

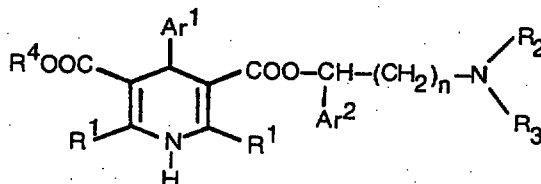
Description

Field of the Invention

The invention relates to esters of 1,4-dihydro-2,6-dimethyl-3-(alkoxycarbonyl or alkoxyalkoxycarbonyl)-4-(substituted phenyl)-pyridine-5-carboxylic acid, to their stereochemical isomers and pharmaceutically acceptable salts, to processes for their production and to pharmaceutical compositions containing them.

Description of the Prior Art

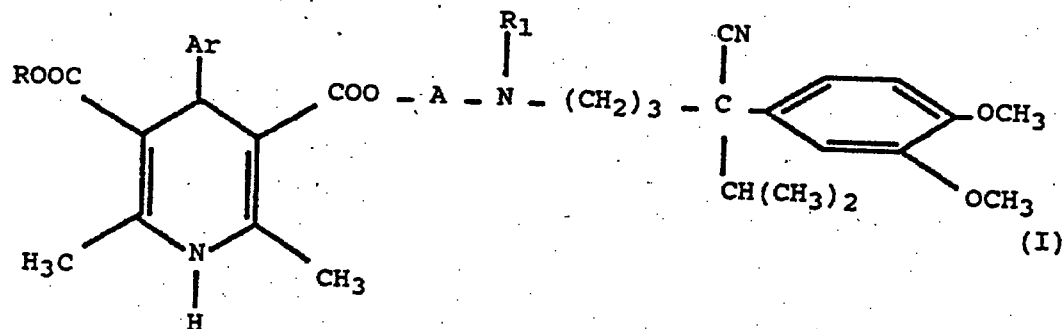
EP—A—60897 describes 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of the general formula



wherein Ar^1 and Ar^2 represent aryl groups, R^1 represents a lower alkyl group, R^2 and R^3 (which may be the same or different) each represents a lower alkyl or aralkyl group, R^4 represents a lower alkyl group and n is 1 or 2. These compounds are useful as hypotensives and therapeutic agents for disturbance of heart and brain circulation.

Description of the Invention

The invention provides esters of 1,4-dihydro-2,6-dimethyl-3-(alkoxycarbonyl or alkoxyalkoxycarbonyl)-4-(substituted phenyl)-pyridine-5-carboxylic acid, the esters having the general formula I



wherein

Ar represents a 3-nitrophenyl or 2,3-dichlorophenyl group,

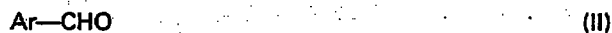
A represents a straight chain or branched chain alkylene group having from 2 to 6 carbon atoms,

R represents a straight chain or branched chain alkyl group having from 1 to 6 carbon atoms, optionally mono-substituted by an alkoxy group having from 1 to 6 carbon atoms, and

R_1 represents an alkyl group having from 1 to 4 carbon atoms,

and further provides pharmaceutically acceptable acid addition salts of such esters.

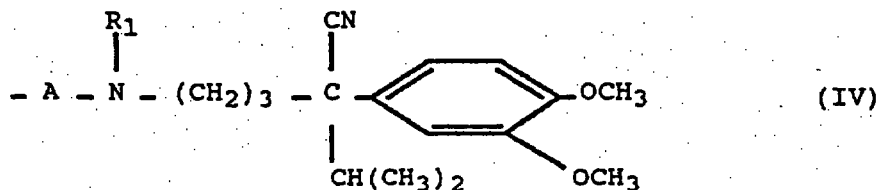
The invention further provides a process for the preparation of the esters of the general formula I, the process comprising condensing a compound of the general formula II



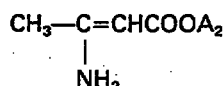
wherein Ar is as above defined with a compound of the general formula III



wherein A_1 represents one of (a) a group R as above defined, (b) a group of the general formula IV

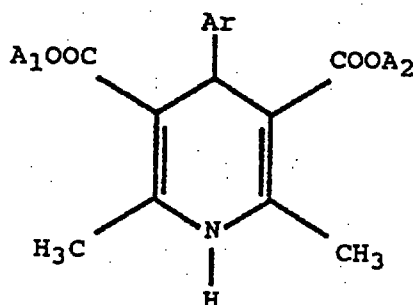


wherein A and R₁ are as above defined and (c) a group of the general formula —AX wherein A is as above defined and X represents a halogen atom, reacting the condensate with a compound of the general formula V



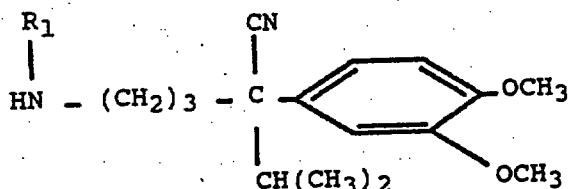
(V)

wherein if A₁ represents the group defined in (a) then A₂ represents either of the groups defined in (b) and (c) and if A₁ represents either of the groups defined in (b) and (c) then A₂ represents the group defined in (a) to give a compound of the general formula (VI)



(VI)

wherein A₁, A₂ and Ar are as above defined, and if one of the groups A₁ and A₂ represents a group defined in (c) then reacting the compound of the general formula VI with a 4-cyano-4-(3,4-dimethoxyphenyl)-5-methyl-hexylamine derivative of the general formula VII



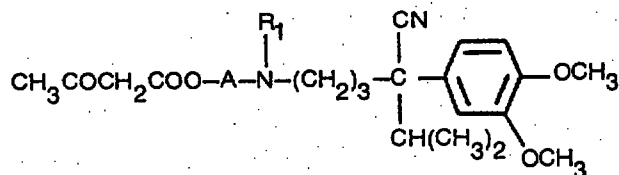
(VII)

wherein R₁ is as above defined.

It will be understood that various synthetic routes are encompassed within the above process. The reaction scheme below, wherein X represents a halogen atom and the other variables are as above defined, illustrates some of these.

