

PATENT SPECIFICATION

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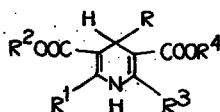
(54) NEW ESTERS, THEIR PRODUCTION, AND THEIR MEDICINAL USE

(71) We, BAYER AKTIENGESSELLSCHAFT, formerly known as Farbenfabriken Bayer Aktiengesellschaft, a body corporate organised under the laws of Germany, of Leverkusen, 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 certain new unsymmetrical 1,4-dihydropyridine-dicarboxylic acid esters, to process for their production, and to their medicinal use, especially as coronary agents.

It has already been disclosed that 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester is obtained if benzylideneacetoacetic acid ethyl ester is reacted with β -aminocrotonic acid ethyl ester or acetoacetic acid ethyl ester and ammonia (Knoevenagel, Ber. 31, 743 (1898)). Symmetrical dihydropyridines have been manufactured by this method, whilst the unsymmetrical esters of the 1,4-dihydropyridines have hitherto not yet become known.

The present invention now provides unsymmetrical 1,4-dihydropyridine-dicarboxylic acid esters of the general formula:—



(I)

in which

R is a phenyl radical carrying at least one nitro, nitrile, azido, or $-\text{SO}_n-$ 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 pyrrol radical optionally carrying at least one alkyl or alkoxy group or halogen atom as a substituent;

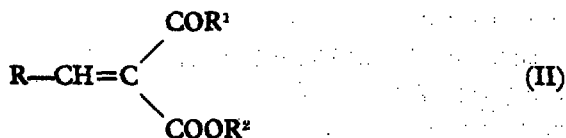
R¹ and R³ are identical or different and are each a hydrogen atom or a straight- or branched-chain alkyl group; and

R² and R⁴ 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.

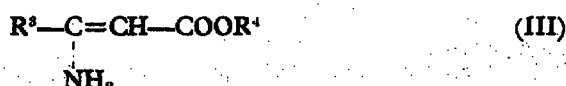
These new compounds display a strong coronary action and anti-hypertensive properties.

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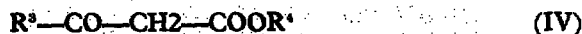
The invention also provides a process for the production of the unsymmetrical 1,4-dihydropyridinedicarboxylic acid ester compounds of general formula (I) in which an ylidene- β -ketocarboxylic acid ester of the general formula:—



is reacted either with an enamino-carboxylic acid ester of the general formula:—



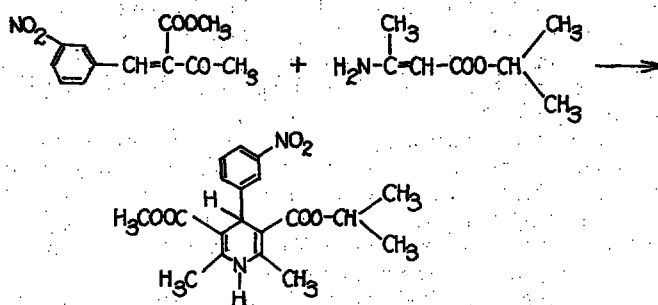
or with ammonia and a β -ketocarboxylic acid ester of the general formula:—



[in which general formulae (II), (III) and (IV) R, R¹, R², R³ and R⁴ are as defined above] in water or an inert organic solvent as diluent.

Surprisingly, the unsymmetrical compounds of the invention show a substantially higher coronary-dilating action than the known symmetrical 1,4-dihydropyridines. The compounds of the invention thus represent an enrichment of pharmacy.

The reaction used in the process of the invention may be illustrated by the following equation, in which 3'-nitrobenzylideneacetoacetic acid methyl ester and β -amino-crotonic acid isopropyl ester are used as starting compounds



In the general formulae (I), (II), (III) and (IV), R preferably represents a phenyl radical which is monosubstituted or disubstituted by one or more nitro, nitrile, azido or SO_n-alkyl groups (n=0—2), especially by nitro or nitrile groups, and which is optionally additionally substituted by one or more alkyl, alkoxy or halogen radicals, preferably by halogen, especially by chlorine, the total number of the substituents being at most 3, preferably 1 or 2; or represents a naphthyl, quinolyl, isoquinolyl, pyridyl, pyrimidyl, thenyl, furyl or pyrrol radical which is optionally substituted by alkyl, alkoxy or halogen; the alkyl and alkoxy groups optionally substituent on R preferably contain 1 or 2 carbon atoms, and halogen is to be understood as fluorine, chlorine or bromine. The abovementioned pyridyl, pyrrol, thenyl and furyl radicals are preferably substituted by an alkyl radical with 1—2 carbon atoms and the pyrimidyl radical is preferably additionally substituted by 1 or 2 methoxy or ethoxy groups. R¹ and R³, which are identical or different, preferably represent hydrogen or a straight-chain or branched alkyl radical with 1—4 carbon atoms, especially the methyl group. R² and R⁴, which must always be different from one another, each represent a straight-chain, branched or cyclic, saturated or unsaturated hydrocarbon radical, preferably with 1—6 carbon atoms, especially an aliphatic hydrocarbon chain with 1—3 carbon atoms, the hydrocarbon chain being optionally interrupted by 1 or 2 oxygen atoms, preferably by one oxygen atom, and/or substituted by a hydroxyl group.

The starting compounds which can be used according to the invention are already known or can be manufactured according to known methods. As examples there may be mentioned:

