PATENT SPECIFICATION (11) 1 516 793

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(54) A 1,4-DIHYDROPYRIDINE-3.5-DICARBOXYLIC ACID DI-ESTER DERIVATIVE, SEVERAL PROCESSES FOR ITS PREPARATION, AND ITS USE AS A CORONARY THERAPEUTIC AGENT

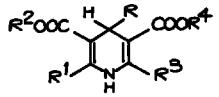
(71) We, BAYER AKTIENGESELLSCHAFT, a body corporate, organised under the laws of Germany, of Leverkusen, Bayerwerk, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to the new isobutyl methyl 1,4-dihydro-2.6-dimethyl-4-(2-nitrophenyl)-3.5-pyridinedicarboxylate, several processes for its preparation and its use as a coronary therapeutic agent.

It has already been disclosed that diethyl-1.4-dihydro-2.6-dimethyl-4-phenyl-3.5-pyridinedicarboxylate is obtained when benzylideneacetoacetic acid ethyl ester is reacted with β-aminocrotonic acid ethyl ester or acetoacetic acid ethyl ester and ammonia (Knoevenagel, Ber. dtsch. chem. Ges. *31*, 743 (1898)). Further, it is known that certain 1,4-dihydropyridines exhibit interesting pharmacological properties (F. Bossert and W. Vater, Naturwissenschaften *58*, 578 (1971)).

Further, it has been disclosed, in the applicant's earlier German Offenlegungsschriften (German Published Specifications) 2,117,571 and 2,117,573 that similar dihydropyridines can be used as coronary agents.

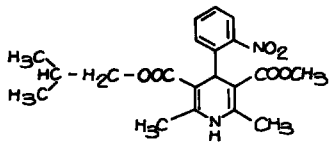
Our British Patent Specification No. 1,358,951 describes and claims unsymmetrical 1,4-dihydropyridine dicarboxylic acid ester compounds of the general formula:—



in which

R is a phenyl radical carrying at least one nitro, nitrile, azido, or $-SO_n-$alkyl group [*n* being 0, 1 or 2] as substituent and optionally also carrying at least one alkyl or alkoxy group or halogen atom as substituent, the total number of substituents carried by R being at most three;
or a naphthyl, quinolyl, isoquinolyl, pyridyl, pyrimidyl, thenyl, furyl or pyrryl radical optionally carrying at least one alkyl or alkoxy group or halogen atom as a substituent;
R^1 and R^3 are identical or different and are each a hydrogen atom or a straight- or branched-chain alkyl group; and
R^2 and R^4 are different straight- or branched-chain or cyclic, saturated or unsaturated hydrocarbon radicals, the carbon chain of each of which can be interrupted by one or two oxygen atoms and can carry a hydroxyl group as a substituent.

According to the present invention, we now provide isobutylmethyl 1.4-dihydro-2.6-dimethyl-4-(2-nitrophenyl)-3.5-pyridine dicarboxylate of the formula (I).

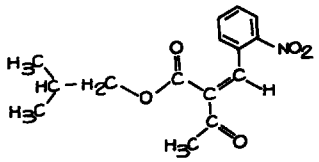


(I)

The compound of the invention exhibits a very powerful and long-lasting coronary action.

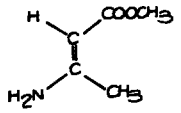
Further, the new active compound of the formula (I) is obtained when

A) 2'-nitrobenzylideneacetoacetic acid isobutyl ester (formula (II))



(II)

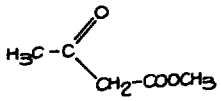
is reacted with β-aminocrotonic acid methyl ester (formula III))



(III)

if appropriate in the presence of water or inert organic solvents, or

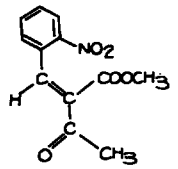
B) 2'-nitrobenzylideneacetoacetic acid isobutyl ester (formula (II)) is reacted with acetoacetic acid methyl ester (formula (IV))



(IV)

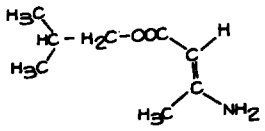
and ammonia, if appropriate in the presence of water or inert organic solvents, or

C) 2'-nitrobenzylideneacetoacetic acid methyl ester (formula (V))



(V)

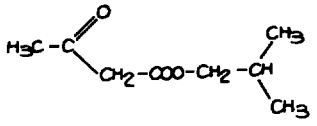
is reacted with β-aminocrotonic acid isobutyl ester (formula (VI))