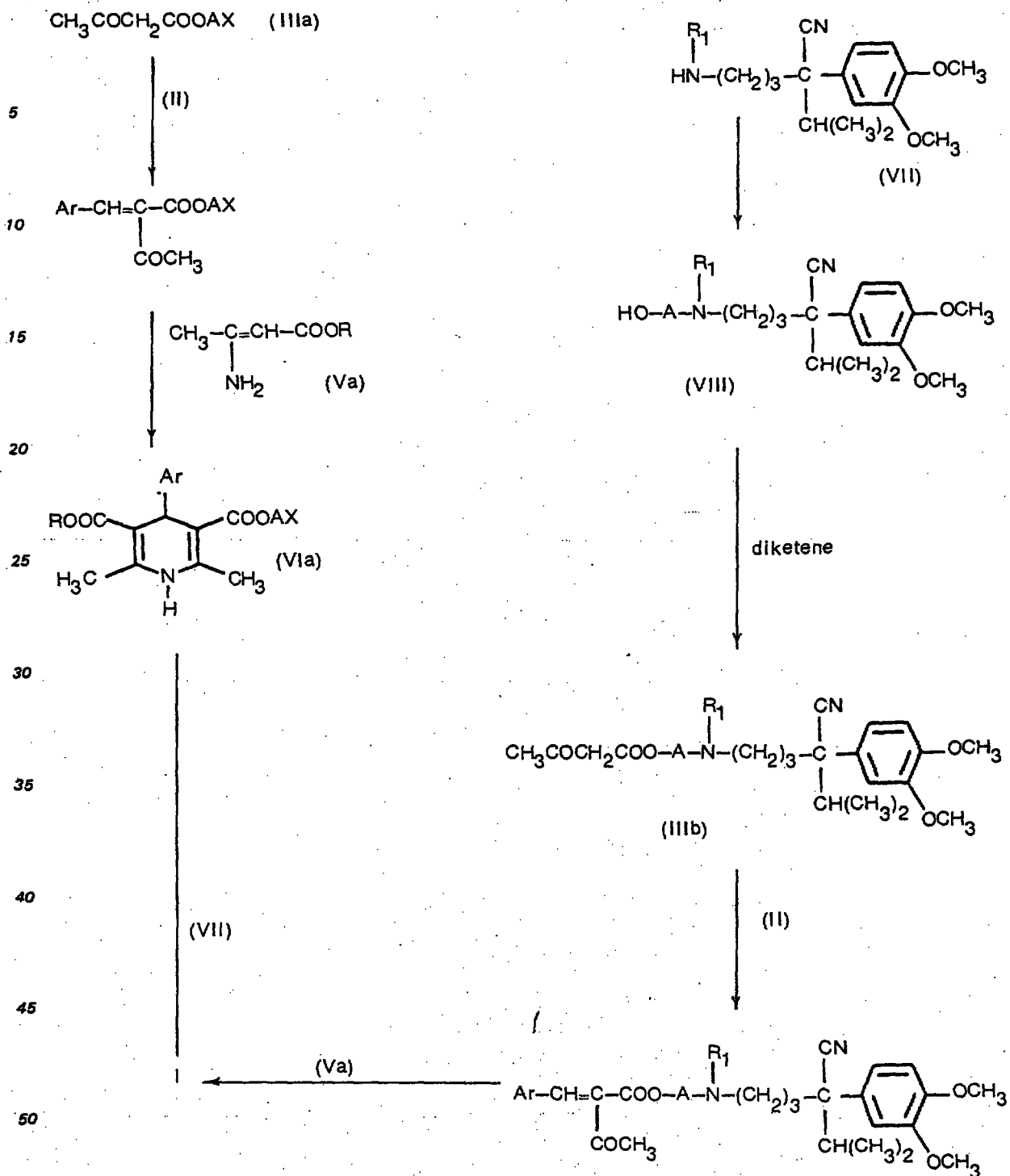
For example, the esters I may be prepared by condensing a haloalkyl acetoacetate IIIa (III: A₁=AX) with an aldehyde II, reacting the condensate with an alkyl or alkoxyalkyl 3-aminocrotonate Va (V: A₂=R), and converting the group AX of the resultant pyridine derivative VIa (VI: A₂=R, A₁=AX) to a group IV by reacting with 4-cyano-4-(3,4-dimethoxyphenyl)-5-methyl-hexylamine or a derivative thereof (VII).

Alternatively the group IV may be introduced into the compound III before ring formation. These routes start from compound IIIb



(IIIb)

This is available from the amine VII by conventional alkylation to introduce a hydroxyalkyl group HO—A (compound VIII), and the reaction of the alkylated amine with diketene. In one route compound IIIb is condensed with an aldehyde II and the product is reacted with a 3-aminocrotonate Va.



The above process includes a synthesis of the pyridine ring. If a pyridine derivative VIa is already available it is only necessary to condense it with an amine VII. This condensation is itself within the scope of the invention. When X represents a chlorine atom, it is preferably carried out in toluene or xylene under reflux, whereas when X represents a bromine atom it may be carried out in dimethylformamide at lower temperature.

The esters I obtained may be purified according to methods known per se. The pharmaceutically acceptable salts according to the invention may be prepared from the bases in a conventional manner. Preferred pharmaceutically acceptable acid addition salts are those of hydrochloric, sulphuric, maleic, succinic, citric, methanesulphonic and toluenesulphonic acids. Their stereoisomers may be separated in a conventional manner.

The esters I and their salts according to the invention possess a valuable antihypertensive activity and are also effective against coronary heart diseases. Accordingly, the invention also provides a

pharmaceutical composition comprising an ester of the general formula I as above defined or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

The LD₅₀ of the compounds according to the invention was determined in the mouse os according to the method described by C. S. Weil (*Biometrics*, 8, 249, 1952).

The antihypertensive activity of the esters according to the invention was evaluated in male hypertensive rats (SHR, Wistar-Kyoto strain, 15—25 weeks old). The determination of blood pressure was performed by an indirect method (M. Gerold et al., *Arzneim. Forsch.*, 18, 1285, 1968). The animals were prewarmed in a heating chamber at a temperature of from 35° to 37°C for a period of 15 minutes before pressure determination. The compounds tested by oral route were dissolved or suspended in a 0.5% methylcellulose solution. Controls were given only the vehicle. Systolic blood pressure and heart rate were measured 1, 3, 5 and 7 hours after drug administration by means of a tail-cuff and a pulse transducer.

Coronary dilating activity was evaluated in anesthetized normotensive rats (weighing about 500 g), as the ability to antagonize methacholine induced coronary spasm. Rats were instrumented for methacholine infusion into the coronary ostium, while spastic activity was detected as ST segment elevation in D₂ ECG recording (K. Sakai et al., *J. Pharm. Meth.*, 5, 325, 1981). The compounds tested by i.v. infusion were dissolved in water:dimethylformamide (9:1 by volume). Activity was detected as normalization of ECG tracing after compounds administration during methacholine infusion.

The results of the tests, given in the Table below, show that the esters are of low toxicity, possess valuable antihypertensive activities and can also be considered effective against coronary heart diseases.

TABLE

Compound	LD ₅₀ mg/kg os	ED ₂₅ SHR os	ED ₅₀ iv
2245	278	6.8	0.301
2392	3000	14.9	—
2404	3000	17.8	—

ED₂₅ = antihypertensive activity mg/kg

ED₅₀ = coronary dilating activity mg/kg

— = not tested

The invention is illustrated by the following Examples.

Example 1

Methyl 2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate

A solution comprising 3.94 g of methyl 2-chloroethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate and 5.78 g of 4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamine in 12 ml of xylene was refluxed under stirring for 7 hours. At the end of the reaction, the mixture was diluted with ethyl acetate and the solution was extracted with dilute hydrochloric acid in order to remove the unreacted amine. The organic solution was dried, the solvent was evaporated off under vacuum, and the residue was washed with diethyl ether, treated with dilute aqueous sodium hydroxide solution and extracted with diethyl ether:ethyl acetate (4:1 by volume). The extract was dried and the solvents were evaporated off under vacuum. The crude product thus obtained was purified by silica gel chromatography, using chloroform as eluent with increasing amounts of ethyl acetate. Pure fractions were collected and evaporated to dryness. The residue was dissolved in methanol, filtered through charcoal, treated with ethanolic hydrogen chloride and evaporated to dryness under vacuum. The residue was washed with warm diethyl ether:acetone mixtures (49:1 and then 24:1 by volume). 2.32 g of the hydrochloride of the title compound (2245) were obtained.

Mp 97—103°C (Kofler).

Example 2

2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethanol

A solution of 18.9 g of 4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamine and 4.5 g of propylene oxide in 40 ml of methanol was allowed to stand for 24 hours at 20°C. A further 0.75 g of propylene oxide was then added, and after 24 hours at 20°C the solution was refluxed for 1 hour and then evaporated to dryness in vacuo. The oil thus obtained was purified by silica gel chromatography using chloroform containing increasing amounts of methanol as eluent. The unitary TLC fractions (chloroform:methanol:5N methanolic ammonia 95:5:0.5 by volume) were evaporated to dryness to give 18.78 g of the title compound as an oil.

Example 3

2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl acetoacetate

2.7 ml of diketene was added, over 10 minutes, to a solution of 11.36 g of the compound prepared in Example 2 in 10 ml of toluene at 80°C. When the exothermic reaction was over, the reaction mixture was heated for 2 hours at 80°C and, after cooling, it was evaporated to dryness in vacuo. The oily residue was then purified by silica gel column chromatography using ethyl acetate containing decreasing amounts of petroleum ether as eluent. The unitary TLC fractions (chloroform:methanol) 95:5 by volume) were evaporated to dryness in vacuo to give 11.61 g of the title compound as an oil.