a) *Ylidene- β -ketocarboxylic acid esters.*

	2'-Nitrobenzylideneacetoacetic acid methyl ester,	
	2'-nitrobenzylideneacetoacetic acid ethyl ester,	
	3'-nitrobenzylideneacetoacetic acid methyl ester,	
5	3'-nitrobenzylideneacetoacetic acid ethyl ester,	5
	3'-nitrobenzylideneacetoacetic acid isopropyl ester,	
	2'-cyanobenzylideneacetoacetic acid methyl ester,	
	2'-cyanobenzylideneacetoacetic acid ethyl ester,	
	2'-cyanobenzylideneacetoacetic acid propyl ester,	
10	2'-cyanobenzylideneacetoacetic acid allyl ester,	10
	4'-nitrobenzylideneacetoacetic acid methyl ester,	
	3'-cyanobenzylideneacetoacetic acid ethyl ester,	
	3'-cyanobenzylideneacetoacetic acid propargyl ester,	
	4'-cyanobenzylideneacetoacetic acid ethyl ester,	
15	3'-nitro-4'-chlorobenzylideneacetoacetic acid t-butyl ester,	15
	3'-nitro-4'-chlorobenzylideneacetoacetic acid isopropyl ester,	
	3'-nitro-6'-chlorobenzylideneacetoacetic acid cyclohexyl ester,	
	3'-nitro-6'-chlorobenzylideneacetoacetic acid ethyl ester,	
	3'-nitro-4'-methoxybenzylideneacetoacetic acid methyl ester,	
20	2'-nitro-4'-methoxybenzylideneacetoacetic acid methyl ester,	20
	2'-cyano-4'-methylbenzylideneacetoacetic acid ethyl ester,	
	2'-azidobenzylideneacetoacetic acid methyl ester,	
	2'-azidobenzylideneacetoacetic acid ethyl ester,	
	3'-azidobenzylideneacetoacetic acid propargyl ester,	
25	4'-azidobenzylideneacetoacetic acid methyl ester,	25
	4'-methylmercaptobenzylideneacetoacetic acid ethyl ester,	
	2'-methylmercaptobenzylideneacetoacetic acid ethyl ester,	
	2'-sulphinylmethylbenzylideneacetoacetic acid methyl ester,	
	2'-sulphonylmethylbenzylideneacetoacetic acid isopropyl ester,	
30	4'-sulphonylmethylbenzylideneacetoacetic acid ethyl ester,	30
	(1'-naphthylidene)acetoacetic acid methyl ester,	
	(1'-naphthylidene)acetoacetic acid ethyl ester,	
	(2'-naphthylidene)acetoacetic acid ethyl ester,	
35	2'-ethoxy-(1'-naphthylidene)acetoacetic acid methyl ester,	35
	2'-methoxy-(1'-naphthylidene)acetoacetic acid ethyl ester,	
	5'-bromo-(1'-naphthylidene)acetoacetic acid methyl ester,	
	(2'-quinolyl)methylideneacetoacetic acid ethyl ester,	
	(3'-quinolyl)methylideneacetoacetic acid ethyl ester,	
40	(4'-quinolyl)methylideneacetoacetic acid ethyl ester,	40
	(8'-quinolyl)methylideneacetoacetic acid ethyl ester,	
	(1'-isoquinolyl)methylideneacetoacetic acid methyl ester,	
	(3'-isoquinolyl)methylideneacetoacetic acid methyl ester,	
	α -pyridylmethylideneacetoacetic acid methyl ester,	
	α -pyridylmethylideneacetoacetic acid ethyl ester,	
45	α -pyridylmethylideneacetoacetic acid allyl ester,	45
	α -pyridylmethylideneacetoacetic acid propargyl ester,	
	α -pyridylmethylideneacetoacetic acid cyclohexyl ester,	
	β -pyridylmethylideneacetoacetic acid β -methoxyethyl ester,	
	β -pyridylmethylideneacetoacetic acid ethyl ester,	
50	γ -pyridylmethylideneacetoacetic acid methyl ester,	50
	6'-methyl- α -pyridylmethylideneacetoacetic acid ethyl ester,	
	4',6'-dimethoxy-(5'-pyrimidyl)-methylideneacetoacetic acid ethyl ester,	
	(2'-thenyl)-methylideneacetoacetic acid ethyl ester,	
	(2'-furyl)-methylideneacetoacetic acid allyl ester,	
55	(2'-pyrryl)-methylideneacetoacetic acid methyl ester,	55
	3'-nitro- α -benzylidenepropionylacetic acid ethyl ester and	
	α -pyridylmethylidenepropionylacetic acid methyl ester.	

b) *B-Ketocarboxylic acid esters.*

Formylacetic acid ethyl ester,
 acetoacetic acid methyl ester,
 acetoacetic acid ethyl ester,
 acetoacetic acid propyl ester,
 acetoacetic acid isopropyl ester,
 acetoacetic acid butyl ester,
 acetoacetic acid t-butyl ester,
 acetoacetic acid (α - or β -)-methoxyethyl ester,
 acetoacetic acid (α - or β -)-ethoxyethyl ester,
 acetoacetic acid (α - or β -)-propoxyethyl ester,
 acetoacetic acid (α - or β -)-hydroxyethyl ester,
 acetoacetic acid allyl ester,
 acetoacetic acid propargyl ester,
 acetoacetic acid cyclohexyl ester,
 propionylacetic acid methyl ester,
 propionylacetic acid ethyl ester,
 propionylacetic acid isopropyl ester and
 butyrylacetic acid ethyl ester.

c) *Enaminocarboxylic acid esters.*

β -Aminocrotonic acid methyl ester,
 β -aminocrotonic acid ethyl ester,
 β -aminocrotonic acid isopropyl ester,
 β -aminocrotonic acid propyl ester,
 β -aminocrotonic acid allyl ester,
 β -aminocrotonic acid butyl ester,
 β -aminocrotonic acid β -methoxyethyl ester,
 β -aminocrotonic acid β -ethoxyethyl ester,
 β -aminocrotonic acid β -propoxyethyl ester,
 β -aminocrotonic acid t-butyl ester,
 β -aminocrotonic acid cyclohexyl ester and
 β -amino- β -ethylacrylic acid ethyl ester.

Possible diluents for use in the process of the invention are water and all inert organic solvents. These include, preferably, alcohols such as ethanol and methanol, ethers such as dioxane and diethyl ether, or glacial acetic acid, pyridine, dimethylformamide, dimethylsulphoxide or acetonitrile.

The reaction temperatures can be varied over a wide range. In general, the reaction is carried out at between about 20 and about 200° C, preferably at the boiling point of the solvent.

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

In carrying out the process according to the invention, the substances participating in the reaction are generally each employed in about molar amounts. The ammonia used is approximately added in excess.

The following may be mentioned individually as new active substances.

2,6-Dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester.

2,6-Dimethyl-4-(2'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester.

2,6-Dimethyl-4-(2'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-methyl ester.

2,6-Dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-methyl ester.

2,6-Dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5- β -methoxyethyl ester.

2,6-Dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-propyl ester-5-isopropyl ester.

2,6-Dimethyl-4-(2'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-allyl ester-5-isopropyl ester.

2,6-Dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-propargyl ester.

2,6-Dimethyl-4-(3'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-methyl ester

2,6-Dimethyl-4-(3'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester.

