

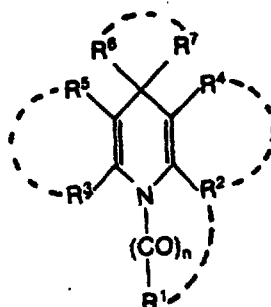


Description

The present invention relates to the use of novel and known dihydropyridines in medicaments having a positive inotropic action, novel compounds from this class of substances, medicaments containing them and their preparation.

It has already been disclosed that 1,4-dihydropyridines have vasodilating properties and can be used as coronary agents and antihypertensives (cf. British Patent 1,173,062; British Patent 1,358,951; German Offenlegungsschrift 2,629,892 and German Offenlegungsschrift 2,752,820). Furthermore, it is known that 1,4-dihydropyridines inhibit the contractility of smooth and cardiac muscles and can be used for the treatment of coronary and vascular diseases (cf. A. Fleckenstein, Ann. Rev. Pharmacol. Toxicol. 17, 149-166 (1977)). Knowing these properties of the dihydropyridines, it was not foreseeable that the compounds according to the invention from this class of substances do not have a contraction-inhibiting but a contraction-augmenting, positive inotropic action on heart muscles.

The invention relates to the use of 1,4-dihydropyridines of the general formula (I)



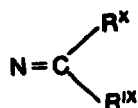
in which

n stands for 0, 1 or 2,
 R^1

- a) stands for hydrogen, a straight-chain, branched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical which optionally contains 1 to 3 identical or different hetero chain members from the group consisting of O, CO, SO_m ($m = 0.1$ or 2), $=N-$, NR^I and $SiR^{II}R^{III}$, this hydrocarbon radical being unsubstituted or substituted by halogen, NO_2 , CN, N_3 , hydroxyl, aryl or heteroaryl or
- b) stands for an aryl or heteroaryl radical, these

radicals optionally carrying 1 to 5 identical or different substituents from the group consisting of aryl, alkyl, alkenyl, alkynyl, alkenoxy, alkinoxy, aralkyl, acyl, alkylene, dioxyalkylene, halogen, CF₃, OCF₃, SCF₃, NO₂, NO, CN, N₃, COR^{IV}, COOR^V, OR^{VI}, NR^I or NR^{VIII}R^{VIII}, it
 5 being possible for the alkyl, alkoxy and aryl radicals of the abovementioned substituents in their turn also to be substituted by halogen, COR^V or NR^{VII}R^{VIII} or
 c) stands for the radical NR^{VII}R^I, the radicals R^I, R^{II},
 10 R^{III}, R^{IV}, R^V, R^{VI}, R^{VII} and R^{VIII} mentioned under a), b) and c) having the meaning given below,
 R²

a) stands for one of the substituents mentioned under R¹ but does not have to be identical thereto, or
 15 b) stands for the radicals NHR^I or



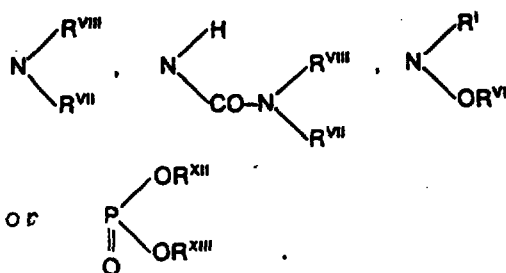
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R^I, R^{IX} and R^X having the meaning given below, or the substituents R¹ and R² together form a 5- to 8-membered, saturated or unsaturated ring which optionally contains 1,
 25 2 or 3 identical or different ring members from the group consisting of O, S, NR^I and CO and which contains 1 to 3 identical or different substituents from the group consisting of halogen, hydroxyl, alkyl, alkoxy, aryl or aralkyl,
 R³ stands for one of the substituents mentioned under R²
 30 and is identical thereto or differs therefrom, only one of the two substituents R² or R³ each standing for alkoxy, alkythio or NHR^I,

R⁴
 a) stands for hydrogen, NO₂, NO, CN, SO_m-R^{XI} (m = 0, 1 or
 35 2), halogen,

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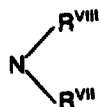
5
10 R^{I} , R^{VII} , R^{VIII} , R^{XI} and R^{XIII} having the meaning given below, or

b) stands for a branched or unbranched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical which is unsubstituted or substituted by halogen, OH, CN, alkoxy, alkylthio, aryloxy, COOR^{V} or

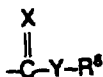


15
 R^{V} , R^{VII} and R^{VIII} having the meaning given below, or

20 c) stands for an aromatic hydrocarbon radical or for a 5- to 7-membered saturated or unsaturated hetero ring having 1 to 4 identical or different hetero members from the group consisting of O, S, $-\text{N}=$ and NR^{I} , this hetero ring being linked to the dihydropyridine ring either via a
25 carbon atom or a nitrogen atom, it being possible for the aromatic hydrocarbon radical and the hetero rings to carry 1 to 3-identical or different substituents from the group consisting of halogen, OH, CN, CF_3 , OCF_3 , SCF_3 , NO_2 , alkyl, alkoxy, aryl and



30
35 d) stands for the radical



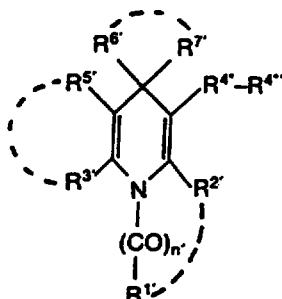
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in which X denotes oxygen, sulphur or NR^{I} , and Y stands for a single bond, O, S or NR^{I} , and R^8 has the meaning given for R^1 and is identical to the substituent R^1 or differs therefrom, or

5 e) stands for the radical



10

in which
 15 n^1 , $\text{R}^{1'}$, $\text{R}^{2'}$, $\text{R}^{3'}$, $\text{R}^{5'}$, $\text{R}^{6'}$ and $\text{R}^{7'}$ have the meaning given for n , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 and are identical thereto or differ therefrom, and R^{4*} and R^{4**} are identical or
 20 R^2 and R^4 together form a branched, unbranched, saturated or unsaturated 5- to 8-membered ring which can contain 1, 2 or 3 identical or different ring members from the group consisting of O, CO, CS, $\text{C}=\text{NR}^{\text{I}}$, $=\text{N}-$, NR^{I} , SO_m ($m = 0, 1$ or 2) and $\text{SiR}^{\text{II}}\text{R}^{\text{III}}$, and which is unsubstituted or substituted
 25 by halogen, hydroxyl, alkoxy, aryl, aralkyl

or



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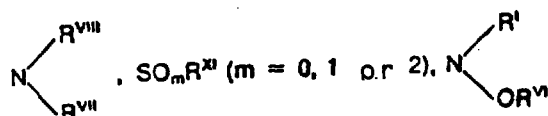
or disubstituted by a straight-chain or branched alkylene chain having 3 to 8 carbon atoms, it being possible for this common ring of R^2 and R^4 also to be directly fused to the common ring of R^1 and R^2 , the radicals R^{I} , R^{II} , R^{III} ,
 35 R^{VII} and R^{VIII} having the meaning given below,
 R^5 has the meaning given for R^4 and is identical to R^4 or differs therefrom, or
 R^5 and R^3 together form a ring which is identical to the ring formed by R^2 and R^4 or differs therefrom,



R^6 stands for hydrogen, alkyl or halogenoalkyl, and
 R^7

a) stands for a saturated, unsaturated, cyclic, straight-chain or branched aliphatic hydrocarbon radical which is
 5 unsubstituted or substituted by halogen, aryl or hetero-aryl, or

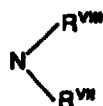
b) stands for an aryl or heteroaryl radical which can contain 1 to 5 identical or different substituents from the group consisting of NO_2 , CN , N_3 , NO , CF_3 , halogen,
 10 COR^{IV} , $COOR^V$, OR^{VI} ,



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alkyl, aryl, alkenyl, alkynyl, alkenoxy, alkinoxy, aralkyl, acyl, alkylene and dioxyalkylene, it being possible for the abovementioned alkyl and aryl substituents in their turn also to be substituted by $COOR^V$ or

20



25 and in the abovementioned definitions of the substituents R^1 to R^8 ,

R^I stands for hydrogen, alkyl, aryl, aralkyl, heteroaryl or acyl,

R^{II} and R^{III} are identical or different and each stand for
 30 alkyl, aryl, aralkyl or heteroaryl,

R^{IV} , R^V and R^{VI} are each identical or different and stand for hydrogen, alkyl, aryl, aralkyl or heteroaryl, the alkyl and acyl radicals being unsubstituted or substituted by halogen, alkylthio, alkoxy, trifluoromethyl, nitro or

35 R^{VII} and R^{VIII} are each identical or different and stand for hydrogen, aryl or aralkyl, or stand for alkyl which is uninterrupted or interrupted by O , S or NR^I , or, together with the nitrogen atom, form a 5- to 7-membered ring which can contain 1 or 2 identical or different hetero ring





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members from the group consisting of O, S and NR^{I} , or one of the radicals R^{VIII} or R^{VIII} stands for an aliphatic acyl group having up to 6 carbon atoms, R^{IX} , R^{X} , R^{XI} , R^{XII} and R^{XIII} are each identical or different and stand for
5 alkyl, aryl or aralkyl, the alkyl, aryl, aralkyl, hetero-aryl and acyl radicals mentioned under R^1 to R^8 and under R^{I} to R^{XIII} , and the hetero ring formed with R^{VII} and R^{VIII} , in their turn being unsubstituted or substituted by OH, CF_3 , OCF_3 , CN, NO_2 , halogen, lower thioalkyl, lower
10 alkyl, lower alkoxy, aryl or aralkyl, and the following substituents being mentioned as heteroaryl:
thienyl, furyl, pyryl, pyridyl, quinolyl, isoquinolyl, pyrimidyl, pyridazinyl, quinazolyl, quinoxalyl, benzo-
15 thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, oxydiazolyl, pyrazinyl, oxazinyl, thiazinyl, indoliziny, indolyl, benzofuranyl, indazolyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzoxadiazolyl, cinnolinyl, phthalaziny, naphthyridinyl or benzotriazinyl,
20 in the form of isomers, isomer mixtures, racemates and optical antipodes, and of their pharmaceutically acceptable salts, for the preparation of medicaments having a positive inotropic action, which are in particular suitable as cardiac stimulants. This contraction-augmenting
25 effect is also due to the increase in the Ca^{++} influx into the cell caused by the compounds according to the invention which also makes them suitable for treatment of hypotensive circulatory conditions, for reducing blood sugar,
30 for decreasing the swelling of mucous membranes and for influencing the salt and fluid balance.

The compounds of the general formula (I) are those which, from a concentration of 10^{-5} g/ml upwards, cause an at least 25% augmentation of the contraction of the isolated left atrium of the guinea pig heart.
35

The experimental setup is as follows:

The left atria of guinea pig hearts are isolated and suspended in a thermostat-controlled organ bath, which contains an isotonic mineral salt solution, which is

adapted to the ionic medium and the pH of body fluids, and suitable nutrients. This organ bath is treated with a gas mixture consisting of oxygen and carbon dioxide, the carbon dioxide content being such that the pH of the organ bath remains constant. The left atria are clamped into the organ bath, the tension is recorded by means of a force transducer, which is set to a certain baseline tone. The left atria are then continuously stimulated electrically at certain intervals and the resulting contractions recorded. After the addition of the active substance, recording of the contractions is continued. An augmentation of the contraction of at least 25% is considered a significant positive inotropic action.

The compounds according to the invention of the general formula (I) can be prepared in different ways using conventional methods, for example

A) by building up the dihydropyridine structure using known dihydropyridine syntheses or

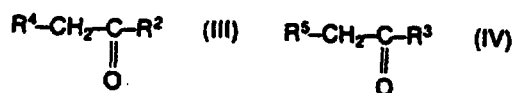
B) by converting functional groups on the dihydropyridine skeleton using known reaction schemes.

A) Buildup of the 1,4-dihydropyridine basic structure

The buildup of the 1,4-dihydropyridine basic structure can be carried out by process in which
a) carbonyl compounds of the general formula (II)



in which R^6 and R^7 have the abovementioned meaning, are reacted with ketones of the formula (III) and (IV)



in which R^2 , R^3 , R^4 and R^5 have the abovementioned meaning, and primary amines of the formula (V)

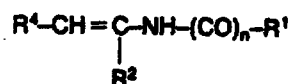




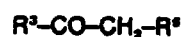
- in which $n = 0$ and R^1 has the abovementioned meaning,
 5 in the presence or absence of inert solvents, or
 b) carbonyl compounds of the formula (II)



- 10 in which R^6 and R^7 have the abovementioned meaning,
 are reacted with enamines of the formula (VI)

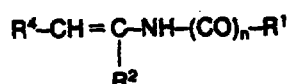


- 15 in which R^1 , R^2 , R^4 and n have the abovementioned meaning,
 and ketones of the formula (IV)

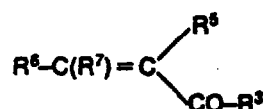


- 20 in which R^3 and R^5 have the abovementioned meaning,
 in the presence or absence of inert solvents or
 c) enamines of the formula (VI)

25



- in which R^1 , R^2 , R^4 and n have the abovementioned meaning,
 30 are reacted with ylidene compounds of the formula (VII)



- 35 in which R^3 , R^5 , R^6 and R^7 have the abovementioned meaning,
 in the presence or absence of inert solvents.

B) Conversion of functional groups

By converting one or more functional groups of known dihydropyridines or alternatively of novel



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dihydropyridines obtained by process A) a) to c), compounds of the general formula (I) can also be prepared according to the invention by conventional methods (cf. Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry, Georg Thieme Verlag, Stuttgart 1966; Organicum, VEB Deutscher Verlag der Wissenschaften, Berlin 1969; W. Foerst, Neuere Methoden der präparativen organischen Chemie (New Methods of Preparative Organic Chemistry), Vol. 1-5, Verlag Chemie, Weinheim 1961; C. Ferri, Reaktionen der organischen Chemie (Reactions of Organic Chemistry), Georg Thieme Verlag, Stuttgart 1978; Fieser + Fieser, Reagents for Organic Synthesis, Vol. 1-8, J. Wiley & Sons, Inc., London 1967.

Preferred conversion reactions are: acid- or base-catalysed hydrolysis, esterification or transesterification, lactamization, condensation, acylation, reduction or cyclization with reagents suitable for each case or of the intramolecular type. A particularly preferred reaction is lactonization. For this reaction, compounds of the general formula (I) in which the substituents R^2 and R^4 and/or R^3 and R^5 contain hydroxyl and carboxylic acid functions, which are free and/or blocked by protective groups, are cyclized under suitable base- or acid-catalysed reaction conditions, if desired, after a previous complete or partial elimination of the protective groups to give the lactones according to the invention of the general formula (I).

In German Offenlegungsschrift No. 2,629,892, a few of the possible preparative methods are described in more detail.

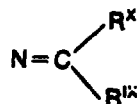
Preference is given to compounds of the general formula (I) in which n stands for 0, 1 or 2, R^1

a) stands for hydrogen, a straight-chain, branched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical having up to 10 C atoms which optionally contains 1 or 2 identical or different hetero chain members from the group consisting of O, CO, S, SO₂, =N- and NR^I, this hydrocarbon

radical being unsubstituted or substituted by halogen, NO₂, CN, N₃, hydroxyl having 1 to 4 C atoms, phenyl, naphthyl or heteroaryl or

- b) stands for a phenyl, naphthyl or heteroaryl radical,
 5 these radicals optionally carrying 1 to 3 identical or different substituents from the group consisting of phenyl, alkyl, alkenyl, alkynyl, alkenoxy, alkinoxy, each having up to 4 C atoms, aralkyl having 7 to 14 C atoms, acyl having up to 6 C atoms, alkylene, dioxyalkylene having up to 4
 10 carbon atoms in the alkylene chain, halogen, CF₃, OCF₃, SCF₃, NO₂, CN, N₃, COR^{IV}, COOR^V, OR^{VI}, NR^I or NR^{VII}R^{VIII}, it being possible for the alkyl, alkoxy and aryl radicals of the abovementioned substituents in their turn also to be substituted by halogen, COOR^V or NR^{VII}R^{VIII} or
 15 c) stands for the radical NR^{VII}R^I, the radicals R^I, R^{II}, R^{III}, R^{IV}, R^V, R^{VI}, R^{VII} and R^{VIII} mentioned under a), b) and c) having the meaning given below,
 R²

- a) stands for one of the substituents mentioned under R¹
 20 but does not have to be identical thereto or
 b) stands for the radicals NHR^I or



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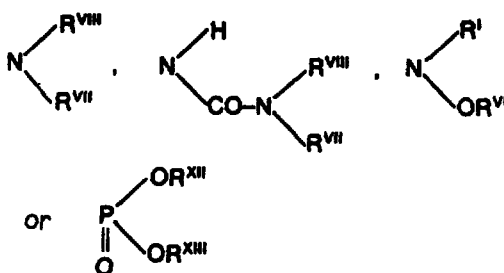
- R^I, R^{IX} and R^X having the meaning given below, or the substituents R¹ and R² together form a 5- to 7-membered saturated or unsaturated ring which optionally contains one or two identical or different ring members from the
 30 group consisting of O, S, NR^I and CO and which can contain one to three identical or different substituents from the group consisting of halogen, hydroxyl, alkyl, alkoxy, each having 1 to 4 C atoms, phenyl, naphthyl or aralkyl having 7 to 14 C atoms,
 35 R³ stands for one of the substituents mentioned under R² and is identical thereto or differs therefrom, only one of the two substituents R² or R³ each standing for alkoxy, or NHR¹,



R^4

a) stands for hydrogen, NO_2 , NO , CN , $\text{SO}_m\text{-R}^{\text{IX}}$ ($m = 0$ or 2), halogen,

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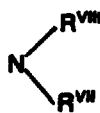


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R^{I} , R^{VII} , R^{VIII} , R^{XI} and R^{XIII} having the meaning given below, or

b) stands for a branched or unbranched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical having up to 10 C atoms, which is unsubstituted or substituted by halogen, OH, CN, alkoxy, alkylthio, each having 1 to 4 carbon atoms, phenyloxy, naphthoxy, COOR^{V} or

20



R^{V} , R^{VII} and R^{VIII} having the meaning given below, or

c) stands for an aromatic hydrocarbon radical having 6 to 10 C atoms or for a 5- to 7-membered saturated or unsaturated hetero ring having 1 to 3 identical or different hetero members from the group consisting of O, S, $-\text{N}=\text{}$ and NR^{I} , this hetero ring being linked to the dihydropyridine ring either via a carbon atom or a nitrogen atom, the aromatic hydrocarbon radical and it being possible for the hetero rings to carry 1 to 3 identical or different substituents from the group consisting of halogen, OH, CN, CF_3 , OCF_3 , SCF_3 , NO_2 , alkyl, alkoxy, each having 1 to 4 C atoms, phenyl, naphthyl and

35



or



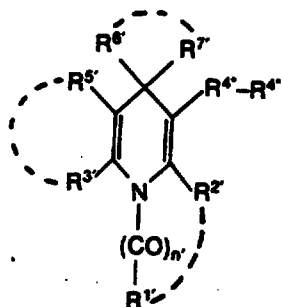
d) stands for the radical

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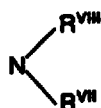


in which X denotes oxygen, sulphur or NR^{I} , and Y stands
 5 for a single bond, O, S or NR^{I} , and R^8 has the meaning
 given for R^1 and is identical to the substituent R^1 or
 differs therefrom, or
 e) stands for the radical

10



in which
 15 n^1 , $\text{R}^{1'}$, $\text{R}^{2'}$, $\text{R}^{3'}$, $\text{R}^{5'}$, $\text{R}^{6'}$ and $\text{R}^{7'}$ have the meaning given
 for n , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 and are identical thereto
 or differ therefrom, and R^{4*} and R^{4**} are identical or
 different and each stand for a radical, minus one hydrogen,
 of the substituents mentioned for R^4 under a) to d), or
 20 R^2 and R^4 together form a branched, unbranched, saturated
 or unsaturated 5- to 7-membered ring which can contain 1,
 2 or 3 identical or different ring members from the group
 consisting of O, CO, CS, $\text{C}=\text{NR}^{\text{I}}$, $=\text{N}-$, NR^{I} and SO_m ($m = 0$ or
 2) and which is unsubstituted or substituted by halogen,
 25 hydroxyl, alkoxy having 1 to 4 C atoms, phenyl, naphthyl,
 aralkyl having 7 to 14 C atoms, or



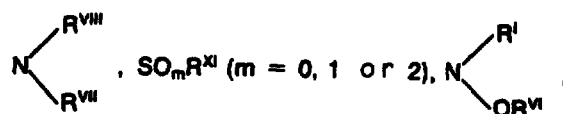
30 or disubstituted by a straight-chain or branched alkylene
 chain having 3 to 8 carbon atoms, it being possible for
 this common ring of R^2 and R^4 also to be directly fused to
 the common ring of R^1 and R^2 , the radicals R^{I} , R^{II} , R^{III} ,
 R^{VII} and R^{VIII} having the meaning given below,
 35 R^5 has the meaning given for R^4 and is identical to R^4 or
 differs therefrom,
 R^6 stands for hydrogen, alkyl or halogenoalkyl each having
 1 to 4 C atoms and