Example 4

2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl α -acetyl-3-nitrocinnamate hydrochloride

A solution of 7.80 g of the compound prepared in Example 3 and 3.26 g of 3-nitrobenzaldehyde in 25 ml of chloroform was saturated with hydrogen chloride at 0°C. After 24 hours at 20°C, the reaction mixture was evaporated to dryness in vacuo and the oil residue was solidified by treatment with diethyl ether. The solid thus obtained was washed with diethyl ether:ethyl acetate 95:5 by volume (6 x 30 ml) until no trace of 3-nitrobenzaldehyde could be discovered.

8.70 g of the title compound, melting at 75—100°C, were obtained, as an E—Z isomeric mixture, which was used as such for further reactions.

Example 5

2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ether α -acetyl-2,3-dichlorocinnamate hydrochloride

Operating as described in Example 4, but employing 2,3-dichlorobenzaldehyde instead of 3-nitrobenzaldehyde, the title compound was obtained as a brown oil. The compound was an E—Z isomeric mixture and was used as such for further reactions.

Example 6

Isopropyl 2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate

A solution of 1.38 g of the compound prepared in Example 4 and 0.33 g of isopropyl 3-aminocrotonate in 4 ml of isopropanol was refluxed for 2.5 hours. After cooling, the mixture was evaporated to dryness in vacuo and the residue was dissolved in dichloromethane and washed with an aqueous solution of sodium bicarbonate. The organic phase was dried and evaporated in vacuo to dryness. The residue was purified by flash chromatography on silica gel using petroleum ether containing increasing amounts of acetone as eluent. The unitary TLC fractions (petroleum ether:acetone 7:3 by volume) were evaporated to dryness. The residue was dissolved in diethyl ether and acidified with hydrogen chloride in diethyl ether to give a solid which was collected, washed with diethyl ether and dried. 0.87 g of the hydrochloride hemihydrate of the title compound (2432) melting at 90—105°C, was obtained.

Example 7

Isobutyl 2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-pyridine-3,5-dicarboxylate

Operating as described in Example 6, but starting from isobutyl 3-aminocrotonate and the compound prepared in Example 5, the hydrochloride hydrate of the title compound (2392), melting at 120—123.5°C, was obtained.

Example 8

2-Propoxy-ethyl 2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-pyridine-3,5-dicarboxylate

Operating as described in Example, but starting from 2-propoxy-ethyl 3-aminocrotonate and the compound prepared in Example 5, the hydrochloride hydrate of the title compound (2404), melting at 102—105°C, was obtained.

Claims for the Contracting States: BE CH/LI DE FR GB IT LU NL SE

1. An ester of 1,4-dihydro-2,6-dimethyl-3-(alkoxycarbonyl or alkoxyalkoxycarbonyl)-4-(substituted phenyl)-pyridine-5-carboxylic acid, the ester having the general formula I

Example 3

2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl acetoacetate

2.7 ml of diketene was added, over 10 minutes, to a solution of 11.36 g of the compound prepared in Example 2 in 10 ml of toluene at 80°C. When the exothermic reaction was over, the reaction mixture was heated for 2 hours at 80°C and, after cooling, it was evaporated to dryness in vacuo. The oily residue was then purified by silica gel column chromatography using ethyl acetate containing decreasing amounts of petroleum ether as eluent. The unitary TLC fractions (chloroform:methanol) 95:5 by volume) were evaporated to dryness in vacuo to give 11.61 g of the title compound as an oil.

Example 4

2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl α -acetyl-3-nitrocinnamate hydrochloride

A solution of 7.80 g of the compound prepared in Example 3 and 3.26 g of 3-nitrobenzaldehyde in 25 ml of chloroform was saturated with hydrogen chloride at 0°C. After 24 hours at 20°C, the reaction mixture was evaporated to dryness in vacuo and the oil residue was solidified by treatment with diethyl ether. The solid thus obtained was washed with diethyl ether:ethyl acetate 95:5 by volume (6 $\times$ 30 ml) until no trace of 3-nitrobenzaldehyde could be discovered.

8.70 g of the title compound, melting at 75—100°C, were obtained, as an E—Z isomeric mixture, which was used as such for further reactions.

Example 5

2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ether α -acetyl-2,3-dichlorocinnamate hydrochloride

Operating as described in Example 4, but employing 2,3-dichlorobenzaldehyde instead of 3-nitrobenzaldehyde, the title compound was obtained as a brown oil. The compound was an E—Z isomeric mixture and was used as such for further reactions.

Example 6

Isopropyl 2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate

A solution of 1.38 g of the compound prepared in Example 4 and 0.33 g of isopropyl 3-aminocrotonate in 4 ml of isopropanol was refluxed for 2.5 hours. After cooling, the mixture was evaporated to dryness in vacuo and the residue was dissolved in dichloromethane and washed with an aqueous solution of sodium bicarbonate. The organic phase was dried and evaporated in vacuo to dryness. The residue was purified by flash chromatography on silica gel using petroleum ether containing increasing amounts of acetone as eluent. The unitary TLC fractions (petroleum ether:acetone 7:3 by volume) were evaporated to dryness. The residue was dissolved in diethyl ether and acidified with hydrogen chloride in diethyl ether to give a solid which was collected, washed with diethyl ether and dried. 0.87 g of the hydrochloride hemihydrate of the title compound (2432) melting at 90—105°C, was obtained.

Example 7

Isobutyl 2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-pyridine-3,5-dicarboxylate

Operating as described in Example 6, but starting from isobutyl 3-aminocrotonate and the compound prepared in Example 5, the hydrochloride hydrate of the title compound (2392), melting at 120—123.5°C, was obtained.

Example 8

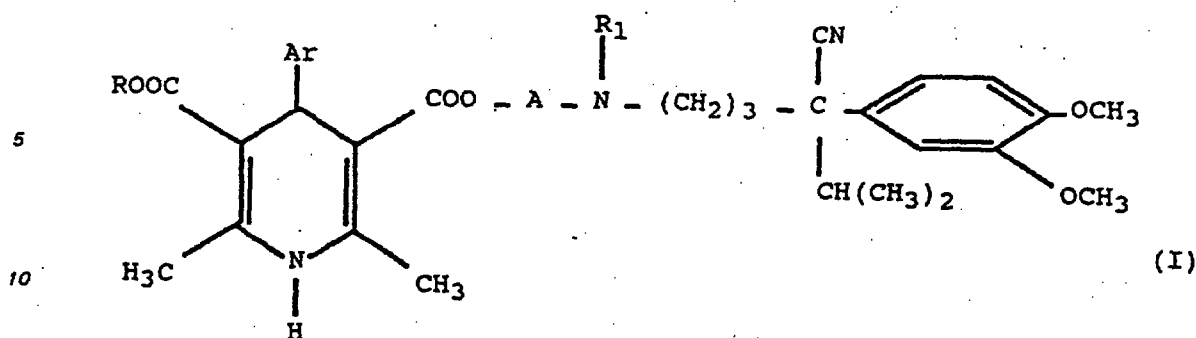
2-Propoxy-ethyl 2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-pyridine-3,5-dicarboxylate

Operating as described in Example, but starting from 2-propoxy-ethyl 3-aminocrotonate and the compound prepared in Example 5, the hydrochloride hydrate of the title compound (2404), melting at 102—105°C, was obtained.