2-Methyl-6-ethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-carboxylic acid 3-methyl ester-5-ethyl ester.

2 - Methyl - 6 - isopropyl - 4 - (3' - nitrophenyl) - 1,4 - dihydropyridine - 3,5-dicarboxylic acid 3-ethyl ester-5-isopropyl ester.

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5- β -methoxyethyl ester.

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5- β -propoxyethyl ester.

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester.

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-propargyl ester.

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-isopropyl ester.

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-allyl ester.

2,6 - Dimethyl - 4 - (3' - nitro - 6' - chlorophenyl) - 1,4 - di - hydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester.

The new compounds according to the invention can be used as medicines. They have a broad and diverse pharmacological spectrum of action.

In detail, the following main effects were demonstrable in animal experiments:

1) On parenteral and oral, preferably perlingual, administration the new compounds give rise to a distinct and long-lasting dilation of the coronary vessels. This action on the coronary vessels is boosted by a simultaneous nitrite-like effect of reducing the load on the heart. Both as regards the absolute intensity of action and as regards perlingual resorption the new compounds are distinctly superior to the known symmetrical dihydropyridinecarboxylic acid esters. They influence or modify the heart metabolism in the sense of a saving of energy.

2) The excitability of the impulse formation and stimulus conduction system in the heart is reduced so that at therapeutic doses a detectable anti-fibrillation action results.

3) The tone of the smooth vascular muscle is greatly reduced under the action of the compounds.

4) The new compounds reduce the blood pressure of normotonic and hypertonic animals and can hence be used as anti-hypertensive agents.

5) The new compounds possess a strong muscular-spasmolytic action which manifests itself on the smooth muscle of the stomach, intestinal tract, urogenital tract and respiratory system.

The new compounds prepared in the preparative Examples had detectable coronary effects at the following doses:

	Compound of Example				Coronary effect at			
				1		0.001	mg/kg i.v.	
				2		0.001	mg/kg i.v.	
				3		0.005	mg/kg i.v.	
				4		0.001	mg/kg i.v.	
5				5		0.001	mg/kg i.v.	5
				6		0.005	mg/kg i.v.	
				7		0.01	mg/kg i.v.	
				8		0.005	mg/kg i.v.	
				9		0.01	mg/kg i.v.	
10				10		0.005	mg/kg i.v.	10
				11		0.005	mg/kg i.v.	
				12		0.01	mg/kg i.v.	
				13		0.001	mg/kg i.v.	
				14		0.0005	mg/kg i.v.	
15				15		0.003	mg/kg i.v.	15
				16		0.1	mg/kg i.v.	
				17		0.02	mg/kg i.v.	
				18		0.01	mg/kg i.v.	
				19		0.01	mg/kg i.v.	
20				20		0.01	mg/kg i.v.	20
				21		0.005	mg/kg i.v.	
				22		0.005	mg/kg i.v.	
				24		0.005	mg/kg i.v.	
				25		0.005	mg/kg i.v.	
25				26		0.005	mg/kg i.v.	25
				27		3	mg/kg i.v.	
				28		0.05	mg/kg i.v.	
				29		0.1	mg/kg i.v.	
				30		0.1	mg/kg i.v.	
30				31		0.05	mg/kg i.v.	30
				32		0.1	mg/kg i.v.	
				33		0.2	mg/kg i.v.	
				34		0.05	mg/kg i.v.	
				35		0.01	mg/kg i.v.	
35				36		0.2	mg/kg i.v.	35
				38		0.2	mg/kg i.v.	
				39		0.2	mg/kg i.v.	
				40		0.05	mg/kg i.v.	
				41		3	mg/kg i.v.	
40				42		0.005	mg/kg i.v.	40
				43		0.001	mg/kg i.v.	
				44		2	mg/kg i.v.	
				45		0.1	mg/kg i.v.	
				46		0.1	mg/kg i.v.	
45				47		0.5	mg/kg i.v.	45
				48		0.01	mg/kg i.v.	
				49		0.1	mg/kg i.v.	
				50		0.01	mg/kg i.v.	
50				51		0.5	mg/kg i.v.	50
				52		0.01	mg/kg i.v.	
				53		0.005	mg/kg i.v.	

The following Table shows the toxicity towards mice (expressed as DL_{50} in terms of mg. active compound perorally administered per kg. body weight), and minimum dosage (expressed as mg. active compound perorally administered per kg. body weight) at which a depression of the blood pressure appeared in hypertensive rats, for the new compounds according to the invention the preparation of which is described in the preparative Examples.

Compound of Example:-	Toxicity (Mouse) DL ₅₀ mg/kg p.o.	Blood pressure effect (hypertensive rat) mg/kg p.o.
1	3000	from 0.3
2	800	from 1.0
3	2000	from 1.0
4	630	from 3.1
5	3000	from 0.03
6	2000	from 10.0
7	800	from 3.1
8	3000	from 1.0
9	1000	from 3.1
10	3000	from 1.0
11	800	from 3.1
12	3000	from 1.0
13	2000	from 3.1
14	200	from 0.3
15	200	from 0.3
16	3000	
17	3000	from 1.0
18	3000	from 3.1
19	3000	from 1.0

Compound of Example:-	Toxicity (Mouse) DL ₅₀ mg/kg p.o.	Blood pressure effect (hyperten- sive rat) mg/kg p.o.
20	3000	from 1.0
21	2000	from 1.0
22	200	from 1.0
24		from 0.3
25	800	from 3.1
26	1000	from 1.0
27	3000	
28	3000	from 31.5
29	3000	from 10.0
30	2000	from 31.5
31	1000	from 10.0
32	3000	from 31.5
33	2000	from 10.0
34	3000	from 10.0
35	3000	from 10.0
36	3000	from 1.0
38	630	from 31.5
39	2000	from 1.0
41	3000	
42	320	from 1.0
43	3000	from 3.1
45	800	from 100
46	3000	from 10.0

Compound of Example:-	Toxicity (Mouse) DL ₅₀ mg/kg p.o.	Blood pressure effect (Hyperten- sive rat) mg/kg p.o.
47	3000	from 100
50	1000	from 0.3
51	2000	from 1.0

As stated above, the invention also relates to the use in human and veterinary medicine of the new unsymmetrical 1,4-dihydro-pyridinecarboxylic acid ester compounds of the invention.

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

The invention also provides a medicament in dosage unit form comprising a compound of the invention either alone or in admixture with a diluent.

