ethyl ester having hypotensive properties, process for its preparation and pharmaceutical preparations containing it.

DESCRIPTION

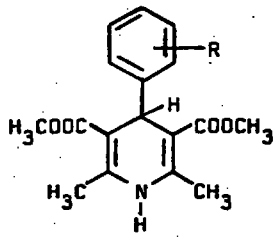
TECHNICAL FIELD

The present invention relates to a new compound having valuable antihypertensive properties, process for its preparation, method for lowering blood pressure in mammals including man, and pharmaceutical preparations containing said compound.

The object of the present invention is to obtain a new antihypertensive agent, which lower blood pressure in the peripheral vessels in lower doses than it lower blood pressure in the heart vessels, by selective dilation of peripheral blood vessels.

BACKGROUND OF THE INVENTION

Compounds of the formula



wherein R is nitro or trifluoromethyl in 2 or 3 position are known to possess cerebral vasodilating effect, effect against angina pectoris or blood pressure lowering effect.

In the US Patent Specification S/N 3,799,936 it has been shown that asymmetric 2,6-dimethyl-4(substituted phenyl)-1,4-dihydropyridine-3,5-dicarboxylates possess cardiovascular properties. This US Patent Specification corresponds mainly to the German Patent Specifications 2,117,572 and 2,117,573 with regard to the compounds disclosed.

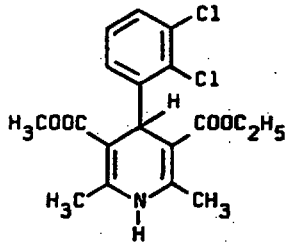
It is further known from German Patent Specification S/N 2,629,892 that compounds of the similar structure possess cardiovascular properties. According to the main concept of said patent specification symmetric compounds with regard to the 3,5-dicarboxylic acid ester functions are disclosed.

Agents which relax vascular smooth muscle may be used for treatment of arterial hypertension since such patients suffer from elevated peripheral resistance to blood flow. Compounds which interfere with vascular smooth muscle activity have been used clinically for several years. However, their usefulness has often been limited due to insufficient efficacy and/or due to adverse effects. Side effects (outside the cardiovascular system) have often been connected with properties of the agent not relevant to the smooth muscle relaxant effect. Sometimes the vasodilating agents have also exerted a negative effect on the contractility of the heart.

It appears that the development of specific smooth muscle relaxants devoid of adverse effects, can offer a therapeutic advantage in arterial hypertension and for treatment of ischaemic heart disease and of the acutely failing heart. Furthermore, such agents can also be useful in treatment of other conditions with excessive activation of smooth muscle of the visceral type.

DISCLOSURE OF THE INVENTION

It has now surprisingly been shown that the compound of the formula I



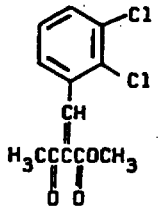
(I)

possesses specific muscle relaxing effect related to the peripheral vascular system whereby the compound is devoid of adverse effects.

The substance is intended to be administered orally or parenterally for acute and chronic treatment of above mentioned cardiovascular disorders.

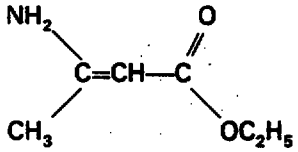
The biological effects of the new compound have been tested, and the different tests carried out will be shown and explained below.

a[1]) a compound of formula IIa



(IIa)

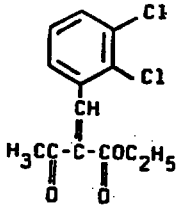
is reacted with a compound of formula IIIa



(IIIa)

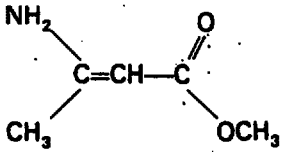
to give a compound of formula I, or

a[2]) a compound of formula IIb



(IIb)

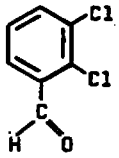
is reacted with a compound of formula IIIb



(IIIb)