(VI)

if appropriate in the presence of water or inert solvents, or

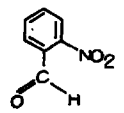
D) 2'-nitrobenzylideneacetoacetic acid methyl ester (formula (V)) is reacted with acetoacetic acid isobutyl ester (formula (VII))



(VII)

and ammonia, if appropriate in the presence of water or inert organic solvents, or

E) β-aminocrotonic acid isobutyl ester (Formula (VI)) is reacted with 2-nitrobenzaldehyde (formula (VIII))



(VIII)

and acetoacetic acid methyl ester (formula (IV)), if appropriate in the presence of water or inert organic solvents, or

F) β-aminocrotonic acid methyl ester (formula (III)) is reacted with 2-nitrobenzaldehyde (formula (VIII)) and acetoacetic acid isobutyl ester (formula (VII)) as such or in water or in inert organic solvents.

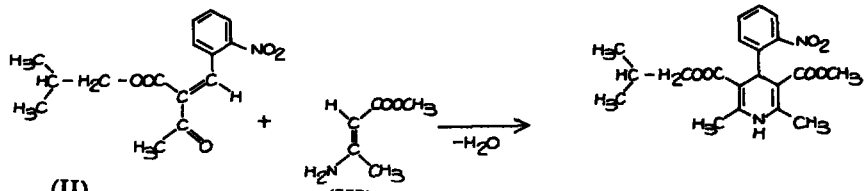
Surprisingly, the substance according to the invention, of the formula (I), has a particularly strong coronary action.

Amongst the series of the similar 1,4-dihydropyridine derivatives known from the state of the art, such a strong and long-lasting coronary action, especially after enteral administration, has hitherto not been demonstrated. In addition, the compound according to the invention is less unstable to light than corresponding dihydropyridines which are known from the state of the art. It thus represents in respect of these special properties, an enrichment of pharmacy.

The compound according to the invention is chiral and can exist in stereoisomeric forms which have an image/relationship to each other (enantiomers, antipodes). These can, in turn again occur in different conformations. Both the racemic form and the antipodes are included within the present invention.

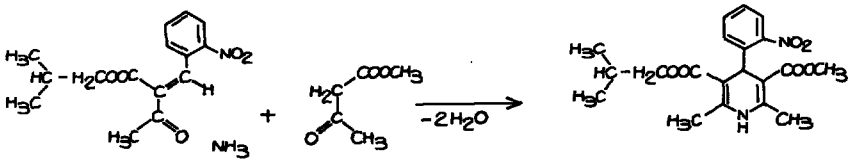
Depending on the nature of the starting materials used, the synthesis of the compound according to the invention can be represented by the following equations:

A)



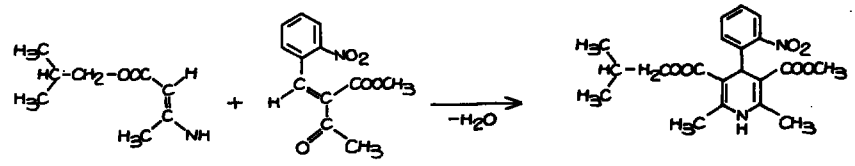
(II) (III)

B)

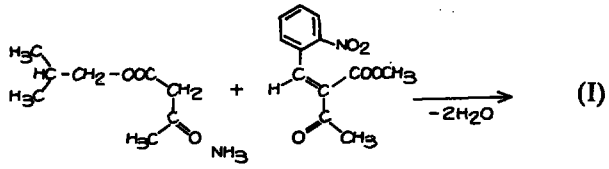


(II) (IV)

C)

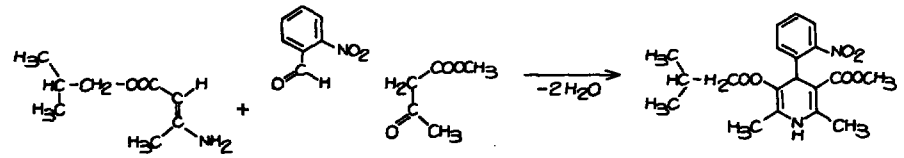


(VI) (V)