Claims for the Contracting States: BE CH/LI DE FR GB IT LU NL SE

1. An ester of 1,4-dihydro-2,6-dimethyl-3-(alkoxycarbonyl or alkoxyalkoxycarbonyl)-4-(substituted phenyl)-pyridine-5-carboxylic acid, the ester having the general formula I



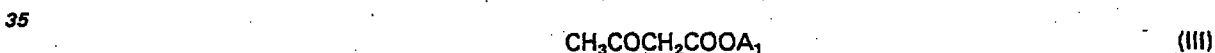


wherein

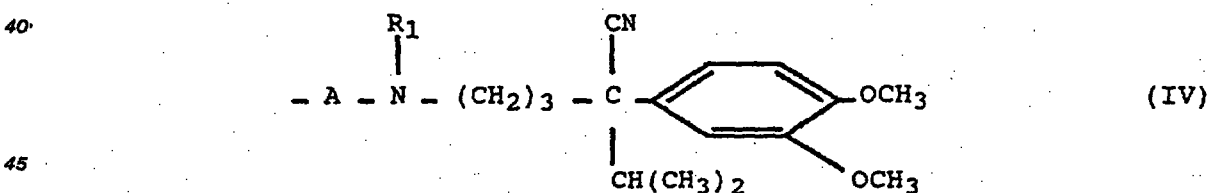
- 15 Ar represents a 3-nitrophenyl or 2,3-dichlorophenyl group,
 A represents a straight chain or branched chain alkylene group having from 2 to 6 carbon atoms,
 R represents a straight chain or branched chain alkyl group having from 1 to 6 carbon atoms, optionally
 mono-substituted by an alkoxy group having from 1 to 6 carbon atoms, and
 R₁ represents an alkyl group having from 1 to 4 carbon atoms,
 20 or a stereoisomer or pharmaceutically acceptable acid addition salt of such an ester.
 2. Methyl 2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-ethyl 1,4-dihydro-2,6-
 dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate or its hydrochloride.
 3. Isopropyl 2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl 1,4-
 dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate or its hydrochloride hemihydrate.
 25 4. Isobutyl 2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl 1,4-dihydro-
 2,6-dimethyl-4-(2,3-dichlorophenyl)-pyridine-3,5-dicarboxylate or its hydrochloride hydrate.
 5. 2-Propoxy-ethyl 2-[4-cyano-4-(3,4-dimethoxyphenyl)-5,N-dimethyl-hexylamino]-1-methyl-ethyl 1,4-
 dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-pyridine-3,5-dicarboxylate or its hydrochloride hydrate.
 6. A process for the preparation of an ester according to claim 1, the process comprising condensing a
 30 compound of the general formula II



wherein Ar is as defined in claim 1 with a compound of the general formula III



wherein A₁ represents one of (a) a group R as defined in claim 1, (b) a group of the general formula IV



wherein A and R₁ are as defined in claim 1 and (c) a group of the general formula -AX wherein A is as
 50 defined in claim 1 and X represents a halogen atom, reacting the condensate with a compound of the
 general formula V

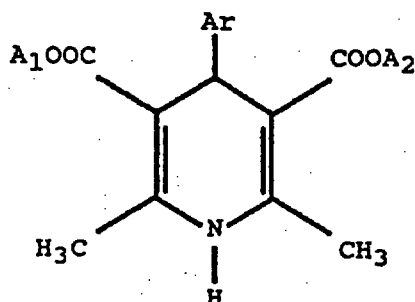


55 wherein if A₁ represents the group defined in (a) then A₂ represents either of the groups defined in (b) and
 (c) and if A₁ represents either of the groups defined in (b) and (c) then A₂ represents the group defined in (a)
 to give a compound of the general formula (VI)

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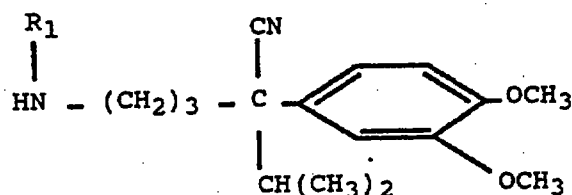
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(VI)

wherein A_1 and A_2 are as defined in this claim and Ar is as defined in claim 1, and if one of the groups A_1 and A_2 represents a group defined in (c) then reacting the compound of the general formula VI with a 4-cyano-4-(3,4-dimethoxyphenyl)-5-methyl-hexylamine derivative of the general formula VII



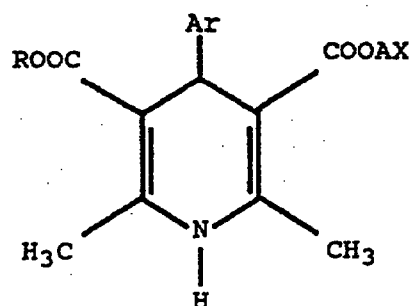
(VII)

wherein R_1 is as defined in claim 1.

7. A process according to claim 6 in which A_1 represents a group of the formula $-\text{AX}$ and A_2 represents a group R.

8. A process according to claim 6 in which A_1 represents a group of the general formula IV and A_2 represents a group R.

9. A process for the preparation of an ester according to claim 1, the process comprising condensing a pyridine derivative of the general formula VIa



(VIa)

wherein Ar, R and A are as defined in claim 1 and X represents a halogen atom with a compound of the general formula VII as defined in claim 6.

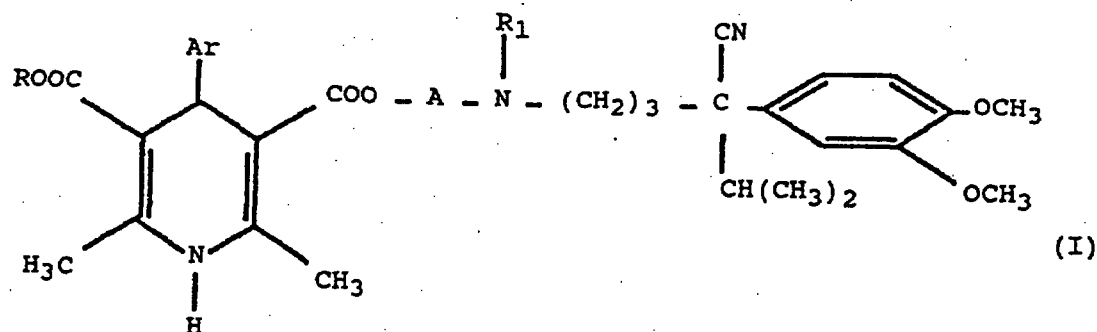
10. A pharmaceutical composition comprising an ester according to any of claims 1 to 5 or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.



0 164 213

Claims for the Contracting State: AT

1. A process for the preparation of an ester of 1,4-dihydro-2,6-dimethyl-3-(alkoxycarbonyl or alkoxy-alkoxycarbonyl)-4-(substituted phenyl)-pyridine-5-carboxylic acid, the ester having the general formula I



wherein

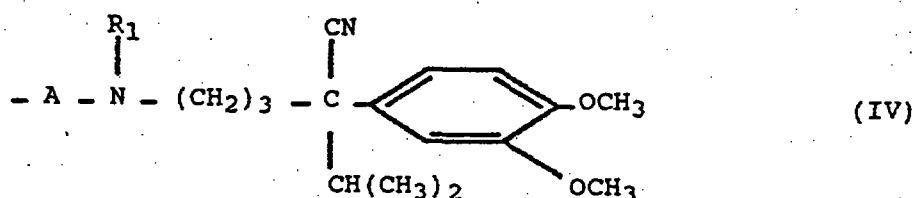
Ar represents a 3-nitrophenyl or 2,3-dichlorophenyl group,
 A represents a straight chain or branched chain alkylene group having from 2 to 6 carbon atoms,
 R represents a straight chain or branched chain alkyl group having from 1 to 6 carbon atoms, optionally mono-substituted by an alkoxy group having from 1 to 6 carbon atoms, and
 R₁ represents an alkyl group having from 1 to 4 carbon atoms,
 the process comprising condensing a compound of the general formula II



wherein Ar is as defined in this claim with a compound of the general formula III



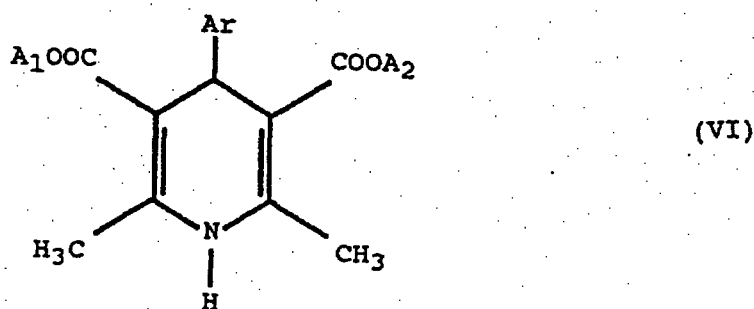
wherein A₁ represents one of (a) a group R as defined in this claim, (b) a group of the general formula IV