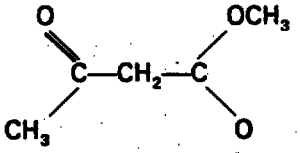
to the formation of a compound of formula I; or;

b[1]) a compound of formula IV

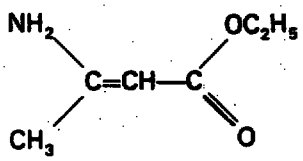


(IV)

is reacted with the compounds for formulas Va and IIIa

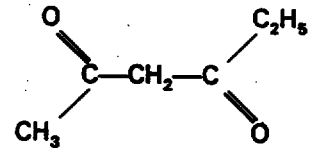


(Va)

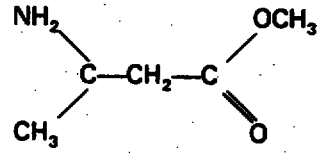


(IIIa)

b[2]) a compound of formula IV above is reacted with the compounds of formulas Vb and VIb



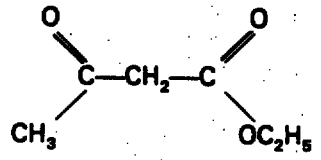
(Vb)



(VIb)

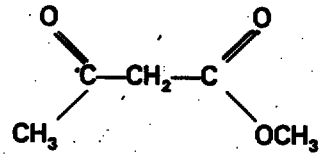
to the formation of a compound of formula I; or

c[1]) a compound of formula IIa is reacted with a compound of the formula VIa



in the presence of ammonia, to the formation of a compound of the formula I, or

c[2]) a compound of formula IIb is reacted with a compound of formula VIb



(VIb)

in the presence of ammonia, to the formation of a compound of the formula I; or

d) a compound of formula IV above is reacted with the compounds of the formulas Va and Vb above, in the presence of ammonia to the formation of a compound of the formula I.

The new compounds may, depending on the choice of starting materials and process, be present as optical antipodes or racemate, or, if it contains at least two asymmetric carbon atoms, be present as an isomer mixture (racemate mixture).

The isomer mixture (racemate mixture) obtained may, depending on physical-chemical differences of the components, be separated into the two stereoisomeric (diastereomeric) pure racemates e.g. by means of chromatography and/or fractional crystallization.

The racemate obtained can be separated according to known methods, e.g., by means of recrystallization from an optically active solvent, by means of microorganisms, or by a reaction with optically active acids forming salts of the compound, and separating the salts thus obtained, e.g. by means of the different solubility of the diastereomeric salts, from which the antipodes may be set free by the action of a suitable agent. Suitably useable optically active acids are e.g. the L- and D-forms of tartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulfonic acid or quinic acid. Preferably the more active part of the two antipodes is isolated.

The starting materials are known or may, if they are novel, be obtained according to processes known *per se*.

In clinical use the compound of the invention is usually administered orally, or rectally in the form of a pharmaceutical preparation, which contains the active component as free base in combination with a pharmaceutically acceptable carrier.

Thus the mentioning of the new compound of the invention is here related to the free amine base even if the compound is generally or specifically described, provided that the context in which such expressions are used, e.g., in the example with this broad meaning should not correspond. The carrier may be a solid, semi-solid or liquid diluent or a capsule. These pharmaceutical preparations are a further object of the invention.

Usually the amount of active compound is between 0.1 and 99% by weight of the preparation,

In the preparation of pharmaceutical preparations containing the compounds of the present invention in the form of dosage units for oral administration the compound may be mixed with a solid, pulverulent carrier, as e.g., with lactose, saccharose, sorbitol, mannitol, starch, such as potatoe starch, corn starch, amylopectin, cellulose derivatives or gelatine, as well as with an antifriction agent such as magnesium stearate, calcium stearate, polyethyleneglycol waxes or the like, and be pressed into tablets. If coated tablets are wanted, the above prepared core may be coated with concentrated solution of sugar, which solution may contain, e.g., gum arabicum, gelatine, talc, titandioxide or the like. Furthermore, the tablets may be coated with a laquer dissolved in an easily volatile organic solvent or mixture of solvents. To this coating a dye may be added in order to easily distinguish between tablets with different active compounds or with different amounts of the active compound present.

In the preparation of soft gelatine capsules (pearl-shaped, closed capsules), which consist of gelatine and, e.g., glycerine, or in the preparation of similar closed capsules, the active compound is mixed with a vegetable oil. Hard gelatine capsules may contain granules of the active compound in combination with a solid, pulverulent carrier as lactose, saccharose, sorbitol, mannitol, starch (as, e.g., potatoe starch, corn starch or amylopectin), cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared in the form of suppositories, which contain the active substance in a mixture with a neutral fat base, or they may be prepared in the form of gelatine-rectal capsules which contain the active substance in a mixture of vegetable oil or paraffin oil.