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

"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 portions suitable for medical administration each containing a daily dose or a multiple (up to four times) or sub-multiple (down to a fortieth) of a daily dose of the compound of the invention. 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 ointments, gels, pastes, creams, sprays (including aerosols), lotions, 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 composition (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 cellulose 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. quarternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol mono-stearate; (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 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 or waxes.

The ingredient can also be made up in micro-encapsulated form together with one or several of the above-mentioned 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 esters [e.g. C₁₄-alcohol and C₁₈-fatty acid]) or mixtures of these diluents.

The pharmaceutical compositions which are ointments, pastes, creams and gels can for example contain the usual diluents, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures of these substances.

The pharmaceutical compositions which are powders and sprays can for example contain the usual diluents, e.g. lactose, talc, silicic acid, aluminium hydroxide, calcium silicate, and polyamide powder or mixtures of these substances. Aerosol sprays can for example contain the usual propellants, e.g. chlorofluorohydrocarbons.

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 preferably contain about 0.1 to 99.5, more preferably from about 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 according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Any diluent in the medicaments of the present invention may be any of these 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 (whether in dosage unit form or not) 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 intravenous administration of the medicaments of the invention is 0.0001 to 1 mg of active ingredient per kg. body weight, preferably 0.0005 to 0.1 mg/kg body weight. For oral administration the preferred daily dose is 0.005 to 10 mg/kg. body weight, preferably 0.05 to 5 mg/kg body weight.

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 for lowering blood pressure in non-human animals, which comprises administering to the animal a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

It is envisaged that these active compounds will be administered in any of the customary ways, but preferably perorally or parenterally (for example intramuscularly, intraperitoneally or intravenously) and especially perlingually or intravenously. Preferred pharmaceutical compositions and medicaments are therefore those adapted for perlingual and intravenous administration. Administration in the method of the invention is preferably intravenous or perlingual.

It can at times be necessary to deviate from the above-mentioned dosage rates,

and in particular to do so as a function of the nature and body weight of the human or animal subject to be treated, the individual reaction of this subjection to the treatment, the type of formulation in which the active ingredient is administered and the mode in which the administration is carried out, and the point in the progress of the disease or interval at which it is to be administered. Thus it may in some case suffice to use less than the above mentioned minimum dosage, whilst other cases the upper limit mentioned must be exceeded to achieve the desired results. Where larger amounts are administered it can be advisable to divide these into several individual administrations over the course of the day.

Preparative Examples.

Example 1.

Boiling a solution of 13.4 g of 3'-nitrobenzylideneacetoacetic acid ethyl ester and 5.8 g of β -amino-crotonic acid methyl ester in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester of melting point 158° C (from ethanol). Yielded 67% of theory.

Example 2.

Heating a solution of 12.7 g of 3'-nitro-benzylideneacetoacetic acid methyl ester and 7.2 g of β -amino-crotonic acid propyl ester in 50 ml of methanol for 8 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester of melting point 147° C (from ethanol). Yield 70% of theory.

Example 3.

Boiling a solution of 14.0 g of 3'-nitro-benzylideneacetoacetic acid allyl ester and 5.8 g of β -amino-crotonic acid methyl ester in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-allyl ester of melting point 110° C (from ethylacetate/petroleum ether). Yield 63% of theory.

Example 4.

Boiling a solution of 12.7 g of 3'-nitro-benzylideneacetoacetic acid methyl ester, 7.0 g of acetoacetic acid propargyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-propargyl ester of melting point 111—113° C (from petroleum ether/ethyl acetate). Yield 70% of theory.

Example 5.

Heating a solution of 13.4 g of 3'-nitrobenzylideneacetoacetic acid ethyl ester and 7.2 g of β -aminocrotonic acid isopropyl ester in 50 ml of isopropanol for 10 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-isopropyl ester of melting point 148° C (from ethanol). Yield 60% of theory.

Example 6.

Heating a solution of 13.4 g of 3'-nitrobenzylideneacetoacetic acid ethyl ester, 9.2 g of acetoacetic acid β -propoxyethyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5- β -propoxyethyl ester of melting point 75° C (from petroleum ether/ethyl acetate). Yield 46% of theory.

Example 7.

Heating a solution of 14.9 g of 3'-nitrobenzylideneacetoacetic acid β -methoxyethyl ester and 6.5 g of β -aminocrotonic acid ethyl ester in 50 ml of methanol for 10 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5- β -methoxyethyl ester of melting point 108° C (from ethanol/water). Yield 51% of theory.

Example 8.

Boiling a solution of 13.4 g of 3'-nitrobenzylideneacetoacetic acid ethyl ester, 7.1 g of acetoacetic acid allyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-allyl ester of melting point 125—126° C (from ethyl acetate/petroleum ether). Yield 55% of theory.

Example 9.

Boiling a solution of 13.4 g of 3'-nitrobenzylideneacetoacetic acid ethyl ester, 7.0 g of acetoacetic acid propargyl ester and 6.0 ml of concentrated ammonia in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-propargyl ester of melting point 132—133° C (from ethanol). Yield 54% of theory.

Example 10.

Boiling a solution of 13.4 g of 3'-nitrobenzylideneacetoacetic acid ethyl ester and 9.2 g of β -aminocrotonic acid cyclohexyl ester in 50 ml of methanol for 8 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-cyclohexyl ester of melting point 135° C (from ethanol/water). Yield 44% of theory.

Example 11.

Heating a solution of 14.2 of 3'-nitrobenzylideneacetoacetic acid isopropyl ester and 7.1 g of β -aminocrotonic acid allyl ester in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-isopropyl ester-5-allyl ester of melting point 96—97° C (from ethanol/water). Yield 58% of theory.

Example 12.

Boiling a solution of 14.1 g of 3'-nitrobenzylideneacetoacetic acid isopropyl ester, 7.0 g of acetoacetic acid propargyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-isopropyl ester-5-propargyl ester of melting point 143.5° C (from ethyl acetate/petroleum ether). Yield 59% of theory.

Example 13.

Boiling a solution of 14.1 g of 3'-nitrobenzylideneacetoacetic acid isopropyl ester, 7.2 g of acetoacetic acid propyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-isopropyl ester of melting point 109—110° C (from ethanol/water). Yield 54% of theory.

Example 14.

