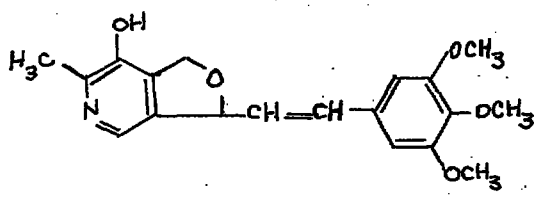
SPECIFICATION

Pyridine derivative

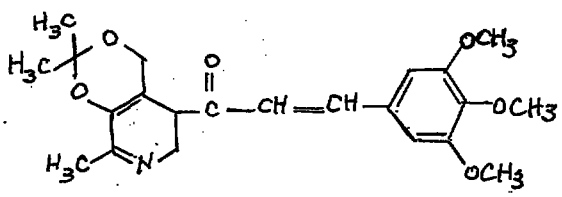
The invention relates to a pyridine derivative, to a process for its preparation and to therapeutic compositions containing it.

The new compound according to the invention is 1, 3 - dihydro - 3 - (3', 4', 5' - trimethoxy - styryl) - 6 - methyl - 7 - hydroxy - furo - [3, 4 - c] pyridine which has the formula:



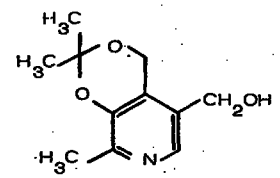
The empirical formula of the above compound is $C_{19}H_{21}NO_5$ and its molecular weight is 343. It is of interest because of its diuretic activity. It has shown a low toxicity: *per os* LD 50 on mice is over 2.4 g/kg.

The invention also provides a process for the preparation of the above compound which comprises reducing, using sodium borohydride, the keto group of a compound of the formula



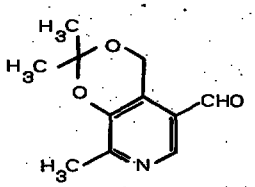
to a secondary alcohol group, followed by treatment of the product with an alcoholic solution of formic and hydrochloric acids to break the isopropylidene bridge and induce an internal condensation. This leads to the hydrochloride salt of the compound of the invention. The free base may be obtained by neutralisation of the hydrochloride salt with a suitable mild alkali, for example sodium bicarbonate.

The above process is illustrated as steps (5) and (6) of the following reaction sequence, together with reaction steps (1) to (3) indicating one possible way of preparing isopropylidene blocked 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - acetyl - pyridine, and reaction step (4) illustrating its conversion by reacting with 3, 4, 5 - trimethoxy - benzaldehyde in the presence of a strong base in solution in aqueous alcohol at or slightly above room temperature to the keto compound used in reaction step (5). The reaction sequence uses as starting material pyridoxine in which the 3- and 4-hydroxy groups are blocked with an isopropylidine bridge. This starting material may be obtained as described in British Patent Specification No. 1,286,161.