R⁷

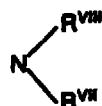
- a) stands for a saturated, unsaturated, cyclic, straight-chain or branched aliphatic hydrocarbon radical having up to 10 C atoms, which is unsubstituted or substituted by halogen, phenyl, naphthyl or heteroaryl or
- b) stands for a phenyl, naphthyl or heteroaryl radical which optionally contains 1 to 3 identical or different substituents from the group consisting of NO₂, halogen, CN, N₃, NO, CF₃, COR^{IV}, COOR^V, OR^{VI},

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- alkyl having 1 to 4 C atoms, phenyl, naphthyl, alkenyl, alkynyl, alkenoxy, alkinoxy, each having up to 4 C atoms, aralkyl having 7 to 14 C atoms, acyl having 1 to 4 C atoms, alkylene and dioxyalkylene, each having up to 4 C atoms, it being possible for the abovementioned alkyl and aryl substituents in their turn also to be substituted by halogen, COOR^V or

25



- and in the abovementioned definitions of the substituents R^I to R⁷,
- R^I stands for hydrogen, alkyl having 1 to 6 C atoms, phenyl, naphthyl, aralkyl having 7 to 12 C atoms, heteroaryl or acyl having up to 7 C atoms,
- R^{II} and R^{III} are identical or different and each stand for alkyl having 1 to 6 C atoms, phenyl, naphthyl, aralkyl having 7 to 12 C atoms or heteroaryl,
- R^{VII}, R^V and R^{VI} are each identical or different and stand for hydrogen, alkyl having 1 to 6 C atoms, phenyl, naphthyl, aralkyl having 7 to 12 C atoms or heteroaryl,
- R^{VII} and R^{VIII} are each identical or different and stand for hydrogen, phenyl, naphthyl or aralkyl having 7 to 12 C atoms or stand for alkyl having 1 to 6 C atoms which is

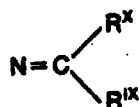


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- uninterrupted or interrupted by O, S, or NR^{I} , or, together with the nitrogen atom, form a 5- to 7-membered ring which can contain 1 or 2 identical or different hetero ring members from the group consisting of O, S and NR^{I} , or
- 5 one of the radicals R^{VII} and R^{VIII} stands for an aliphatic acyl group having up to 6 carbon atoms, R^{IX} , R^{X} , R^{XII} and R^{XIII} are each identical or different and stand for alkyl having 1 to 6 C atoms, phenyl, naphthyl or aralkyl having 7 to 12 C atoms, the alkyl, aryl,
- 10 aralkyl, heteroaryl and acyl radicals mentioned under R^1 to R^8 and under R^{I} to R^{VIII} , and the hetero ring formed with R^6 and R^7 , in their turn being unsubstituted or substituted by OH, CF_3 , OCF_3 , CN, NO_2 , halogen, alkyl having 1 to 4 C atoms, alkoxy having 1 to 4 C atoms, phenyl or benzyl,
- 15 and the following substituents being mentioned as hetero-aryl:
- thienyl, furyl, pyryl, pyridyl, quinolyl, isoquinolyl, pyrimidyl, pyridazinyl, quinazolyl, quinoxalyl, benzo-
- 20 thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, oxydiazolyl, pyrazinyl, oxazinyl, thiazinyl, indolizinyl, indolyl, benzofuranyl, indazolyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzotriazolyl, benzoxadiazolyl, cinnolinyl, phthalazinyl, naphthyridinyl or benzotriazinyl,
- 25 in the form of isomers, isomer mixtures, racemates and optical antipodes, and of their pharmaceutically acceptable salts.

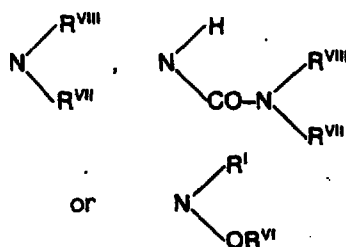
- Of particular interest are compounds of the general formula (I) in which
- 30 n stands for 0 or 1, R^1
- a) stands for hydrogen, a straight-chain, branched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical having up to 10 C atoms which can contain one or two identical or different hetero chain members from the group consisting
- 35 of O, CO, S, =N- and NR^{I} , this hydrocarbon radical being unsubstituted or substituted by F, Cl, Br, NO_2 , CN, OH, phenyl or pyridyl or
- b) stands for a phenyl, naphthyl or pyridyl radical, it being possible for these radicals to carry 1 or 2 identical

- or different substituents from the group consisting of phenyl, alkyl, alkenyl, alkoxy, alkenoxy, each having up to 4 C atoms, benzyl, acetyl, alkylene, dioxyalkylene having 2 to 4 C atoms, fluorine, chlorine, bromine, CF_3 , OCF_3 , SCF_3 , NO_2 , CN , COOR^{V} , OR^{VI} , NR^{I} and $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$, it being possible for the alkyl, alkoxy and aryl radicals of the abovementioned substituents in their turn also to be halogen-substituted or
- c) stands for the radical $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$, the radicals R^{I} to R^{VIII} mentioned under a), b) and c) having the meaning given below,
- R^2
- a) stands for one of the substituents mentioned under R^{I} but does not have to be identical thereto or
- b) stands for the radicals NHR^{I} or



- R^{I} , R^{IX} and R^{X} having the meaning given below, or the substituents
- R^{I} and R^2 together form a 5- to 7-membered saturated or unsaturated ring which optionally contains 1 or 2 identical or different ring members from the group consisting of O, S, NR^{I} and CO and which can contain 1 or 2 identical or different substituents from the group consisting of halogen, hydroxyl, alkyl, alkoxy, each having 1 to 4 C atoms, phenyl and benzyl,
- R^3 stands for one of the substituents mentioned under R^2 and is identical thereto or differs therefrom, only one of the two substituents R^2 or R^3 each standing for alkoxy, alkylthio or NHR^{I} ,
- R^4
- a) stands for hydrogen, NO_2 , CN , SR^{XI} , $\text{SO}_2\text{R}^{\text{XI}}$, R^{I} , R^{VI} , R^{VII} , R^{VIII} and R^{IX} having the meaning given below,





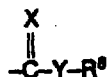
- 5
10 b) stands for a branched or unbranched alkyl or cycloalkyl radical having up to 8 C atoms, which is unsubstituted or substituted by halogen, hydroxyl, cyano, alkoxy having 1 to 4 C atoms, phenyloxy, COOR^{V} or



- 15 R^{V} , R^{VII} and R^{VIII} having the meaning given below
or

- 20 c) stands for an aromatic hydrocarbon radical having 6 to 10 C atoms or for a 5- to 7-membered saturated or unsaturated hetero ring having 1 to 3 identical or different hetero members from the group consisting of O, S, =N- and NR^{I} , this hetero ring being linked to the dihydropyridine ring either via a carbon atom or a nitrogen atom, the aromatic hydrocarbon radical and the hetero rings optionally
25 carrying 1 or 2 identical or different substituents from the group consisting of halogen, hydroxyl, cyano, CF_3 , NO_2 , phenyl, alkyl and alkoxy, each having 1 to 4 C atoms,
or

- 30 d) stands for the radical



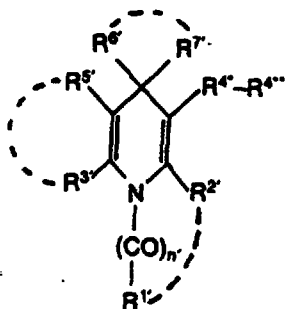
- 35 in which X stands for oxygen or NR^{I} and Y stands for a single bond, oxygen or NR^{I} and R^8 has the meaning given for R^1 and is identical to the substituent or differs therefrom, or

- e) stands for the radical





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- 5 in which n' , $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{5'}$, $R^{6'}$ and $R^{7'}$ have the meaning given for n , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 and are identical thereto or differ therefrom, and R^{4*} and R^{4**}
- 10 are identical or different and stand each for a radical, minus one hydrogen, of the substituents mentioned for R^4 under a) to d), or
- R^2 and R^4 together form a branched, unbranched, saturated or unsaturated 5- to 7-membered ring which can contain
- 15 1 or 2 identical or different ring members from the group consisting of O, CO, CS, $C=NR^I$, $=N-$ and NR^I and which is unsubstituted or substituted by halogen or hydroxyl, R^1 having the meaning given below,
- R^5 has the meaning given for R^4 and is identical to R^4 or
- 20 differs therefrom or
- R^5 and R^3 together form a ring of the kind defined for R^2 and R^4 and which is identical thereto or differs therefrom,
- R^6 stands for hydrogen or alkyl having 1 to 4 C atoms which is unsubstituted or substituted by fluorine, chlorine
- 25 or bromine and
- R^7
- a) stands for a saturated, unsaturated, cyclic, straight-chain or branched aliphatic hydrocarbon radical having up to 8 C atoms, which is unsubstituted or substituted by
- 30 halogen, or
- b) stands for a phenyl or heteroaryl radical which optionally contains 1 to 3 identical or different substituents from the group consisting of NO_2 , CN, N_3 , CF_3 , halogen, COR^{IV} , COR^V , OR^{VI} , SR^{XI} ,

35



phenyl, alkyl having 1 to 4 C atoms, benzyl and acyl



having 1 to 4 C atoms,

and in the abovementioned definitions of the substituents R^1 to R^8 ,

R^I stands for hydrogen, alkyl having 1 to 6 C atoms,
5 phenyl, naphthyl, benzyl, phenethyl, heteroaryl or acyl
having up to 4 C atoms,

R^{II} and R^{III} are identical or different and each stand for
alkyl having 1 to 6 C atoms, phenyl, naphthyl, benzyl or
heteroaryl,

10 R^{IV} , R^V and R^{VI} are each identical or different and stand
for hydrogen, alkyl having 1 to 6 C atoms, phenyl,
naphthyl, benzyl or heteroaryl,

R^{VII} and R^{VIII} are each identical or different and stand
for hydrogen, phenyl or benzyl or stand for alkyl having 1
15 to 6 carbon atoms, which is uninterrupted or interrupted
by 0 or NR^I , or, together with the nitrogen atom, form a
5- to 7-membered ring which can contain 1 or 2 identical
or different hetero ring members from the group O, S and
 NR^I

20 or

one of the radicals R^{VII} or R^{VIII} stands for an aliphatic
acyl group having up to 6 carbon atoms and R^{IX} , R^X , R^{XI} ,
 R^{XII} and R^{XIII} are each identical or different and stand
for alkyl having 1 to 6 C atoms, phenyl or benzyl,

25 and the following substituents being mentioned as
heteroaryl:

thienyl, furyl, pyryl, pyridyl, quinolyl, isoquinolyl,
pyrimidyl, pyridazinyl, quinazolyl, quinoxalyl, benzo-
thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl,
30 thiazolyl, triazolyl, oxydiazolyl, pyrazinyl, oxazinyl,
thiazinyl, indolyl, benzofuranyl, indazolyl, benzothienyl,
benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazol-
yl, benzotriazolyl or benzoxadiazolyl.

Particular preference is given to compounds of the
35 general formula (I) in which

n stands for 0,

R^1

a) stands for hydrogen, an aliphatic hydrocarbon radical
having up to 6 C atoms, which can contain a hetero chain

- 19 -

member from the group consisting of O, CO, =N- and NR^{I} and which is unsubstituted or substituted by halogen, nitro, hydroxyl or phenyl or

b) stands for a phenyl or pyridyl radical which is unsubstituted or substituted by halogen, NO_2 , CF_3 , OCF_3 , CN, COOR^{V} or $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$,

R^2 stands for one of the substituents mentioned under R^1 but does not have to be identical thereto or stands for one of the radicals NHR^{I} or $\text{N}=\text{CR}^{\text{X}}\text{R}^{\text{XI}}$,

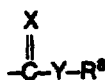
R^3 stands for one of the substituents mentioned under R^2 and is identical thereto or differs therefrom, R^4

a) stands for hydrogen, NO_2 , $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$, $\text{NH-CO-NR}^{\text{VII}}\text{R}^{\text{VIII}}$ or halogen, or

b) stands for an alkyl radical having 1 to 4 C atoms, which is unsubstituted or substituted by halogen, OH, CN, alkoxy having 1 to 4 C atoms, COOR^{V} or $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$ or

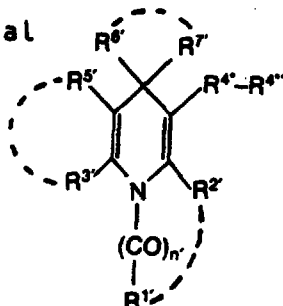
c) stands for phenyl, pyridyl or thienyl, which are unsubstituted or substituted by halogen, OH, CN, alkyl or alkoxy, each having 1 to 4 C atoms or by $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$ or

d) stands for the radical



in which X denotes oxygen and Y stands for a single bond, oxygen or NR^{I} and R^8 has the meaning given for R^1 and is identical to the substituent R^1 or differs therefrom or

e) stands for the radical



in which n' , $\text{R}^{1'}$, $\text{R}^{2'}$, $\text{R}^{3'}$, $\text{R}^{5'}$, $\text{R}^{6'}$ and $\text{R}^{7'}$ have the meaning given for n , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 and are identical thereto or differ therefrom, and R^{4*} and R^{**} are identical or different and each stand for a radical, minus

one hydrogen, of the substituents mentioned for R^4 under a) to d), or
 R^2 and R^4 together form a 5- to 7-membered ring which can contain 1 or 2 different ring members from the group consisting of O, CO, CS and $C=NR^I$ and which is unsubstituted or substituted by halogen,
 R^5 has the meaning given for R^4 and is identical to R^4 or differs therefrom,
 R^6 stands for hydrogen or alkyl having 1 to 4 C atoms and
10 R^7 has the abovementioned meaning,
the substituents R^I to R^{VIII} marked with Roman numerals in the abovementioned definitions having the meaning given above.

Very particular preference is given to compounds in
15 which at least one of the substituents R^4 and R^5 stands for NO_2 ,
and/or
in which R^2 and R^4 together or R^3 and R^5 together form a lactone ring.

20 The preparation of the 1,4-dihydropyridine derivatives according to the invention, which have a positive inotropic action, is carried out by conventional methods which are known for the preparation of 1,4-dihydropyridines (cf. for example British Patent 1,305,793; British Patent
25 1,358,951; German Offenlegungsschrift 2,752,820; German Offenlegungsschrift 2,847,237; German Offenlegungsschrift 2,629,892; German Offenlegungsschrift 2,658,804).

A few of the compounds usable according to the invention are already known from the prior art. The
30 compounds of the preparation examples 1 to 10, 19 to 23, 26, 28, 29, 30, 31, 32, 35 to 38, 41, 42, 43, 45 and 46 to 254 are novel. These novel compounds are in part covered by general substituent definitions of the prior art without, however, having been named before.

35 Novel compounds are also those from the general formula I in which at least one of the substituents R^4 and R^5 stands for the group





in which R^{VIII} and R^{VII} and the substituents R^1 , R^2 , R^3 , R^6 and R^7 and n have the abovementioned meaning, and those compounds from the general formula I in which at least one of the substituents R^4 and R^5 stands for methyl, R^1 , R^2 , R^3 , R^6 and R^7 and n having the abovementioned meaning, and those compounds from the general formula I in which one of the radicals R^4 or R^5 denotes hydrogen, R^1 stands for hydrogen and n stands for 0, and R^2 , R^3 , R^6 and R^7 and also the other radical of R^4 or R^5 have the abovementioned meaning, and those compounds from the general formula I in which one of the radicals R^4 or R^5 denotes halogen, and R^1 , R^2 , R^3 , R^6 , R^7 and n and also the other radical of R^4 or R^5 have the abovementioned meaning.

The present invention also relates to the novel compounds of the general formula (I), their preparation and use in medicaments having a positive inotropic action.

Compounds of the general formula (I) in which R^2 is different from R^3 or R^4 is different from R^5 can be obtained as racemic mixtures or in the form of optical isomers due to the presence of an asymmetric carbon atom in the 4-position of the dihydropyridine ring. Some of the compounds according to the invention which contain at least 2 asymmetric carbon atoms can be obtained in the form of individual diastereomers or in the form of mixtures thereof. The diastereomeric mixture can be resolved by using conventional methods. For example by fractional recrystallization or by chromatographic methods. Racemic mixtures can be separated by conventional methods, for example by resolution into the corresponding optical isomers by fractional recrystallization of a salt with optically active acids.

The definition of the substituents of the general formula (I) also covers some compounds which do not have a positive inotropic action. However, by using the abovementioned test on isolated atria of guinea pigs, a person skilled in the art will have no problems in recognizing

the compounds according to the invention which have a positive inotropic action and in distinguishing them from those compounds which may have been included and which have a negative inotropic action.

The present invention refers to those compounds which, from a concentration of 10^{-5} g/ml upwards, cause an at least 25% augmentation of the contraction of the isolated left atrium of the guinea pig heart.

The examples in the table which follows show the positive inotropic or contraction-augmenting action by at least 25% of some of the compounds according to the invention.

Table

Example No.	Concentration of active substance in g/ml	Example No.	Concentration of active substance in g/ml
1	10^{-7}	33	10^{-7}
2	10^{-8}	35	10^{-6}
3	10^{-6}	36	10^{-6}
4	3×10^{-7}	37	10^{-6}
5	10^{-8}	38	10^{-6}
6	10^{-7}	40	10^{-6}
7	10^{-7}	41	10^{-6}
8	10^{-6}	42	10^{-6}
9	10^{-7}	43	10^{-6}
10	10^{-7}	44	10^{-6}
11	10^{-8}	45	10^{-6}
12	10^{-6}	49	10^{-6}
13	10^{-6}	55	10^{-7}
14	10^{-6}	56	10^{-6}
15	10^{-8}	59	10^{-6}
16	10^{-6}	60	3×10^{-6}
17	10^{-7}	64	10^{-6}
18	3×10^{-6}	65	10^{-6}
19	10^{-8}	67	3×10^{-7}
20	3×10^{-7}	68	3×10^{-7}
21	10^{-7}	69	10^{-7}
22	10^{-6}	72	10^{-7}
23	3×10^{-7}	73	10^{-7}
24	10^{-8}	77	10^{-6}
25	10^{-6}	78	3×10^{-6}
26	10^{-7}	79	10^{-7}
27	10^{-7}	80	10^{-7}
29	10^{-7}	86	10^{-6}
31	10^{-6}	88	10^{-6}
32	10^{-7}	92	10^{-6}
		93	10^{-6}



Example No.	Concentration of active substance in g/ml	Example No.	Concentration of active substance in g/ml
94	10^{-6}	219	10^{-5}
98	10^{-7}	220	10^{-6}
99	10^{-5}	221	10^{-6}
101	10^{-6}	222	10^{-6}
102	10^{-6}	223	3×10^{-6}
104	3×10^{-7}	224	10^{-6}
105	10^{-7}	225	10^{-6}
108	10^{-6}	226	10^{-6}
111	3×10^{-6}	227	10^{-6}
112	10^{-7}	228	10^{-6}
114	10^{-6}	229	10^{-5}
117	10^{-6}	230	10^{-7}
118	10^{-7}	231	10^{-6}
124	10^{-7}	232	10^{-6}
126	10^{-6}	233	10^{-6}
132	10^{-7}	234	10^{-6}
144	10^{-7}	235	3×10^{-5}
145	10^{-7}	236	10^{-6}
146	10^{-6}	239	3×10^{-7}
147	10^{-7}	240	3×10^{-8}
148	10^{-7}	241	10^{-7}
149	10^{-7}	242	3×10^{-7}
152	10^{-7}	245	3×10^{-7}
156	3×10^{-7}	246	3×10^{-7}
157	10^{-6}	247	10^{-6}
158	10^{-7}	248	3×10^{-7}
159	10^{-6}	250	3×10^{-7}
164	10^{-6}	251	10^{-7}
167	10^{-5}	257	3×10^{-7}
170	10^{-6}		
173	10^{-7}		
174	10^{-6}		
175	10^{-6}		
177	10^{-6}		
179	3×10^{-7}		
181	10^{-6}		
186	10^{-7}		
187	10^{-7}		
189	3×10^{-7}		
190	10^{-6}		
191	10^{-6}		
193	10^{-7}		
195	3×10^{-6}		
196	10^{-6}		
197	3×10^{-6}		
198	3×10^{-7}		
199	3×10^{-7}		
200	10^{-7}		
202	10^{-7}		
203	10^{-6}		
208	10^{-7}		
210	3×10^{-6}		
211	10^{-6}		
212	3×10^{-7}		
214	3×10^{-6}		
215	3×10^{-7}		
216	10^{-6}		
217	10^{-5}		
218	10^{-6}		

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The compounds according to the invention show an unexpected and valuable pharmacological spectrum of action. They can serve as cardiac stimulants for improving cardiac contractility. Furthermore, by virtue of the fact that
5 they increase the Ca^{++} influx into the cells, they can be used as antihypotensives, for reducing blood sugar, for decreasing the swelling of mucous membranes and for influencing the salt and fluid balance.

