the new salt has been determined on mice. *Per os* value for LD 50 was 1.4 g/kg whereas I.P. was 0.380 g/kg. By comparison with vincamine, the compound of the invention appears a little bit more toxic *per os* but far less toxic I.P.

PHARMACOLOGY

The new compound has been submitted to various pharmacological tests.

A - Action on per-hypocapno-anemic cerebral syndrome on dogs

From this test it has been noticed that the same results could be obtained by administering by venous perfusion 0.42 mg/kg of the compound of the invention (which corresponds theoretically to 0.25 mg/kg of vincamine) as by administering by the same way 1 mg/kg of vincamine. The indication is thus that for the same amount of vincamine 4 times more active than vincamine alone.

B - Action on a functional coronary insufficiency provoked by pitressine (dogs)

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With this test the new salt of the invention showed a very favourable action for the correction of hemodynamic and metabolic troubles (at the dose of 1 mg/kg) whereas in the same indications, vincamine does not present any activity.

5 C - Action on the perturbations on the electrogenesis generated by the cerebral ischemia (rabbits)

In this test, the compound of the invention had a very good action at doses of 50 to 100 $\mu\text{g/kg}$. Some action was obtained with 1000 $\mu\text{g/kg}$ of vincamine (intravenous route). The indication is that for this test, the action of vincamine pyridoxal phosphate is at least 10 times that of vincamine.

10 D - Action of EEG disturbances generated by a unilateral cerebral oedema (rabbits)

The new salt of the invention and vincamine were administered at various doses. The dose of 4.2 mg/kg of vincamine pyridoxal phosphate (i.e. 2.5 mg/kg of vincamine) was found to have the same effect as the administration of 10 mg/kg of vincamine base. In this test also the activity of vincamine pyridoxal phosphate appeared 4 times better than that of vincamine.

15 POSOLOGY-PRESENTATION

For *per os* use, the preferred presentation is enteric coated tablets dosed at 5 mg of vincamine pyridoxal phosphate. For injections, the form is opaque phials containing 3mg of lyophilized product, to be dissolved in 2 ml of isotonic solution.

Posology is from 2 to 8 tablets *per diem*, *per os*, or 1 or 2 phials *per diem*, intravenously.

20 The invention according also provides a therapeutic composition comprising the new salt in admixture with one or more therapeutically acceptable diluents or carriers.

The new salt may be prepared according to the invention by reacting a suspension of vincamine in a mixture of water and a lower alkanol, preferably a 50% mixture by weight, at about 105°C with pyridoxal-5-phosphate. The reagents are preferably used in stoichiometric proportions vincamine pyridoxal phosphate with a high yield. The term "lower alkanol" is used to define an alkanol having up to 6 carbon atoms.

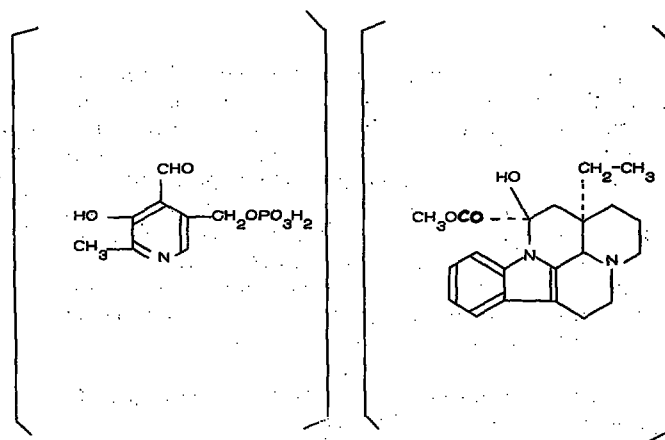
The invention is illustrated by the following Example.

EXAMPLE

30 Into a reactor fitted with stirring and warming means there were poured 2 litres of a 50% by weight solution of methanol in water and 141.75 g (0.4 mol) of vincamine. This mixture was stirred and warmed to 40°C to give a suspension to which was added 106.5 g (0.4 mol) of pyridoxal-5-phosphate monohydrate. The mixture was warmed to 105°C whilst stirring to give a clear solution from which the methanol was removed at 35°C under reduced pressure. After filtration of the remaining solution to remove some small amounts of impurities, the solution was lyophilized to give 223 g of yellow powder, melting at about 150°C (pasty melting). Yield: 93%. Analysis showed a good correspondence with the formula $\text{C}_{29}\text{H}_{36}\text{N}_3\text{O}_9\text{P}$.

WHAT WE CLAIM IS:

1. Vincamine pyridoxal-5-phosphate, having the formula:



2. A process for the preparation of the compound of claim 1 comprising reacting a suspension of vincamine in a mixture of water and a lower alkanol as herein defined, at about 105 °C with pyridoxal-5-phosphate.

3. A process for the preparation of the compound of claim 1, substantially as described in the Example herein.

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With this test the new salt of the invention showed a very favourable action for the correction of hemodynamic and metabolic troubles (at the dose of 1 mg/kg) whereas in the same indications, vincamine does not present any activity.

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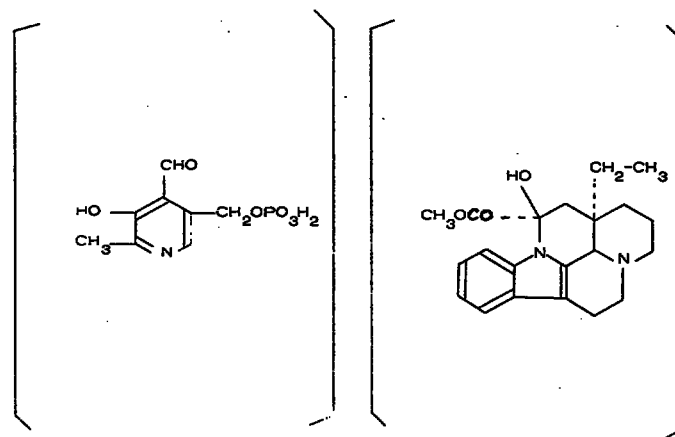
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3. A process for the preparation of the compound of claim 1, substantially as described in the Example herein.



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4. A therapeutic composition comprising the compound of claim 1 in admixture with one more therapeutically acceptable diluents or carriers.

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