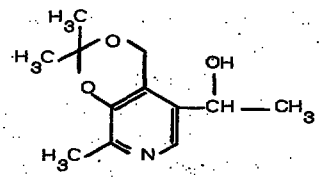
$C_{11}H_{15}NO_3$ MW: 209

(1) MnO_2



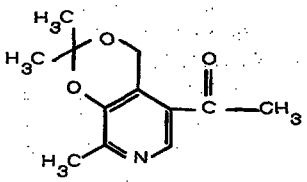
$C_{11}H_{13}NO_3$ MW:207

(2) CH_3I + Mg



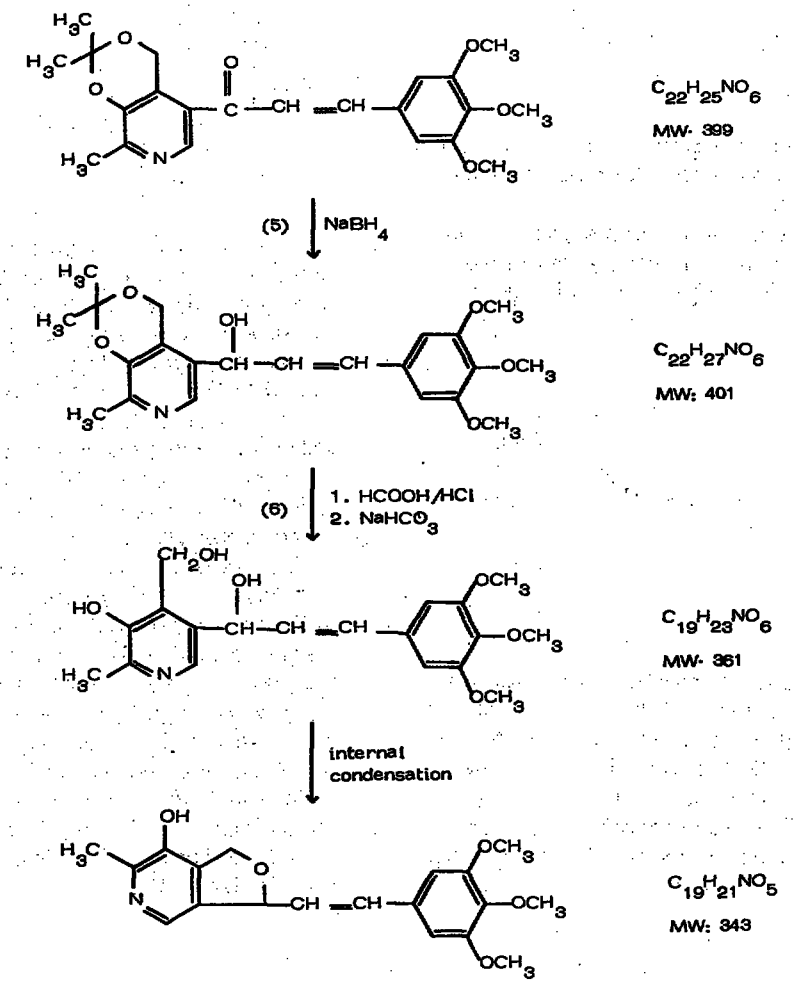
$C_{12}H_{17}NO_3$ MW:223

(3) Pyridinium chlorochromate



$C_{12}H_{15}NO_3$ MW:221

(4) 3,4,5-trimethoxy-benzaldehyde



$C_{22}H_{25}NO_6$ MW: 399

$C_{22}H_{27}NO_6$ MW: 401

$C_{19}H_{23}NO_6$ MW: 361

$C_{19}H_{21}NO_5$ MW: 343

The following Example illustrates this invention.

EXAMPLE

Pyridoxine in which the 3- and 4-hydroxy groups are blocked by an isopropylidine bridge was obtained as indicated in British Patent 1,286,161, and was treated conventionally by MnO_2 to give the corresponding 5-aldehyde. This compound, after separation and purification, was treated with methyl iodide in the presence of magnesium to give the corresponding 5-(2'-hydroxyethyl) compound. This compound in turn was transformed into the corresponding 5-acetyl derivative by treatment with pyridinium chlorochromate and dry sodium acetate, in solution in drymethylene dichloride. These reactions are well known and do not need further description. The following steps will now be described in more detail.

In a two-litre reactor there were poured 221 g (1 mole) of the 3, 4 - isopropylidene blocked 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - acetyl - pyridine, 42.8 g (1.1 mole) of sodium hydroxide, 0.5 litre of water and 0.25 litre of ethanol. The reaction proceeded as in reaction step (4) above. The mixture was stirred at room temperature and there were slowly added, whilst stirring and at about 40°C, 196 g (1 mole) of trimethoxybenzaldehyde. Stirring was maintained for 4 hours at the same temperature. There was then added 0.75 litre of water, and a precipitate formed. Stirring was maintained for one hour. The precipitate was separated, washed with water, then with ethanol, recrystallized from methanol and dried. Yield 335 g (84%).

300 g (0.75 mole) of this product were treated according to reaction step (5) above at 0°C to 5°C, in a 5-litre reactor containing 2.5 litres of methanol, with 88.5 g (2.34) of $NaBH_4$ which were slowly added whilst stirring. A precipitate appeared and 3 hours after the end of the addition there was added dropwise a sufficient amount of acetic acid to reach pH6. The precipitate was separated, washed and recrystallized from a 50/50 water-ethanol mixture. There was obtained 235 g (78%) of the secondary alcohol.

For the final step, (reaction step (6) above), 214 g (0.534 mole) of the compound thus obtained were treated in a reactor by 0.7 litre of HCl (1.9N) and 0.87 litre of 1% formic acid in 1.5 litres of ethanol over a water bath for 30 minutes. The solution was then filtered, evaporated and retreated with diethyl ether, filtered, dried and finally dissolved in 2 litres of water and treated by $NaHCO_3$ (pH 7-8) with stirring. The precipitate obtained was separated, washed with water and recrystallied from methanol.

Yield: 171 g (87%) of a product analysis of which showed a good correspondence with the formula $C_{19}H_{21}NO_5$. The structure of the product was confirmed by nuclear magnetic resonance.