The compounds according to the invention can be
10 converted in a known manner to the customary formulations.

The novel active substances can be converted in a known manner to the customary formulations such as tablets, capsules, sugar-coated tablets, pills, granulates, aerosols, syrups, emulsions, suspensions and solutions, by
15 using inert, non-toxic, pharmaceutically suitable vehicles or solvents. In each case, the therapeutically active compound should be present at concentrations of about 0.5 to 90% by weight of the total mixture, that is in amounts which are sufficient to obtain the dosage range given.

20 The formulations are prepared, for example, by extending the active substances with solvents and/or vehicles, if desired, by using emulsifiers and/or dispersing agents, it being possible, for example, if water is used as the diluent, to use organic solvents as auxiliary
25 solvents.

Auxiliary substances are, for example:

Water, non-toxic organic solvents such as paraffins (for example crude oil fractions), vegetable oils (for example peanut/sesame oil), alcohols (for example ethyl
30 alcohol, glycerol), glycols (for example propylene glycol, polyethylene glycol), solid vehicles such as, for example, natural mineral powders (for example kaolins, clays, talcum, chalk), synthetic mineral powders (for example highly dispersed silica, silicates), sugars (for example
35 cane and milk sugar and glucose), emulsifiers (for example polyoxyethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, alkylsulphonates and arylsulphonates), dispersing agents (for example lignin, sulphite waste liquors, methylcellulose, starch and polyvinylpyrrolidone)



- 25 -

and lubricants (for example magnesium stearate, talcum, stearic acid and sodium lauryl sulphate).

The administration is carried out in the conventional manner, preferably orally or parenterally, in particular perlingually or intravenously. In the case of oral use, tablets can, of course, also contain, in addition to the vehicles mentioned, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with a variety of adjuvants such as starch, preferably potato starch, gelatin and the like. Furthermore, lubricants such as magnesium stearate, sodium lauryl sulphate and talcum can also be used for tablet-making. In the case of aqueous suspensions and/or elixirs which are intended for oral use, besides the abovementioned auxiliaries a variety of taste-improving agents or dyes can be added to the active substances.

For parenteral administration, solutions of the active substances in combination with suitable liquid vehicles can be used.

In general, it is advantageous in intravenous administration to give amounts of about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg of body weight to obtain effective results, and in oral administration the dosage is about 0.01 to 20 mg/kg, preferably 0.1 to 10 mg/kg of body weight.

Nevertheless, in some cases it may be necessary to deviate from the amounts mentioned, depending on the body weight of the test animal or on the method of administration and also depending on the type of animal and its individual behaviour towards the medicament or the type thereof on its formulation and the date or interval at which it is given. Thus, in some cases it may be sufficient to make do with less than the predetermined minimum amount, whereas in other cases the upper limit mentioned must be exceeded. If larger amounts are given it is recommended to spread them over a day in several individual doses. An identical dosage range is intended for use in human medicine. What has been said above equally applies there.

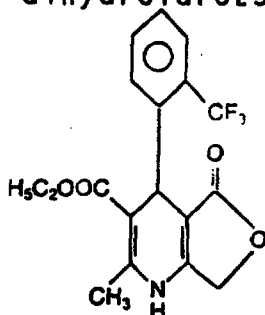


Preparation Examples

Example 1

Ethyl 2-methyl-4-(2-trifluoromethylphenyl)-5-oxo-1,4-dihydro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate

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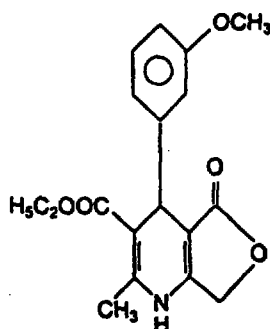
50 mmol each of ethyl 4-acetoxy-3-oxobutyrates, ethyl 3-aminocrotonate and 2-trifluoromethylbenzaldehyde were refluxed in 100 ml of ethanol for 24 hours, subsequently treated with 2 g of potassium hydroxide and boiled for another hour. After cooling, the product was precipitated with a water/sodium chloride mixture and recrystallized from methanol.

Yield: 45% of theory; m.p.: 195°C.

Example 2

Ethyl 2-methyl-4-(3-methoxyphenyl)-5-oxo-1,4-dihydro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate

25

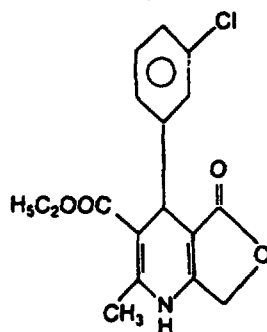


Preparation analogous to Example 1 using 3-methoxybenzaldehyde instead of 2-trifluoromethylbenzaldehyde. Yield: 30% of theory; m.p.: 180°C.

Example 3

Ethyl 2-methyl-4-(3-chlorophenyl)-5-oxo-1,4-dihydro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate

- 27 -



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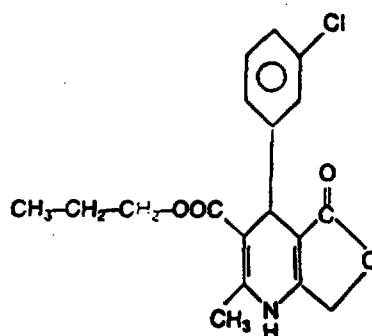
Preparation analogous to Example 1 using 3-chlorobenzaldehyde instead of 2-trifluoromethylbenzaldehyde.

10 Yield: 50% of theory; m.p.: 196°C.

Example 4

Propyl 2-methyl-4-(3-chlorophenyl)-5-oxo-1,4-dihydro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate

15



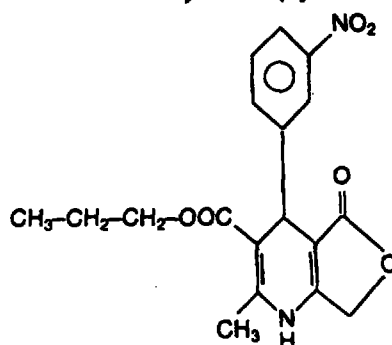
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Preparation analogous to example 1 using 3-chlorobenzaldehyde instead of 2-trifluoromethylbenzaldehyde and propyl 3-aminocrotonate instead of ethyl 3-aminocrotonate. Yield: 42% of theory; m.p.: 166°C.

25 Example 5

Propyl 2-methyl-4-(3-nitrophenyl)-5-oxo-1,4-dihydro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate

30



35 Preparation analogous to Example 1 using 3-nitrobenzaldehyde instead of 2-trifluoromethylbenzaldehyde and propyl 3-aminocrotonate instead of ethyl 3-aminocrotonate. Yield: 50% of theory; m.p.: 196°C.

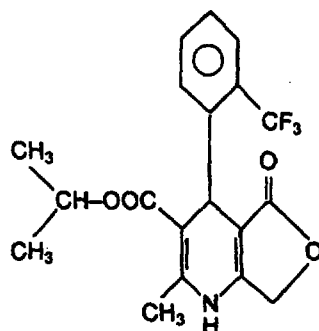


Example 6

Isopropyl 2-methyl-4-(3-trifluoromethylphenyl)-5-oxo-1,4-dihydro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate

5

10



Preparation analogous to Example 1 using isopropyl 3-aminocrotonate instead of ethyl 3-aminocrotonate.

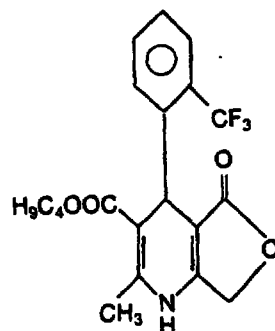
15 Yield: 18% of theory; m.p.: 219-223°C.

Example 7

Butyl 2-methyl-4-(2-trifluoromethylphenyl)-5-oxo-1,4-dihydro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate

20

25



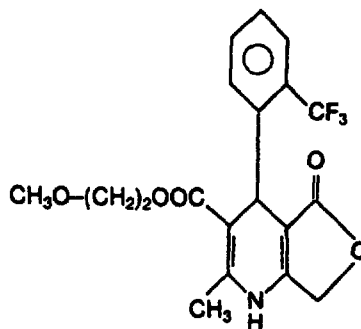
Preparation analogous to Example 1 using butyl 3-aminocrotonate instead of ethyl 3-aminocrotonate.

Yield: 10% of theory; m.p.: 194-195°C.

Example 8

30 2-Methoxyethyl 2-methyl-4-(2-trifluoromethylphenyl)-5-oxo-1,4-dihydro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate

35



Preparation analogous to Example 1 using 2-methoxyethyl



- 29 -

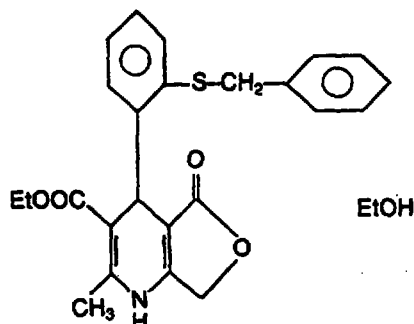
3-aminocrotonate instead of ethyl 3-aminocrotonate.

Yield: 16% of theory; m.p.: 196-197°C.

Example 9

Ethyl 2-methyl-4-(2-benzylthiophenyl)-5-oxo-1,4-dihydro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate

10



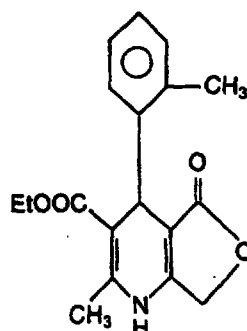
Preparation analogous to Example 1 using 2-benzylthio-benzaldehyde instead of 2-trifluoromethylbenzaldehyde.

Yield: 31% of theory; m.p.: 189-190°C (from EtOH).

Example 10

Ethyl 2-methyl-4-(2-methylphenyl)-5-oxo-1,4-dihydro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate

20



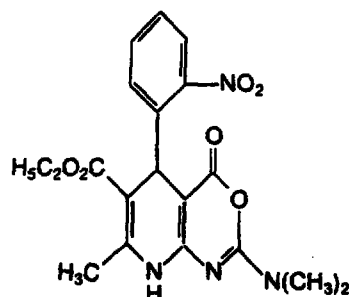
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Preparation analogous to Example 1 using 2-methylbenzaldehyde instead of 2-trifluoromethylbenzaldehyde.

Yield: 45%, m.p. 196-198°C.

Example 11

30



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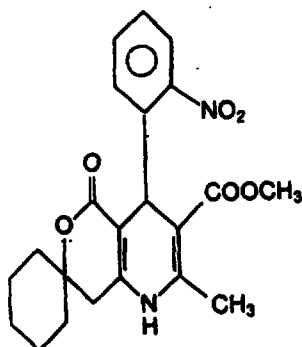
33.8 g (90 mmol) of diethyl 2-amino-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate were stirred together with 14.6 g (90 mmol) of dichloromethyl-enedimethylammonium chloride in 200 ml of chlorobenzene

- 30 -

for 2 hours at 80°C. The mixture was then cooled with ice, and the precipitate was filtered off with suction and taken up in a cold 10% strength sodium bicarbonate solution. The aqueous phase was extracted several times with methylene chloride. Drying of the extracts over Na₂SO₄ and removal of the solvent by distillation gave 16.6 g (46% of theory) of the reaction product of melting point m.p.: 216-218°C.

Example 12

10 Methyl 1,4-dihydro-2-methyl-5-oxo-7,7-pentamethylene-4-(2'-nitrophenyl)-7H-pyrano[4,3-b]pyridine-3-carboxylate

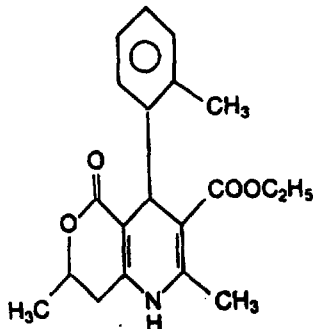


15

20 4.6 g of 6,6-pentamethylenetetrahydropyran-2,4-dione, 3.8 g of 2-nitrobenzaldehyde and 2.9 g of methyl 3-amino-crotonate are refluxed in 100 ml of ethanol/glacial acetic acid (5:1) for 10 hours. After cooling to room temperature, the precipitate is filtered off with suction. Recrystallization from ethanol gives 6 g (58% of theory) of m.p.: 228°C.

Example 13

30 Ethyl 1,4-dihydro-2,7-dimethyl-4-(2'-methylphenyl)-5-oxo-7H-pyrano[4,3-b]pyridine-3-carboxylate



35

A solution of 4.3 g of 6-methyltetrahydropyran-2,4-dione, 4.0 g of 2-methylbenzaldehyde and 4.3 g of ethyl



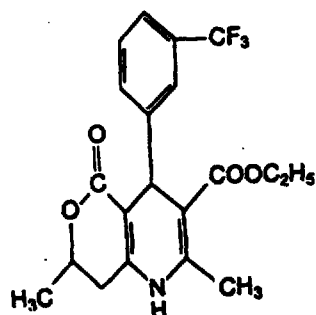
- 31 -

3-aminocrotonate is refluxed in 80 ml of ethanol/glacial acetic acid (5:1) for 10 hours. The mixture is concentrated in vacuo, and the residue is recrystallized from ethanol: 5.3 g (50% of theory) of m.p.: 213°C.

The following were obtained analogously:

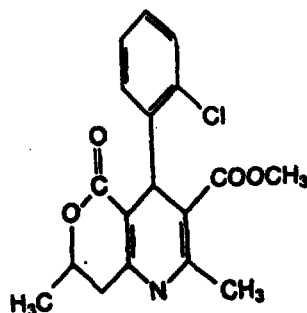
Example 14

Ethyl 1,4-dihydro-2,7-dimethyl-4-(3'-trifluoromethylphenyl)-5-oxo-7H-pyrano[4,3-b]pyridine-3-carboxylate of m.p.: 210°C.



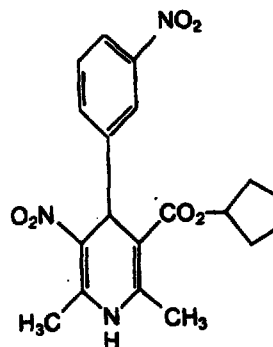
Example 15

Methyl 1,4-dihydro-2,7-dimethyl-4-(2'-chlorophenyl)-5-oxo-7H-pyrano[4,3-b]pyridine-4-carboxylate of m.p.: 252-254°C.



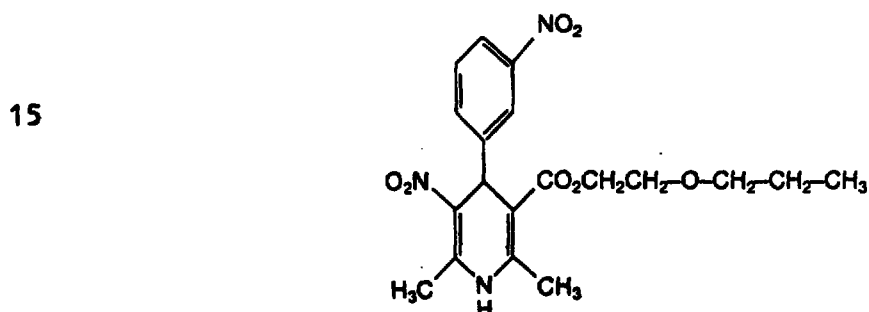
Example 16

Cyclopentyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(3-nitrophenyl)pyridine-5-carboxylate



15.1 g (0.1 mol) of 3-nitrobenzaldehyde are refluxed together with 16.9 g (0.1 mol) of cyclopentyl β -aminocrotonate and 10.3 g (0.1 mol) of nitroacetone in 150 ml

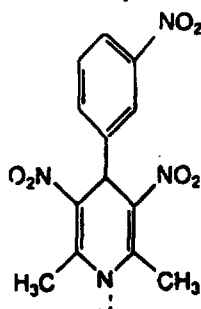
β-n-propoxyethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(3-nitrophenyl)pyridine-5-carboxylate



15.1 g (0.1 mol) of 3-nitrobenzaldehyde are refluxed together with 18.8 g (0.1 mol) of β -n-propoxyethyl acetoacetate and 10.2 g (0.1 mol) of 2-amino-1-nitro-1-propene in 150 ml of ethanol for 6 hours. After cooling, the solvent is distilled off in vacuo, the oily residue is taken up in a small amount of chloroform and chromatographed on a silica gel column using chloroform with the addition of methanol. The fractions containing the product are concentrated, the residue is taken up in a small amount of isopropanol, nitrodihydropyridine crystallized in yellow crystals of melting point 161°C.

Yield: 41% of theory.

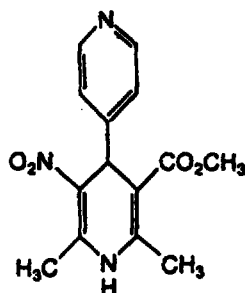
1,4-dihydro-2,6-dimethyl-3,5-dinitro-4-(3-nitro-phenyl)pyridine



- 33 -

23.6 g (0.1 mol) of 2-nitro-1-(3-nitrophenyl)-1-buten-3-one and 10.2 g (0.1 mol) of 2-amino-1-nitro-1-propene are refluxed in 150 ml of ethanol for 12 hours. After cooling, the solvent is distilled off in vacuo, the oily residue is taken up in chloroform and chromatographed on a silica gel column using chloroform with the addition of methanol. The product forms yellow crystals of melting point 237-240°C (Dec.) in isopropanol. Yield: 38% of theory.

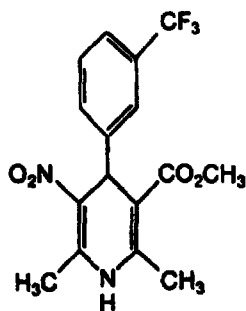
10 Example 19



15

Analogously to Example 16, methyl 1,4-dihydro-2,6-dimethyl-4-(4-pyridyl)-3-nitropyridine-5-carboxylate of melting point 210°C (Dec.) (isopropanol) was obtained by reaction of 50 mmol of pyridine-4-aldehyde with 50 mmol of methyl acetoacetate and 50 mmol of 2-amino-1-nitro-1-propene in ethanol. Yield: 19% of theory.

25 Example 20



30

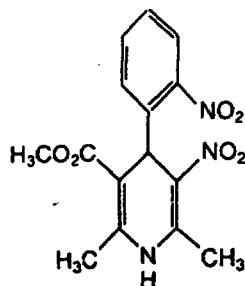
Analogously to Example 16, methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(3-trifluoromethylphenyl)pyridine-5-carboxylate of melting point 175°C (isopropanol) was obtained by reaction of 50 mmol of 3-trifluoromethylbenzaldehyde with 50 mmol of nitroacetone and 50 mmol of methyl β-aminocrotonate. Yield: 42% of theory.



- 34 -

Example 21

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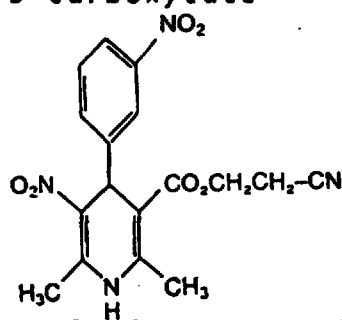
Analogously to Example 16, methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-nitrophenyl)pyridine-5-carboxylate of melting point 190°C (isopropanol) was obtained by reaction of 50 mmol of 2-nitrobenzaldehyde with 50 mmol of nitroacetone and 50 mmol of methyl β -aminocrotonate as a very light-sensitive compound.

Yield: 12% of theory.

15 Example 22

β -Cyanoethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(4-nitrophenyl)pyridine-5-carboxylate

20

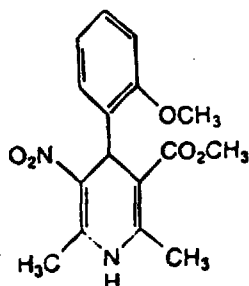


Analogously to Example 18, β -cyanoethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(3-nitrophenyl)pyridine-5-carboxylate of melting point 210°C (isopropanol) was obtained by reaction of 50 mmol of 2-nitro-1-(3-nitro-phenyl)-1-butene-3-one with 50 mmol of β -cyanoethyl aminocrotonate in 100 ml of ethanol.

Yield: 33% of theory.

Example 23

35



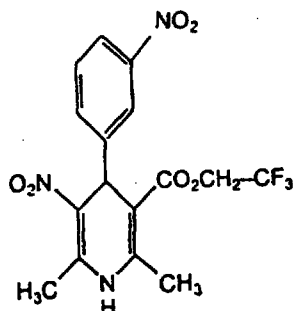
Analogously to Example 18, methyl 1,4-dihydro-2,6-dimethyl-4-(2-methoxyphenyl)-3-nitropyridine-5-carboxylate of melting point 206°C (ethanol) was obtained by reaction

- 35 -

of 50 mmol of methyl 2-methoxybenzylidene acetoacetate and 50 mmol of 2-amino-1-nitro-1-propene [sic] in ethanol. Yield: 44% of theory.

