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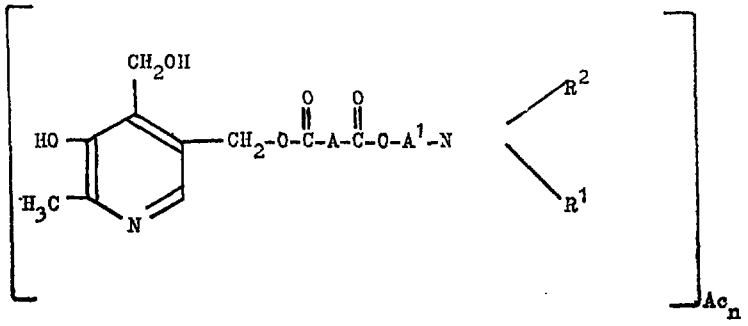
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(54) PYRIDOXINE MONO-ESTERS

(71) We, SOCIETE D'ETUDES DE PRODUITS CHIMIQUES, a company organised and existing under the laws of France of 16 rue Kleber, 92 Issy Les Moulineaux, 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:—

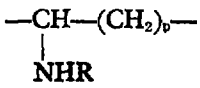
The invention relates to salts of pyridoxine mono-esters and to a process for their manufacture.

The invention provides a salt of a pyridoxine mono-ester having the general formula:

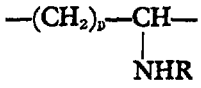


in which:

A and A^1 each represents an alkylene radical with a chain of up to 16 carbon atoms or a divalent amino-substituted aliphatic hydrocarbon radical for example an amino-alkylene residue such as



or



in which:

R represents a hydrogen atom or a CH_3CO group, and p is 1 or 2;

R^1 and R^2 each represents an alkyl radical containing up to 5 carbon atoms, or R^1 and R^2 form, together with the nitrogen atom, a heterocyclic ring;

Ac represents a pharmaceutically acceptable acid; and

n is 1, 2 or 3

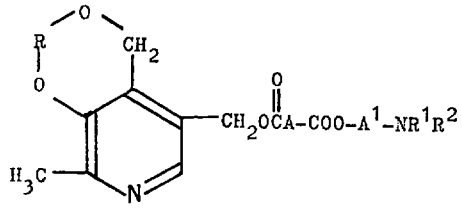
The salts of pyridoxine mono-esters according to the invention have therapeutic activity and may be prepared according to the invention by reacting pyridoxine which

[*Price 25p*]

has the —OH and —CH_2OH groups at its 3- and 4-positions blocked, with an acyl chloride having the general formula:

$$ClCO—A—COO—A^1—NR^1R^2$$

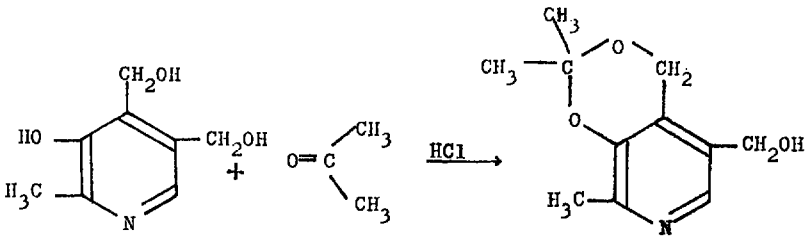
in which the symbols are as above defined to obtain an intermediate having the general formula



in which R represents a blocking group that can be removed by hydrolysis to liberate the —OH and —CH_2OH groups at the 3- and 4-positions of the pyridoxine ring.

