

PATENT SPECIFICATION

(11) 1447 338

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 (72) Inventor ANDRE ESANU

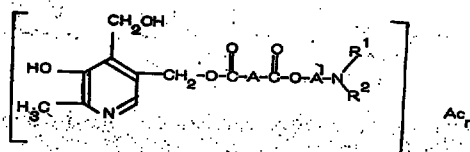


(54) SALTS OF PYRIDOXINE MONO-ESTERS

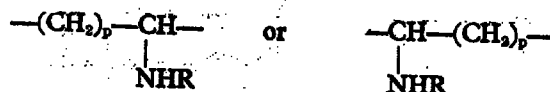
(71) We, SOCIETE D'ETUDES DE PRODUITS CHIMIQUES, a company organised and existing under the laws of France, of 16 rue Kleber 92130 Issy-Les-Moulineaux, France, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly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



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. British Patent No. 1,367,592 is a Patent of Addition to British Patent No. 1,286,161 and relates to an improved or modified process for the manufacture of the above pyridoxine mono-ester. The present invention relates to a further improved or modified process for the manufacture of the above pyridoxine mono-esters.

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



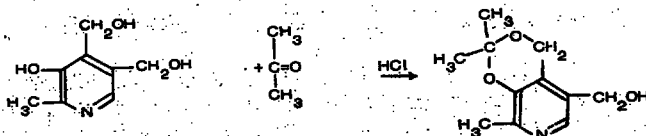
in which A is as above defined, converting the resulting acid monoester intermediate into its acid chloride, reacting the acid chloride with a tertiary amine of the general

formula $\text{HO}-\text{A}^1-\text{NR}^1\text{R}^2$ in which the symbols are as above defined; reacting the resulting compound with a pharmaceutically acceptable acid to give a pharmaceutically acceptable acid addition salt and removing the group blocking the two hydroxyl groups at the 3- and 4-positions by heating the mono-ester preferably to about 90°C . An aqueous solution of the mono-ester may for example be heated to remove the blocking group.

The reaction sequence is illustrated below:

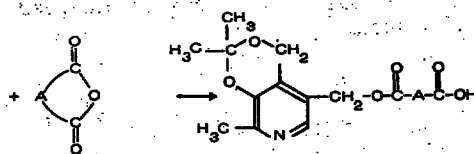
a. Blocking of two hydroxyl groups of pyridoxine:

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



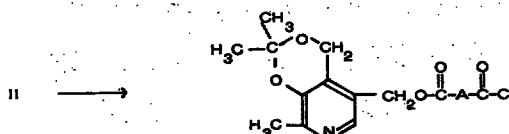
The choice of acetone is not essential, and any other blocking agent may be used.

b. Reaction of the compound I obtained in (a) with the appropriate acid anhydride to form an intermediate II



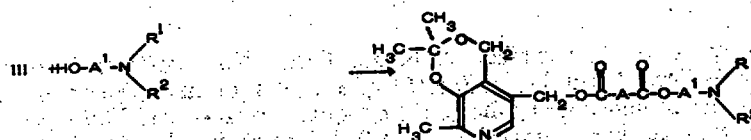
This reaction step is preferably carried out in dichloroethane as solvent for the reasons given in Patent Specification No. 1,367,592.

c. Conversion of the intermediate II into its acid chloride III.



The chlorinating agent may be, for example, thionyl chloride under the usual conditions for conversion of an acid into its acid chloride.

d. Reaction of the acid chloride III with a suitable tertiary aminoalcohol.



e. Formation of an appropriate acid addition salt and liberating the 2 alcohol functions at the 3- and 4-positions of the pyridoxine ring. This new process gives favourable yields of generally between 75% and 90%. The invention is illustrated by the following Examples.

Example 1

Salts of 5 α -pyridoxyl succinate dimethyl-aminoethanol ester

The blocking of the alcohol functions in positions 3 and 4 of pyridoxine was performed as described in British patent 1,268,161 to give (4,3,0)-isopropylidene pyridoxine. 83.6 g (0.4 mol) of this compound were poured at 50°C into a one litre reactor containing a suspension of 40 g (0.4 mol) of succinic anhydride in 350 ml of dichloroethane. The mixture was refluxed for 30 minutes, and there were then

added dropwise 29 ml (0.4 mol) of thionyl chloride. Boiling was maintained for a further 30 minutes and 40 ml (0.4 mol) of dimethyl aminoethanol were added dropwise. The mixture was allowed to cool whilst stirring and was then poured into 0.5 litres of iced water. To the aqueous mixture was then added 100 ml of aqueous sodium hydroxide to bring the pH to 10 and after decantation the aqueous phase was extracted with 200 ml of dichloroethane. The dichloroethane extracts were washed twice with 200 ml of water and then mixed with a solution of 116 g (1 mol) of maleic acid in 200 ml of water.