Example 24

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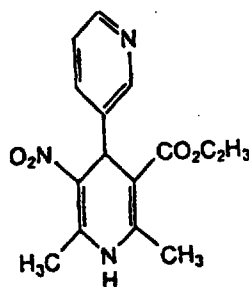
10

Analogously to Example 18, β -trifluoroethyl 1,4-di-hydro-2,6-dimethyl-3-nitro-4-(3-nitrophenyl)pyridine-5-carboxylate of melting point 196°C (ethanol) was obtained by reaction of β -trifluoroethyl 3-nitrobenzylidene acetoacetate with 2-amino-1-nitro-1-propene in ethanol. Yield: 28% of theory.

15

Example 25

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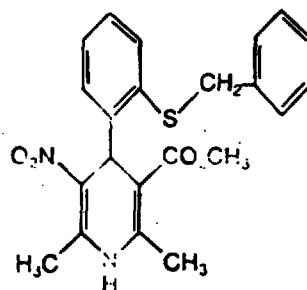
25

Analogously to Example 16, ethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(pyridyl)-3-pyridine-5-carboxylate of melting point 264°C (isopropanol) was obtained by reaction of pyridine-3-aldehyde with ethyl β -aminocrotonate and nitroacetone in ethanol. Yield: 34% of theory.

30

Example 26

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Analogously to Example 17, methyl 4-(2-benzylthiophenyl)-1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate of melting point 173°C (isopropanol) was obtained by reaction

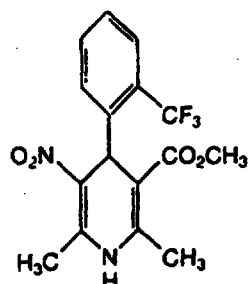


of 2-benzylthiobenzaldehyde with 2-amino-1-nitro-1-propene and methyl acetoacetate in ethanol.

Yield: 21% of theory.

Example 27

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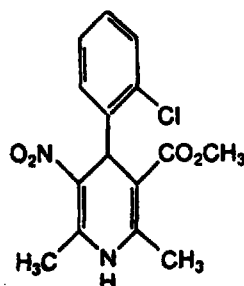


10 Analogously to Example 16, methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate of melting point 176°C (ethanol) was obtained by reaction of 2-trifluoromethylbenzaldehyde with methyl β-aminocrotonate and nitroacetone in ethanol.

15 Yield: 36% of theory.

Example 28

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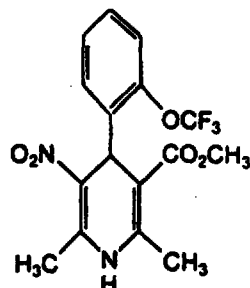


Analogously to Example 16, methyl 4-(2-chlorophenyl)-1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate of
25 melting point 167°C (isopropanol) was obtained by reaction of 2-chlorobenzaldehyde with methyl β-aminocrotonate and nitroacetone in ethanol.

Yield: 42% of theory.

Example 29

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35

Analogously to Example 18, methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethoxyphenyl)pyridine-5-carboxylate of melting point 175°C (isopropanol) was obtained by reaction of 50 mmol of methyl 2-trifluoro-

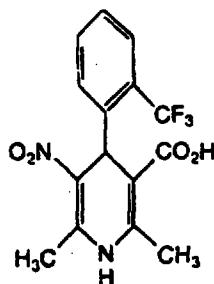
- 37 -

methoxybenzylideneacetoacetate with 50 mmol of 2-amino-1-nitro-1-propene in ethanol.

Yield: 39% of theory.

Example 30

5



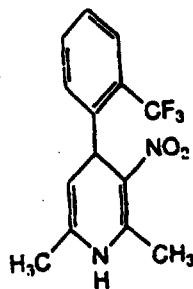
The treatment of β -cyanoethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate in [sic] 1.2 equivalents of potassium hydroxide in aqueous ethylene glycol dimethyl ether at room temperature gives, after acidification with dilute HCl, 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylic acid of melting point 183°C (decomposition) (methanol).

15

Yield: 89% of theory.

Example 31

20



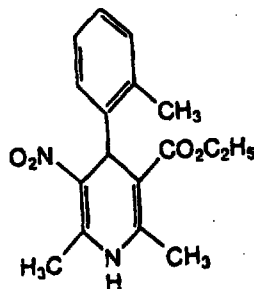
25

1,4-Dihydro-2,6-dimethyl-3-nitro-4-(trifluoromethylphenyl)pyridine-5-carboxylic acid (Example 30) is decarboxylated to give 1,4-dihydro-2,6-dimethyl-3-nitro-4-(trifluoromethylphenyl)pyridine with quantitative yield upon heating in ethanol with the addition of a trace of sulphuric acid. Melting point: 201°C .

30

Example 32

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Analogously to Example 18, ethyl 1,4-dihydro-2,6-dimethyl-

- 38 -

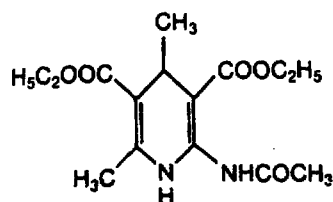
4-(2-tolyl)-3-nitropyridine-5-carboxylate of melting point 155°C (isopropanol) was obtained by reaction of ethyl 2-methylbenzylidene acetoacetate with 2-amino-1-nitro-1-propene in ethanol.

5 Yield: 42% of theory.

Example 33

Diethyl 2-acetylamino-4,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

10



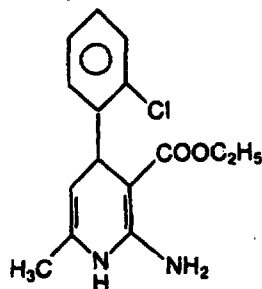
8 g (0.03 mol) of diethyl 2-amino-4,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate are refluxed in 100 ml of acetic anhydride for 4 hours. The mixture is evaporated to dryness in vacuo, and the residue is recrystallized from ethanol.

Yield: 5.4 g (58% of theory) of m.p.: 105°C.

20 Example 34

Ethyl 2-amino-6-methyl-1,4-dihydro-4-(2'-chlorophenyl)-pyridine-3-carboxylate

25



After boiling a solution of 18.1 g of 2'-chlorobenzylidene acetone and 13.0 g of ethyl amidinoacetate in 150 ml of ethanol for 2 hours, the solvent is removed in vacuo.

The residue is recrystallized from ethanol.

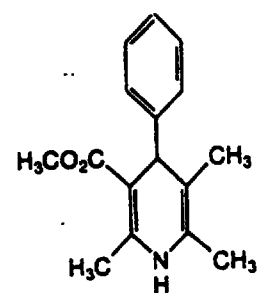
Yield: 62% of theory, m.p.: 171°C.

Example 35 .

35 Methyl 1,4-dihydro-4-phenyl-2,3,6-trimethylpyridine-5-carboxylate



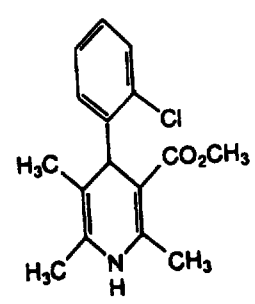
5



24.1 g (80 mmol) of methyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate [sic] are added in portions at 60°C with stirring to a solution of 12.2 g (320 mmol) of LiAlH₄ in 400 ml of absolute tetrahydrofuran (N₂ atmosphere), and the mixture is stirred for 6 to 7 hours at 60°C. After cooling, 19.7 ml of ethyl acetate, 15.9 ml of water, 19.6 ml of N[sic] NaOH and 15.9 ml of water are added dropwise in succession. The mixture is then filtered with suction, the precipitate is thoroughly washed with ether, and the filtrate is evaporated in vacuo. The syrup-like residue is dissolved in 50 ml of ether and allowed to crystallize in the cold, 7.4 g, i.e. 36% of theory. After recrystallization from acetonitrile, colourless prisms; melting point 120°C.

Example 36

25



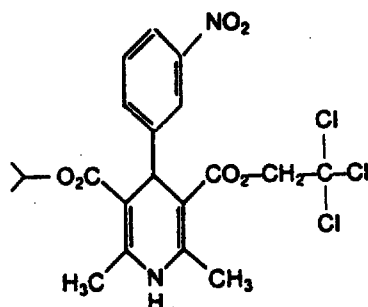
Analogously to Example 35, methyl 4-(2-chlorophenyl)-1,4-dihydro-2,3,6-trimethylpyridine-5-carboxylate of melting point 164°C (acetonitrile) was obtained at [sic] 4-(2-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate by reduction with LiAlH₄ in THF. Yield: 30% of theory.

Example 37

Isopropyl 2,2,2-trichloroethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.



- 40 -

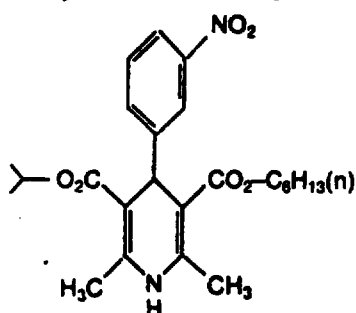


5

A solution of 30.2 g (0.2 mol) of 3-nitrobenzaldehyde, 46.6 g (0.2 mol) of 2,2,2-trichloroethyl acetoacetate and 28.6 g (0.2 mol) of isopropyl 3-aminocrotonate in 200 ml of ethanol was heated to boiling for 12 hours under nitrogen. The solvent [sic] was concentrated in vacuo, the solid residue was recrystallized from ethanol. Melting point :192°C; Yield 46 g (47% of theory).

15 Example 38

n-Hexyl isopropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitro-phenyl)pyridine-3,5-dicarboxylate

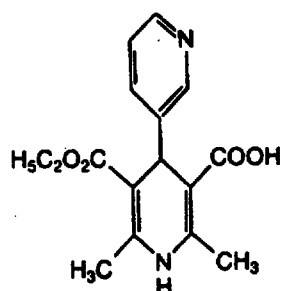


20

25 Prepared analogously to Example 32 from 0.2 mol of 3-nitrobenzaldehyde, 0.2 mol of n-hexyl acetoacetate and 0.2 mol of isopropyl 3-aminocrotonate. Melting point 87°C; yield 75%.

Example 39

30 Monoethyl 1,4-dihydro-2,6-dimethyl-4-(pyridyl)-3-pyridine-3,5-dicarboxylate



35

Prepared according to German Offenlegungsschrift 2,847,237 (Example No. 14). Melting point 205°C (Dec.);

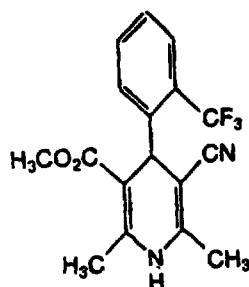


Yield: 32% of theory.

Example 40

Methyl 3-cyano-1,4-dihydro-2,6-dimethyl-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate

5



10

Prepared according to German Offenlegungsschrift 2,658,804 (Example No. 17). Melting point 171°C;

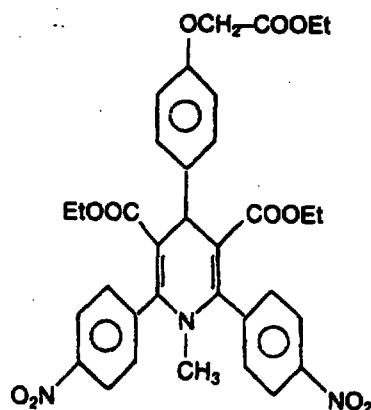
Yield: 42% of theory.

Example 41

15

Diethyl 2,6-di-(4-nitrophenyl)-4-(4-ethoxycarbonylmethoxy)-1-methyl-1,4-dihydropyridine-3,5-dicarboxylate

20



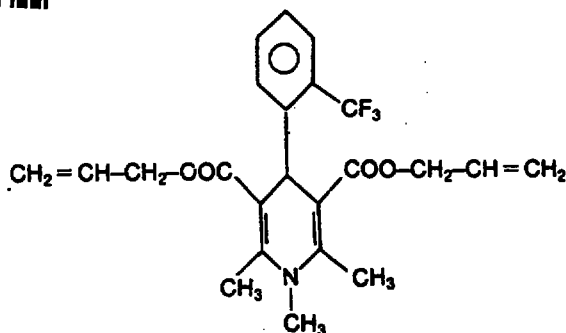
25

100 mmol of 4-(ethoxycarbonylmethoxy)benzaldehyde were heated at 100°C for 5 hours with 200 mmol of ethyl 4-nitrobenzoylacetate and 100 mmol of methylamine hydrochloride in 60 ml of pyridine. The mixture was poured into icewater and the product filtered off with suction. Yield 11% of theory; m.p.: 136°C.

Example 42

Diallyl 2,6-dimethyl-4-(2-trifluoromethyl)-1-methyl-1,4-dihydropyridine-3,5-dicarboxylate

- 42 -



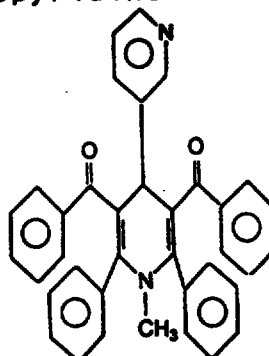
5

100 mmol of 2-trifluoromethylbenzaldehyde, 200 mmol of allyl acetoacetate and 120 mmol of methylamine hydrochloride were heated in 50 ml of pyridine at 110°C for 5 hours, poured into water and the product was filtered off with suction.

Yield: 5% of theory; m.p.: 90 to 91°C.

Example 43

15 2,6-Diphenyl-3,5-di(phenylcarbonyl)-1-methyl-4-(pyridiyl[sic])-1,4-dihydropyridine



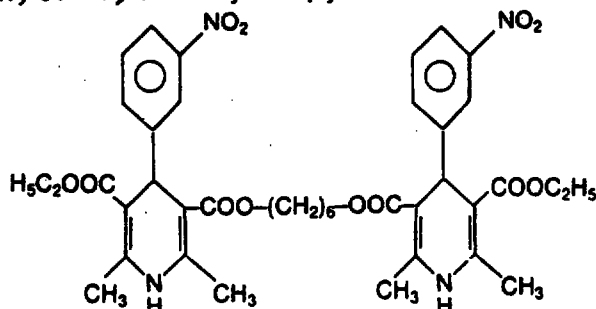
20

1.3 ml of pyridine-3-carbaldehyde, 6 g of dibenzoylmethane and 1 g of methylaminehydrochloride are heated at 100°C overnight in 10 ml of pyridine, then poured into ice water, the product is filtered off with suction and recrystallized from methanol.

Yield: 15% of theory; m.p.: 238°C.

30 Example 44

Hexane-1,6-diyl bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



35

25 mmol of hexane-1,6-diyl bis-3-aminocrotonate are

- 43 -

refluxed together with 50 mmol of ethyl 3-nitrobenzylideneacetoacetate in 100 ml of ethanol for 14 hours.

After cooling, the solvent is distilled off in vacuo, and the residue is taken up in 50% strength aqueous ethanol.

5 The semi-solid residue was recrystallized from methanol.

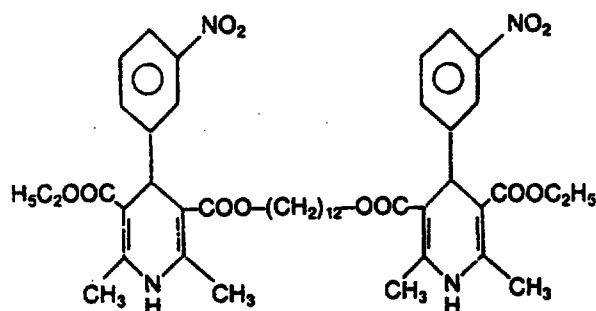
Yield: 37% of theory; m.p.: 177 to 179°C.

Example 45

Dodecane-1,12-diyl bis[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]

10

15

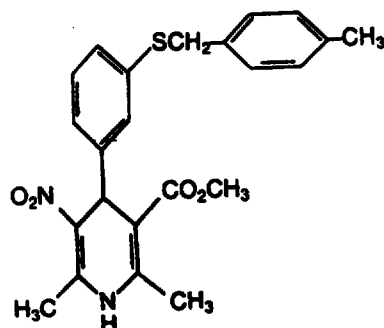


Preparation analogous to Example 44 using dodecane-1,12-diyl bis-3-aminocrotonate instead of hexane-1,6-diyl bis-3-aminocrotonate.

20 Yield: 10% of theory; m.p.: 103 to 120°C.

Example 46

25

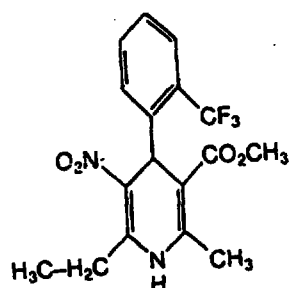


Analogously to Example 17, methyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzylthio)phenyl]-3-nitropyridine-5-carboxylate of melting point 160°C (isopropanol) was obtained by reaction of 2-(4-methylbenzylthio)benzaldehyde with 2-amino-1-nitro-1-propene and methyl acetoacetate in ethanol. Yield: 28% of theory.

30

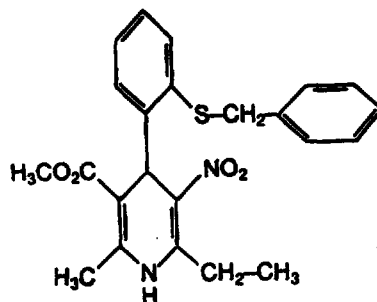


Example 47



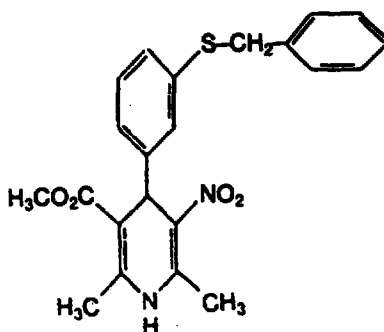
Analogously to Example 16, methyl 1,4-dihydro-2-ethyl-6-methyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate of melting point 199°C (isopropanol)[sic] was obtained by reaction of 2-trifluoromethylbenzaldehyde with methyl β -aminocrotonate and 1-nitro-2-butanone in ethanol. Yield: 31% of theory.

Example 48



Analogously to Example 16, methyl 4-(2-benzylthiophenyl)-1,4-dihydro-2-ethyl-6-methyl-3-nitropyridine-5-carboxylate of melting point 122°C (isopropanol) was obtained by reaction of 2-benzylthiobenzaldehyde with methyl β -aminocrotonate and 1-nitro-2-butanone in ethanol. Yield: 21% of theory.

Example 49



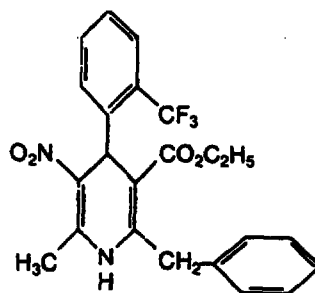
Analogously to Example 16, methyl 4-(3-benzylthiophenyl)-1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate of melting point 155°C (ethanol) was obtained by reaction of 3-benzylthiobenzaldehyde with methyl β -aminocrotonate and

nitroacetone in ethanol.

Yield: 35% of theory.

Example 50

5

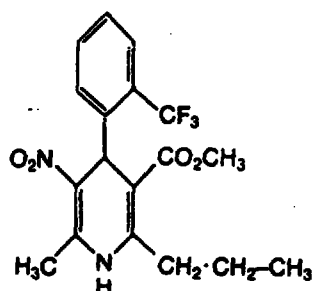


10 Analogously to Example 17, ethyl 2-benzyl-1,4-dihydro-6-methyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate of melting point 168°C was obtained by reaction of 2-trifluoromethylbenzaldehyde with ethyl γ -phenylacetoacetate and 2-amino-1-nitro-1-propene in ethanol.

15 Yield: 12% of theory.

Example 51

20

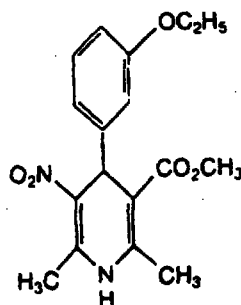


25 Analogously to Example 17, methyl 1,4-dihydro-2-methyl-3-nitro-6-propyl-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate of melting point 168°C (isopropanol) was obtained by reaction of 2-trifluoromethylbenzaldehyde with 2-amino-1-nitro-1-propene and methyl 3-oxohexanoate in ethanol.

Yield: 19% of theory.

Example 52

35



Analogously to Example 16, methyl 1,4-dihydro-2,6-dimethyl-4-(3-ethoxyphenyl)-3-nitropyridine-5-carboxylate of melting point 127°C was obtained by reaction of 3-ethoxybenzaldehyde

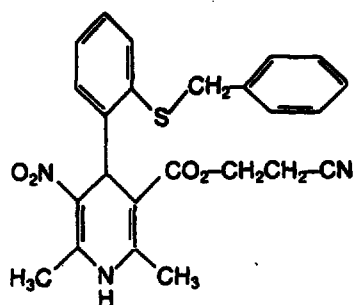
- 46 -

with nitroacetone and methyl β -aminocrotonate.