The blocking group R of the intermediate is then removed to liberate the —OH and —CH_2OH groups at the 3- and 4-positions of the pyridoxine ring. The esters thus obtained are then treated by a pharmaceutically acceptable acid to obtain a pharmaceutically acceptable salt according to the invention. The reaction sequence is illustrated below:

a. Blocking of two alcohol functions of pyridoxine:

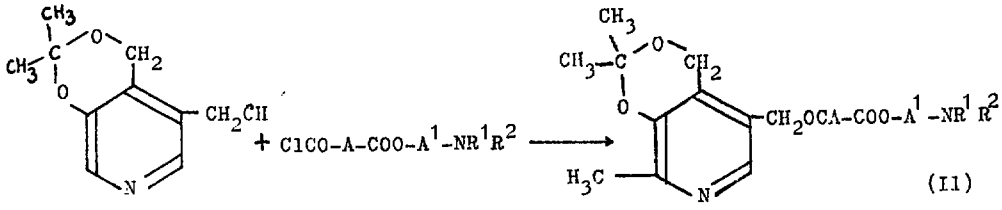


(I)

The resulting compound I is obtained in the form of its hydrochloride and is reacted with Na_2CO_3 to obtain the free base.

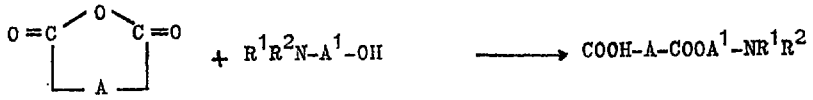
The choice of acetone is not critical: any other suitable blocking agent may alternatively be used.

b. Treatment of the compound obtained in (a) with the appropriate acyl chloride to form an intermediate.



(II)

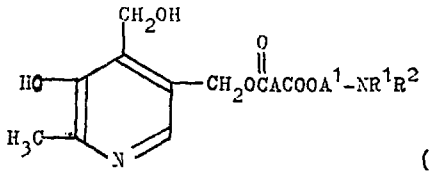
The acyl chloride used in the above reaction step may be obtained by the reaction of the anhydride of the corresponding acid with a suitably substituted amino alkanol, to form a substituted amino alkanol mono-ester according to the reaction scheme:



and this mono-ester, treated with $SOCl_2$, gives the acyl chloride:

$$ClCO—A—COOA^1—NR^1R^2$$

c. Liberation of the —OH and —CH_2OH in the 3- and 4-positions of the pyridoxine ring by reacting compound (II) with an acid to form the pyridoxine mono-ester:



(III)

The hydrolysis may not necessarily be an acid hydrolysis when a different blocking agent is used instead of acetone in step *a*.

d. The compound (III) is reacted with an acid to give a pharmaceutically acceptable acid addition salt according to the invention.

The salts of pyridoxine mono-esters according to the invention have interesting psycho-stimulant properties as exemplified by the maleate salt of the dimethylamino ethanol mono-ester of 5-α-pyridoxine succinate maleate. The compound shows at doses from 10 mg/kg, per os, an antagonistic action against the hypodermic and ptosic action of reserpine. Moreover a very favourable action has been noticed on the disfunctioning of the memory in rat and a high rate activity has been noticed on the cortex of the cat with doses of a level of 25 mg/kg I.V.

These compounds present also a low toxicity (in the case of the above mentioned compound it is: DL 50 on mice, 1.55 g/kg per os or 1.0 g/kg I.P.).

The invention also provides a therapeutic composition comprising a pharmaceutically acceptable salt according to the invention in admixture with a pharmaceutically acceptable diluent or carrier.

In human therapy, very good results have been obtained on patients suffering from psychasthenia, neurotonic depressing syndrome, subjective cranial traumatic syndrome by a treatment comprising the administration, per diem, of 4 to 6 gelatin capsules containing each 0.250 g of the same compound. In all the cases of administration the tolerance has been perfect.

The following Examples illustrate the invention.

EXAMPLE 1

Salts of the Dimethylamino Ethanol Monoester of 5-α-Pyridoxine Succinate

a. Blocking of two alcohol functions of pyridoxine:

Into a four litre flask provided with a stirrer there were poured 2.1 litres of pure and anhydrous acetone, and 100 g of dried pyridoxine hydrochloride were added under stirring. The mixture was cooled whilst stirring at 0°C and then gaseous HCl was bubbled through the solution for 6 hours. After another hour the temperature was allowed to rise to room temperature and the stirring was maintained for a further hour. The mixture was then cooled to −15°C and the corresponding 3,4-isopropylidene pyridoxine was obtained in the form of its hydrochloride (100 g). The free base was obtained by neutralization with a solution of Na_2CO_3.