Boiling a solution of 12.7 g of 2'-nitrobenzylideneacetoacetic acid methyl ester and 7.1 g of β -aminocrotonic acid isopropyl ester in 50 ml of methanol for 10 hours yielded 2,6-dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester of melting point 174° C (from ethanol). Yield 48% of theory.

Example 15.

Heating a solution of 12.7 g of 2'-nitrobenzylideneacetoacetic acid methyl ester, 7.2 g of acetoacetic acid propyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-propyl ester of melting point 127—128° C (from isopropanol). Yield 54% of theory.

Example 16.

Boiling a solution of 13.4 g of 4'-nitrobenzylideneacetoacetic acid ethyl ester and 5.8 g of β -aminocrotonic acid methyl ester in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(4'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester of melting point 150° C (from ethanol). Yield 85% of theory.

Example 17.

Boiling a solution of 15.2 g of 3'-nitro-6'-chlorobenzylideneacetoacetic acid ethyl ester and 5.8 g of β -aminocrotonic acid methyl ester in 50 ml of methanol for 10 hours yielded 2,6-dimethyl-4-(3'-nitro-6'-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester of melting point 163—164° C (from ethanol/water). Yield 40% of theory.

Example 18.

Heating a solution of 15.2 g of 3'-nitro-6'-chlorobenzylideneacetoacetic acid ethyl ester and 7.2 g of β -aminocrotonic acid isopropylester in 50 ml of methanol for 8 hours yielded 2,6-dimethyl-4-(3'-nitro-6'-chlorophenyl)-1,4-dihydropyridine-3,5-di-

carboxylic acid 3-ethyl ester-5-isopropyl ester of melting point 152° C (from petroleum ether/ethyl acetate). Yield 41% of theory.

Example 19.

5 Heating a solution of 14.5 g of 3'-nitro-6'-chlorobenzylideneacetoacetic acid methyl ester and 7.2 g of β -aminocrotonic acid isopropyl ester in 50 ml of methanol for 10 hours yielded 2,6-dimethyl-4-(3'-nitro-6'-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester of melting point 163° C. Yield 54% of theory. 5

Example 20.

10 Boiling a solution of 13.4 g of 3'-nitrobenzylideneacetoacetic acid ethyl ester, 7.2 g of acetoacetic acid propyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-propyl ester of melting point 131—133° C (from petroleum ether/ethyl acetate). Yield 49% of theory. 10

Example 21.

15 Boiling a solution of 12.2 g of 2'-cyanobenzylideneacetoacetic acid ethyl ester and 5.8 g of β -aminocrotonic acid methyl ester in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(2'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester of melting point 178° C (from ethanol). Yield 65% of theory. 15

Example 22.

20 Heating a solution of 12.2 g of 2'-cyanobenzylideneacetoacetic acid ethyl ester and 7.2 g of β -aminocrotonic acid isopropyl ester in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(2'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-isopropyl ester of melting point 152° C (from ethanol). Yield 49% of theory. 20

Example 23.

25 Boiling a solution of 12.2 g of 2'-cyanobenzylideneacetoacetic acid ethyl ester, 7.1 g of acetoacetic acid allyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(2'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-allyl ester of melting point 148° C (from ethyl acetate/petroleum ether). Yield 24% of theory. 25

Example 24.

30 Boiling a solution of 12.9 g of 2'-cyanobenzylideneacetoacetic acid propyl ester and 5.8 g of β -aminocrotonic acid methyl ester in 50 ml of methanol for 8 hours yielded 2,6-dimethyl-4-(2'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-propyl ester of melting point 188° C (from ethanol). Yield 51% of theory. 30

Example 25.

40 Heating a solution of 11.5 g of 3'-cyanobenzylideneacetoacetic acid methyl ester, 6.5 g of acetoacetic acid ethyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(3'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester of melting point 150° C (from ethanol). Yield 68% of theory. 40

Example 26.

45 Boiling a solution of 12.2 g of 3'-cyanobenzylideneacetoacetic acid ethyl ester and 7.1 g of β -aminocrotonic acid isopropyl ester in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(3'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-isopropyl ester of melting point 133—134° C (from petroleum ether/ethyl acetate). Yield 55% of theory. 45

Example 27.

50 Heating a solution of 12.5 g of 4'-methylmercaptobenzylideneacetoacetic acid methyl ester, 6.5 g of acetoacetic acid ethyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(4'-methylmercaptophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester of melting point 163° C (from ethanol). Yield 60% of theory. 50

Example 28

Boiling a solution of 10.5 g of 2'-thenylmethylideneacetoacetic acid methyl ester and 6.5 g of β -aminocrotonic acid ethyl ester in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(2'-thenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester of melting point 142° C (from methanol). Yield 45% of theory.

Example 29.

Heating a solution of 10.5 g of 2'-thenylmethylideneacetoacetic acid methyl ester and 7.2 g of β -aminocrotonic acid isopropyl ester in 50 ml of methanol for 8 hours yielded 2,5-dimethyl-4-(2'-thenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester of melting point 121—122° C (from ethanol). Yield 41% of theory.

Example 30.

Boiling a solution of 10.9 g of α -pyridylmethylideneacetoacetic acid ethyl ester and 5.8 g of β -aminocrotonic acid methyl ester in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(α -pyridyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester of melting point 199—200° C (from ethanol). Yield 63% of theory.

Example 31.

Heating a solution of 10.2 g of α -pyridylmethylideneacetoacetic acid methyl ester and 7.2 g of β -aminocrotonic acid isopropyl ester in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(α -pyridyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester of melting point 188° C (from ethanol). Yield 40% of theory.

Example 32.

Boiling a solution of 11.6 g of α -pyridylmethylideneacetoacetic acid isopropyl ester, 7.2 g of acetoacetic acid propyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(α -pyridyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-propyl ester-5-isopropyl ester of melting point 153—154° C (from ethyl acetate/petroleum ether). Yield 45% of theory.

Example 33.

Heating a solution of 10.2 g of α -pyridylmethylideneacetoacetic acid methyl ester and 7.0 g of β -aminocrotonic acid propargyl ester in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(α -pyridyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-propargyl ester of melting point 194—195° C (from ethanol). Yield 42% of theory.

Example 34.

Heating a solution of 13.4 g of α -naphthylideneacetoacetic acid ethyl ester and 7.2 g of β -aminocrotonic acid isopropyl ester in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(α -naphthyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-isopropyl ester of melting point 167° C. Yield 38% of theory.