Yield: 42% of theory.

Example 53

5

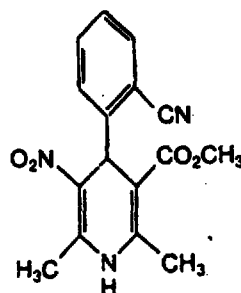


10 Analogously to Example 16, β -cyanoethyl 4-(2-benzylthiophenyl)-1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate of melting point 173°C (isopropanol) was obtained by reaction of 2-benzylthiobenzaldehyde with nitroacetone and β -cyanoethyl β -aminocrotonate in ethanol-[sic].

15 Yield: 28% of theory.

Example 54

20

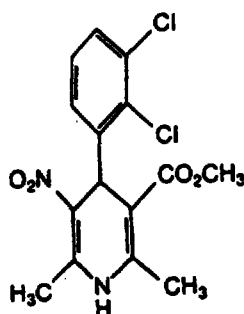


25 Analogously to Example 16, methyl 4-(2-cyanophenyl)-1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate of melting point 182°C (isopropanol) was obtained by reaction of 2-cyanobenzaldehyde with nitroacetone and methyl β -aminocrotonate in ethanol.

Yield: 28% of theory.

30 Example 55

35



Analogously to Example 16, methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate of melting point 184°C was obtained by reaction of

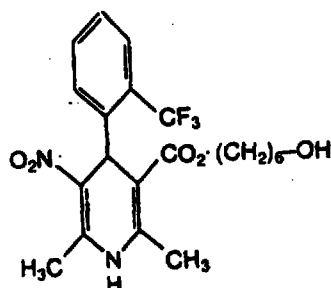
- 47 -

2,3-dichlorobenzaldehyde with nitroacetone and methyl β -aminocrotonate in ethanol.

Yield: 39% of theory.

Example 56

5



10

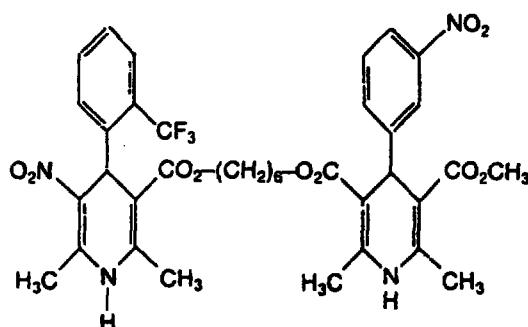
Analogously to Example 16, 6-hydroxyhexyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate of melting point 174°C was obtained by reaction of 2-trifluoromethylbenzaldehyde with nitroacetone and 6-hydroxyhexyl β -aminocrotonate in ethanol.

15

Yield: 32% of theory.

Example 57

20



Methyl 5-6-[2,6-dimethyl-5-nitro-4-(2-trifluoromethylphenyl)-1,4-dihydropyrid-3-ylcarboxy]hexyloxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate is obtained as an amorphous, yellow substance by reaction of 1 equivalent of 6-hydroxyhexyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate with 1 equivalent of 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-carboxymethylpyridine-5-carboxylic acid and 1.1 equivalents of dicyclohexylcarbodiimide in the [sic] methylene chloride.

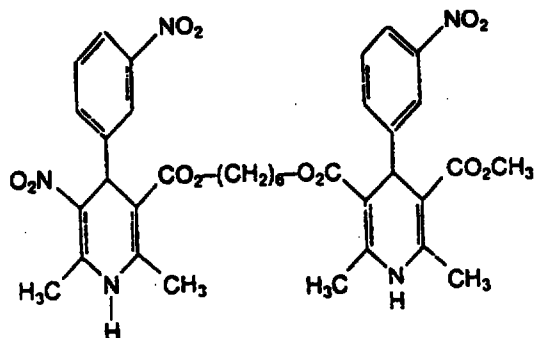
Yield: 68% m/e: 756 $\hat{=}$ M^+ .

Elemental analysis	C	H	N	F
calculated	58.7%	5.2%	7.4%	7.5%
found	58.5%	5.2%	7.2%	7.0%



Example 58

5



Analogously to the previous example, methyl 5-6-[2,3-
 10 dimethyl-5-nitro-4-(3-nitrophenyl)-1,4-dihydropyrid-3-ylcarboxyl]hexyloxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate is obtained as an amorphous, yellow substance by reaction of 6-hydroxyhexyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(3-nitrophenyl)pyridine-5-
 15 carboxylate with 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-carboxymethylpyridine-5-carboxylic acid and dicyclohexylcarbodiimide in methylene chloride is obtained [sic].

Yield: 73%

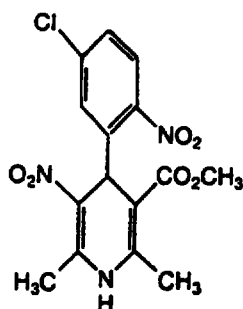
20 $m/e: 733 \hat{=} M^+$

Elemental analysis

	C	H	N
calculated	58.9%	5.3%	9.5%
found	58.7%	5.2%	9.6%

Example 59

25



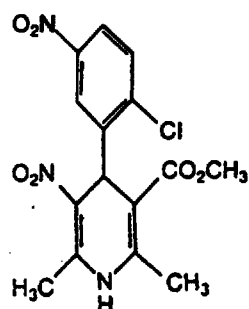
30

Analogously to Example 16, methyl 4-(5-chloro-2-nitrophenyl)-2,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate of melting point 221°C (isopropanol) was obtained
 35 by reaction of 5-chloro-2-nitrobenzaldehyde with nitroacetone and methyl β -aminocrotonate in ethanol.
 Yield: 43% of theory.



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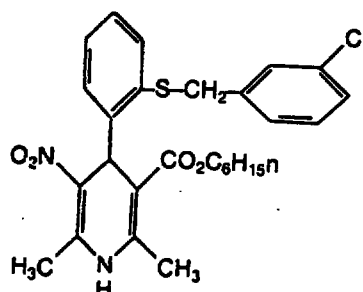
Example 60



Analogously to Example 16, methyl 4-(2-chloro-5-nitrophenyl)-1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate of melting point 219°C was obtained by reaction of 2-chloro-5-nitrobenzaldehyde with nitroacetone and methyl β -aminocrotonate in ethanol.

Yield: 39% of theory.

Example 61



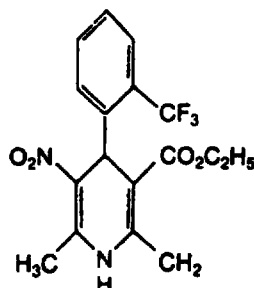
Analogously to Example 16, n-hexyl 4-(3-chlorobenzylthio)phenyl)-1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate was obtained after chromatography by reaction of 2-(3-chlorobenzylthio)-benzaldehyde with nitroacetone and n-hexyl β -aminocrotonate in ethanol.

Yield: 21% of theory.

Elemental analysis

	C	H	Cl	N	S
calculated	62.9%	6.2%	6.9%	5.4%	6.2%
found	62.7%	6.1%	6.4%	5.3%	6.1%

Example 62



Methyl 6-amino-1,4-dihydro-2-methyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate of melting point 210°C



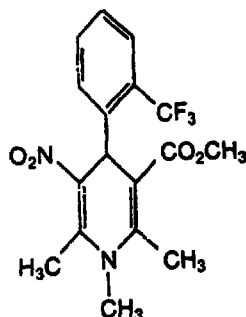
- 50 -

(isopropanol) was obtained by reaction of 10 mmol each of 2-trifluoromethylbenzaldehyde, nitroacetone, ethylamidinoacetate hydrochloride and sodium methylate in 60 ml of boiling ethanol.

5 Yield: 36% of theory.

Example 63

10

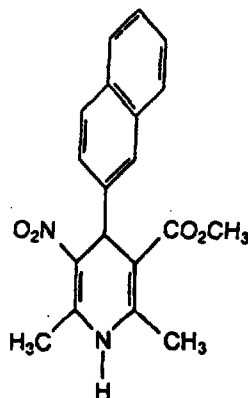


Methyl 1,4-dihydro-3-nitro-4-(2-trifluoromethylphenyl)-
15 1,2,6-trimethylpyridine-5-carboxylate was obtained by
reaction of 10 mmol each of 2-trifluoromethylbenzaldehyde,
methyl acetoacetate, nitroacetone and methylamine hydro-
chloride in 50 ml of glacial acetic acid at 60°C for 12
hours.

20 Yield: 15% of theory.

Example 64

25



30

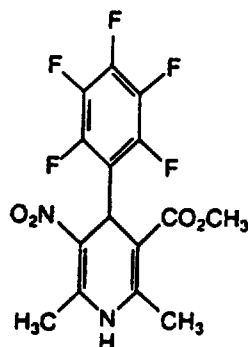
Analogously to Example 16, methyl 1,4-dihydro-2,6-dimethyl-
4-β-naphthyl-3-nitropyridine-5-carboxylate of melting point
163°C (isopropanol) was obtained by reaction of β-naphthyl-
aldehyde, methyl β-aminocrotonate and nitroacetone in
35 ethanol.

Yield: 42% of theory.



Example 65

5

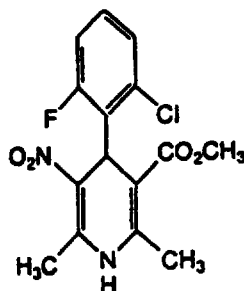


Analogously to Example 16, methyl 1,4-dihydro-2,6-dimethyl-
10 3-nitro-4-pentafluorophenylpyridine-5-carboxylate of melting point 231°C was obtained by reaction of pentafluorobenzaldehyde with nitroacetone and β -aminocrotonate in ethanol.

Yield: 38% of theory.

15 Example 66

20

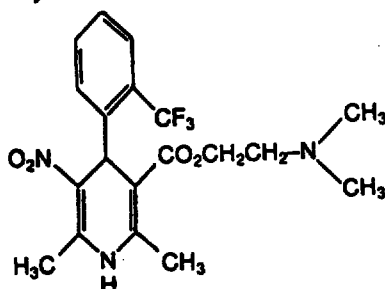


Analogously to Example 16, methyl 4-(2-chloro-6-fluorophenyl)-1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate of melting point 190°C was obtained by reaction of
25 2-chloro-6-fluorobenzaldehyde with nitroacetone and methyl β -aminocrotonate.

Yield: 28% of theory.

Example 67

30

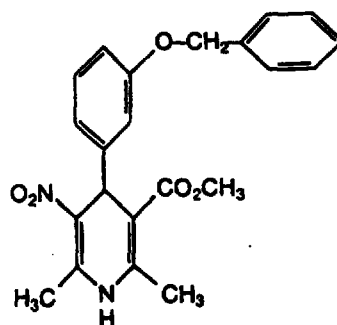


β -Dimethylaminoethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-
35 (2-trifluoromethylphenyl)pyridine-5-carboxylate of melting point 132°C was obtained by reaction of 1 equivalent each of 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylic acid with dimethylaminoethanol and DCC in the [sic] methylene chloride.



Yield: 84% of theory.

Example 68

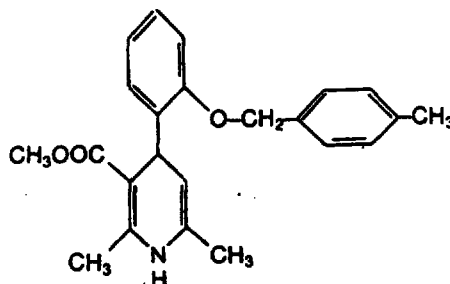


- 10 Analogously to Example 16, methyl 4-(3-benzyloxyphenyl)-1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate of melting point 181°C (isopropanol) is obtained by reaction of 3-benzyloxybenzaldehyde with nitroacetone and methyl β -aminocrotonate.

15 Yield: 34% of theory.

Example 69

Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3-carboxylate



- 20 A) Preparation of methyl α -acetyl-2-(4-methylbenzyloxy) cinnamate
- 25 g (110.6 mmol) of 2-(4-methylbenzyloxy)benzaldehyde are stirred together with 11.9 ml (110.6 mmol) of methyl acetoacetate in 66 ml of isopropanol and treated with a
- 30 freshly prepared solution of 0.64 ml of piperidine and 0.38 ml of glacial acetic acid in 5.5 ml of isopropanol. The mixture is stirred for 1 hour at 60°C and for 4 hours at 40°C, cooled and concentrated. The evaporation residue is dissolved in ether and the solution is successively
- 35 washed with about 100 ml of 1 N hydrochloric acid, twice with water, with saturated sodium bicarbonate solution and again twice with water. The ether phase is dried, filtered and concentrated. This gives 35.3 g (98.51% of theory) of a dark yellow oil which is further reacted without

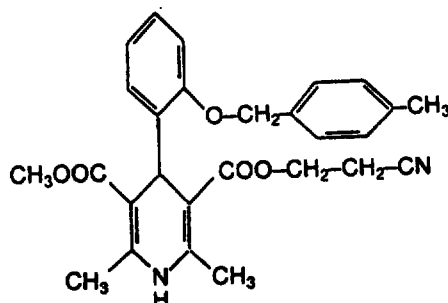


purification.

B) Methyl 2-cyanoethyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate

5

10



15

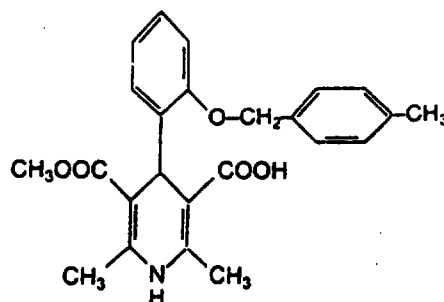
20

35.3 g (108.35 mmol) of methyl α -acetyl-2-(4-methylbenzyloxy)cinnamate are refluxed with 16.8 g (108.95 mmol) of 2-cyanoethyl β -aminocrotonate in 160 ml of ethanol for 18 hours. The solution is concentrated, the evaporation residue is taken up in ethyl acetate and extracted twice with water. The ethyl acetate phase is dried, filtered, and concentrated. The evaporation residue obtained crystallizes upon stirring with methanol. The product is filtered off with suction and washed with methanol. This gives 20.2 g (40.53% of theory) of a slightly yellow product of melting point 165°C with decomposition.

C) Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate

25

30



35

17.5 g (38 mmol) of methyl 2-cyanoethyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate are suspended in a solution of 4.6 g (115 mmol) of sodium hydroxide in 115 ml of water and treated with 57.5 ml of dimethoxyethane. Gradually, a clear solution is obtained. The mixture is stirred for 20 hours, treated with 100 ml of water and extracted three times with methylene chloride. While stirring, the aqueous



- 54 -

phase is acidified dropwise with concentrated hydrochloric acid, which precipitates the acid. The product is filtered off with suction, washed with water and dried. This gives 12.2 g (78.9% of theory) of a beige-coloured solid product of melting point starting at 169°C with decomposition.

D) 3 g of monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate are suspended in 30 ml of diethylene glycol and heated to 170 to 180°C with stirring, resulting in a clear solution with the evolution of gas. The mixture is stirred at 180°C for about 5 minutes and cooled. The viscous solution is dissolved in an ether/water mixture with vigorous stirring, the phases are separated, the aqueous phase is extracted with ether and the combined ether phases are washed with 1 N sodium hydroxide and twice with water. The organic phase is dried, filtered and concentrated. The resulting syrup-like residue is crystallized with isopropanol or acetonitrile in an ice bath and filtered off with suction. This gives 1.6 g of methyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)-phenyl]pyridine-3-carboxylate of melting point 107°C to 109°C.

The following were prepared analogously:

Example 70

25 Ethyl 1,4-dihydro-2,6-dimethyl-4-(2-trifluoromethylphenyl)pyridine-3-carboxylate of melting point 125 to 128°C.

Example 71

30 Isopropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3-carboxylate, isolated as an oil. R_f value: 0.525; TLC aluminium roll, layer thickness: 0.2 mm, silica gel: 60 F 254, Merck; eluent: petroleum ether/ethyl acetate in a ratio of 2:1 by volume.

35 Example 72

Methyl 1,4-dihydro-1,2,6-trimethyl-4-(2-chlorophenyl)pyridine-3-carboxylate of melting point 142 to 144°C.



Example 73

Methyl 1,4-dihydro-2,6-dimethyl-4-(3-chlorophenyl)-pyridine-3-carboxylate of melting point 129 to 133°C.

Example 74

- 5 Methyl 1,4-dihydro-2,6-dimethyl-4-(2-methylphenyl)-pyridine-3-carboxylate of melting point 127 to 130°C.

Example 75

Methyl 1,4-dihydro-2,6-dimethyl-4-(2-chlorophenyl)-pyridine-3-carboxylate of melting point 143-146°C.

- 10 Example 76

Methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3-carboxylate of melting point 110 to 112°C.

Example 77

- 15 Methyl 1,4-dihydro-2,6-dimethyl-4-(2-phenylthio-methoxyphenyl)pyridine-3-carboxylate as an oil.

NMR spectrum at 250 MHz in CDCl₃

Singlet at δ = 1.6 ppm (3H, 6-CH₃)

Singlet at δ = 2.38 ppm (3H, 2-CH₃)

Singlet at δ = 3.42 ppm (3H, COOCH₃)

- 20 2 duplets at δ = 4.65 and 4.96 ppm (1H each for 5H and 4H)

Singlet at δ = 5.16 ppm (1H for $\begin{array}{c} \diagup \\ \text{N} \\ \diagdown \\ \text{H} \end{array}$)

AB system at δ = 5.5 to 5.64 ppm (2H for -O-CH₂-S-)

- 25 Multiplet at δ = 6.9 to 7.65 ppm (9H, aromatics)

Example 78

Methyl 1,4-dihydro-2,6-dimethyl-4-(2-benzyloxyphenyl)pyridine-3-carboxylate of melting point 81 to 83°C.

Example 79

- 30 Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-chloro-benzyloxy)phenyl]pyridine-3-carboxylate of melting point 90 to 94°C.

Example 80

- 35 Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(2-chloro-benzyl-oxy)phenyl]pyridine-3-carboxylate of melting point 75 to 77°C.

Example 81

Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(2,6-dichloro-benzyloxy)phenyl]pyridine-3-carboxylate of melting point



125 to 128°C.

Example 82

Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(3,4-dichloro-phenyloxy)phenyl]pyridine-3-carboxylate,
5 isolated as a foam. R_f value: 0.65, TLC plates precoated with silica gel 60 F 254, eluent: chloroform/ethyl acetate in a ratio of 5:1 by volume.

Example 83

Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyl-
10 oxy)naphthyl]pyridine-3-carboxylate,
isolated as a foam.

Mass spectrum:

The most important peaks are found at $m/e = 413$ (molecular ion); $m/e = 308$; $m/e = 248$; $m/e = 166$.

15 Example 84

Isopropyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3-carboxylate of melting point starting at 99°C.

Example 85

20 Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-trifluoromethylbenzylthio)phenyl]pyridine-3-carboxylate, isolated as an oil. R_f value: 0.84, TLC aluminium roll, layer thickness: 0.2 mm, silica gel 60 F 254, eluent: chloroform/ethyl acetate in a ratio of 5:1 by volume.

25 Example 86

Isobutyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3-carboxylate of melting point starting at 57°C.

Example 87

30 Methyl 1,4-dihydro-2,6-dimethyl-4-naphthyl-pyridine-3-carboxylate, isolated as a foam.

Mass spectrum:

The most important mass peaks are $m/e = 293$ (molecular ion); $m/e = 166$ (M - naphthyl).

35 Example 88

Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-trifluoromethylbenzyloxy)phenyl]pyridine-3-carboxylate of melting point 134°C.



Example 89

Sec.-butyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3-carboxylate of melting point starting at 78°C.

5 Example 90

Methyl 1,4-dihydro-2,6-dimethyl-4-(3-benzyloxyphenyl)-pyridine-3-carboxylate, isolated as an oil. R_f value: 0.69, TLC aluminium roll, layer thickness 0.2 mm, silica gel 60 G 254, Merck; eluent: chloroform/ethyl acetate in a ratio of 7:1 by volume.

Example 91

Isobutyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-trifluoromethylbenzyloxy)phenyl]pyridine-3-carboxylate, isolated as an oil.

Mass spectrum:

The most important mass peaks are:

m/e = 459 (molecular ion);

20 m/e = 402 (M-CH₂-CH(CH₃)₂)

m/e = 208 (M-C₁₄H₁₀F₃O).

Example 92

25 Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-nitrobenzyloxy)phenyl]pyridine-3-carboxylate of melting point 117 to 118°C.

Example 93

30 Ethyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-nitrobenzyloxy)phenyl]pyridine-3-carboxylate of melting point from 107 to 109°C.