The interest of the compound of the invention will be understood from the reports of the following pharmacological experiments:

1. *Stabilization on membrane in vitro.*

In this experiment, the stabilizing effect was researched on the red blood corpuscle membrane of

the rabbit, by determination of the hemolysis rate during the incubation in hypotonic conditions (phosphate buffer 10 mM, pH: 7.4, -Na Cl 5.5 g/litre) at 53°C. The tested products were added to the incubation environment at various concentrations and the hemolysis rate was compared to a control. This experiment was carried out comparatively with phenylbutazone, known to have a similar highly favourable action. The results are reported in the following table in which OD means average optical density on 3 assays.

2. *Variation of diuresis on normal animals.*

The compound of the invention induces a selective diuresis which has been evidenced on rats and mice; these experiments have shown a very favourable rate of elimination of sodium compared with potassium, which is of high importance in diuresis. For instance, compared with controls, on the rat, the ratio Na/K is over 200%, either for the compound itself or its pharmaceutically acceptable salts. Similar results are found on the same experiment on the mouse.

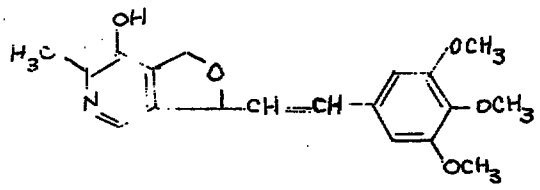
3. The protection in vivo has been evidenced on rats having received high doses of glafenine or tetracycline which are known to provoke alteration or necrosis in the kidney. Antagonist action of the compound of the invention has been measured by the variation of plasmatic urea and creatinine values compared with non-treated animals and with animals treated by glafenine or tetracycline; the variation of hematocrite and of the diuresis were measured at the same time.

For therapeutic use, a unit dosage contains from 0.02 g to 0.5 g of the compound according to the invention or of a therapeutically acceptable salt thereof:

Tested Concentration mM	PHENYLBUTAZONE		Compound of the invention		PHENYLBUTAZONE		Compound of the invention	
	OD	% of PROTECTION	OD	% of PROTECTION	OD	% of PROTECTION	OD	% of PROTECTION
0	561	–	589	–	1290	–	1410	–
0.1	–	–	–	–	826	35	977	23
0.2	380	36	471	20	641	49	979	23
0.5	352	41	381	36	489	61	841	33
1	386	35	361	39	434	66	825	35
5	232	61	276	53	272	79	577	54
10	149	75	247	58	Hemolized	–	805	36
20	Hemolized	–	228	61	Hemolized	–	938	35

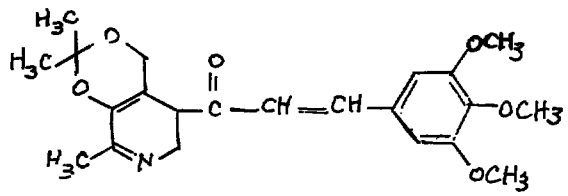
CLAIMS

1. 1,3 - Dihydro - 3 - (3', 4', 5' - trimethoxy - styryl) - 6 - methyl - 7 - hydroxy - furo - [3, 4, *c*] - pyridine having the formula:



and therapeutically acceptable salts thereof.

2. A process for the preparation of the compound of claim 1, the process comprising reducing, using sodium borohydride, the keto group of a compound of the formula



to a secondary alcohol group, treating the resultant product with an alcoholic solution of formic and hydrochloric acids to break the isopropylidene bridge and induce an internal condensation, and neutralizing the solution with a suitable mild alkali to liberate the free base.

3. A process for the preparation of the compound of claim 1, the process being substantially as described herein with reference to the Example.

4. A unit dosage therapeutic composition comprising 0.020 g to 0.5 g of the compound of claim 1 or a therapeutically acceptable salt thereof in admixture with an inert diluent or carrier.

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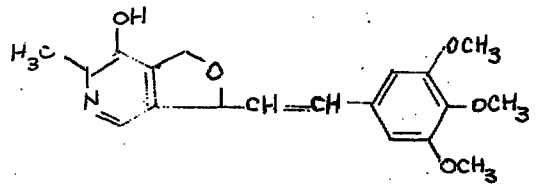
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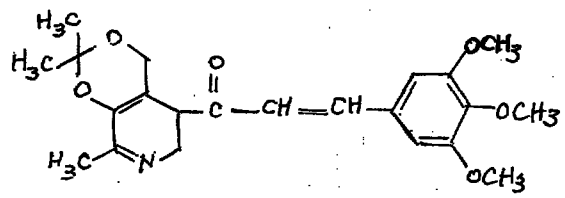
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