Example 35.

Boiling a solution of 13.4 g of α -naphthylideneacetoacetic acid ethyl ester and 5.8 g of β -aminocrotonic acid methyl ester in 50 ml of methanol for 8 hours yielded 2,6-dimethyl-4-(α -naphthyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-methyl ester of melting point 196—197° C (from ethanol). Yield 45% of theory.

Example 36.

Heating a solution of 12.7 g of 4'-quinolylmethylideneacetoacetic acid methyl ester and 6.5 g of β -aminocrotonic acid ethyl ester in 50 ml of methanol for 8 hours yielded 2,6-dimethyl-4-(4'-quinolyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester of melting point 208° C (from ethanol). Yield 74% of theory.

Example 37.

Boiling a solution of 9.7 g of 2'-pyrrylmethylideneacetoacetic acid methyl ester, 6.5 g of acetoacetic acid ethyl ester and 6 ml of concentrated ammonia in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(2'-pyrryl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester of melting point 239° C (from diethyl ether). Yield 36% of theory.

Example 38.

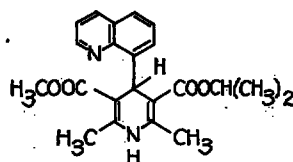
Heating a solution of 10.2 g of β -pyridylmethylideneacetoacetic acid methyl ester and 6.5 g of β -aminocrotonic acid ethyl ester in 50 ml of ethanol for 8 hours yielded 2,6-dimethyl-4-(β -pyridyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester of melting point 191—192° C (from ethanol). Yield 59% of theory.

Example 39.

Boiling a solution of 11.6 g of β -pyridylmethylideneacetoacetic acid isopropyl ester and 5.8 g of β -aminocrotonic acid methyl ester in 50 ml of ethanol for 10 hours yielded 2,6-dimethyl-4-(β -pyridyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester of melting point 164—165° C (from methanol). Yield 52% of theory.

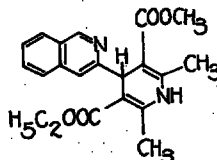
Example 40.

By heating a solution of 12.8 g of quinolyl-8-methylideneacetoacetic acid methyl ester and 7.2 g aminocrotonic acid isopropyl ester in 80 ml ethanol under reflux for 5 hours, 2,6-dimethyl-4-(8'-quinolyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester 5-isopropyl ester of melting point 178—179° C was obtained (alcohol). Yield 69% of theory.



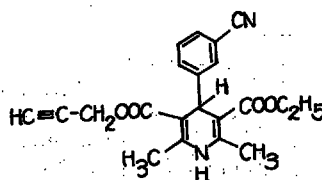
Example 41.

After 8 hours' heating of a solution of 12.8 grams isoquinolyl-3-methylamine acetoacetic acid methyl ester and 6.5 g aminocrotonic acid ethyl ester in 100 ml ethanol, 2,6-dimethyl-4-(3'-isoquinolyl)-3,5-dicarboxylic acid 3-methyl ester 5-ethyl ester of melting point 206° C (ethanol) were obtained. Yield 73% of theory.



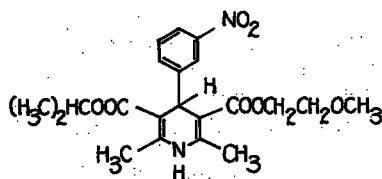
Example 42.

By 10 hours' heating of a solution of 12.2 g 3'-cyanobenzylamine acetoacetic acid ethyl ester and 7.0 g aminocrotonic acid propargyl ester in 80 ml isopropanol, 2,6-dimethyl-4-(3'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methyl ester 5-propargyl ester of melting point 144—145° C (acetic ester/petroleum ether) were obtained. Yield 63% of theory.



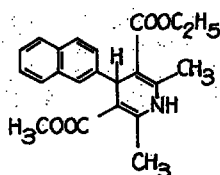
Example 43.

After 8 hours' boiling of a solution of 3.8 grams of 3'-nitro-benzylideneacetoacetic acid isopropyl ester, 8 grams of acetoacetic acid β -methoxyethyl ester and 6 ml conc. ammonia in 80 ml ethanol under reflux, 2,6-dimethyl-4-(3'-nitro-phenyl)-1,4-dihydropyridine 3- β -methoxyethyl ester 5-isopropyl ester of melting point 125° C (petroleum ether/acetic ester) was obtained. Yield 49% of theory.



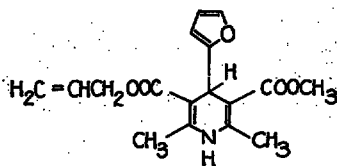
Example 44.

After 7 hours' boiling of a solution of 3.5 g β -naphthylideneacetoacetic acid ethyl ester and 5.8 g aminocrotonic acid methyl ester in 80 ml ethanol, 2,6-dimethyl-4-(β -naphthyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester 5-ethyl ester of melting point 140—142° C (ethanol) was obtained. Yield 47% of theory.



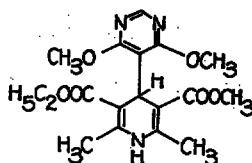
Example 45.

By 8 hours' heating of a solution of 9.7 g 2'-furfurylideneacetoacetic acid methyl ester, 7.1 g acetoacetic acid allyl ester and 6 ml conc. ammonia in 100 ml ethanol, 2,6-dimethyl-4-(2'-furyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester 5-allyl ester of melting point 134—135° C (ethanol) was obtained. Yield 59% of theory.



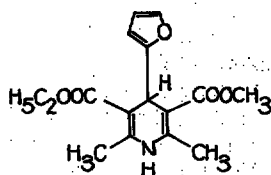
Example 46.

By 10 hours' heating of a solution of 14.0 g 4,6-dimethoxypyrimidine 5-methylideneacetoacetic acid ethyl ester and 5.8 g aminocrotonic acid methylester in 100 ml ethanol, 2,6-dimethyl-4-(4',6'-dimethoxypyrimidyl-5')-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester 5-ethyl ester of melting point 245° C (ethanol/water) was obtained. Yield 68% of theory.



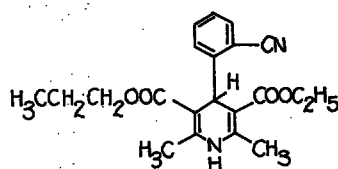
Example 47.