Liquid preparations for oral administration may be present in the form of sirups or suspensions, e.g. solutions containing from about 0.2% by weight to about 20% by weight of the active substance described, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent.

The preparation of pharmaceutical tablets for peroral use is carried out in accordance with the following method:

The solid substances included are ground or sieved to a certain particle size. The binding agent is homogenized and suspended in a certain amount of solvent. The therapeutic compound and necessary auxiliary agents are mixed with continuous and constant mixing with the binding agent solution and are moistened so that the solution is uniformly divided in the mass without overmoistening any parts. The amount of solvent is usually so adapted that the mass obtains a consistency reminding of wet snow. The moistening of the pulverulent mixture with the binding agent solution causes the particles to gather together slightly to aggregates and the real granulating process is carried out in such a way that the mass is pressed through a sieve in the form of a net of stainless steel having a mesh size of about 1 mm. The mass is then placed in thin layers on a tray to be dried in a drying cabinet. This drying takes place during 10 hours and has to be standardized carefully as the damp degree of the granulate is of outmost importance for the following process and for the feature of the tablets. Drying in a fluid bed may possibly be used. In this case the mass is not put on a tray but is poured into a container having a net bottom.

After the drying step the granules are sieved so that the particle size wanted is obtained. Under certain circumstances powder has to be removed.

To the so called final mixture, disintegrating, antifriction agents and antiadhesive agents are added. After this mixture the mass shall have its right composition for the tabletting step.

The cleaned tablet punching machine is provided with a certain set of punches and dies, whereupon the suitable adjustment for the weight of the tablets and the degree of compression is tested out. The weight of the tablet is decisive for the size of the dose in each tablet and is calculated starting from the amount of therapeutic agent in the granules. The degree of compression affects the size of the tablet, its strength and its ability of disintegrate in water. Especially with regard to the two later properties the choice of compression pressure (0.5 to 5 ton) means something of a compromise. When the right adjustment is set, the preparation of tablets is started and is carried out with a rate of 20.000 to 200.000 tablets per hour. The pressing of the tablets requires different times and depends on the size of the batch.

The tablets are freed from adhering pulver in a specific apparatus and are then stored in closed packages until they are delivered.

Many tablets, especially those which are rough or bitter, are coated with a coating. This means that they are coated with a layer of sugar or some other suitable coating.

The tablets are usually packed by machines having an electronic counting device. The different types of packages consist of glass or plastic gallipots but also boxes, tubes and specific dosage adapted packages.

The daily dose of the active substance varies and is dependent on the type of administration, but as a general rule it is 100 to 1000 mg/day of active substance at peroral administration.

BEST MODE OF CARRYING OUT THE INVENTION

The following illustrates the principle and the adaptation of invention, however, without being limited thereto. Temperature is given in degree Celsius.

Preparation of 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester.

2.87 g of 2,3-dichlorobenzylideneacetylacetic acid-methylester and 1.3 g of 3-aminocrotonic acid ethylester were dissolved in 10 mls of t.-butanol. The reaction mixture was allowed to stand at ambient temperature for 4 days, whereupon the t.-butanol was evaporated and the residue was dissolved and was stirred with a small amount of isopropylether, whereby the compound crystallized. After recrystallization from isopropylether pure 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester was obtained. M.p. 145°C. Yield 75%.

Example 2
(method c1, c^2)

5.74 g of 2,3-dichlorobenzylideneacetylacetic acid methylester, 2.6 g of ethylacetoacetate and 2.8 mls of conc. NH_3 were dissolved in 25 mls tert.-butanol. The reaction mixture was allowed to stand at ambient temperature for 5 days, whereupon the tert.-butanol was evaporated and the residue was dissolved in isopropylether. After cooling the compound crystallized and after recrystallization from isopropylether pure 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester was obtained. M.p. 145°C. Yield 59%.