82 g of base (compound A) were obtained melting at 111°C.

b. Preparation and reaction of the acyl chloride of dimethylamino ethanol monosuccinate:

100 g of succinic anhydride, 100 g of dimethylamino ethanol and 100 ml of anhydrous acetone were placed into a two litre flask and were there refluxed for 3 hours. The solution was then concentrated to one third of its original volume by evaporation and cooled. A precipitate appeared, which was separated and recrystallized from acetone.

140 g of product were obtained, with a melting point of 78°C.

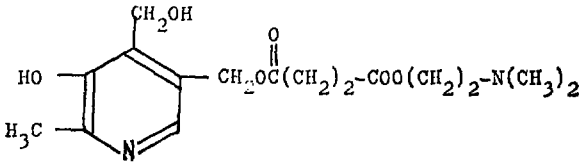
The acyl chloride was prepared from this compound by reaction of 420 g of the compound with freshly distilled $SOCl_2$ (1.85 litre). After elimination of non-reacted $SOCl_2$ the product obtained was washed with benzene and dried to yield 620 g of the hydrochloride of the acyl chloride.

120 g of the compound of step (a) above (0.57 mole) were dissolved in 0.5 litre of pyridine. After cooling there were slowly added at about 5°C during 90 minutes, 170 g (0.69 mole) of the hydrochloride of the acyl chloride previously obtained, dis-

solved in 0.2 litre of chloroform. The solution was stirred for 10 hours, then evaporated to dryness (350 g). The residue was dissolved in 0.3 litre of water and was neutralized by an aqueous solution of NH_3 saturated by K_2CO_3. There was obtained an oily substance which was extracted with chloroform. The extract was concentrated to dryness (170 g).

c. Liberation of —OH and —CH_2OH in the 3- and 4- positions by treating compound (II) with an acid:

In this step the blocking group linking the —OH in position 3 to the —CH_2OH in position 4 of the pyridoxine ring was broken by hydrolysis with formic acid. 52 g of the product of step (b) above were mixed with 1.650 litre of a 1% solution of formic acid and 0.250 litre of ethyl alcohol. The mixture was boiled for 30 minutes, evaporated, again mixed with ethyl alcohol and evaporated. There were obtained 37 g of an oily substance having the formula:



d. Salt formation

1. Maleate

The maleate was obtained by reacting 37 g (0.115 mole) of the above product of step (c) dissolved in 120 ml of acetone with 27 g (0.230 mole) of maleic acid dissolved in 130 ml of acetone.

Yield: 51 g.

Melting point: 134°C.

The fumarate was prepared by an exactly analogous process.

2. N-acetyl aspartate

The N-acetyl aspartate as obtained in an analogous manner to the preparation of the maleate by reacting 22 g (0.64 mole) of the substance of step (c) dissolved in 0.1 litre of ethyl alcohol with 22.4 g of N-acetyl aspartic acid (1.28 mole) dissolved in 0.3 litre of ethyl alcohol. The compound was very hydroscopic.

Yield: 31.5 g.

EXAMPLE 2

The Dimethyl Ethanol Monoester of 5-α-Pyridoxine Glutarate Maleate

Step (a) was identical to step (a) of Example 1. In step (b), glutaric anhydride was used instead of succinic anhydride.

Step (c) was similar to step (c) of Example 1.

There is thus obtained an oily substance which is reacted with maleic acid as in step (d) of Example 1.

There was obtained an ochre-white crystalline product melting at 100—102°C.

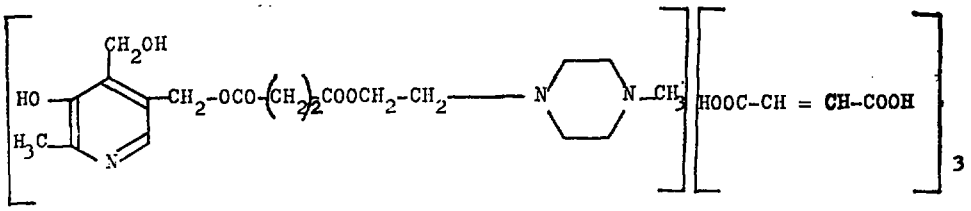
EXAMPLE 3

The N-Methyl N′-Ethanol Piperazine Monoester of 5-α-Pyridoxine Succinate Trimaleate

Step (a) was the same as in Example 1.