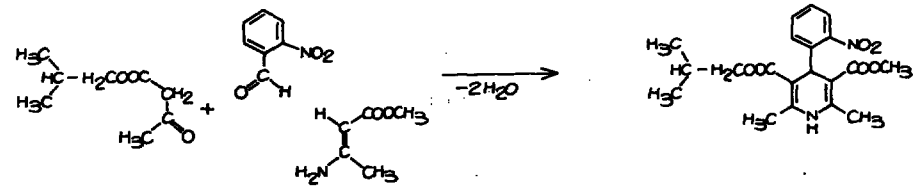


(VII) (V) (I)

E)



F)



The substances of the formulae (II)—(VIII) used as starting materials are known from the literature or can be prepared in accordance with methods known from the literature (literature: Org. Reactions XV, 204 et seq. (1967); A. C. COPE, J. Amer. chem. Soc. *67*, 1,017 (1945); and Houben-Weyl, Methoden der Organ. Chemie (Methods of Organic Chemistry) VII/4, 230 et seq. (1968)).

In carrying out processes A—F according to the invention the compounds participating in the reaction are in each case employed approximately in equimolar amounts. The ammonia used is advantageously added in excess.

Diluents which can be used are water and all inert organic solvents. These preferentially include alcohols such as ethanol and methanol, ethers such as dioxane or diethyl ether, or glacial acetic acid, pyridine, dimethylformamide, dimethylsulphoxide or acetonitrile.

The reaction temperatures can be varied within a substantial range. In general, the reaction is carried out at a temperature of from 20 to 200°C, preferably at 50 to 120°C and especially at the boiling point of the solvent.

The reaction can be carried out under normal pressure but also under elevated pressure. In general, normal pressure is used.

The preceding processes of preparation are given solely for clarification and the preparation of the compound (I) is not restricted to these processes; instead, any modification of these processes can be used in the same manner for the preparation of the compound (I).

The compound according to the invention is a substance which can be used as a medicament. When used enterally or parenterally it produces a powerful and long-lasting increase in myocardial perfusion and can therefore be employed for the prophylaxis and treatment of ischaemic heart diseases, especially if they are combined with hypertension.

The present invention provides a pharmaceutical composition containing as active ingredient the compound of the invention in admixture with a solid or liquefied gaseous diluent, or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 (preferably less than 350) except in the presence of a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient the compound of the invention in the form of a sterile or isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising the comound of the invention.

The invention also provides a medicament in the form of tablets (including lozenges and granules), dragees, capsules, pills, ampoules or suppositories comprising the compound of the invention.

"Medicament" as used in this Specification means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as used in this Specification means physically discrete coherent units suitable for medical administration each containing a daily dose or a multiple (up to four times) or submultiple (down to a fortieth) of a daily dose of the compound of the invention in association with a carrier and/or enclosed within an envelope. Whether the medicament contains a daily dose or, for example, a half, a third, or a quarter of a daily dose will depend on whether the medicament is to be administered once or, for example, twice, three times or four times a day respectively.

The pharmaceutical compositions according to the invention may, for example, take the form of suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granules or powders.

The diluents to be used in pharmaceutical compositions (e.g. granulates) adapted to be formed into tablets, dragees, capsules and pills include the following: (a) fillers and extenders, e.g. starch, sugars, mannitol, and silicic acid; (b) binding agents, e.g. carboxymethyl celllose and other cellulose derivatives, alginates, gelatine and polyvinyl pyrrolidone; (c) moisturizing agents, e.g. glycerol; (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium bicarbonate; (e) agents for retarding dissolution e.g. paraffin; (f) resorption accelerators, e.g. quaternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g. kaolin and bentonite; (i) lubricants, e.g. talc, calcium and magnesium stearate and solid polyethylene glycols.

The tablets, dragees, capsules and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, of polymeric substances waxes.

The ingredient can also be made up in microencapsulated form together with one or several of the abovementioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble or water-insoluble diluents, such as polyethylene glycols and fats (e.g. cocoa oil and high ester [e.g. C_{14}-alcohol with C_{16}-fatty acid]) or mixture of these diluents.

The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above-mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils [for example ground nut oil], glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

For parenteral administration, the solutions and emulsions should be sterile, and, if appropriate, blood-isotonic.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols polyoxyethylene sorbite and sorbitane esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures thereof.

All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives as well as perfumes and flavouring additions (e.g. peppermint oil and eucalyptus oil) and sweetening agents (e.g. saccharin).

The pharmaceutical compositions according to the invention in general contain from 0.1 to 99.5, more usually from 0.5 to 95% of the active ingredient by weight of the total composition.