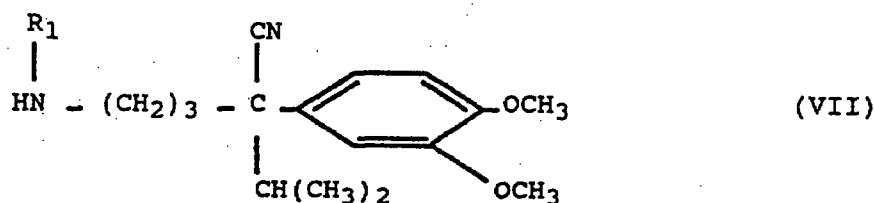
wherein A and R₁ are as defined in this claim and (c) a group of the general formula —AX wherein A is as defined in this claim and X represents a halogen atom, reacting the condensate with a compound of the general formula V



wherein if A₁ represents the group defined in (a) then A₂ represents either of the groups defined in (b) and (c) and if A₁ represents either of the groups defined in (b) and (c) then A₂ represents the group defined in (a) to give a compound of the general formula (VI)



wherein A_1 , A_2 and Ar are as defined in this claim, and if one of the groups A_1 and A_2 represents a group defined in (c) then reacting the compound of the general formula VI with a 4-cyano-4-(3,4-dimethoxyphenyl)-5-methyl-hexylamine derivative of the general formula VII

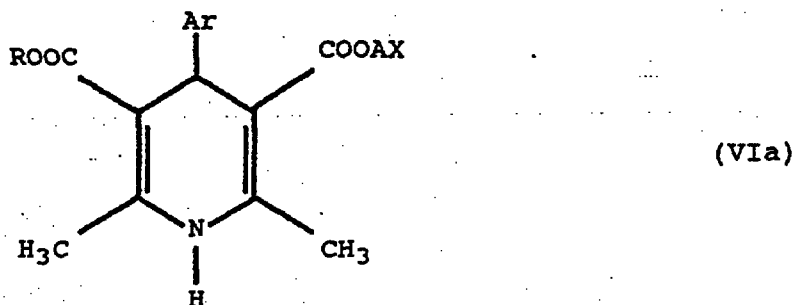


wherein R_1 is as defined in this claim.

2. A process according to claim 1 in which A_1 represents a group of the formula $-AX$ and A_2 represents a group R .

3. A process according to claim 1 in which A_1 represents a group of the general formula IV and A_2 represents a group R .

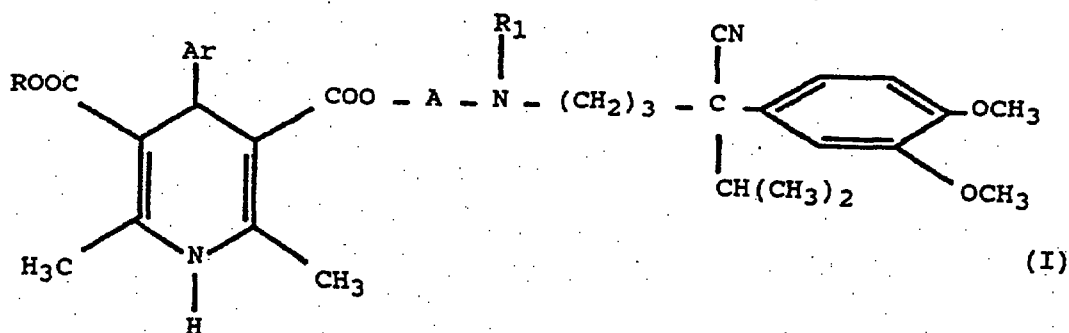
4. A process for the preparation of an ester having the general formula I as defined in claim 1, the process comprising condensing a pyridine derivative of the general formula VIa



wherein Ar , R and A are as defined in claim 1 and X represents a halogen atom with a compound of the general formula VII as defined in claim 1.

Patentansprüche für die Vertragsstaaten: BE CH/LI DE FR GB IT LU NL SE

1. Ester von 1,4-Dihydro-2,6-dimethyl-3-(alkoxycarbonyl oder alkoxyalkoxycarbonyl)-4-(substituiertes phenyl)-pyridin-5-carbonsäure, welcher Ester die allgemeine Formel I



besitzt, worin Ar eine 3-Nitrophenyl oder 2,3-Dichlorphenylgruppe bedeutet, A eine gerade oder verzweigte Alkylengruppe mit 2 bis 6 C-Atomen bedeutet, R eine gerade oder verzweigte, gegebenenfalls durch eine Alkoxygruppe mit 1 bis 6 C-Atomen monosubstituierte Alkylgruppe mit 1 bis 6 C-Atomen bedeutet und R_1 eine Alkylgruppe mit 1 bis 4 C-Atomen bedeutet oder ein Stereoisomeres oder pharmazeutisch anwendbares Säureadditionssalz eines solchen Esters.

2. Methyl-2-[4-cyano-4-(3,4-dimethoxyphenyl)-5 N-dimethyl-hexylamino]-äthyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridin-3,5-dicarboxylat oder sein Hydrochlorid.

3. Isopropyl-2-[4-cyano-4-(3,4-dimethoxyphenyl)-5 N-dimethyl-hexylamino]-1-methyl-äthyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridin-3,5-dicarboxylat oder sein Hydrochlorid-Hemihydrat.

4. Isobutyl-2-[4-cyano-4-(3,4-dimethoxyphenyl)-5 N-dimethyl-hexylamino]-1-methyl-äthyl-1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorphenyl)-pyridin-3,5-dicarboxylat oder sein Hydrochlorid-Hydrat.

5. 2-Propoxy-äthyl-2-[4-cyano-4-(3,4-dimethoxyphenyl)-5 N-dimethyl-hexylamino]-1-methyl-äthyl-1,4-



dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-pyridin-3,5-dicarboxylat oder sein Hydrochlorid-Hydrat.

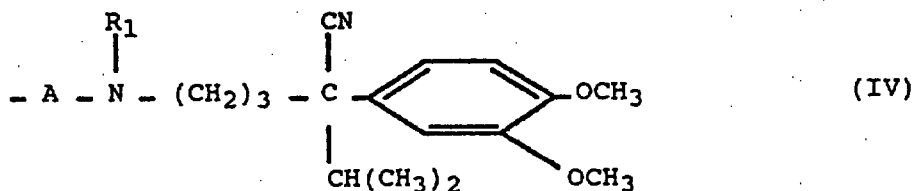
6. Verfahren zur Herstellung eines Esters nach Anspruch 1, welches Verfahren darin besteht, dass eine Verbindung der allgemeinen Formel II



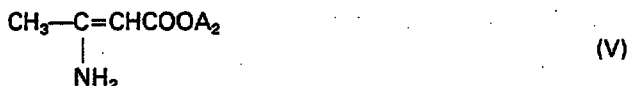
worin Ar wie in Anspruch 1 definiert ist, mit einer Verbindung der allgemeinen Formel III



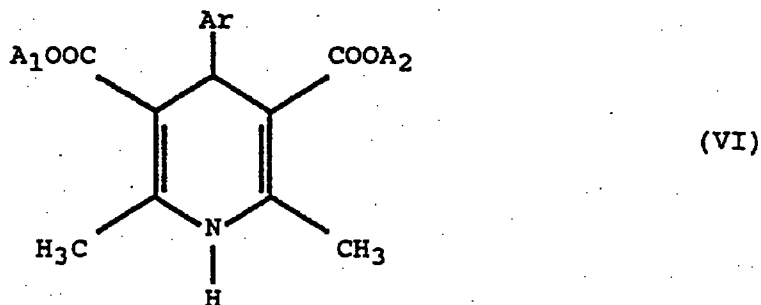
worin A_1 entweder (a) eine Gruppe R wie in Anspruch 1 definiert, (b) eine Gruppe der allgemeinen Formel IV