The mono-chloride of the mono-succinate of N-methyl N′-ethanol piperazine was prepared by the same way as described in Example 1 step (b), from succinic anhydride and N-methyl N′-ethanol piperazine in stoecchiometric proportions refluxed in acetone (which led to the formation of the mono-succinate of N-methyl N′-ethanol piperazine; melting point: 80—82°C) and the further reaction of this compound with $SOCl_2$.

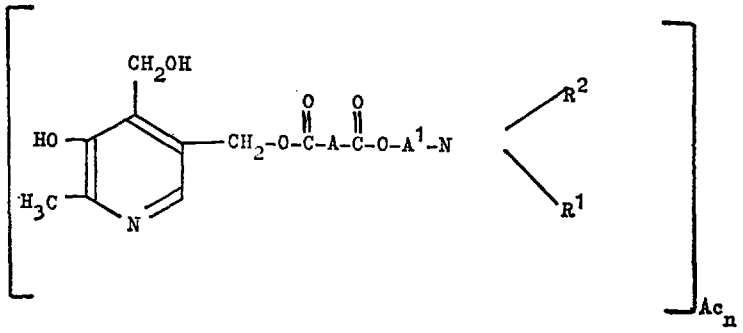
Step (c) was carried out as in Example 1 step (c) and there was obtained an oily substance in a yield of 73%. Analysis showed this compound to correspond to the formula:



Step (d) — The compound of step (c) was transformed into a salt by maleic acid as in Example 1 step (d). With 3 molecules of maleic acid there was obtained the corresponding tri-maleate which was a white product with a bitter and salt taste, melting at about 142°C.

WHAT WE CLAIM IS:—

1. A pharmaceutically acceptable salt of a pyridoxine monoester having the general formula:



in which:

A and A^1 each represents an alkylene radical with a chain of up to 16 carbon atoms or a divalent amino-substituted aliphatic hydrocarbon radical;

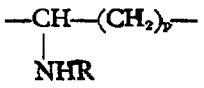
R^1 and R^2 each represents an alkyl radical containing up to 5 carbon atoms or R^1 and R^2 form, together with the nitrogen atom, a heterocyclic ring;

Ac represents a pharmaceutically acceptable acid; and

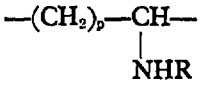
n is 1, 2 or 3.

2. A pharmaceutically acceptance salt according to claim 1 in hich A and/or A^1 represents an amino-alkylene radical.

3. A salt according to claim 2 wherein A and/or A^1 represents a group



or



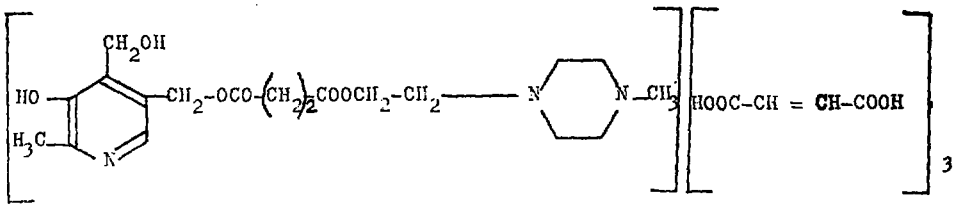
in which R represents a hydrogen atom or a CH_3CO— group and p is 1 or 2.

4. A pharmaceutically acceptable salt according to any preceding claim wherein A represents an alkylene radical with a chain of up to 16 carbon atoms or a divalent amino-substituted aliphatic hydrocarbon radical and A^1 represents an alkylene radical with a chain of up to 16 carbon atoms.

5. A pharmaceutically acceptable salt according to claim 4 wherein each of the symbols R^1 and R^2 represents an alkyl radical containing up to 5 carbon atoms.