In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds.

Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent.

The discrete coherent portions constituting the medicament according to the invention will generally be adapted, by virtue of their shape or packaging, for medical administration, and may be, for example, any of the following: tablets, (including lozenges and granules), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The preferred daily dose for administration of the medicaments of the invention is 0.005 mg to 1 g of active ingredient.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

This invention further provides a method of combating (including prevention, relief and cure of) the above-mentioned diseases in non-human animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

Preferably, the compound of the invention is administered in an amount of from 0.0001 to 10 mg per kg body weight per day.

It is envisaged that these active compounds will be administered perorally, enterally, parenterally (for example intramuscularly, intraperitoneally or intravenously), rectally, preferably enterally or parenterally, especially perlingually or intravenously. Preferred pharmaceutical compositions and medicaments are therefore those adapted for enteral or parenteral administration.

In general it has proved advantageous, in the case of intravenous administration, to administer amounts of 0.0001 to 1 mg/kg, preferably 0.0005 to 0.01 mg/kg of body weight daily to achieve effective results, whilst in the case of enteral administration the dosage is 0.0005 to 10 mg/kg, preferably 0.001 to 0.1 mg/kg of body weight daily.

Nevertheless it can at times be necessary to deviate from the amounts mentioned and in particular to do so as a function of the body weight of the test animals or of the nature of the administration route, but also because of the species of animal and its individual behaviour towards the medicine or interval at which it is administered. Thus it may suffice, in some cases, to manage with less than the above-mentioned minimum amount whilst in other cases the upper limit mentioned must be exceeded. Where major amounts are administered it can be advisable to divide these into several individual administrations over the course of the day. The same dosage range is envisaged for administration in human medicine. Here, again, the general sense of the above comments applies.

To demonstrate the perfusion-assisting action in heart muscle, the substance was administered to dogs and the myocardial perfusion was measured with the aid of an electromagnetic flow meter.

The substance increases the perfusion of the heart, after intravenous and enteral administration. A particular advantage is its rapid and complete resorption after perlingual administration, so that the substance has a strong and long-lasting action even when used in this way, in very low doses.

The results of the investigations on dogs after sub-lingual administration are shown in the table which follows.

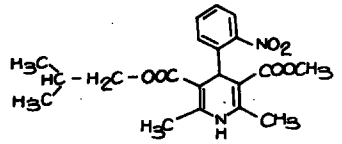
Dose, mg/kg, administered sublingually	Increase in heart perfusion by %	Increase in heart perfusion half-life of the duration of action, in minutes	Lowering of blood pressure in %
0.003	23	100	Ø
0.01	46	133	5
0.1	142	184	13

It can be seen that the compound according to the invention increases the perfusion of the heart muscle, as a function of the dose, and, surprisingly, the effective doses are very low. The action of the substance starts a few minutes after sublingual administration and lasts, depending on the dose, for 2 to 6 hours (in the table, the half-life of the action is given as a more accurate yardstick of the duration of action). At the same time, it causes a slight and equally long-lasting

lowering of the blood pressure, which as a rule represents an additional advantage in the therapy of coronary illnesses.

The compound according to the invention is therefore suitable for the prophylaxis and therapy of acute and chronic ischaemic heart diseases in the broadest sense. The substance can be used as an agent for the prophylaxis and therapy of angina pectoris complaints and attacks, and for the therapy of conditions after a heart infarct. It is particularly suitable for the therapy of cases in which one of the abovementioned heart diseases is combined with hypertension.

The following Examples illustrate the alternative methods of preparation of isobutyl methyl 1.4-dihydro-2.6-dimethyl-4-(2-nitrophenyl)-3.5-pyridine dicarboxylate in accordance with the invention.



Example 1 (Process A).

14.6 g (50 mmols) of 2'-nitrobenzylideneacetoacetic acid isobutyl ester together with 5.8 g (50 mmols) of β-aminocrotonic acid methyl ester, in 80 ml of ethanol, were heated for 20 hours under reflux. After the reaction mixture had cooled, the solvent was distilled off in vacuo and the oily residue was mixed with a little ethanol. The product crystallised completely after a short time and was filtered off and recrystallised from ethanol. Melting point: 151—152°C yield: 15.2 g (78%).

Example 2 (Process B).