Example 3

A syrup containing 2% (weight per volume) of active substance was prepared from the following ingredients:

2,6-dimethyl-4-(2,3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester	2.0	g
Saccharine	0.6	g
Sugar	30.0	g
Glycerine	5.0	g
Flavouring agent	0.1	g
Ethanol 96%	10.0	g
Distilled water	ad 100.0	ml

Sugar, saccharine and the active substance were dissolved in 60 g of warm water. After cooling, a glycerine and solution of flavouring agents dissolved in ethanol were added. To the mixture water was then added to 100 ml.

BIOLOGICAL TESTS

The *antihypertensive effect* of the compound was tested in conscious, unrestrained spontaneously hypertensive rats (SHR) of the Okamoto strain. The animals had been prepared by prior implantation of indwelling catheters in the abdominal aorta via the femoral artery. Mean arterial blood pressure (MABP) and heart rate was continuously monitored. After a 2 hour control period the compound under study was administered by oral intubation at 2 hour intervals, suspended in methocel solution (5 ml/kg bodyweight). The cumulated doses were 1, 5 and 25 μmoles/kg bodyweight. The antihypertensive response, *i.e.* the BP reduction to each dose, was expressed as a percentage of the initial control BP level and plotted against the dose on a logarithmic scale. The dose which would give 20 per cent BP reduction was then determined by interpolation. The results are shown in table I.

The *specificity* towards *smooth muscle relaxation* was examined as follows: The isolated portal vein preparation of Wistar rats was mounted in an organ bath together with a paced isolated papillary heart muscle preparation of the same animal. The integrated contractile activity of the portal vein smooth muscle and the peak force amplitude of the papillary, myocardial, preparation were recorded. The respective activities during a 30 min control period were set as 100 per cent and the ensuing activities under the influence of the agent under study were expressed as a percentage thereof. The agent was administered at 10 min intervals and the potency for vasodilation(-log ED_{50} of portal vein) and that of myocardial depression (-log ED_{50} of papillary muscle) were determined by interpolation from the concentration-effect relationships determined in each experiment. A "separation" value was determined for each compound by averaging the differences of the -log ED_{50} values for vasodilatation and myocardial depression respectively, obtained in the experiments. This logarithmic separation value was transformed into numeric format and entered into table I.

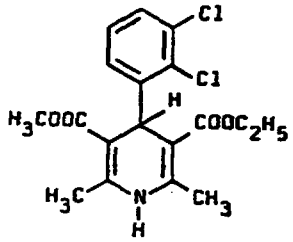
The compound of the invention was compared with Nifedipin [2,6-dimethyl-4-(2-nitrophenyl)-1.4-dihydropyridine-3,5-dicarboxylic acid-3,5-dimethylester).

TABLE I

Compound according to Ex.	SHR ED_{20} µmoles/kg bodyweight	Ratio heart / vasc.
1	4	98
Nifedipin	5	15

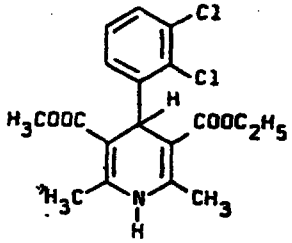
Claims for the Contracting States: BE, GH, DE, FR, GB, IT, LU, NL, SE

1. A compound of formula I



(I)

2. Pharmaceutical preparation, which comprises as an active ingredient a therapeutically effective dose of a antihypertensive compound having vascular smooth muscle relaxing properties which compound has the formula I

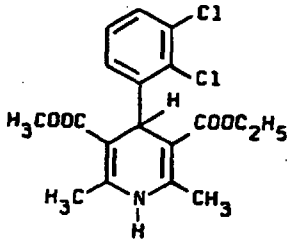


(I)

3. A pharmaceutical preparation according to claim 2 wherein the compound of the formula I comprises 0.1 to 99% by weight of the preparation.