6. A pharmaceutically acceptable salt of a pyridoxine mono-ester as disclosed in any of the Examples herein.

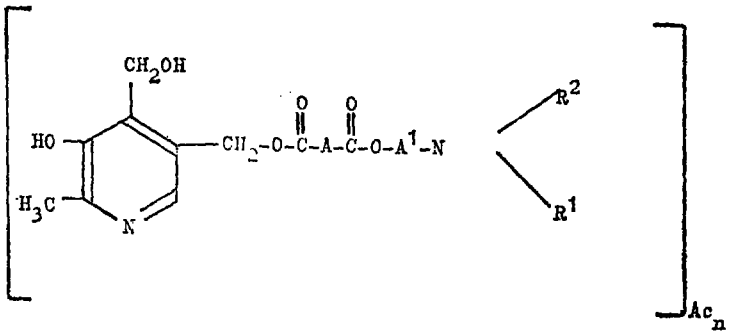
7. A therapeutic composition comprising a pharmaceutically acceptable salt



Step (d) — The compound of step (c) was transformed into a salt by maleic acid as in Example 1 step (d). With 3 molecules of maleic acid there was obtained the corresponding tri-maleate which was a white product with a bitter and salt taste, melting at about 142°C.

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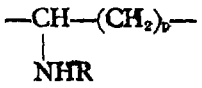
R^1 and R^2 each represents an alkyl radical containing up to 5 carbon atoms or R^1 and R^2 form, together with the nitrogen atom, a heterocyclic ring;

Ac represents a pharmaceutically acceptable acid; and

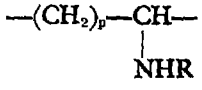
n is 1, 2 or 3.

2. A pharmaceutically acceptance salt according to claim 1 in hich A and/or A' represents an amino-alkylene radical.

3. A salt according to claim 2 wherein A and/or A^1 represents a group



or



in which R represents a hydrogen atom or a CH_3CO— group and p is 1 or 2.

4. A pharmaceutically acceptable salt according to any preceding claim wherein A represents an alkylene radical with a chain of up to 16 carbon atoms or a divalent amino-substituted aliphatic hydrocarbon radical and A^1 represents an alkylene radical with a chain of up to 16 carbon atoms.

5. A pharmaceutically acceptable salt according to claim 4 wherein each of the symbols R^1 and R^2 represents an alkyl radical containing up to 5 carbon atoms.

6. A pharmaceutically acceptable salt of a pyridoxine mono-ester as disclosed in any of the Examples herein.

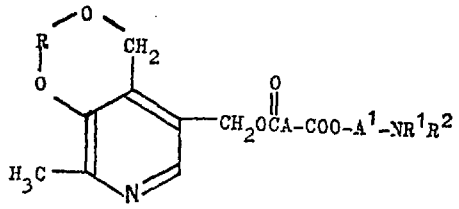
7. A therapeutic composition comprising a pharmaceutically acceptable salt

according to any preceding claim in almixture with a pharmaceutically acceptable diluent or carrier.

8. A process for preparing a pharmaceutically acceptable salt according to any preceding claim, which comprises blocking the two alcohol functions in the 3- and 4- positions of pyridoxine, reacting the compound thus obtained with a compound having the general formula

$$ClCO—A—COO—A^1—NR^1R^2$$

in which A, A^1, R^1 and R^2 are as defined in any of claims 1 to 5, to obtain an intermediate having the general formula:



in which R is a blocking group that can be removed by hydrolysis to liberate the —OH and $—CH_2OH$ groups in the 3- and 4- positions of the pyridoxine ring, liberating the —OH and $—CH_2OH$ groups by the hydrolytic removal of the blocking group and reacting the resulting compound with a pharmaceutically acceptable acid to obtain a pharmaceutically acceptable acid addition salt.

9. A process according to claim 8 wherein the blocking agent is acetone.

10. A process according to claim 8 or claim 9 wherein the blocking group is removed by acid hydrolysis and the resulting compound is neutralized with sodium bicarbonate prior to the formation of the acid addition salt.

11. A process for preparing a salt of a pyridoxine mono-ester substantially as disclosed in any of the Examples herein.

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