14.6 g (50 mmols) of 2'-nitrobenzylideneacetoacetic acid isobutyl ester together with 5.8 g (50 mmols) of acetoacetic acid methyl ester and 6 ml (88 mmols) of a 25 per cent strength aqueous ammonia solution, in 80 ml of methanol, were heated for 24 hours under reflux. The solvent was then distilled off in vacuo and the oily residue was mixed with a little ethanol. The product crystallised completely after a short time and was filtered off and recrystallised from ethanol.

Melting point: 150—152°C, yield: 11.9 g (61%).

Example 3 (Process C).

12.5 g (50 mmols) of 2'-nitrobenzylideneacetoacetic acid methyl ester together with 7.85 g (50 mmols) of β-aminocrotonic acid isobutyl ester in 80 ml of ethanol were heated for 20 hours under reflux. After the reaction mixture had cooled, the solvent was distilled off in vacuo and the solid residue was triturated with ether, filtered off and recrystallised from ethanol.

Melting point: 150—152°C, yield: 14.5 (74%).

Example 4 (Process D).

12.5 g (50 mmols) of 2'-nitrobenzylideneacetoacetic acid methyl ester together with 7.85 g (50 mmols) of acetoacetic acid isobutyl ester and 6 ml (88 mmols) of a 25 per cent strength aqueous ammonia solution, in 80 ml of isobutanol, were heated for 15 hours under reflux. After the reaction mixture had cooled, the solvent was distilled off in vacuo. The oily residue crystallised completely overnight and was triturated with ether, filtered off and recrystallised from ethanol.

Melting point: 150—152°C, yield: 10.9 (56%).

Example 5 (Process E).

7.85 (50 mmols) of β-aminocrotonic acid isobutyl ester together with 7.6 g (50 mmols) of 2-nitrobenzaldehyde and 5.8 g (50 mmols) of acetoacetic acid methyl ester in 80 ml of ethanol were heated for 24 hours under reflux. After the reaction mixture had cooled, the solvent was concentrated in vacuo and the solid residue was triturated with ether, filtered off and recrystallised from ethanol.

Melting point: 151—152°C, yield: 14.5 g (75%).

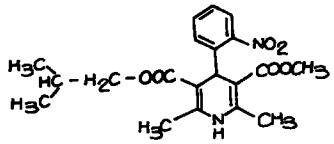
Example 6 (Process F).

5.8 g (50 mmols) of β-aminocrotonic acid methyl ester together with 7.6 g (50 mmols) of 2-nitrobenzaldehyde and 7.85 g (50 mmols) of acetoacetic acid isobutyl

ester, in 80 ml of ethanol, were heated to the boil for 24 hours. The solvent was then distilled off in vacuo and the solid residue was recrystallised from ethanol.
Melting point: 151—152°C, yield: 13.6 g (70%).

WHAT WE CLAIM IS:—

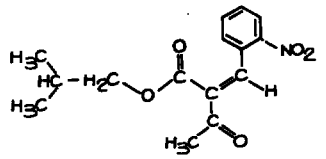
1. Isobutyl methyl 1.4-dihydro-2.6-dimethyl-4-(2-nitrophenyl)-3.5-pyridine-dicarboxylate of the formula (I)



(I)

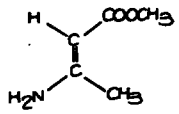
2. A process for preparing isobutyl methyl 1.4-dihydro-2.6-dimethyl-4-(2-nitrophenyl)-3.5-pyridine-dicarboxylate in which

A) 2'-nitrobenzylideneacetoacetic acid isobutyl ester (formula (II))



(II)

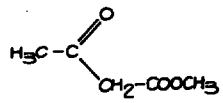
is reacted with β-aminocrotonic acid methyl ester (formula (III))



(III)

if appropriate in the presence of water or inert organic solvents, or

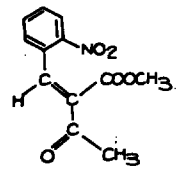
B) 2'-nitrobenzylideneacetoacetic acid isobutyl ester (formula (II)) is reacted with acetoacetic acid methyl ester (formula (IV))



(IV)

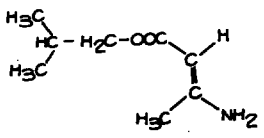
and ammonia, if appropriate in the presence of water or inert organic solvents, or

C) 2'-nitrobenzylideneacetoacetic acid methyl ester (formula (V))



(V)

is reacted with β-aminocrotonic acid isobutyl ester (formula (VI))



(VI)

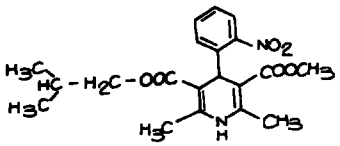
if appropriate in the presence of water or inert solvents, or

ester, in 80 ml of ethanol, were heated to the boil for 24 hours. The solvent was then distilled off in vacuo and the solid residue was recrystallised from ethanol.