Claims for the Contracting State: AT

1. A process for preparing a compound of the formula I



(I)

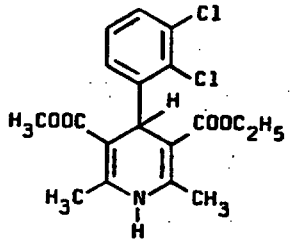
characterized in that

TABLE I

Compound according to Ex.	SHR ED_{20} μmoles/kg bodyweight	Ratio heart / vasc.
1	4	98
Nifedipin	5	15

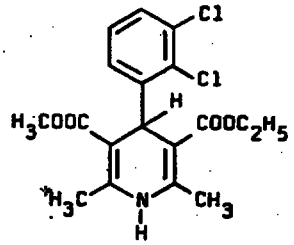
Claims for the Contracting States: BE, GH, DE, FR, GB, IT, LU, NL, SE

1. A compound of formula I



(I)

2. Pharmaceutical preparation, which comprises as an active ingredient a therapeutically effective dose of a antihypertensive compound having vascular smooth muscle relaxing properties which compound has the formula I

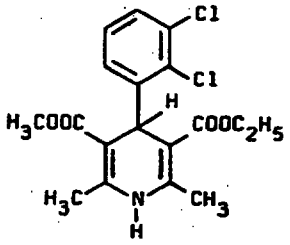


(I)

3. A pharmaceutical preparation according to claim 2 wherein the compound of the formula I comprises 0.1 to 99% by weight of the preparation.

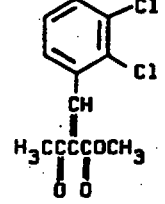
Claims for the Contracting State: AT

1. A process for preparing a compound of the formula I



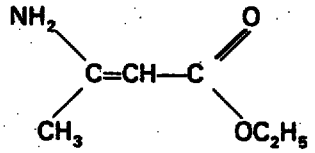
(I)

characterized in that



(IIa)

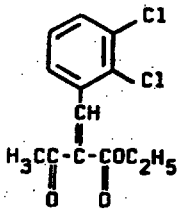
is reacted with a compound of formula IIIa



(IIIa)

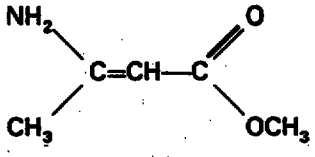
to the formation of a compound of the formula I; or

a[2]) a compound of formula IIb



(IIb)

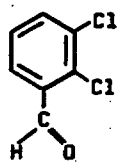
is reacted with a compound of formula IIIb



to the formation of a compound of formula I.

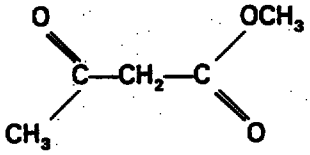
2. A process for preparing a compound of formula I defined in claim 1, characterized in that

b[1]) a compound of formula IV

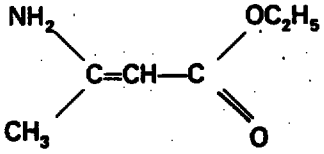


(IV)

is reacted with the compounds of formulas Va and IIIa

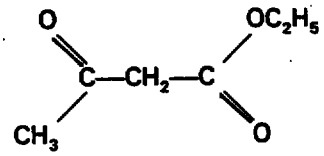


(Va)

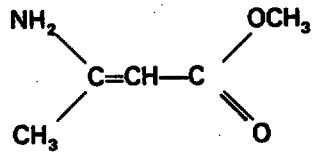


(IIIa)

b[2]) a compound of formula IV above is reacted with the compounds of formula Vb and IIIb



(Vb)

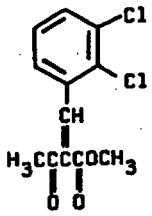


(IIIb)

to the formation of a compound of formula I.

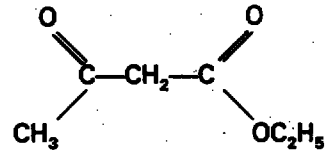
3. A process for preparing a compound of formula I, defined in claim 1, characterized in that

c[1]) a compound of formula IIa



(IIa)

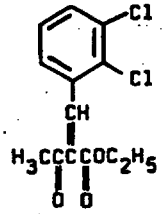
is reacted with a compound of formula VIa



(VIa)

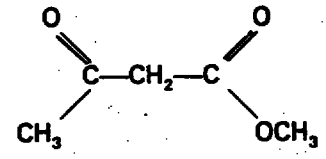
in the presence of ammonia, to the formation of a compound of the formula I, or

c[2]) a compound of formula IIb



(IIb)

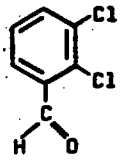
is reacted with a compound of formula VIb



