PATENT SPECIFICATION (11) 1367592

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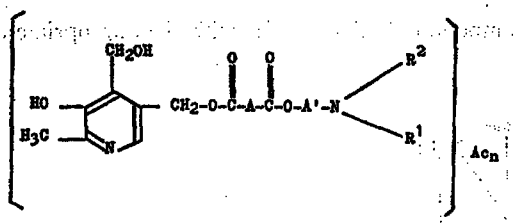
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(54) PYRIDOXINE MONO-ESTERS

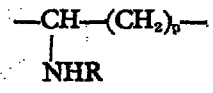
(71) We, SOCIETE D'ETUDES DE PRODUITS CHIMIQUES, a company organised and existing under the laws of France, of 16 rue Kleber 92130 Issy-Les-Moulineaux, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to the manufacture of salts of pyridoxine mono-esters, and provides an improvement in or modification of the process described and claimed in British Patent No. 1,286,161.

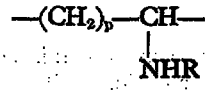
British Patent No. 1,286,161 relates to a salt of a pyridoxine mono-ester having the general formula:



in which A and A′ 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,

and to a process for its manufacture.

The process according to the present invention comprises blocking the two hydroxyl groups in the 3- and 4-positions of pyridoxine in acid conditions, reacting the acid compound thus obtained with a compound having the general formula

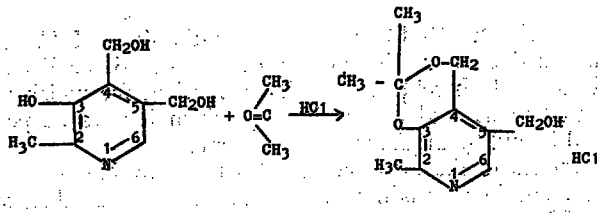
$$ClCO—A—COO—A^1—NR^1R^2$$

in which A, A^1, R^1 and R^2 are as above defined, in solution in dichloroethane, reacting the resulting compound with a pharmaceutically acceptable acid to obtain a pharmaceutically acceptable acid addition salt and removing the group blocking the two hydroxyl groups at the 3- and 4-positions by heating the salt preferably to about 90°C. An aqueous solution of the salt may for example be heated to remove the blocking group.

The reaction sequence is illustrated below:

a. Blocking of two hydroxyl groups of pyridoxine:

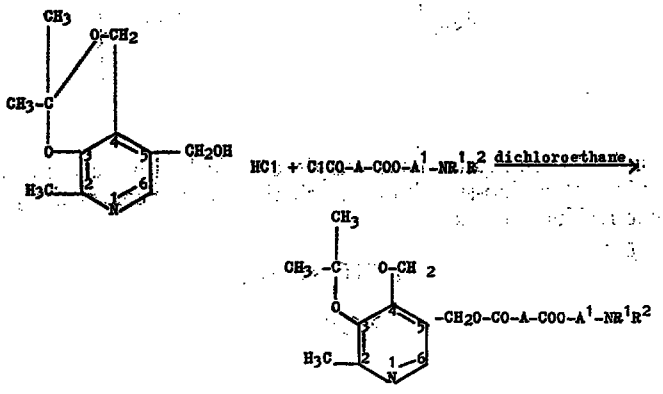
The blocking of the hydroxyl groups in positions 3 and 4 of pyridoxine is carried out under the same conditions as described in the main Patent. The only difference is that the compound obtained in the form of hydrochloride is not neutralized but is used as such.



I

The choice of acetone is not critical, and any other blocking agent may be used. The resulting compound I is obtained and used in the form of its hydrochloride.

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



II

The choice of dichloroethane as solvent for this reaction has advantages over the pyridine used in the Examples of Patent No. 1,286,161. It has been found that pyridine is a little bit too basic and cannot be used in the following steps whereas this is possible with dichloroethane. Moreover, the isopropylidene compound obtained in this step is soluble in dichloroethane but insoluble in the aqueous phase whereas its hydrochloride is soluble in the aqueous phase and insoluble in dichloroethane. This causes, during neutralization, separation of the initially obtained product into different phases. The product in the form of its hydrochloride is found in the water phase and the resulting neutralized product is found in the dichloroethane phase, which provides an automatic separation of the compounds. The acid chloride in the above-mentioned reaction scheme may be obtained as described in the main Patent but preferably by replacing the acetone by dichloroethane.

c. Formation of the Acid Addition Salt.

At the end of the previous step there is obtained an isopropylidene derivative which is directly reacted with the selected acid, preferably by using the anhydride of

a suitable acid, to give the salt of the isopropylidene derivative. The salt of the pyridoxine mono-ester derivative may then be obtained by mere heating of the reaction mixture at about 90°C. In this process of preparation, one stage of the previous synthesis disappears and moreover the possibility that the same solvent may be used to obtain the acid chloride and to condense the acid chloride with the isopropylidene pyridoxine renders the process easier, with a corresponding increase of the yield which according to the present invention may reach from 70% to 90%.

The invention is illustrated by the following Examples.

Example 1

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

(a) Blocking of the hydroxyl groups in positions 3 and 4 of pyridoxine

This was obtained as described in Example 1 of the main Patent except that there was no treatment by sodium carbonate and the hydrochloride obtained is separated, washed with acetone and dried under reduced pressure at room temperature before being used in the following step. The yield of isopropylidene pyridoxine hydrochloride was 95% with respect to the initial pyridoxine hydrochloride.