Melting point: 151—152°C, yield: 13.6 g (70%).

WHAT WE CLAIM IS:—

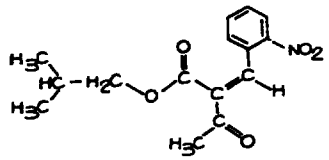
1. Isobutyl methyl 1.4-dihydro-2.6-dimethyl-4-(2-nitrophenyl)-3.5-pyridine-dicarboxylate of the formula (I)



(I)

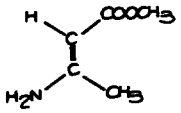
2. A process for preparing isobutyl methyl 1.4-dihydro-2.6-dimethyl-4-(2-nitrophenyl)-3.5-pyridine-dicarboxylate in which

A) 2'-nitrobenzylideneacetoacetic acid isobutyl ester (formula (II))



(II)

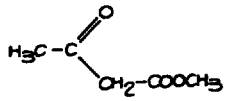
is reacted with β-aminocrotonic acid methyl ester (formula (III))



(III)

if appropriate in the presence of water or inert organic solvents, or

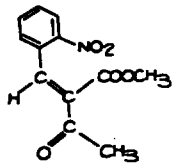
B) 2'-nitrobenzylideneacetoacetic acid isobutyl ester (formula (II)) is reacted with acetoacetic acid methyl ester (formula (IV))



(IV)

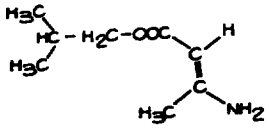
and ammonia, if appropriate in the presence of water or inert organic solvents, or

C) 2'-nitrobenzylideneacetoacetic acid methyl ester (formula (V))



(V)

is reacted with β-aminocrotonic acid isobutyl ester (formula (VI))

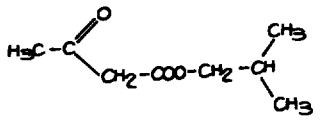


(VI)

if appropriate in the presence of water or inert solvents, or

* C L M S *

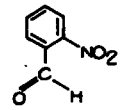
D) 2'-nitrobenzylideneacetoacetic acid methyl ester (formula (V)) is reacted with acetoacetic acid isobutyl ester (Formula (VII))



(VII)

and ammonia, if appropriate in the presence of water or inert organic solvents, or

E) β-aminocrotonic acid isobutyl ester (formula (VI)) is reacted with 2-nitrobenzaldehyde (formula (VIII)) and acetoacetic acid methyl ester



(VIII)

(formula (IV)), if appropriate in the presence of water or inert organic solvents, or

F) β-aminocrotonic acid methyl ester (formula (III)) is reacted with 2-nitrobenzaldehyde (formula (VIII)) and acetoacetic acid isobutyl ester (formula (VII)), as such or in water or in inert organic solvents.

3. A process according to claim 2 wherein the reaction is carried out at a temperature of from 20 to 200°C.

4. A process for the production of a compound according to claim 1 substantially as hereinbefore described in any one of the Examples.

5. A compound according to claim 1 whenever prepared by a process according to any one of claims 2 to 4.

6. A pharmaceutical composition containing as an active ingredient a compound according to claim 1 or 5 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface-active agent.

7. A pharmaceutical composition containing as an active ingredient a compound according to claim 1 or 5 in the form of a sterile or isotonic aqueous solution.

8. A composition according to claim 6 or 7 containing from 0.5 to 95% by weight of the said active ingredient.

9. A medicament in dosage unit form comprising a compound according to claim 1 or 5.

10. A medicament in the form of tablets, pills, dragees, capsules, ampoules, or suppositories comprising a compound according to claim 1 or 5.

11. A method of combating coronary disease in non-human animals which comprises administering to the animals an active compound according to claim 1 or 5 either alone or in admixture with a diluent or in the form of a medicament according to claim 9 or 10.

12. A method according to claim 11 in which the active compound is administered in an amount of from 0.0001 to 10 mg per kg body weight per day.

13. A method according to claim 11 or claim 12 in which the active compound is administered enterally or parenterally.

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