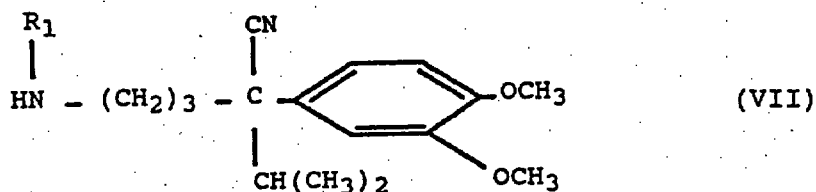
worin A und R_1 wie in Anspruch 1 definiert sind oder (c) eine Gruppe der allgemeinen Formel $-\text{AX}$, worin A wie in Anspruch 1 definiert ist und X ein Halogenatom darstellt, bedeutet, kondensiert wird und das Kondensat mit einer Verbindung der allgemeinen Formel V



worin für den Fall, dass A_1 die unter (a) definierte Gruppe bedeutet, A_2 eine der unter (b) und (c) definierten Gruppen bedeutet, und für den Fall, dass A_1 eine der unter (b) und (c) definierten Gruppen bedeutet, A_2 die unter (a) definierte Gruppe bedeutet, zur Reaktion gebracht wird, um eine Verbindung der allgemeinen Formel VI



zu ergeben, worin A_1 und A_2 wie in diesem Anspruch definiert sind und Ar wie in Anspruch 1 definiert ist, und für den Fall, dass eine der Gruppen A_1 und A_2 eine unter (c) definierte Gruppe bedeutet, dann die Verbindung der allgemeinen Formel VI mit einem 4-Cyano-4-(3,4-dimethoxyphenyl)-5-methyl-hexylamin-Derivat der allgemeinen Formel VII



worin R_1 wie in Anspruch 1 definiert ist, zur Reaktion gebracht wird.

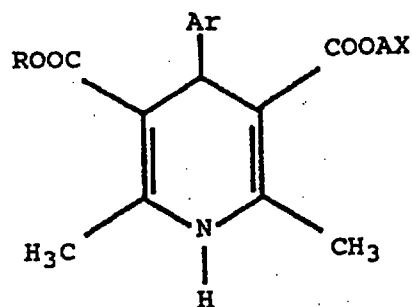
7. Verfahren nach Anspruch 6, wobei A_1 eine Gruppe der Formel $-\text{AX}$ und A_2 eine Gruppe R bedeutet.

8. Verfahren nach Anspruch 6, wobei A_1 eine Gruppe der allgemeinen Formel IV und A_2 eine Gruppe R bedeutet.

9. Verfahren zur Herstellung eines Esters gemäss Anspruch 1, welches Verfahren darin besteht, dass ein Pyridin-Derivat der allgemeinen Formel IVa



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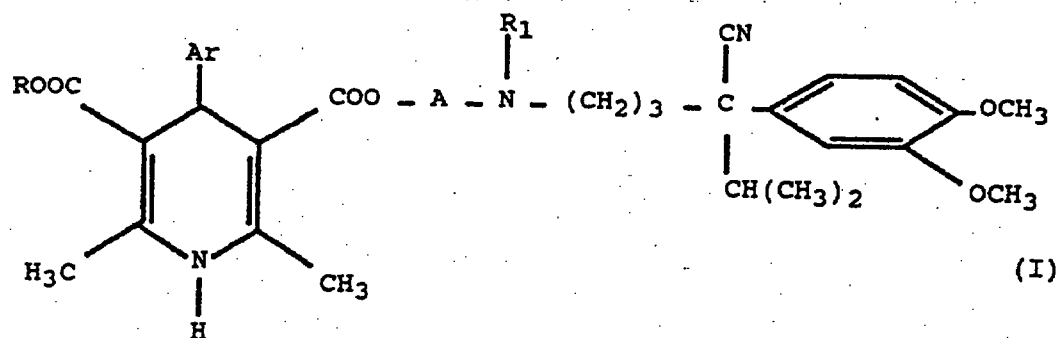
(VIa)

worin Ar, R und A wie in Anspruch 1 definiert sind und X ein Halogenatom bedeutet mit einer Verbindung der allgemeinen Formel VII wie in Anspruch 6 definiert, kondensiert wird.

10. Pharmazeutische Zubereitung enthaltend einen Ester nach einem der Ansprüche 1 bis 5 oder ein pharmazeutisch anwendbares Säureadditionssalz davon in Mischung mit einem pharmazeutisch anwendbaren Verdünnungsmittel oder Trägerstoff.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines Esters von 1,4-Dihydro-2,6-dimethyl-3-(alkoxycarbonyl oder alkoxyalkoxycarbonyl)-4-(substituiertes phenyl)-pyridin-5-carbonsäure, welcher Ester der allgemeinen Formel I



(I)

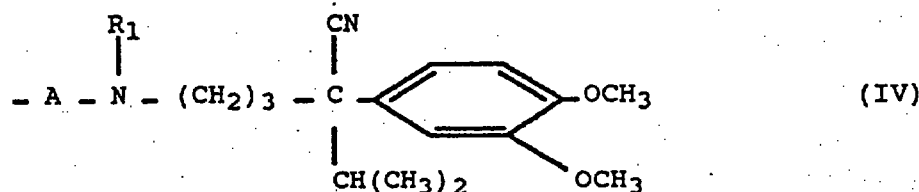
entspricht, worin Ar eine 3-Nitrophenyl oder 2,3-Dichlorophenylgruppe bedeutet, A eine gerade oder verzweigte Alkylengruppe mit 2 bis 6 C-Atomen bedeutet, R eine gerade oder verzweigte, gegebenenfalls durch eine Alkoxygruppe mit 1 bis 6 C-Atomen monosubstituierte Alkylgruppe mit 1 bis 6 C-Atomen bedeutet und R₁ eine Alkylgruppe mit 1 bis 4 C-Atomen bedeutet, welches Verfahren darin besteht, dass eine Verbindung der allgemeinen Formel II



worin Ar wie in diesem Anspruch definiert ist, mit einer Verbindung der allgemeinen Formel III



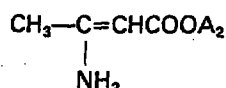
worin A₁ entweder (a) eine Gruppe R wie in diesem Anspruch definiert, (b) eine Gruppe der allgemeinen Formel IV



(IV)

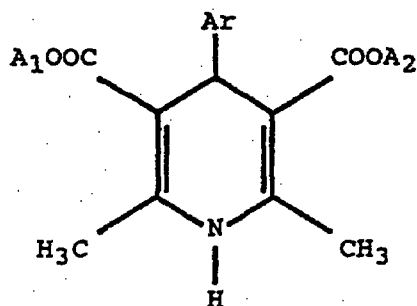
worin A und R₁ wie in diesem Anspruch definiert sind oder (c) eine Gruppe der allgemeinen Formel -AX, worin A wie in diesem Anspruch definiert ist und X ein Halogenatom bedeutet, kondensiert wird und das Kondensat mit einer Verbindung der allgemeinen Formel V





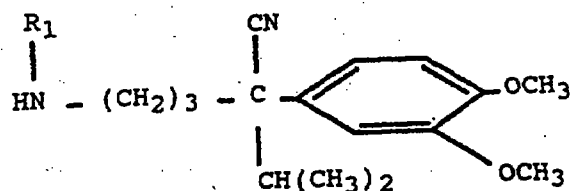
(V)

worin für den Fall, dass A₁ die unter (a) definierte Gruppe bedeutet, A₂ eine der unter (b) und (c) definierten Gruppen bedeutet, und für den Fall, dass A₁ eine der unter (b) und (c) definierten Gruppen bedeutet, A₂ die unter (a) definierte Gruppe bedeutet, zur Reaktion gebracht wird, um eine Verbindung der allgemeinen Formel VI



(VI)

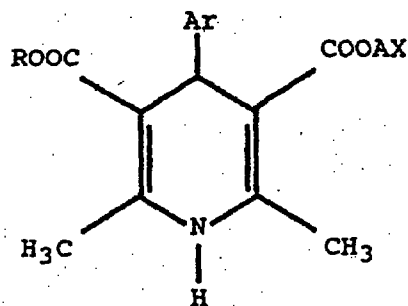
zu ergeben, worin A₁, A₂ und Ar wie in diesem Anspruch definiert sind, und für den Fall, dass eine der Gruppen A₁ und A₂ eine unter (c) definierte Gruppe bedeutet, dann die Verbindung der allgemeinen Formel VI mit einem 4-Cyano-4-(3,4-dimethoxyphenyl)-5-methyl-hexylamin-Derivat der allgemeinen Formel VII



(VII)

worin R₁ wie in diesem Anspruch definiert ist, zur Reaktion gebracht wird.