Example 94

35 Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-fluorobenzyloxy)phenyl]pyridine-3-carboxylate of melting point 68 to 70°C.

Example 95

Sec.butyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-trifluoromethylbenzyloxy)phenyl]pyridine-3-carboxylate, isolated as an oil.

**Mass spectrum:**

The most important mass peaks are:

$m/e = 459$ (molecular ion); $m/e = 402$ (M-57).

Example 96

- 5 Ethyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-fluoro-benzyloxy)phenyl]pyridine-3-carboxylate of melting point 122 to 125°C.

Example 97

- 10 Methyl 1,4-dihydro-2,6-dimethyl-4[2-(3,5-dimethyl-benzyloxy)phenyl]pyridine-3-carboxylate of melting point 127 to 129°C (crystallized with 1 mol of acetonitrile).

Example 98

Ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3-carboxylate of melting point 107 to 108°C.

- 15 **Example 99**

n-Butyl 1,4-dihydro-2,6-dimethyl-4-[2-(3,5-dimethyl-benzyloxy)phenyl]pyridine-3-carboxylate, isolated as an oil.

Mass spectrum:

- 20 The most important peaks are:

$m/e = 417$ (M-2); $m/e = 300$ (M-119) and $m/e = 208$.

Example 100

- 25 n-Butyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-methyl-benzyloxy)phenyl]pyridine-3-carboxylate of melting point 104 to 10°C.

Example 101

Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-methyl-benzyloxy)phenyl]pyridine-3-carboxylate of melting point 58 to 62°C crystallizes with one mole of acetonitrile.

- 30 **Example 102**

Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-fluoro-benzyloxy)phenyl]pyridine-3-carboxylate of melting point 109 to 10°C.

Example 103

- 35 n-Butyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-fluoro-benzyloxy)phenyl]pyridine-3-carboxylate of melting point 105 to 106°C.

Example 104

Methyl 1,4-dihydro-2,6-dimethyl-4-(2-phenylpropyl-

mercaptophenyl)pyridine-3-carboxylate, isolated as an oil.

R_f value: 0.46, TLC aluminium roll, layer thickness: 0.2 mm, silica gel 60 F 254 Merck, eluent: chloroform.

Example 105

5 Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-methoxy-
benzyloxy)phenyl]pyridine-3-carboxylate of melting point
starting at 53°C.

Example 106

Methyl 1,4-dihydro-2,6-dimethyl-4-(2-benzylthio-
10 phenyl)pyridine-3-carboxylate.

Mass spectrum:

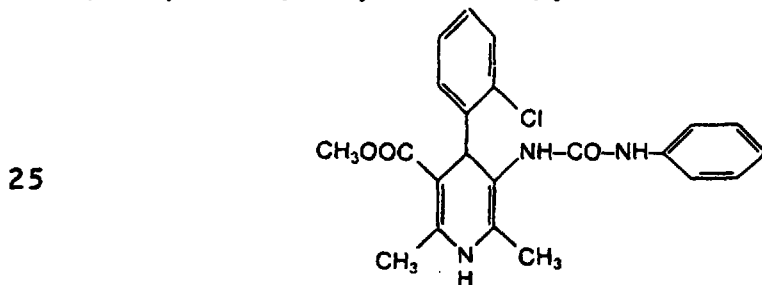
The most important peaks are found at $m/e = 365$ (molecular ion), $m/e = 350$ (M-15), $m/e = 306$ (M-59), $m/e = 274$, $m/e = 166$.

15 Example 107

n-Butyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-methoxybenzyloxy)phenyl]pyridine-3-carboxylate of melting point 144 to 146°C.

Example 108

20. Methyl 1,4-dihydro-2,6-dimethyl-4-(2-chloro-phenyl)-5-phenyl-ureidopyridine-3-carboxylate



9.65 g (30 mmol) of monoethyl 1,4-dihydro-2,6-dimethyl-4-(2-chlorophenyl)-3,5-dicarboxylate are refluxed with 6.4 mol (30 mmol) of diphenylphosphoryl azide and 4.2 ml (30 mmol) of triethylamine for 1 hour. The mixture is cooled, treated with 2.8 ml (30 mmol) of aniline and boiled for 1 hour. The mixture is concentrated, the solid evaporation residue is dissolved in warm ethyl acetate, the solution is washed with 1 N hydrochloric acid, water, 2 N sodium hydroxide solution and twice with water, dried and concentrated. The solid evaporation residue is treated with 100 ml of hot ethyl acetate, cooled with stirring, filtered off with suction and washed with ethyl acetate.



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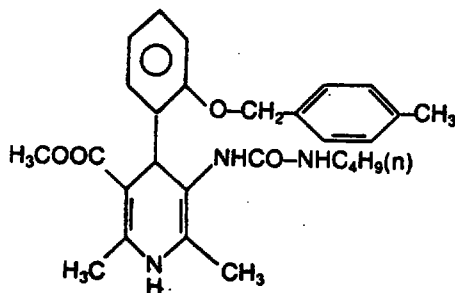
This gives 4.6 g of methyl 1,4-dihydro-2,6-dimethyl-4-(2-chlorophenyl)-5-phenylureidopyridine-3-carboxylate of melting point 203 to 205°C.

The following were prepared analogously:

5 Example 109

Methyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]-5-n-butylureidopyridine-3-carboxylate of melting point 194 to 196°C.

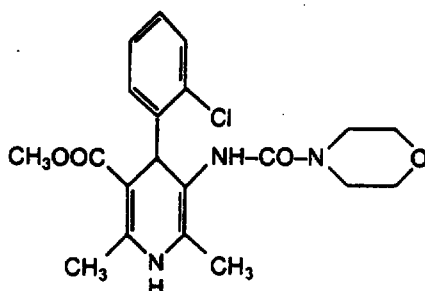
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15 Example 110

Methyl 1,4-dihydro-2,6-dimethyl-4-(2-chlorophenyl)-5-N-morpholinyl)carbonylaminopyridine-3-carboxylate of melting point 245 to 249°C.

20

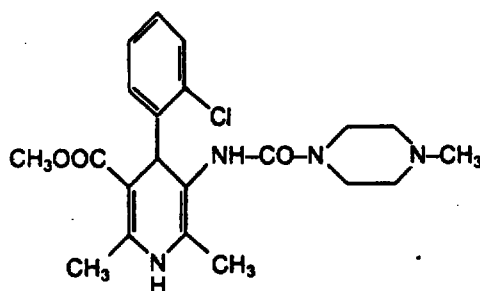


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Example 111

Methyl 1,4-dihydro-2,6-dimethyl-4-(2-chlorophenyl)-5-(4-N-methylpiperazinyl-carbonylamino)pyridine-3-carboxylate of melting point 231°C.

35



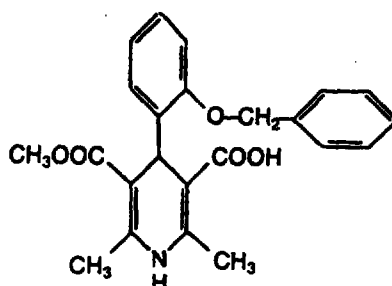
Example 112

Monomethyl 1,4-dihydro-2,6-dimethyl-4-(2-benzyl-



oxyphenyl)pyridine-3,5-dicarboxylate

5



- 10.6 g (24 mmol) of methyl β -cyanoethyl 1,4-dihydro-2,6-dimethyl-4-(2-benzyloxyphenyl)pyridine-3,5-dicarboxylate are suspended in a solution of 2.88 g (72 mmol) of sodium hydroxide in 72 ml of water and treated with 45 ml of dimethoxyethane. The mixture is stirred overnight, treated with 100 ml of water and extracted three times with ether.
- 15 The aqueous phase is distilled for a short time on a rotary evaporator and is then, with stirring, acidified dropwise with concentrated hydrochloride acid. The precipitated product is filtered off with suction, washed with water and dried. This gives 6.2 g of a beige-coloured product of melting point 160°C with decomposition.
- 20 The following were prepared analogously to 112:

Example 113

- Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 169°C with decomposition.

Example 114

Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-chlorobenzyl)phenyl]pyridine-3,5-dicarboxylate of melting point 156°C with decomposition.

30 Example 115

Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(2-chlorobenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 153°C with decomposition.

Example 116

- 35 Monomethyl 1,4-dihydro-2,6-dimethyl-4-(2-phenylmercaptomethoxyphenyl)pyridine-3,5-dicarboxylate of melting point 95°C with decomposition.

Example 117

Monomethyl 1,4-dihydro-2,6-dimethyl-4-(2-phenethyl-



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oxyphenyl)pyridine-3,5-dicarboxylate of melting point 100 to 103°C with decomposition.

Example 118

5 Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(2,6-dichlorobenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 198 to 201°C with decomposition.

Example 119

10 Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(3,4-dichlorobenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 138 to 140°C with decomposition.

Example 120

Monomethyl 1,4-dihydro-2,6-dimethyl-4-(3-propoxyphenyl)pyridine-3,5-dicarboxylate of melting point 175 to 177°C with decomposition.

15 Example 121

Monomethyl 1,4-dihydro-2,6-dimethyl-4-(3-benzyloxyphenyl)pyridine-3,5-dicarboxylate of melting point 148°C with decomposition.

Example 122

20 Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)naphthyl]pyridine-3,5-dicarboxylate of melting point 171 to 179°C with decomposition.

Example 123

25 Monomethyl 1,4-dihydro-2,6-dimethyl-4-naphthylpyridine-3,5-dicarboxylate of melting point 175 to 179°C with decomposition.

Example 124

30 Monoisopropyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 101°C with decomposition.

Example 125

Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-trifluoromethylbenzylthio)phenyl]pyridine-3,5-dicarboxylate of melting point 90°C with decomposition.

35 Example 126

Monoisobutyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 85°C with decomposition.



Example 127

Monosec.-butyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-methylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 133 to 140°C with decomposition.

5 Example 128

Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-trifluoromethylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 182°C with decomposition.

Example 129

10 Monoisobutyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-trifluoromethylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 150 to 153°C with decomposition.

Example 130

15 Monosec.-butyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-trifluoromethylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 144°C with decomposition.

Example 131

20 Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-nitrobenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 167°C with decomposition.

Example 132

Monoethyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-nitrobenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 172°C with decomposition.

25 Example 133

Monoethyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-fluorobenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 154 to 156°C with decomposition.

Example 134

30 Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(4-fluorobenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting point 181 to 186°C with decomposition.

Example 135

35 Monomethyl 1,4-dihydro-2,6-dimethyl-4-(2-phenylpropylmercaptophenyl)pyridine-3,5-dicarboxylate of melting point starting at 94°C with decomposition.

Example 136

Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(3,5-dimethylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate of



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melting point starting at 98°C with decomposition.

Example 137

- Mono-n-butyl 1,4-dihydro-2,6-dimethyl-4-[2-(3,5-dimethylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate of
5 melting point starting at 85°C with decomposition.

Example 138

Monomethyl 1,4-dihydro-2,6-dimethyl-4-[3-methylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate of melting
point 140 to 145°C with decomposition.

10 Example 139

Mono-n-butyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-methylbenzyloxy)phenyl]pyridine-3,5-dicarboxylate of
melting point 132 to 139°C with decomposition.

Example 140

- 15 Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-fluorobenzyloxy)phenyl]pyridine-3,5-dicarboxylate of
melting point 146 to 149°C with decomposition.

Example 141

- 20 Mono-n-butyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-fluorobenzyloxy)phenyl]pyridine-3,5-dicarboxylate of
melting point 141 to 144°C with decomposition.

Example 142

- 25 Monomethyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-methoxybenzyloxy)phenyl]pyridine-3,5-dicarboxylate of
melting point 155 to 160°C with decomposition.

Example 143

- 30 Mono-n-butyl 1,4-dihydro-2,6-dimethyl-4-[2-(3-methoxybenzyloxy)phenyl]pyridine-3,5-dicarboxylate of
melting point 145 to 149°C with decomposition.

30 Example 144

Ethyl 1-ethyl-2-methyl-4-[2-(3-trifluoromethylbenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]-
pyridine-3-carboxylate.

M.p.: 117 to 119°C.

35 Example 145

2-Methoxyethyl 2-methyl-4-[2-(3-trifluoromethylbenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]-
pyridine-3-carboxylate.

M.p. 124 to 125°C.



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Example 146

Butyl 2-methyl-4-[2-(3-trifluoromethylbenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

5 M.p.: 112 to 120°C.

Example 147

Ethyl 2-methyl-4-[2-(3-trifluoromethylbenzyloxy)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate

10 M.p.: 180 to 183°C.

Example 148

Ethyl 2-methyl-4-[2-(3-nitrobenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 164 to 166°C.

15 Example 149

n-Butyl 2-methyl-4-[2-(3-nitrobenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 137 to 139°C.

Example 150

20 Ethyl 2-methyl-4-[2-(3-methylbenzylsulphanyl)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate:
M.p.: 243-245°C.

Example 151

25 Ethyl 4-[2-(benzylthio)phenyl]-2-methyl-5-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxylate.
M.p.: 243 to 246°C.

Example 152

30 Ethyl 4-[2-(benzylsulphonyl)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 150 to 152°C.

Example 153

35 Methyl 2-methyl-4-[2-(3-trifluoromethylbenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]-3-carboxylate.
M.p.: 178 to 181°C.

Example 154

Butyl 4-[2-(4-tert.-butylbenzylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-



carboxylate.

M.p.: 103°C.

Example 155

Ethyl 2-methyl-4-[2-(3-trifluoromethylbenzyl)-
5 phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-
carboxylate.

M.p.: 189°C.

Example 156

Ethyl 2-methyl-4-[2-(3-methylbenzylthio)phenyl]-
10 5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxy-
late.

M.p.: 150 to 155°C.

Example 157

Butyl 4-[2-(3-chlorobenzylthio)phenyl]-2-methyl-5-
15 oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 167 to 170°C.

Example 158

Ethyl 4-[2-(4-ethoxycarbonylbenzylthio)phenyl]-2-
methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-
20 carboxylate.

M.p.: 157 to 160°C.

Example 159

Ethyl 4-[2-(benzylthio)phenyl]-2-propyl-5-oxo-
1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

25 M.p.: 167 to 169°C.

Example 160

Ethyl 4-[2-(chlorobenzylthio)phenyl]-2-methyl-5-
oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 87 to 89°C.

30 Example 161

Methyl 4-[2-(benzylthio)phenyl]-2-ethyl-5-oxo-
1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 174 to 176°C.

Example 162

35 Ethyl 4-[2-(4-tert.-butylbenzylthio)phenyl]-2-
methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-
carboxylate.

M.p.: 127 to 130°C.

Example 163

Ethyl 2-methyl-4-[2-(3-methylbenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 114 to 116°C.

5 Example 164

Methyl 4-[2-(4-tert.-butylbenzylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 112 to 113°C.

10 Example 165

Methyl 2-methyl-4-[2-(3-methylbenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 166 to 168°C.

15 Example 166

Methyl 4-[2-(3-chlorobenzylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 209 to 211°C.

20 Example 167

Octyl 2-methyl-4-[2-(4-methylbenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
¹H-NMR (CDCl₃): δ = 0.9 (t, J = 7 Hz, 3H), 1.0-1.5 (m, 12H), 2.3 and 2.35 (2s, je 3H), 3.75-4.1 (m, 2H),
25 4.1 and 4.15 (2d, J = 14 Hz, je 1H), 4.45 (s, 2H), 5.5 (s, 1H) 7.0-7.4 (m, 8H), 8.1 (s, NH) ppm.

Example 168

Butyl 2-methyl-4-[2-(4-methylbenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
30 M.p.: 87 to 89°C.

Example 169

Ethyl 4-[2-benzylthio)phenyl]-2-methyl-5-oxo-1-propyl-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
35 M.p.: 132°C.

Example 170

Ethyl 1-allyl-4-[2-benzylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 115 to 177°C.



Example 171

Ethyl 2-methyl-4-[2-(4-methylbenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 137 to 139°C.

5 Example 172

Ethyl 2-methyl-4-[2-(4-methylbenzyloxy)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 208 to 209°C.

Example 173

- 10 Ethyl 4-[2-(benzylthio)phenyl]-1-ethyl-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 80 to 82°C.

Example 174

- 15 Ethyl 4-[2-(benzylthio)phenyl]-1,2-dimethyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 188-190°C.

Example 175

- 20 Ethyl 4-[3-(benzylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 183 to 185°C.

Example 176

- 25 Ethyl 4-[2-(4-methoxycarbonylbenzylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 102 to 110°C.

Example 177

- 30 Ethyl 2-methyl-4-[2-(1-phenylethylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 93 to 110°C (2:3 mixtures of diastereomers).

Example 178

- 35 Ethyl 2-methyl-4-[2-(2-methylbenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 217 to 219°C.

Example 179

Ethyl 2-methyl-5-oxo-4-[3-phenylpropylsulphinyl]-phenyl]-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 185 to 186°C.



Example 180

Ethyl 2-methyl-4-[2-(4-nitrobenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 168 to 170°C.

5 Example 181

Ethyl 4-[2-(methoxycarbonyl)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 240 to 249°C.

Example 182

10 Ethyl 4-[2-(butylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 163 to 167°C.

Example 183

15 Ethyl 4-[2-(2,5-dichlorobenzylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 244 to 250°C.

Example 184

20 Ethyl 4-[2-(4-methoxybenzylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 83 to 85°C.

Example 185

25 Ethyl 4-[2-(4-chlorobenzylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 97 to 99°C.

Example 186

30 Ethyl 2-methyl-4-[2-(1-methylethylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 193 to 194°C.

Example 187

Ethyl 2-methyl-5-oxo-4-[2-(3-phenylpropylthio)phenyl]-1,4,5,7-tetrahydro[3,4-b]pyridine-3-carboxylate.
M.p.: 179 to 180°C.

35 Example 188

Ethyl 2-methyl-5-oxo-4-[2-(tetralin-2-ylmethylthio)phenyl]-1,4,5,7-tetrahydrofuro-[3,4-b]pyridine-3-carboxylate.
M.p.: 102 to 104°C.



Example 189

Ethyl 4-(2,3-dimethylphenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 225 to 227°C.

5 Example 190

Ethyl 2-methyl-5-oxo-[2-(2[phenylcarbonyloxy]-ethylthio)phenyl]-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 190 to 196°C.

10 Example 191

Ethyl 2-methyl-4-[2-(1-naphthylmethylthio)-phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 93 to 100°C.

15 Example 192

Ethyl 4-[2-(benzylsulphinythio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 250°C.

20 Example 193

Ethyl 4-[2-(3,4-dichlorobenzylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 90 to 95°C.

25 Example 194

Ethyl 4-[3-benzyloxyphenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 103 to 104°C.

Example 195

30 Ethyl 4-[2-(2-hydroxyethylthio)phenyl]-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 130 to 134°C.

Example 196

35 Ethyl 4-(2-benzylphenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 239 to 240°C.

Example 197

Ethyl 4-(2-ethylthio)phenyl-2-methyl-5-oxo-



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1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 235 to 236°C.

Example 198

5 Ethyl 2-methyl-4-[2-(methylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 233 to 234°C.

Example 199

10 Ethyl 2-methyl-4-[2-(2-phenylethylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 184 to 185°C.

Example 200

15 Ethyl 2-methyl-4-[2-(4-methylbenzylthio)phenyl]-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 132 to 134°C.

Example 201

20 Methyl 4-(2-benzyloxyphenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate. M.p.: 245 to 246°C.

Example 202

Ethyl 4-(2-ethylphenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 197 to 200°C.

25 Example 203

Octyl 4-(2-benzylthiophenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate. M.p.: 212°C.

Example 204

30 Butyl 4-(2-benzylthiophenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (amorphous substance).

Example 205

35 Ethyl 4-(2-benzyloxyphenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate. M.p.: 177°C.

Example 206

Methyl 4-(2-benzylthiophenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.



M.p.: 215°C.

Example 207

Ethyl 2-methyl-5-oxo-4-(2-trifluoromethyl-phenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

5

M.p.: 228 to 230°C.

Example 208

Isopropyl 4-(2-benzylthiophenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

10

M.p.: 158 to 161°C.

Example 209

Ethyl 2-methyl-5-oxo-4-(2-phenylphenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 217 to 220°C.

15

Example 210

Isopropyl 2-methyl-4-(2-methylphenyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 208°C.

Example 211

20

Butyl 2-methyl-4-(2-methylphenyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 167 to 176°C.

Example 212

25

Allyl 2-methyl-4-(2-methylphenyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 170 to 175°C.

Example 213

3-Acetyl-4-(2-benzylthiophenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine.

30

M.P.: 212°C.

Example 214

Methyl 2-methyl-5-oxo-4-(2-trifluoromethyl-phenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

35

M.p.: 229 to 233°C.

Example 215

Methyl 2-methyl-5-oxo-4-(2-methylphenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 196 to 201°C.



Example 216

2-methoxyethyl 4-(3-chlorophenyl)-1,2-dimethyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 128 to 133°C.