(b) Preparation and reaction of the acyl chloride of dimethylamino ethanol mono-succinate

The hydrochloride was obtained by suspending, in 1.2 litres of dichloroethane, 0.3 kg of succinic anhydride in a dry reactor fitted with drying means. There was then added, slowly, 0.3 litre of dimethylamino ethanol whilst stirring. The temperature rose to 50—55°C. After a few minutes of stirring the dissolution was complete and the reaction mixture was heated to 60°C and 0.415 litre of thionyl chloride was added thereto (i.e. an excess of 100%). After the end of the addition the mixture was allowed to stand for two hours at about 50°C and the excess of thionyl chloride and the dichloroethane were removed under reduced pressure.

For purification, the product then obtained was finally dissolved twice in 0.3 litre of dichloroethane which was again removed under reduced pressure. The resulting product was dissolved in 0.4 litre of dichloroethane and reacted with 0.615 kg (2.5 mols) of the pyridoxine isopropylidene chloride obtained in step (a). The reaction mixture was refluxed, whilst stirring, for 30 minutes and appeared to be homogeneous. It was allowed to cool to room temperature and then part of the hydrochloric acid was eliminated under a slightly reduced pressure. The reaction mixture then received a mixture of 0.8 litre of water and 1,700 kg of ice at pH 10 (soda wash). After stirring and decantation the hydrochloride of the corresponding succinate of 3,4-isopropylidene-5-α-pyridoxine and dimethylamino ethanol was found in solution in the aqueous phase where it was neutralized and gave the succinate of 3,4-isopropylidene-5-α-pyridoxine and dimethylamino ethanol which was insoluble in water and passed into the dichloroethane phase. The aqueous phase was then extracted twice with 0.6 litre of dichloroethane and the resulting dichloroethane solutions were rinsed with slightly alkaline water (sodium sulphate), decolourized with charcoal and filtered. There was thus obtained a solution in dichloroethane of the succinate of 3,4 - isopropylidene - 5 - α - pyridoxine and dimethylamino ethanol.

(c) Salt formation

1. Maleate

The solution obtained from the previous step was reacted with maleic anhydride dissolved in water whilst stirring. The maleate was soluble in water, and the resulting aqueous solution was decolourized with charcoal, filtered, then heated at 90°C (for the transformation of the isopropylidene pyridoxine form to the pyridoxine form) for about 30 minutes. The solution was allowed to cool to 60°C under reduced pressure to remove the water.

There was thus obtained an oily compound which was twice dissolved in 1.25 litres of ethanol to remove impurities and dissolved in 7.5 litres of boiling ethanol. After separation and washing with ethanol the resulting product was dried at 50°C.

There was finally obtained 1.200 kg of the maleate of the dimethylamino ethanol ester of 5-α-pyridoxine succinate with a yield over 80% compared to the pyridoxine hydrochloride which was the most expensive starting material. Melting point: 134°C.

2. N-acetyl aspartate

This salt was obtained exactly as the maleate but by using the N-acetyl aspartic acid.

Example 2

Maleate of the Dimethylamino Ethanol Monoester of 5-α-Pyridoxine Glutarate

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

There was thus obtained an oily product which was reacted with maleic anhydride as in step (c) of Example 1 to give a crystalline product melting at 100—101°C.

Example 3

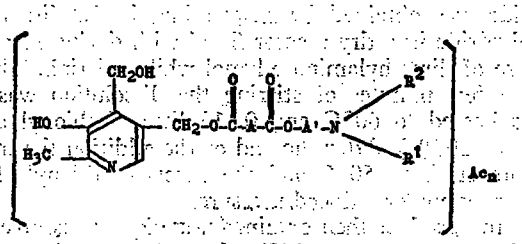
Dimaleate of the N-Methyl N'-Ethanol Piperazine Monoester of 5-α-Pyridoxine Succinate

This compound was obtained as in Example 1 except that N-methyl N'-ethanol piperazine replaced the dimethylamino ethanol in step (b).

There was thus obtained an oily product which when reacted with maleic anhydride as in step (c) of Example 1 gave a di-maleate, a white crystalline product melting at 141—142°C.

WHAT WE CLAIM IS:—

1. A process for the preparation 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;

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

Ac represents a pharmaceutically acceptable acid; and

n is 1, 2 or 3, comprising blocking the two hydroxyl groups in the 3- and 4-positions of pyridoxine in acid conditions, reacting the acid 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 above defined in solution in dichloroethane, reacting the resulting compound with a pharmaceutically acceptable acid to obtain an acid addition salt and removing the group blocking the two hydroxyl groups at the 3- and 4-positions by heating the salt.

2. A process according to claim 1, wherein A and/or A^1 represents an amino-alkylene radical.

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

$$—\underset{\displaystyle NHR}{\underset{|}{CH}}—(CH_2)_p—$$

or

$$—(CH_2)_p—\underset{\displaystyle NHR}{\underset{|}{CH}}—$$

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

4. A process according to any preceding claim, wherein the blocking agent is acetone.

5. A process according to any preceding claim, wherein the group blocking the

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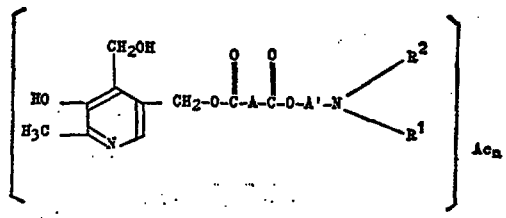
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$$—(CH_2)_p—\underset{\displaystyle NHR}{\underset{|}{CH}}—$$

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

4. A process according to any preceding claim, wherein the blocking agent is acetone.

5. A process according to any preceding claim, wherein the group blocking the

* C L M S *

two hydroxyl groups in the 3- and 4-positions of the pyridoxine ring is removed by heating the salt in aqueous solution.

6. A process according to any preceding claim, wherein the removal of the blocking group is carried out by heating the salt to about 90°C.

7. A process for preparing a salt of a pyridoxine monoester substantially as disclosed in any of the Examples herein.

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