2. Verfahren nach Anspruch 1, wobei A₁ eine Gruppe der Formel —AX und A₂ eine Gruppe R bedeutet.
3. Verfahren nach Anspruch 1, wobei A₁ eine Gruppe der allgemeinen Formel IV und A₂ eine Gruppe R bedeutet.
4. Verfahren zur Herstellung eines Esters, welcher die in Anspruch 1 definierte allgemeine Formel I besitzt, welches Verfahren darin besteht, dass ein Pyridin-Derivat der allgemeinen Formel VIa



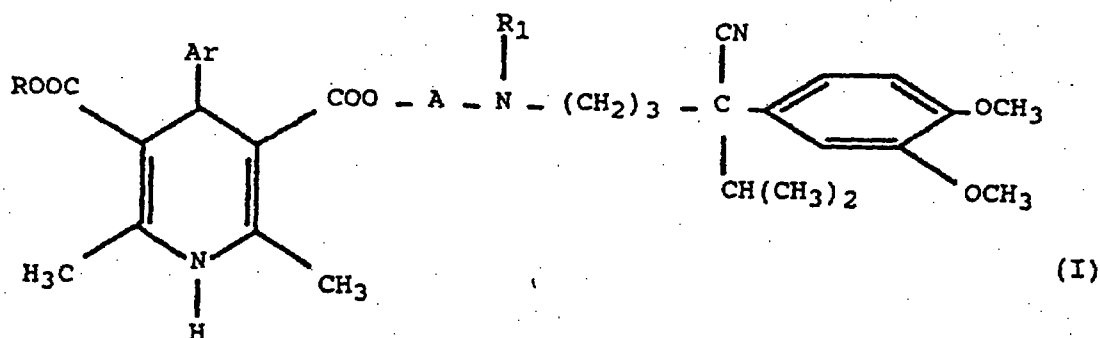
(VIa)

worin Ar, R und A wie in Anspruch 1 definiert sind und X ein Halogenatom bedeutet, mit einer Verbindung der allgemeinen Formel VII wie in Anspruch 1 definiert, kondensiert wird.

Revendications pour les Etats contractants: BE CH/LI DE FR GB IT LU NL SE

1. Un ester de l'acide dihydro-1,4 diméthyle-2,6 (alcoxycarbonyl ou alcoxyalcoxycarbonyl)-3 (phényl substitué)-4 hydroxycarbonyl-5 pyridine, répondant à la formule générale I





dans laquelle

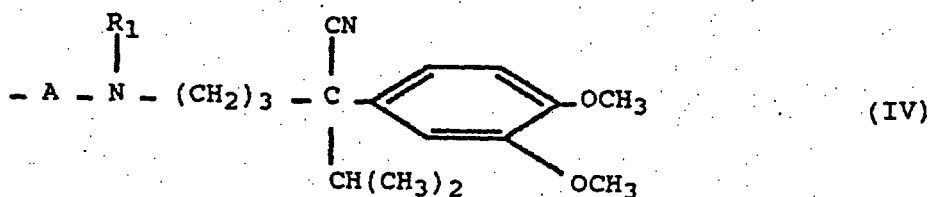
- 15 Ar représente un groupe nitro-3 phényle ou un groupe dichloro-2,3 phényle,
 A représente une chaîne alcoylène droite ou ramifiée, comportant de 2 à 6 atomes de carbone,
 R représente une chaîne alcoyle droite ou ramifiée comportant de 1 à 6 atome(s) de carbone,
 éventuellement mono-substituée par un groupement alcoxy comportant de 1 à 6 atome(s) de carbone, et
 R₁ représente un groupe alcoyle comportant de 1 à 4 atome(s) de carbone,
 20 ou un stéréoisomère ou un sel d'addition acide pharmaceutiquement acceptable d'un tel ester.
 2. Dihydro-1,4 diméthyle-2,6 méthoxycarbonyl-3 (nitro-3 phényle)-4 {[cyano-4 (diméthoxy-3,4
 phényle)-4 diméthyle-5,N hexylamino]-2 éthoxycarbonyl}-5 pyridine ou son chlorhydrate.
 3. Dihydro-1,4 diméthyle-2,6 isopropoxyxycarbonyl-3 (nitro-3 phényle)-4 {[cyano-4 (diméthoxy-3,4
 phényle)-4 diméthyle-5,N hexylamino]-2 méthyl-1 éthoxycarbonyl}-5 pyridine ou son chlorhydrate
 25 hémihydraté.
 4. Dihydro-1,4 diméthyle-2,6 isobutyloxyxycarbonyl-3 (dichloro-2,3 phényle)-4 {[cyano-4 (diméthoxy-3,4
 phényle)-4 diméthyle-5,N hexylamino]-2 méthyl-1 éthoxycarbonyl}-5 pyridine ou son chlorhydrate
 hydraté.
 5. Dihydro-1,4 diméthyle-2,6 (dichloro-2,3 phényle)-4 propoxy-2 éthoxycarbonyl-3 {[cyano-4
 30 (diméthoxy-3,4 phényle)-4 diméthyle-5,N hexylamino]-2 méthyl-1 éthoxycarbonyl}-5 pyridine ou son
 chlorhydrate hydraté.
 6. Un procédé pour la préparation d'un ester selon la revendication 1, ledit procédé comprenant l'étape
 de condensation d'un composé de formule générale II



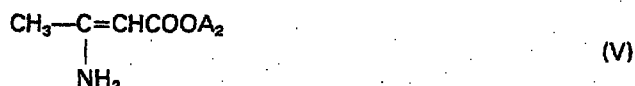
dans laquelle Ar est défini comme dans la revendication 1 sur un composé de formule générale III



dans laquelle A₁ représente soit (a) un groupe R comme défini dans la revendication 1, soit (b) un groupe de
 formule générale IV

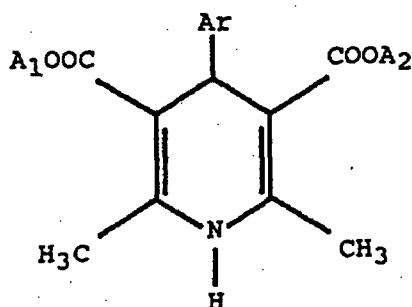


dans laquelle A et R₁ sont définis comme dans la revendication 1 soit enfin (c) un groupe de formule
 générale -AX dans laquelle A est défini comme dans la revendication 1 et X représente un atome
 55 d'halogène; l'étape de la réaction du produit résultant de cette condensation avec un composé de formule
 générale V



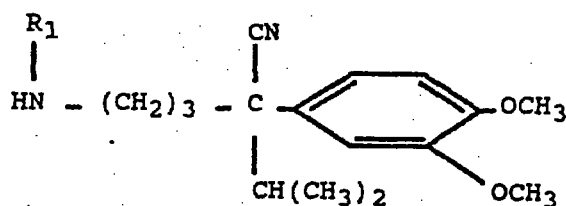
dans laquelle si A₁ représente le groupe défini en (a), A₂ représente l'un des groupes définis en (b) et (c) et si
 A₁ représente l'un des groupes définis en (b) et (c), A₂ représente le groupe défini en (a), pour donner un
 composé de formule générale VI





(VI)

dans laquelle A_1 et A_2 sont définis comme dans la présente revendication et Ar est défini comme dans la revendication 1, et si l'un des groupes A_1 et A_2 représente un groupe défini en (c) l'étape de la réaction du composé de formule générale VI avec un dérivé de la cyano-4-(diméthoxy-3,4 phényl)-4-méthyl-5-hexylamine de formule générale VII



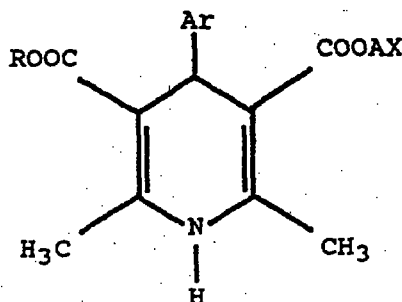
(VII)

dans laquelle R_1 est défini comme dans la revendication 1.