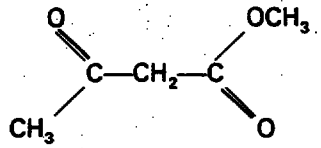
(VIb)

in the presence of ammonia to the formation of a compound of the formula I;

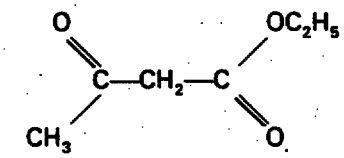
4. A process for preparing a compound of formula I, defined in claim 1, characterized in that a compound of formula IV



(IV)



(Va)



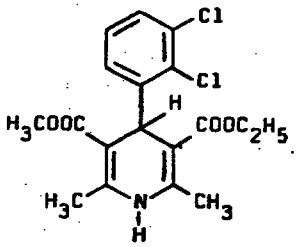
(Vb)

in the presence of ammonia to the formation of a compound of the formula I.

5. A process according to claim 2, wherein 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester is prepared by reacting 2,3-dichlorobenzaldehyde, 3-aminocrotonic acid ethylester and acetylacetic acid methylester.

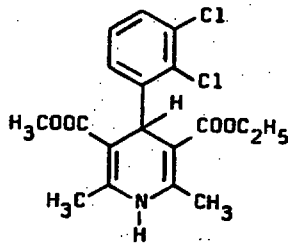
Patentansprüche für die Vertragsstaaten: BE, CH, DE, FR, GB, IT, LU, SE, NL

1. Verbindung der Formel I



(I)

2. Pharmazeutisches Präparat, das als einen aktiven Bestandteil eine therapeutisch wirksame Dosis einer antihypertensiven Verbindung mit die glatte Gefäßmuskulatur entspannenden Eigenschaften enthält, wobei die Verbindung die Formel I besitzt

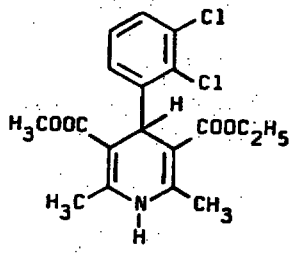


(I)

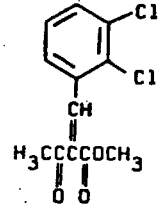
3. Pharmazeutisches Präparat nach Anspruch 2, worin die Verbindung der Formel I 0,1 bis 99% Gewichts-% des Präparates ausmacht.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel I

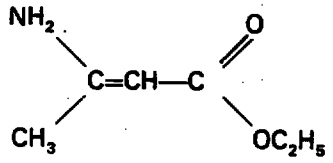


dadurch gekennzeichnet, daß



(IIa)

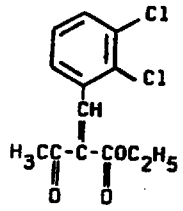
mit einer Verbindung der Formel IIIa



(IIIa)

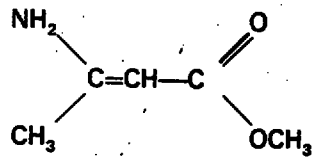
unter Bildung einer Verbindung der Formel I umgesetzt wird oder

a²) eine Verbindung der Formel IIb



(IIb)

mit einer Verbindung der Formel IIIb

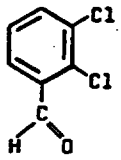


(IIIb)

unter Bildung einer Verbindung der Formel I umgesetzt wird.

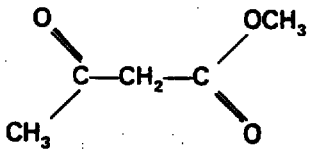
2. Verfahren zur Herstellung einer Verbindung der Formel I gemäß der Definition in Anspruch 1, dadurch gekennzeichnet, daß

b¹) eine Verbindung der Formel IV

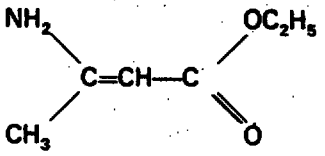


(IV)

mit den Verbindungen der Formeln Va und IIIa

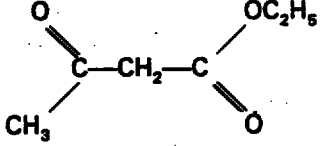


(Va)

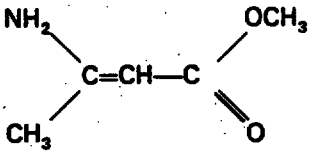


(IIIa)

unter Bildung einer Verbindung der Formel I umgesetzt wird oder



(Vb)

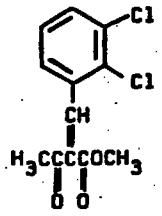


(IIIb)

unter Bildung einer Verbindung der Formel I umgesetzt wird.