By 8 hours' boiling of a solution of 9.7 g 2'-furfurylideneacetoacetic acid methyl ester and 6.5 g aminocrotonic acid ethyl ester in 80 ml ethanol, 2,6-dimethyl-4-(2'-furyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester 5-ethyl ester of melting point 154—155° C (acetic ester) was obtained. Yield 66% of theory.



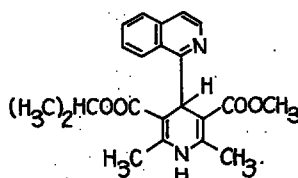
Example 48.

After 10 hours' heating of a solution of 12.2 g 2'-cyanobenzylideneacetoacetic acid ethyl ester, 7.2 g acetoacetic n-propyl ester and 6 ml conc. ammonia in 80 ml ethanol under reflux, 2,6-dimethyl-4-(2'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester 5-n-propyl ester of melting point 156° C (diethyl ether) was obtained. Yield 47% of theory.



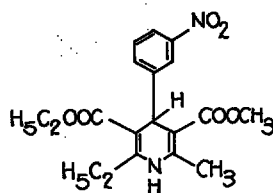
Example 49.

After 6 hours' heating of a solution of 12.8 g isoquinolyl-1-methylideneacetoacetic acid methyl ester and 7.2 g aminocrotonic acid isopropyl ester in 80 ml ethanol, 2,6-dimethyl-4-(1'-isoquinolyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester 5-isopropyl ester of melting point 204° C (ethanol) was obtained. Yield 78% of theory.



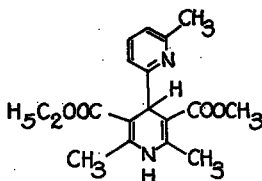
Example 50.

After 8 hours' boiling of a solution of 12.5 g 3'-nitrobenzylideneacetoacetic acid methyl ester and 7.2 g β-ethyl-β-aminoacrylic acid ethyl ester in 70 ml ethanol, 2-methyl-6-ethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester 5-ethyl ester of melting point 123° C (acetic ester/petroleum ether) was obtained. Yield 71% of theory.



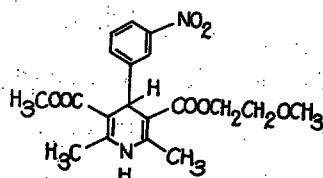
Example 51.

By 8 hours' heating of a solution of 11.7 g 6'-methylpyridyl-2-methylideneacetoacetic acid ethyl ester and 5.8 g aminocrotonic acid methyl ester in 80 ml ethanol, 2,6-dimethyl-4-(6'-methylpyridyl-2')-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester 5-ethyl ester of melting point 162° C (ethanol) was obtained. Yield 62% of theory.



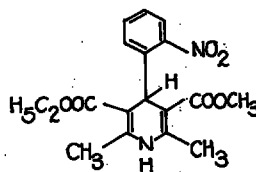
Example 52.

By 9 hours' heating of a solution of 12.5 g 3'-nitrobenzylideneacetoacetic acid methyl ester, 8.0 g acetoacetic acid β -methoxyethyl ester and 6 ml conc. ammonia in 80 ml ethanol, 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3- β -methoxyethyl ester 5-methyl ester of melting point 204° C (acetic ester/petroleum ether) was obtained. Yield 51% of theory.



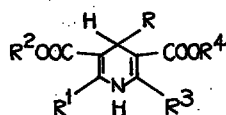
Example 53.

After 8 hours' heating of a solution of 13.2 g 2'-nitrobenzylideneacetoacetic acid ethyl ester and 5.8 g aminocrotonic acid methyl ester in 60 ml ethanol, 2,6-dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester 5-ethyl ester of melting point 117° C (acetic ester/petroleum ether) was obtained. Yield 58% of theory.



WHAT WE CLAIM IS:—

1. Unsymmetrical 1,4-dihydropyridine dicarboxylic acid ester compounds of the general formula:—



(I)

in which

R is a phenyl radical carrying at least one nitro, nitrile, azido, or $-\text{SO}_2$ -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 pyrrol 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.

2. The compounds of claim 1 in which R is a substituted chlorophenyl radical.

3. The compounds of claim 1 or 2 in which R is a mono- or di-substituted phenyl radical.

4. The compounds of claim 1, 2 or 3 in which R carries one or more alkyl or alkoxy groups each having one or two carbon atoms as substituents.

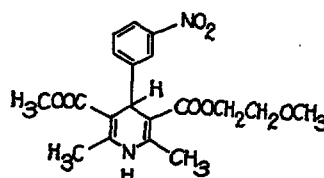
5. The compounds of claim 1 in which R is a pyridyl, pyrrol, thenyl or furyl radical carrying a methyl or ethyl group as a substituent.

6. The compounds of claim 1 in which R is a pyrimidyl radical carrying one or two methoxy or ethoxy groups as substituents.



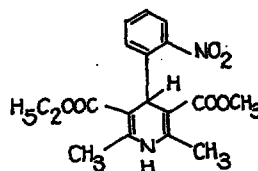
Example 52.

By 9 hours' heating of a solution of 12.5 g 3'-nitrobenzylideneacetoacetic acid methyl ester, 8.0 g acetoacetic acid β -methoxyethyl ester and 6 ml conc. ammonia in 80 ml ethanol, 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3- β -methoxyethyl ester 5-methyl ester of melting point 204° C (acetic ester/petroleum ether) was obtained. Yield 51% of theory.



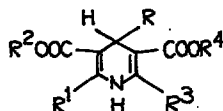
Example 53.

After 8 hours' heating of a solution of 13.2 g 2'-nitrobenzylideneacetoacetic acid ethyl ester and 5.8 g aminocrotonic acid methyl ester in 60 ml ethanol, 2,6-dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester 5-ethyl ester of melting point 117° C (acetic ester/petroleum ether) was obtained. Yield 58% of theory.



WHAT WE CLAIM IS:—

1. Unsymmetrical 1,4-dihydropyridine dicarboxylic acid ester compounds of the general formula:—



(I)

in which

R is a phenyl radical carrying at least one nitro, nitrile, azido, or $-\text{SO}_2-$ 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 pyrrol 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.

2. The compounds of claim 1 in which R is a substituted chlorophenyl radical.

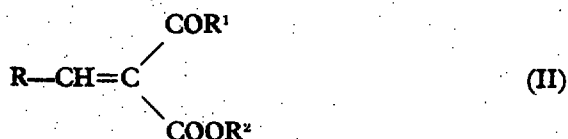
3. The compounds of claim 1 or 2 in which R is a mono- or di-substituted phenyl radical.