After heating the aqueous maleic acid-containing solution at 90°C for 30 minutes there were added 6 g of carbon black and after stirring the mixture was filtered, water was eliminated by concentration under vacuum and the last traces of water were removed by twice adding 100 ml of absolute ethanol, the ethanol being removed after addition by distillation. The resulting oily compound was then dissolved in one litre of ethanol and allowed to crystallize.

The product obtained was separated, washed with ethanol and dried.

There were thus obtained 185.4 g (yield 81%—of the dimaleate of 5-pyridoxine succinate dimethyl-aminoethanol ester which is a white product melting at 134°C. Analysis of the product showed a perfect correspondence with the formula $C_{23}H_{32}O_{13}N_2$.

The N-acetyl aspartate was obtained exactly as the maleate but using N-acetyl aspartic acid in place of the maleic acid.

Example 2

Maleic acid salt of 5 α -pyridoxyl glutarate dimethylaminoethanol ester

This compound was obtained as in Example 1 except that glutaric anhydride replaced the succinic anhydride. There was obtained an oily product which was reacted with maleic anhydride to give a crystalline product melting at 100°C to 101°C. Yield: 77%.

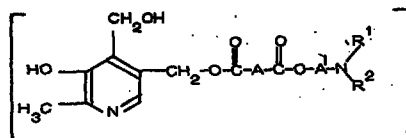
Example 3

Maleic acid salt of 5 α -pyridoxyl succinate 4-methyl-1-piperazinyl-ethanol ester.

This compound was obtained as in Example 1 except that 4-methyl-1-piperazinyl ethanol replaced the dimethylamino ethanol. There was thus obtained an oily product which was reacted with maleic anhydride to give the di-maleate, a white crystalline product melting at 141°C to 142°C. Yield: 88%.

WHAT WE CLAIM IS:—

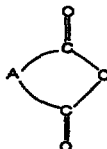
1. A process for the preparation of a pyridoxine mono-ester of the general formula;



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;

R¹ and R² each represents an alkyl radical containing up to 5 carbon atoms, or R¹ and R² 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, reacting the compound thus obtained with an acid anhydride of the general formula



in which A is as above defined, converting the resulting acid monoester intermediate into its acid chloride, reacting the acid chloride with a tertiary amine of the general formula HO—A'—NR¹R² in which the symbols are as above defined, reacting the resulting compound with a pharmaceutically acceptable acid to give a pharma-

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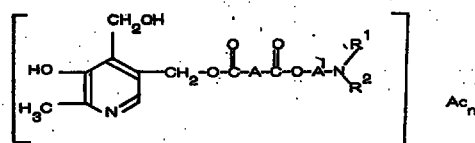
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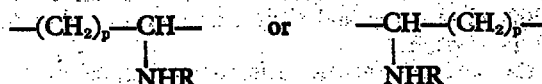
in which A is as above defined, converting the resulting acid monoester intermediate into its acid chloride, reacting the acid chloride with a tertiary amine of the general formula HO—A'—NR¹R² in which the symbols are as above defined, reacting the resulting compound with a pharmaceutically acceptable acid to give a pharma-



ceutically acceptable acid addition salt and removing the group blocking the two hydroxyl groups at the 3- and 4-positions by heating the mono-ester.

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

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



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

10 4. A process according to any preceding claim, wherein the group blocking the two hydroxyl groups at the 3- and 4- positions of the pyridoxine ring is removed by heating the salt in aqueous solution.

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

15 6. A process according to any preceding claim, wherein the conversion of the acid monoester intermediate into its acid chloride is effected by reaction with thionyl chloride.

7. A process according to any preceding claim, wherein the reaction of the blocked pyridoxine with the acid anhydride is carried out under reflux in dichloroethane.

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

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