7. Un procédé selon la revendication 6 dans laquelle A_1 représente un groupe de formule $-AX$ et A_2 représente un groupe R.

8. Un procédé selon la revendication 6 dans laquelle A_1 représente un groupe de formule générale IV et A_2 représente un groupe R.

9. Un procédé pour la préparation d'un ester selon la revendication 1, le procédé comprenant l'étape de la condensation d'un dérivé de la pyridine de formule générale VIa



(VIa)

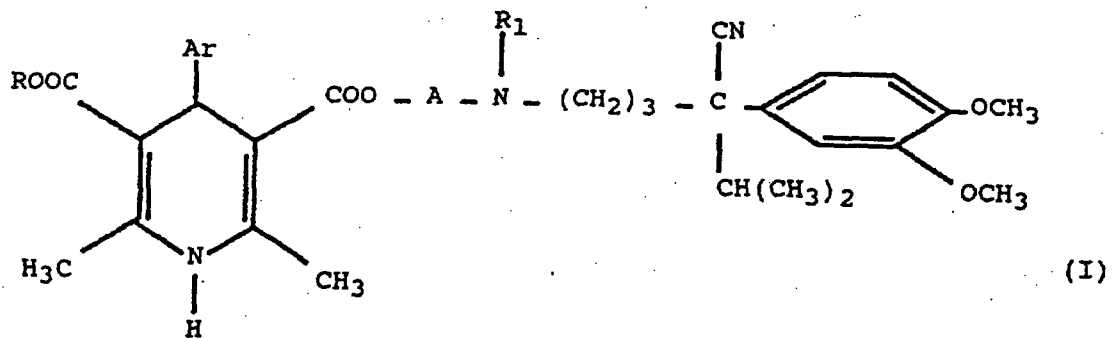
dans laquelle Ar, R et A sont définis comme dans la revendication 1 et X représente un atome d'halogène, avec un composé de formule générale VII défini comme dans la revendication 6.

10. Une composition pharmaceutique comprenant un ester selon l'une des revendications 1 à 5 ou l'un de ses sels d'addition acide pharmaceutiquement acceptables associé à un diluant ou un excipient pharmaceutiquement acceptable.

Revendications pour l'Etat contractant: AT

1. Un procédé pour la préparation d'un ester de l'acide dihydro-1,4 diméthyle-2,6 (alcoyrcarbonyl ou alcoxyalcoyrcarbonyl)-3 (phényl substitué)-4 hydroxycarbonyl-5 pyridine répondant à la formule générale I





dans laquelle

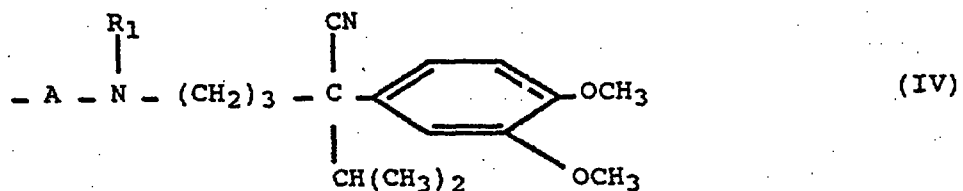
15 Ar représente un groupe nitrophényl-3 ou un groupe dichloro-2,3 phényle,
 A représente une chaîne alcoylène droite ou ramifiée comportant de 2 à 6 atomes de carbone,
 R représente une chaîne alcoyle droite ou ramifiée comportant de 1 à 6 atome(s) de carbone,
 éventuellement mono-substituée par un groupement alcoxy comportant de 1 à 6 atome(s) de carbone, et
 20 R₁ représente un groupe alcoyle comportant de 1 à 4 atome(s) de carbone,
 ledit procédé comprenant l'étape de condensation d'un composé de formule générale II



dans laquelle Ar est défini comme dans la présente revendication sur un composé de formule générale III



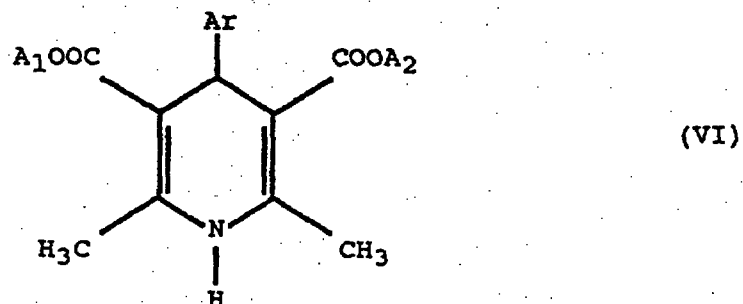
dans laquelle A₁ représente soit (a) un groupe R comme défini dans la présente revendication, soit (b) un groupe de formule générale IV



40 dans laquelle A et R₁ sont définis comme dans la présente revendication soit enfin, (c) un groupe de formule générale -AX dans laquelle A est défini comme dans la présente revendication et X représente un atome d'halogène; l'étape de la réaction du produit résultant de cette condensation avec un composé de formule générale V



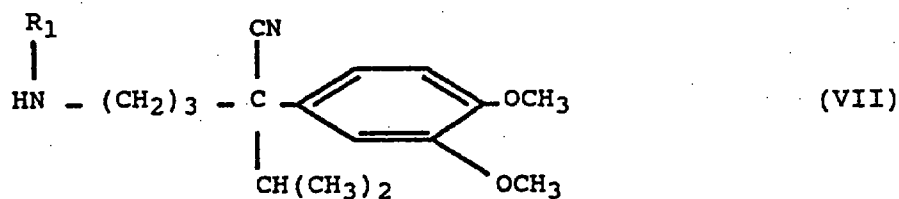
50 dans laquelle si A₁ représente le groupe défini en (a), A₂ représente l'un des groupes définis en (b) et (c) et si A₁ représente l'un des groupes définis en (b) et (c), A₂ représente le groupe défini en (a), pour donner un composé de formule générale VI



65 dans laquelle A₁, A₂ et Ar sont définis comme dans la présente revendication, et si l'un des groupes A₁ et A₂ représente un groupe défini en (c), l'étape de la réaction du composé de formule générale VI avec un dérivé



de la cyano-4 (diméthoxy-3,4 phényl)-4-méthyl-5-hexylamine de formule générale VII

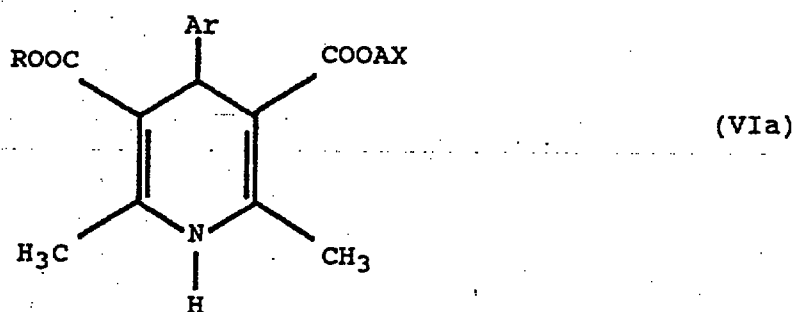


dans laquelle R_1 est défini comme dans la présente revendication.

2. Un procédé selon la revendication 1 dans laquelle A_1 représente un groupe de formule $-\text{AX}$ et A_2 représente un groupe R .

3. Un procédé selon la revendication 1 dans laquelle A_1 représente un groupe de formule générale IV et A_2 représente un groupe R .

4. Un procédé pour la préparation d'un ester de formule générale I défini comme dans la revendication 1, le procédé comprenant l'étape de condensation d'un dérivé de la pyridine de formule générale VIa



dans laquelle Ar , R et A sont définis comme dans la revendication 1 et X représente un atome d'halogène, sur un composé de formule générale VII défini comme dans la revendication 1.