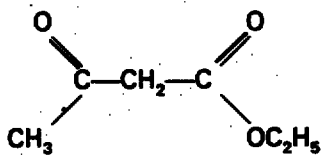
3. Verfahren zur Herstellung einer Verbindung der Formel I, die in Anspruch 1 definiert ist, dadurch gekennzeichnet, daß

c[1]) eine Verbindung der Formel IIa



(IIa)

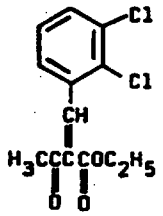
mit einer Verbindung der Formel VIa



(VIa)

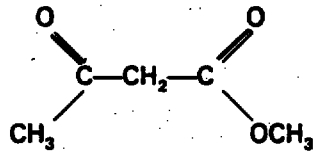
in Gegenwart von Ammoniak unter Bildung einer Verbindung der Formel I umgesetzt wird oder

c[2]) eine Verbindungen der Formel IIb



(IIb)

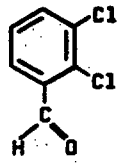
mit einer Verbindung der Formel VIb



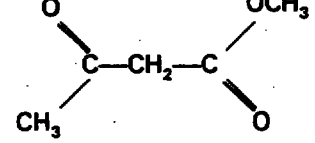
(VIb)

in Gegenwart von Ammoniak unter Bildung einer Verbindung der Formel I umgesetzt wird.

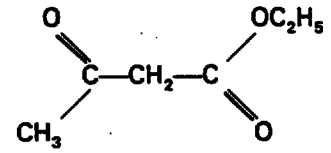
4. Verfahren zur Herstellung einer Verbindung der Formel I, die in Anspruch 1 definiert ist, dadurch gekennzeichnet, daß eine Verbindung der Formel IV



(IV)



(Va)



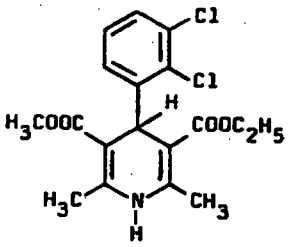
(Vb)

in Gegenwart von Ammoniak unter Bildung einer Verbindung der Formel I umgesetzt wird.

5. Verfahren nach Anspruch 2, worin 2,6-Dimethyl-4-(2,3-dichlorphenyl)-1,4-dihydropyridin-3,5-dicarbonsäure-3-methylester-5-äthylester durch Umsetzung von 2,3-Dichlorbenzaldehyd, 3-Aminocrotonsäureäthylester und Acetylessigsäuremethylester hergestellt wird.

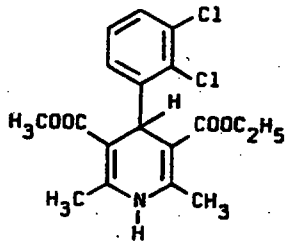
Revendications pour les Etats contractants: BE, CH, DE, FR, GB, IT, LU, NL, SE

1. Composé de formule I



(I)

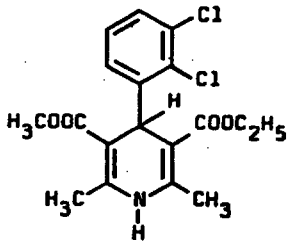
2. Préparation pharmaceutique, caractérisée en ce qu'elle comprend comme composant actif une dose thérapeutiquement efficace d'un composé antihypertenseur ayant des propriétés de relaxation du muscle lisse vasculaire, composé qui répond à la formule I



3. Préparation pharmaceutique selon la revendication 2, caractérisée en ce que is composé de formule I représente 0,1 à 99% en poids de la préparation.