4. The compounds of claim 1, 2 or 3 in which R carries one or more alkyl or alkoxy groups each having one or two carbon atoms as substituents.

5. The compounds of claim 1 in which R is a pyridyl, pyrrol, thenyl or furyl radical carrying a methyl or ethyl group as a substituent.

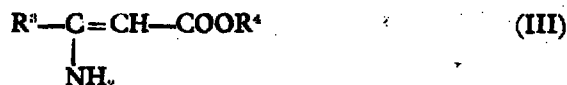
6. The compounds of claim 1 in which R is a pyrimidyl radical carrying one or two methoxy or ethoxy groups as substituents.

7. The compounds of any preceding claim in which R¹ and R³ are both either a hydrogen atom or a straight- or branched-chain alkyl group having up to four carbon atoms.
8. The compounds of claim 7 in which R¹ and R³ are each either a hydrogen atom or a methyl group.
9. The compounds of any preceding claim in which R² and R⁴ both have up to six carbon atoms.
10. The compounds of claim 9 in which R² and R⁴ both have an aliphatic hydrocarbon with up to 3 carbon atoms.
11. The compounds of any preceding claim in which the carbon chain of R¹ and/or R² is interrupted by one oxygen atom.
12. 2,6-Dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester.
13. 2,6-Dimethyl-4-(2'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester.
14. 2,6-Dimethyl-4-(2'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-methyl ester.
15. 2,6-Dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-methyl ester.
16. 2,6-Dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-β-methoxyethyl ester.
17. 2,6-Dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-propyl ester-5-isopropyl ester.
18. 2,6-Dimethyl-4-(2'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-allyl ester-5-isopropyl ester.
19. 2,6-Dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-propargyl ester.
20. 2,6-Dimethyl-4-(3'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-methyl ester.
21. 2,6-Dimethyl-4-(3'-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester.
22. 2-Methyl-6-ethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-ethyl ester.
23. 2-Methyl-6-isopropyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-isopropyl ester.
24. 2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-β-methoxyethyl ester.
25. 2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-β-propoxyethyl ester.
26. 2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester.
27. 2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-propargyl ester.
28. 2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester-5-isopropyl ester.
29. 2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-allyl ester.
30. 2,6-Dimethyl-4-(3'-nitro-6'-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester.
31. The compounds of claim 1 that are hereinbefore specifically mentioned in Examples 1 to 39 but not claimed in any of claims 12 to 30.
32. The compounds of claim 1 that are hereinbefore specifically mentioned in Examples 40—53 but not claimed in any of claims 12 to 30.
33. A process for the production of the compounds of any of claims 1 to 32 in which an ylidene-β-ketocarboxylic acid ester of the general formula:—



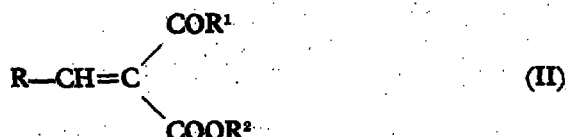
is reacted in water or an inert organic solvent as diluent with an enamino-carboxylic acid ester of the general formula:—





[in which general formulae R, R¹, R², R³ and R⁴ have the meanings set forth in any of claims 1 to 11].

- 5 34. A process for the production of the compounds of any of claims 1 to 32 in which a ylidene- β -ketocarboxylic acid ester of the general formula:—



is reacted in water or an inert organic solvent as diluent with ammonia and a β -ketocarboxylic acid ester of the general formula:—



- 10 [in which general formulae R, R¹, R², R³ and R⁴ have the meanings set forth in any of claims 1 to 11].

35. The process of claim 33 or 34 in which the reaction is carried out in an alcohol or ether, or in glacial acetic acid, pyridine, dimethylformamide, dimethylsulphoxide, or acetonitrile.

- 15 36. The process of claim 33, 34 or 35 in which the reaction is carried out at the boiling point of the diluent.

37. The process of claim 33 or 34 substantially as hereinbefore described or as illustrated in any of Examples 1 to 39.

- 20 38. The process of claim 33 or 34 substantially as hereinbefore illustrated in any of Examples 40 to 53.

39. Unsymmetrical 1,4-dihydropyridine carboxylic acid ester compounds according to claim 1 whenever produced by the process of any of claims 33 to 37.

- 25 40. Unsymmetrical 1,4-dihydropyridine carboxylic acid ester compounds according to claim 1 whenever produced by the process of claim 38.

41. A pharmaceutical composition containing as an active ingredient a compound of any of claims 1 to 31 and 39 in admixture with a solids liquefied gaseous diluent or in admixture with a liquid diluent other than solvents of a molecular weight less than 200 except in the presence of a surface active agent.

- 30 42. A pharmaceutical composition containing as active ingredient a compound of any of claims 1 to 31 and 39 in the form of a sterile or isotonic aqueous solution.

43. The composition of claim 41 or 42 containing from 0.1 to 15 wt % of the said active ingredient.

- 35 44. The composition of claim 41, 42 or 43 containing as the said active ingredient a compound of claim 32 or 40.

45. The pharmaceutical compositions of claim 41 or 42 substantially as hereinbefore described.

- 40 46. A medicament in dosage unit form comprising a compound of any of claims 1 to 31 and 39 either alone or in admixture with a diluent.

47. A medicament in the form of tablets, pills, dragees, capsules and ampoules comprising a compound according to any of claims 1 to 31 and 39 either alone or in admixture with a diluent.

- 45 48. The medicament of claim 46 or 47 comprising a compound of claim 32 or 40.

49. Medicaments of claim 46 or 47 substantially as hereinbefore described.

- 50 50. A method of reducing blood pressure in a non-human animal comprising administering to the animal a compound of any of claims 1 to 31 and 39 alone or in admixture with a diluent or as a medicament of claim 46 or 47.

51. The method of claim 50 in which the compound is administered intravenously at a dosage rate of 0.0005 to 0.1 mg/kg body weight/day.

52. The method of claim 50 in which the compound is perlingually administered at a dosage rate of 0.05 to 5 mg/kg body weight/day.

53. The method of claim 50, 51 or 52 in which the said compound is a compound of claim 32 or 40.

54. The method of claim 50 substantially as hereinbefore described.



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