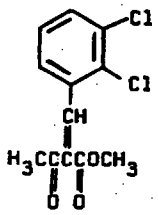
Revendications pour l'Etat contractant: AT

1. Procédé pour la préparation d'une composé de formule I



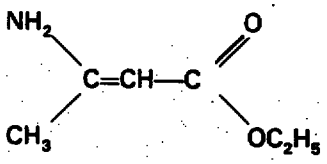
(I)

caractérisé en ce que



(IIa)

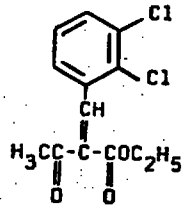
avec un composé de formule IIIa



(IIIa)

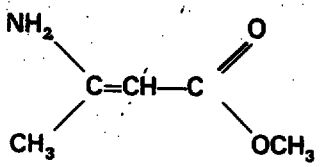
en vue de la formation d'une composé de formule I; ou

a²) on fait réagir un composé de formule IIb



(IIb)

avec un composé de formule IIIb

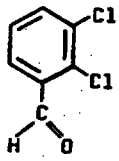


(IIIb)

en vue de la formation d'un composé de formule I.

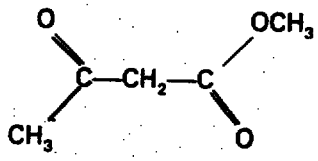
2. Procédé pour la préparation d'un composé de formule I tel que défini dans la revendication 1, caractérisé en ce que

b¹) on fait réagir un composé de formule IV

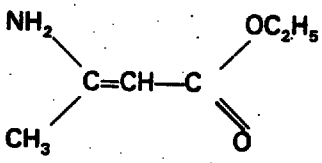


(IV)

avec les composés de formules Va et IIIa

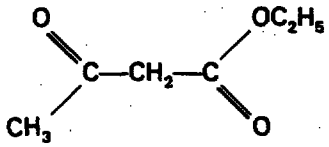


(Va)

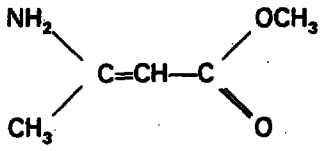


(IIIa)

IIIb



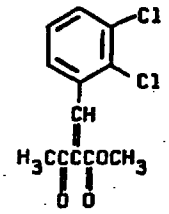
(Vb)



(IIIb)

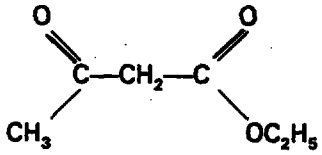
3. Procédé pour la préparation d'un composé de formule I tel que défini dans la revendication 1, caractérisé en ce que.

c[1]) on fait réagir un composé de formule IIa



(IIa)

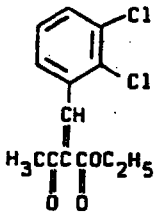
avec un composé de formule VIa



(VIa)

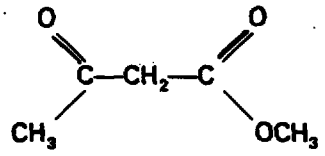
en présence d'ammoniac, en vue de la formation d'un composé de formule I, ou

c[2]) on fait réagir un composé de formule IIb



(IIb)

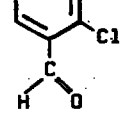
avec un composé de formule VIb



(VIb)

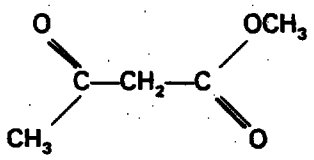
en présence d'ammoniac, en vue de la formation d'un composé de formule I.

4. Procédé pour la préparation d'un composé de formule I tel que défini dans la revendication 1, caractérisé en ce qu'on fait réagir un composé de formule IV

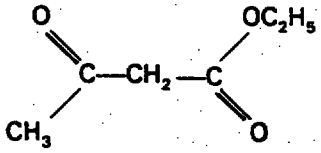


(IV)

avec les composés de formules Va et Vb



(Va)



(Vb)

en présence d'ammoniac, en vue de la formation d'un composé de formule I.

5. Procédé selon la revendication 2, caractérisé en ce que l'ester 3-méthylique-ester-5-éthylique d'acide 2,6-diméthyl-4-(2,3-dichlorphényl)-1,4-dihydropyridine-3,5-dicarboxylique est préparé par réaction de 2,3-dichlorobenzaldéhyde, d'ester éthylique d'acide 3-aminocrotonique et d'ester méthylique d'acide acétylacétique.