5 Example 217

3-Acetyl-2-methyl-5-oxo-4-[2-trifluoromethylphenyl]tetrahydrofuro[3,4-b]pyridine.
M.p.: 212 to 213°C.

Example 218

10 Ethyl 2-methoxymethyl-5-oxo-4-(2-trifluoromethylphenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 218 to 219°C.

Example 219

15 Ethyl 4-(3-chlorophenyl)-1,2-dimethyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 188 to 190°C.

Example 220

20 Butyl 4-(3-chlorophenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 142 to 144°C.

Example 221

25 Allyl 4-(3-chlorophenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 164 to 167°C.

Example 222

Methyl 2-methyl-5-oxo-4-(2-trifluoromethylphenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate 82-pyridyl [sic].
30 M.p.: 209 to 210°C.

Example 223

Ethyl 2-methyl-5-oxo-1-propyl-4-(2-trifluoromethylphenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
35 M.p.: 106 to 107°C.

Example 224

Benzyl 2-methyl-5-oxo-4-(2-trifluoromethylphenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.



M.p.: 218 to 219°C.

Example 225

Hexyl 4-(3-chlorophenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

5 M.p.: 130 to 133°C.

Example 226

Ethyl 1-ethyl-2-methyl-5-oxo-4-(2-trifluoromethylphenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

10 M.p.: 157 to 160°C.

Example 227

Octyl 2-methyl-5-oxo-4-(2-trifluoromethylphenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

15 M.p.: 119 to 120°C.

Example 228

Ethyl 4-(2,3-dichlorophenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 249-251°C.

20 Example 229

Ethyl 2-methyl-5-oxo-4-(3-pyridyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 192 to 194°C.

Example 230

25 Ethyl 2-methyl-5-oxo-4-(2-trifluoromethoxyphenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 174 to 176°C.

Example 231

30 Ethyl 2-methyl-4-(2-naphthyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: > 270°C.

Example 232

35 Ethyl 5-oxo-4-(2-trifluoromethylphenyl)-1,2,7-trimethyl-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
M.p.: 171 to 172°C.

Example 233

Ethyl 2-methyl-5-oxo-4-(3-trifluoromethylphenyl)-



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1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 180 to 182°C.

Example 234

Ethyl 2-ethyl-5-oxo-4-(2-trifluoromethylphenyl)-

5 1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 237 to 239°C.

Example 235

Allyl 2-methyl-5-oxo-4-(2-trifluoromethyl-
phenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxy-
10 late.

M.p.: 190 to 192°C.

Example 236

Ethyl 1,2-dimethyl-5-oxo-4-(2-trifluoromethyl-
phenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-
15 carboxylate.

M.p.: 196 to 197°C.

Example 237

Methyl 4-[(2-fluoro-3-chloro)phenyl]-2-methyl-5-
oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

20 M.p.: 220 to 223°C.

Example 238

Butyl 4-[2-(cyclohexylmethylthio)phenyl]-2-
methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-
carboxylate.

25 M.p.: 123 to 128°C.

Example 239

Ethyl 4-[2-(cyclohexylmethylthio)phenyl]-2-
methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-
carboxylate.

30 M.p.: 77 to 82°C.

Example 240

Hexyl 2-methyl-5-oxo-4-(2-trifluoromethyl-
phenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-
carboxylate.

35 M.p.: 164 to 165°C.

Example 241

Ethyl 2-methyl-5-oxo-4-(2-phenylthiophenyl)-
1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 191 to 192°C.



Example 242

Allyl 4-(2-chlorophenyl)-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

M.p.: 206°C.

5 Example 243

Analogously to the method according to Example No. 35, the following compounds are obtained by hydrogenation with lithium aluminium hydride from the corresponding diesters.

- 10 Ethyl 1,4-dihydro-2,3,6-trimethyl-4-(2-chlorophenyl)pyridine-5-carboxylate of melting point 112°C.

Example 244

Methyl 1,4-dihydro-2,3,6-trimethyl-4-(4-chlorophenyl)pyridine-5-carboxylate of melting point 94°C.

15 Example 245

Methyl 1,4-dihydro-2,3,6-trimethyl-4-(2-methylphenyl)pyridine-5-carboxylate of melting point 147 to 153°C.

Example 246

- 20 Methyl 1,4-dihydro-2,3,6-trimethyl-4-[2-(4-methylbenzylthio)phenyl]pyridine-5-carboxylate of melting point 109 to 111°C.

Example 247

- 25 Methyl 1,4-dihydro-2,3,6-trimethyl-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate of melting point 145 to 149°C.

Example 248

- 30 Methyl 1,4-dihydro-2,3,6-trimethyl-4-(4-methylphenyl)pyridine-5-carboxylate of melting point 146 to 150°C.

Example 249

Methyl 1,4-dihydro-2,3,6-trimethyl-4-(3-thienyl)pyridine-5-carboxylate of melting point 150 to 158°C.

Example 250

- 35 Methyl 1,4-dihydro-2,3,6-trimethyl-4-(2-benzoyloxyphenyl)pyridine-5-carboxylate, isolated as a colourless resin.

Mass spectrum: the most important peaks are found at:
m/e = 363, 348, 304, 272, 180.



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Example 251

Methyl 1,4-dihydro-2,3,6-trimethyl-4-[2-(4-chlorobenzoyloxy)phenyl]pyridine-5-carboxylate, isolated as a colourless resin.

5 Mass spectrum: $m/e = 396$ (180).

Example 252

Methyl 1,4-dihydro-2,3,6-trimethyl-4-[2-(2,6-dichlorobenzoyloxy)phenyl]pyridine-5-carboxylate, isolated as an oil.

10 Example 253

Methyl 1,4-dihydro-2,3,6-trimethyl-4-[2-(4-methylbenzoyloxy)phenyl]pyridine-5-carboxylate, isolated as an oil.

Example 254

15 Methyl 1,4-dihydro-2,3,6-trimethyl-4-(2-phenethyloxyphenyl)pyridine-5-carboxylate, isolated as a yellow oil.

Example 255

20 Methyl 1,4-dihydro-2,3,6-trimethyl-4-(2-phenylmercaptomethoxyphenyl)pyridine-5-carboxylate, isolated as a yellow oil.

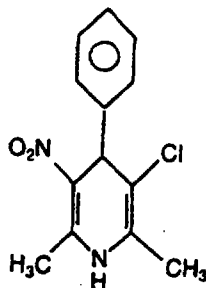
Mass spectrum: $m/e = 395$ (180).

Example 256

25 Methyl 1,4-dihydro-2,3,6-trimethyl-4-[3-(4-methylbenzoyloxy)phenyl]pyridine-5-carboxylate, isolated as a yellow oil.

Example 257

30



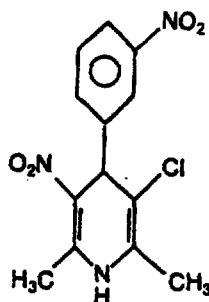
35 Analogously to Example 18, 3-chloro-1,4-dihydro-2,6-dimethyl-5-nitro-4-phenylpyridine of melting point 192°C (isopropanol) is obtained from 0.1 mol of 2-amino-1-nitro-1-propene and 0.1 mol of 2-chloro-1-phenyl-1-butene-3-one by heating in boiling ethanol.
Yield: 28% of theory.



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Example 258

5

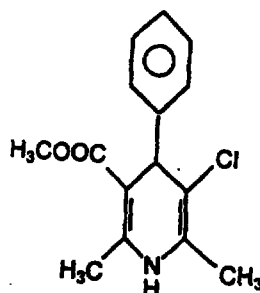


Analogously to Example 18, 0.1 mol of 2-amino-1-nitro-1-propene and 0.1 mol of 2-chloro-1-(3-nitro-phenyl)-1-butene-3-one are heated in boiling ethanol to give 3-chloro-1,4-dihydro-2,6-dimethyl-5-nitro-4-(3-nitrophenyl)-pyridine of melting point 198°C (dec.).

Yield:

Example 259

15



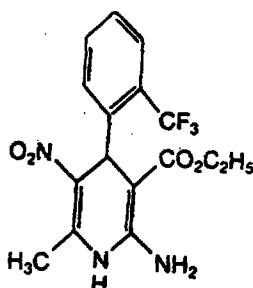
20

Analogously to Example 18, 0.1 mol of methyl aminocrotonate and 2-chloro-1-phenyl-1-butene-3-one are heated in boiling ethanol to give methyl 3-chloro-1,4-dihydro-2,6-dimethyl-4-phenylpyridine-5-carboxylate of melting point 147°C.

Yield: 23% of theory.

Example 260

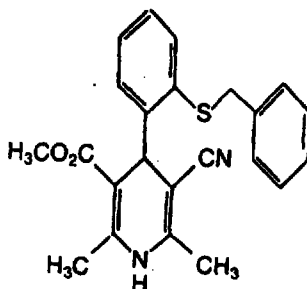
30



Analogously to Example 18, [lacuna] 2-amino-1,4-dihydro-6-methyl-5-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate of melting point 210°C (isopropanol) was obtained by reaction of 2-nitro-1-(2-tri-fluoromethyl-phenyl)-1-butene-3-one and ethyl amidinoacetate in ethanol. Yield: 32% of theory.

Example 261

Methyl 4-(2-benzylthiophenyl)-3-cyano-1,4-dihydro-2,6-dimethylpyridine-5-carboxylate

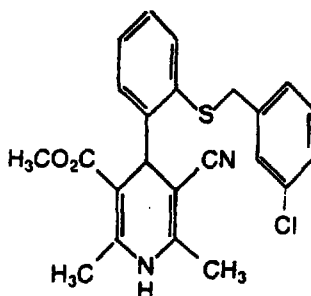


- 5
- 10 A solution of 22.7 g (69 mmol) of methyl 2-(2-benzylthio-benzylidene)acetoacetate and 5.7 g (69 mmol) of β -amino-crotononitrile in 80 ml of methanol was heated to boiling under nitrogen for 12 hours. The solvent [sic] was then concentrated in vacuo and the oily residue was crystallized
- 15 by triturating with a small amount of ether. The crude product was filtered off with suction and recrystallized from methanol.

Melting point: 183-185°C.

Yield: 15.7 g (58%).

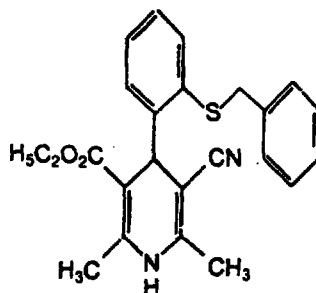
20 Example 262



25

- Analogously to Example 261, methyl 4-(2-(3-chloro-benzylthio)phenyl)-3-cyano-1,4-dihydro-2,6-di-methylpyri-dine-5-carboxylate of m.p.: 155°C (methanol) was obtained
- 30 by reaction of methyl 2-(2-(3-chlorobenzyl-thio)benzylidene)acetoacetate and β -aminocrotononitrile in methanol. Yield: 51% of theory.

Example 263



35

- 80 -

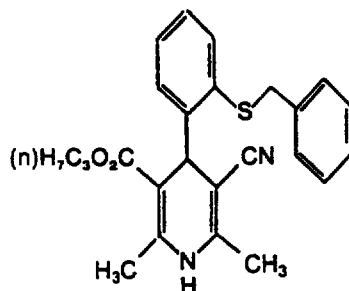
Analogously to Example 261, ethyl 4-(2-benzylthiophenyl)-3-cyano-1,4-dihydro-2,6-dimethylpyridine-5-carboxylate of m.p.: 127°C was obtained by reaction of ethyl 2-(2-benzylthiobenzylidene)acetoacetate and β-amino-

5 crotononitrile in ethanol.

Yield: 49% of theory.

Example 264

10



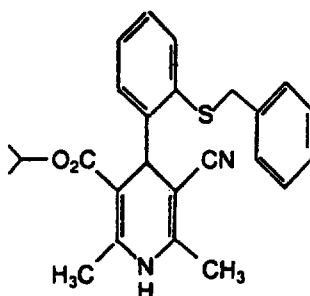
Analogously to Example 261, n-propyl 4-(2-benzylthiophenyl)-3-cyano-1,4-dihydro-2,6-dimethylpyridine-5-

15 carboxylate of m.p.: 101°C was obtained by reaction of n-propyl 2-(2-benzylthiobenzylidene)acetoacetate and β-aminocrotononitrile in ethanol.

Yield: 45% of theory.

20 Example 265

25



Analogously to Example 261, isopropyl 4-(2-benzylthiophenyl)-3-cyano-1,4-dihydro-2,6-dimethylpyridine-5-

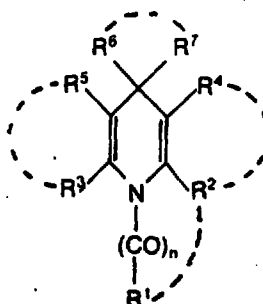
30 carboxylate of m.p.: 152°C was obtained by reaction of isopropyl 2-(2-benzylthiobenzylidene)acetoacetate and β-aminocrotononitrile in ethanol.

Yield: 61% of theory.



Claims

1. Use of 1,4-dihydropyridines of the general formula (I)



in which

n stands for 0, 1 or 2,

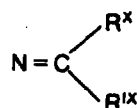
R^1

- a) stands for hydrogen, a straight-chain, branched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical which can contain 1 to 3 identical or different hetero chain members from the group consisting of O, CO, SO_m ($m = 0.1$ or 2), =N-, NR^I and $SiR^{II}R^{III}$, this hydrocarbon radical being unsubstituted or substituted by halogen, NO_2 , CN, N_3 , hydroxyl, aryl or heteroaryl or
 b) stands for an aryl or heteroaryl radical, it being possible for these radicals to carry 1 to 5 identical or different substituents from the group consisting of aryl, alkyl, alkenyl, alkynyl, alkenoxy, alkinoxy, aralkyl, acyl, alkylene, dioxyalkylene, halogen, CF_3 , OCF_3 , SCF_3 , NO_2 , NO, CN, N_3 , COR^{IV} , $COOR^V$, OR^{VI} , NR^I or $NR^{VII}R^{VIII}$, it being possible for the alkyl, alkoxy and aryl radicals of the abovementioned substituents in their turn also to be substituted by halogen, $COOR^V$ or $NR^{VII}R^{VIII}$ or
 c) stands for the radical $NR^{VII}R^I$, the radicals R^I , R^{II} , R^{III} , R^{IV} , R^V , R^{VI} , R^{VII} and R^{VIII} mentioned under a), b) and c) having the meaning given below,

R^2

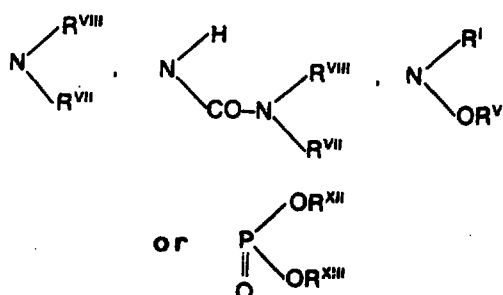
- a) stands for one of the substituents mentioned under R^1 but does not have to be identical thereto, or
 b) stands for the radicals NHR^I or





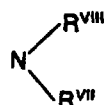
R^{I} , R^{IX} and R^{X} having the meaning given below, or the substituents R^1 and R^2 together form a 5- to 8-membered, saturated or unsaturated ring which can contain 1, 2 or 3 identical or different ring members from the group consisting of O, S, NR^{I} and CO and which can contain 1 to 3 identical or different substituents from the group consisting of halogen, hydroxyl, alkyl, alkoxy, aryl or aralkyl, R^3 stands for one of the substituents mentioned under R^2 and is identical thereto or differs therefrom, only one of the two substituents R^2 or R^3 each standing for alkoxy, alkylthio or NHR^{I} , R^4

a) stands for hydrogen, NO_2 , NO, CN, $\text{SO}_m\text{R}^{\text{XI}}$ ($m = 0, 1$ or 2), halogen,



R^{IVII} , R^{VIII} , R^{XI} and R^{XIII} having the meaning given below, or

b) stands for a branched or unbranched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical which is unsubstituted or substituted by halogen, OH, CN, alkoxy, alkylthio, aryloxy, COOR^{V} or



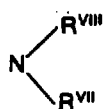
R^{V} , R^{VII} and R^{VIII} having the meaning given below, or

c) stands for an aromatic hydrocarbon radical or for a 5-



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to 7-membered saturated or unsaturated hetero ring having 1 to 4 identical or different hetero members from the group consisting of O, S, -N= and NR^{I} , this hetero ring being linked to the dihydropyridine ring either via a carbon atom or a nitrogen atom, it being possible for the aromatic hydrocarbon radical and the hetero rings to carry 1 to 3 identical or different substituents from the group consisting of halogen, OH, CN, CF_3 , OCF_3 , SCF_3 , NO_2 , alkyl, alkoxy, aryl and

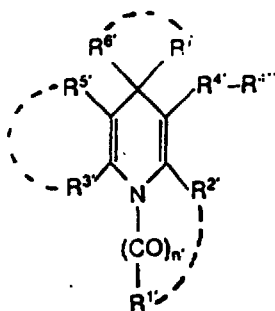


or

d) stands for the radical



in which X denotes oxygen, sulphur or NR^{I} , and Y stands for a single bond, O, S or NR^{I} , and R^8 has the meaning given for R^1 and is identical to the substituent R^1 or differs therefrom, or
e) stands for the radical

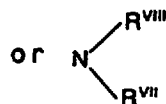


in which n , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 have the meaning given for n , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 and are identical thereto or differ therefrom, and R^{4*} and R^{4**} are identical or different and each stand for a radical, minus one hydrogen,



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of the substituents mentioned for R^4 under a) to d), or R^2 and R^4 together form a branched, unbranched, saturated or unsaturated 5- to 8-membered ring which can contain 1, 2 or 3 identical or different ring members from the group consisting of O, CO, CS, $C=NR^I$, $=N-$, NR^I , SO_m ($m = 0, 1$ or 2) and $SiR^{II}R^{III}$, and which is unsubstituted or substituted by halogen, hydroxyl, alkoxy, aryl, aralkyl



or disubstituted by a straight-chain or branched alkylene chain having 3 to 8 carbon atoms, it being possible for this common ring of R^2 and R^4 also to be directly fused to the common ring of R^1 and R^2 , the radicals R^I , R^{II} , R^{III} , R^{VII} and R^{VIII} having the meaning given below,

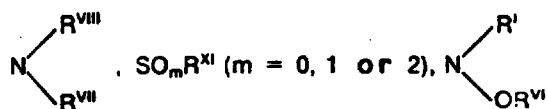
R^5 has the meaning given for R^4 and is identical to R^4 or differs therefrom, or

R^5 and R^3 together form a ring which is identical to the ring formed by R^2 and R^4 or differs therefrom,

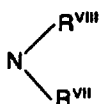
R^6 stands for hydrogen, alkyl or halogenoalkyl, and R^7

a) stands for a saturated, unsaturated, cyclic, straight-chain or branched aliphatic hydrocarbon radical which is unsubstituted or substituted by halogen, aryl or heteroaryl, or

b) stands for an aryl or heteroaryl radical which can contain 1 to 5 identical or different substituents from the group consisting of NO_2 , CN, N_3 , NO, CF_3 , halogen, COR^{IV} , COR^V , OR^{VI} ,



alkyl, aryl, alkenyl, alkynyl, alkenoxy, alkinoxy, aralkyl, acyl, alkylene and dioxyalkylene, it being possible for the abovementioned alkyl and aryl substituents in their turn also to be substituted by halogen, $COOR^V$ or



and in the abovementioned definitions of the substituents R^1 to R^8 ,

R^1 stands for hydrogen, alkyl, aryl, aralkyl, heteroaryl or acyl,

R^{II} and R^{III} are identical or different and each stand for alkyl, aryl, aralkyl or heteroaryl,

R^{IV} , R^{V} and R^{VI} are each identical or different and stand for hydrogen, alkyl, aryl, aralkyl or heteroaryl, the alkyl and aryl radicals being unsubstituted or substituted by halogen, nitro, trifluoromethyl, alkoxy, alkylthio or alkyl, R^{VII} and R^{VIII} are each identical or different and stand for hydrogen, aryl or aralkyl, or stand for alkyl which is uninterrupted or interrupted by O, S or NR^{I} , or, together with the nitrogen atom, form a 5- to 7-membered ring which can contain 1 or 2 identical or different hetero ring members from the group consisting of O, S and NR^{I} , or

one of the radicals R^{VII} or R^{VIII} stands for an aliphatic acyl group having up to 6 carbon atoms, R^{IX} , R^{X} , R^{XI} , R^{XII} and R^{XIII} are each identical or different and stand for alkyl, aryl or aralkyl, the alkyl, aryl, aralkyl, heteroaryl and acyl radicals mentioned under R^1 to R^8 and under R^{I} to R^{XIII} , and the hetero ring formed with R^{VII} and R^{VIII} , in their turn being unsubstituted or substituted by OH, CF_3 , OCF_3 , CN, NO_2 , halogen, lower thioalkyl, lower alkyl, lower alkoxy, aryl or aralkyl,

and the following substituents being mentioned as heteroaryl:

thienyl, furyl, pyryl, pyridyl, quinolyl, isoquinolyl, pyrimidyl, pyradazinyl, quinazolyl, quinoxalyl, benzothienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, oxydiazolyl, pyrazinyl, oxazinyl, thiazinyl, indolizinyll, indolyl, benzofuranyl, indazolyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl,



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benzothiazolyl, benzotriazolyl, benzoxadiazolyl, cinnolyl, phthalazinyl, naphthyridinyl, or benzotriazinyl, in the form of isomers, isomer mixtures, racemates and optical antipodes, and of their pharmaceutically acceptable salts, which, from a concentration of 10^{-5} g/ml upwards, cause an at least 25% augmentation of the contraction of the isolated left atrium of the guinea pig heart, for the preparation of medicaments which increase the influx of Ca^{++} into the cell.

2. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments having a positive inotropic action.

3. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments having a cardiotonic action.

4. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments having an antihypotonic action.

5. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments for reducing blood sugar.

6. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments for decreasing the swelling of mucous membranes.

7. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments for influencing [sic] the salt and fluid balance.

8. Use according to Claims 1 to 7 of compounds of the general formula (I) according to Claim 1, in which n stands for 0, 1 or 2,

R^1

a) stands for hydrogen, a straight-chain, branched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical having up to 10 C atoms which can contain 1 or 2 identical or different hetero chain members from the group consisting of O, CO, S, SO_2 , =N- and NR^{I} , this hydrocarbon radical being unsubstituted or substituted by halogen, NO_2 , CN, N_3 , hydroxyl, having 1 to 4 C atoms, phenyl, naphthyl or heteroaryl or

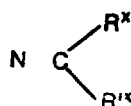


b) stands for a phenyl, naphthyl or heteroaryl radical, these radicals optionally carrying 1 to 3 identical or different substituents from the group consisting of phenyl, alkyl, alkenyl, alkynyl, alkenoxy, each having up to 4 C atoms, aralkyl having 7 to 14 C atoms, acyl having up to 6 C atoms, alkylene, dioxyalkylene having up to 4 carbon atoms in the alkylene chain, halogen, CF_3 , OCF_3 , SCF_3 , NO_2 , CN , N_3 , COR^{IV} , COOR^{V} , OR^{VI} , NR^{I} or $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$, it being possible for the alkyl, alkoxy and aryl radicals of the abovementioned substituents in their turn also to be substituted by halogen, COOR^{V} or $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$ or

c) stands for the radical $\text{NR}^{\text{VII}}\text{R}^{\text{I}}$, the radicals R^{I} , R^{II} , R^{III} , R^{IV} , R^{V} , R^{VI} , R^{VII} and R^{VIII} mentioned under a), b) and c) having the meaning given below,

R^2

a) stands for one of the substituents mentioned under R^1 but does not have to be identical thereto or b) stands for the radicals NHR^{I} or

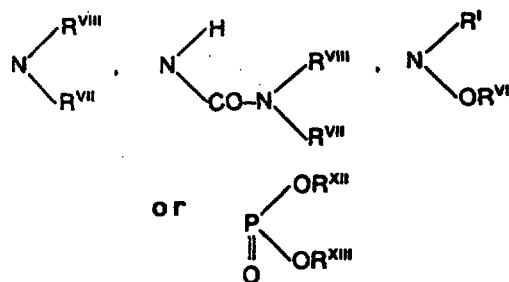


R^{I} , R^{IX} and R^{X} having the meaning given below, or the substituents R^1 and R^2 together form a 5- to 7-membered saturated or unsaturated ring which can contain one or two identical or different ring members from the group consisting of O, S, NR^{I} and CO and which can contain one to three identical or different substituents from the group consisting of halogen, hydroxyl, alkyl, alkoxy, each having 1 to 4 C atoms, phenyl, naphthyl or aralkyl having 7 to 14 C atoms,

R^3 stands for one of the substituents mentioned under R^2 and is identical thereto or differs therefrom, only one of the two substituents R^2 or R^3 in each case standing for alkoxy, alkylthio or NHR^{I} ,

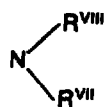
R^4

a) stands for hydrogen, NO_2 , NO , CN , $\text{SO}_m\text{-R}^{\text{IX}}$ ($m = 0$ or 2), halogen,



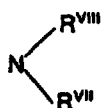
R^{I} , R^{VII} , R^{VIII} , R^{XII} and R^{XIII} having the meaning given below, or

b) stands for a branched or unbranched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical having up to 10 C atoms, which is unsubstituted or substituted by halogen, OH, CN, alkoxy, alkylthio, each having 1 to 4 carbon atoms, phenyloxy, naphthoxy, COOR^{V} or



R^{V} , R^{VII} and R^{VIII} having the meaning given below, or

c) stands for an aromatic hydrocarbon radical having 6 to 10 C atoms or for a 5- to 7-membered saturated or unsaturated hetero ring having 1 to 3 identical or different hetero members from the group consisting of O, S, $-\text{N}=$ and NR^{I} , this hetero ring being linked to the dihydropyridine ring either via a carbon atom or a nitrogen atom, the aromatic hydrocarbon radical and it being possible for the hetero rings to carry 1 to 3 identical or different substituents from the group consisting of halogen, OH, CN, CF_3 , OCF_3 , SCF_3 , NO_2 , alkyl, alkoxy, each having 1 to 4 C atoms, phenyl, naphthyl and



or

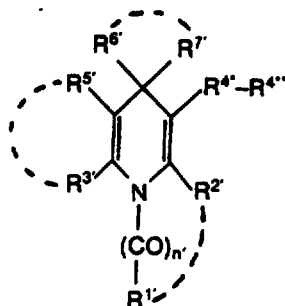
d) stands for the radical $\begin{array}{c} \text{X} \\ \parallel \\ \text{C}-\text{Y}-\text{R}^{\text{B}} \end{array}$

in which X denotes oxygen, sulphur or NR^{I} , and Y stands

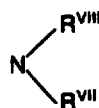


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for a single bond, O, S or NR^{I} , and R^8 has the meaning given for R^1 and is identical to the substituent R^1 or differs therefrom, or e) stands for the radical



in which n' , $\text{R}^{1'}$, $\text{R}^{2'}$, $\text{R}^{3'}$, $\text{R}^{5'}$, $\text{R}^{6'}$ and $\text{R}^{7'}$ have the meaning given for n , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 and are identical thereto or differ therefrom, and R^{4*} and R^{4**} are identical or different and each stand for a radical, minus one hydrogen, of the substituents mentioned for R^4 under a) to d), or R^2 and R^4 together form a branched, unbranched, saturated or unsaturated 5- to 7-membered ring which can contain 1, 2 or 3 identical or different ring members from the group consisting of O, CO, CS, $\text{C}=\text{NR}^{\text{I}}$, $=\text{N}-$, NR^{I} and SO_m ($m = 0$ or 2) and which is unsubstituted or substituted by halogen, hydroxyl, alkoxy having 1 to 4 C atoms, phenyl, naphthyl, aralkyl having 7 to 14 C atoms, or



or disubstituted by a straight-chain or branched alkylene chain having 3 to 8 carbon atoms, it being possible for this common ring of R^2 and R^4 also to be directly fused to the common ring of R^1 and R^2 , the radicals R^{I} , R^{II} , R^{III} , R^{VII} and R^{VIII} having the meaning given below,

R^5 has the meaning given for R^4 and is identical to R^4 or differs therefrom,

R^6 stands for hydrogen, alkyl or halogenoalkyl each having 1 to 4 C atoms and

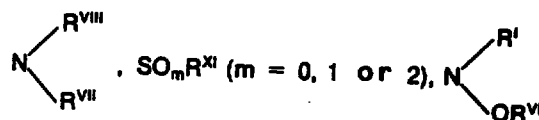
R^7

a) stands for a saturated, unsaturated, cyclic, straight-

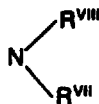


chain or branched aliphatic hydrocarbon radical having up to 10 C atoms, which is unsubstituted or substituted by halogen, phenyl, naphthyl or heteroaryl or

b) stands for a phenyl, naphthyl or heteroaryl radical which optionally contains 1 to 3 identical or different substituents from the group consisting of NO₂, halogen, CN, N₃, NO, CF₃, COR^{IV}, COOR^V, OR^{VI},



alkyl having 1 to 4 C atoms, phenyl, naphthyl, alkenyl, alkynyl, alkenoxy, alkinoxy, each having up to 4 C atoms, aralkyl having 7 to 14 C atoms, acyl having 1 to 4 C atoms, alkylene and dioxyalkylene, each having up to 4 C atoms, it being possible for the abovementioned alkyl and aryl substituents in their turn also to be substituted by halogen, COOR^V or



and in the abovementioned definitions of the substituents R^I to R⁷,

R^I stands for hydrogen, alkyl having 1 to 6 C atoms, phenyl, naphthyl, aralkyl having 7 to 12 C atoms, heteroaryl or acyl having up to 7 C atoms,

R^{II} and R^{III} are identical or different and each stand for alkyl having 1 to 6 C atoms, phenyl, naphthyl, aralkyl having 7 to 12 C atoms or heteroaryl,

R^{VII}, R^V and R^{VI} are each identical or different and stand for hydrogen, alkyl having 1 to 6 C atoms, phenyl, naphthyl, aralkyl having 7 to 12 C atoms or heteroaryl, the alkyl and aryl radicals being unsubstituted or substituted by halogen, nitro, trifluoromethyl, alkoxy, alkylthio and alkyl, each having 1 to 4 C atoms,

R^{VII} and R^{VIII} are each identical or different and stand for hydrogen, phenyl, naphthyl or aralkyl having 7 to 12 C



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atoms or stand for alkyl having 1 to 6 C atoms which is uninterrupted or interrupted by O, S, or NR^{I} , or, together with the nitrogen atom, form a 5- to 7-membered ring which can contain 1 or 2 identical or different hetero ring members from the group consisting of O, S and NR^{I} , or one of the radicals R^{VII} and R^{VIII} stands for an aliphatic acyl group having up to 6 carbon atoms, R^{IX} , R^{X} , R^{XII} and R^{XIII} are each identical or different and stand for alkyl having 1 to 6 C atoms, phenyl, naphthyl or aralkyl having 7 to 12 C atoms, the alkyl, aryl, aralkyl, heteroaryl and acyl radicals mentioned under R^1 to R^8 and under R^{I} to R^{VIII} and the hetero ring formed with R^6 and R^7 in their turn being unsubstituted or substituted by OH, CF_3 , OCF_3 , CN, NO_2 , halogen, alkyl having 1 to 4 C atoms, alkoxy, alkylthio, each having 1 to 4 C atoms, phenyl or benzyl, and the following substituents being mentioned as hetero-aryl:

thienyl, furyl, pyryl, pyridyl, quinolyl, isoquinolyl, pyrimidyl, pyridazinyl, quinazolyl, quinoxalyl, benzothienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, oxydiazolyl, pyrazinyl, oxazinyl, thiazinyl, indolizinyl, indolyl, benzofuranyl, indazolyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzotriazolyl, benzoxadiazolyl, cinnolinyl, phthalazinyl, naphthyridinyl or benzotriazinyl,

in the form of isomers, isomer mixtures, racemates and optical antipodes, and of their pharmaceutically acceptable salts.

9. Use according to Claims 1 to 7 of compounds of the general formula (I) according to Claim 1, in which n stands for 0 or 1,

R^1

a) stands for hydrogen, a straight-chain, branched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical having up to 10 C atoms which can contain by [sic] one or two identical or different hetero chain members from the group consisting of O, CO, S, =N- and NR^{I} , this hydrocarbon



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radical being unsubstituted or substituted by F, Cl, Br, NO₂, CN, OH, phenyl or pyridyl or

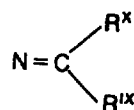
b) stands for a phenyl, naphthyl or pyridyl radical, it being possible for these radicals to carry 1 or 2 identical or different substituents from the group consisting of phenyl, alkyl, alkenyl, alkoxy, alkenoxy, each having up to 4 C atoms, benzyl, acetyl, alkylene, dioxyalkylene having 2 to 4 C atoms, fluorine, chlorine, bromine, CF₃, OCF₃, SCF₃, NO₂, CN, COOR^V, OR^{VI}, NR^I and NR^{VII}R^{VIII}, it being possible for the alkyl, alkoxy and aryl radicals of the abovementioned substituents in their turn also to be halogen-substituted or

c) stands for the radical NR^{VII}R^{VIII}, the radicals R^I to R^{VIII} mentioned under a), b) and c) having the meaning given below,

R²

a) stands for one of the substituents mentioned under R¹ but does not have to be identical thereto or

b) stands for the radicals NHR^I or



R^I, R^{IX} and R^X having the meaning given below, or the substituents

R¹ and R² together form a 5- to 7-membered saturated or unsaturated ring which optionally contains 1 or 2 identical or different ring members from the group consisting of O, S, NR^I and CO and which can contain 1 or 2 identical or different substituents from the group consisting of halogen, hydroxyl, alkyl, alkoxyl, each having 1 to 4 C atoms, phenyl and benzyl,

R³ stands for one of the substituents mentioned under R² and is identical thereto or differs therefrom, only one of the two substituents R² or R³ each standing for alkoxy, alkylthio or NHR^I,

R⁴

a) stands for hydrogen, NO₂, CN, SR^{XI}, SO₂R^{XI}, R^I, R^{VI}, R^{VII}, R^{VIII} and R^{IX} having the meaning given below,



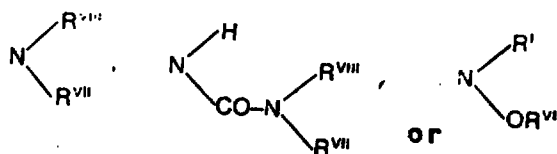
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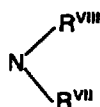


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b) stands for a branched or unbranched alkyl or cycloalkyl radical having up to 8 C atoms, which is unsubstituted or substituted by halogen, hydroxyl, cyano, alkoxy having 1 to 4 C atoms, phenyloxy, COOR^{V} or



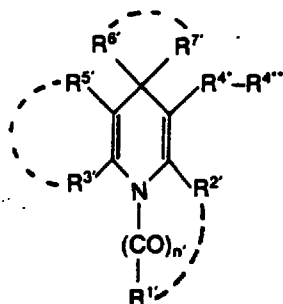
R^{V} , R^{VII} and R^{VIII} having the meaning given below or

c) stands for an aromatic hydrocarbon radical having 6 to 10 C atoms or a 5- to 7-membered saturated or unsaturated hetero ring having 1 to 3 identical or different hetero members from the group consisting of O, S, =N- and NR^{I} , this hetero ring being linked to the dihydropyridine ring either via a carbon atom or a nitrogen atom, it being possible for the aromatic hydrocarbon radical and the hetero rings to carry 1 or 2 identical or different substituents from the group consisting of halogen, hydroxyl, cyano, CF_3 , NO_2 , phenyl, alkyl and alkoxy, each having 1 to 4 C atoms, or

d) stands for the radical
$$\begin{array}{c} \text{X} \\ \parallel \\ \text{C-Y-R}^8 \end{array}$$

in which X stands for oxygen or NR^{I} and Y stands for a single bond, oxygen or NR^{I} and R^8 has the meaning given for R^1 and is identical to the substituent or differs therefrom, or

e) stands for the radical



in which n' , $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{5'}$, $R^{6'}$ and $R^{7'}$ have the meaning given for n , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 and are identical thereto or differ therefrom, and R^{4*} and R^{4**} are identical or different and each stand for a radical, minus one hydrogen, of the substituents mentioned for R^4 under a) to d), or

R^2 and R^4 together form a branched, unbranched, saturated or unsaturated 5- to 7-membered ring which can contain 1 or 2 identical or different ring members from the group consisting of O, CO, CS, $C=NR^I$, $=N-$ and NR^I and which is unsubstituted or substituted by halogen or hydroxyl, R^1 having the meaning given below,

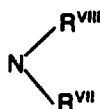
R^5 has the meaning given for R^4 and is identical to R^4 or differs therefrom or

R^5 and R^3 together form a ring of the kind defined for R^2 and R^4 and which is identical thereto or differs therefrom, R^6 stands for hydrogen or alkyl having 1 to 4 C atoms which is unsubstituted or substituted by fluorine, chlorine or bromine and

R^7

a) stands for a saturated, unsaturated, cyclic, straight-chain or branched aliphatic hydrocarbon radical having up to 8 C atoms, which is unsubstituted or substituted by halogen, or

b) stands for a phenyl or heteroaryl radical which optionally contains 1 to 3 identical or different substituents from the group consisting of NO_2 , CN, N_3 , CF_3 , halogen, COR^{IV} , COR^V , OR^{VI} , SR^{XI} ,



phenyl, alkyl having 1 to 4 C atoms, benzyl and acyl



having 1 to 4 C atoms,

and in the abovementioned definitions of the substituents R^1 to R^8 ,

R^I stands for hydrogen, alkyl having 1 to 6 C atoms, phenyl, naphthyl, benzyl, phenethyl, heteroaryl or acyl having up to 4 C atoms,

R^{II} and R^{III} are identical or different and each stand for alkyl having 1 to 6 C atoms, phenyl, naphthyl, benzyl or heteroaryl,

R^{IV} , R^V and R^{VI} are each identical or different and stand for hydrogen, alkyl having 1 to 6 C atoms, phenyl, naphthyl, benzyl or heteroaryl, the alkyl, phenyl and benzyl radicals being unsubstituted or substituted by fluorine, chlorine, nitro, CF_3 , methyl, methoxy and methylthio,

R^{VII} and R^{VIII} are each identical or different and stand for hydrogen, phenyl or benzyl or stand for alkyl having 1 to 6 carbon atoms, which is uninterrupted or interrupted by O or NR^I , or together with the nitrogen atom, form a 5- to 7-membered ring which can contain 1 or 2 identical or different hetero ring members from the group consisting of O, S and NR^I ,

or

one of the radicals R^{VII} or R^{VIII} stands for an aliphatic acyl group having up to 6 carbon atoms and R^{IX} , R^X , R^{XI} , R^{XII} and R^{XIII} are each identical or different and stand for alkyl having 1 to 6 C atoms, phenyl or benzyl, and the following substituents being mentioned as heteroaryl:

thienyl, furyl, pyryl, pyridyl, quinolyl, isoquinolyl, pyrimidyl, pyridazinyl, quinazolyl, quinoxalyl, benzothienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, oxydiazolyl, pyrazinyl, oxazinyl, thiazinyl, indolyl, benzofuranyl, indazolyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzotriazolyl or benzoxadiazolyl.

10. Use according to Claims 1 to 7 of compounds of the general formula (I) according to Claim 1, in which n stands for 0,

R^1

a) stands for hydrogen, an aliphatic hydrocarbon radical



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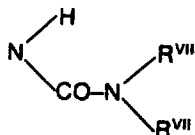
having up to 6 C atoms, which can contain a hetero chain member from the group consisting of O, CO, =N- and NR^{I} and which is unsubstituted or substituted by halogen, nitro, hydroxyl or phenyl or

b) stands for a phenyl or pyridyl radical which is unsubstituted or substituted by halogen, NO_2 , CF_3 , OCF_3 , CN, COOR^{V} or $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$,

R^2 stands for one of the substituents mentioned under R^1 but does not have to be identical thereto or stands for one of the radicals NHR^{I} or $\text{N}=\text{CR}^{\text{X}}\text{R}^{\text{XI}}$,

R^3 stands for one of the substituents mentioned under R^2 and is identical thereto or differs therefrom,
 R^4

a) stands for hydrogen, NO_2 , $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$,



or halogen, or

b) stands for an alkyl radical having 1 to 4 C atoms, which is unsubstituted or substituted by halogen, OH, CN, alkoxy having 1 to 4 C atoms, COOR^{V} or $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$ or

c) stands for phenyl, pyridyl or thienyl, which are unsubstituted or substituted by halogen, OH, CN, alkyl or alkoxy, each having 1 to 4 C atoms, or by $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$ or

d) stands for the radical



in which X denotes oxygen and Y stands for a single bond, oxygen or NR^{I} and R^8 has the meaning given for R^1 and is identical to the substituent R^1 or differs therefrom or

e) stands for the radical

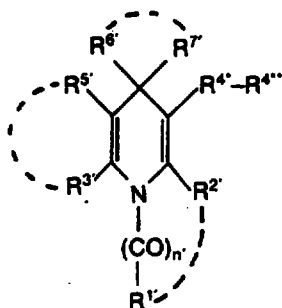


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in which n' , $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{5'}$, $R^{6'}$ and $R^{7'}$ have the meaning given for n , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 and are identical thereto or differ therefrom, and R^{4*} and R^{**} are identical or different and each stand for a radical, minus one hydrogen, of the substituents mentioned for R^4 under a) to d), or

R^2 and R^4 together form a 5- to 7-membered ring which can contain 1 to 2 different ring members from the group consisting of O, CO, CS and $C=NR^I$ and which is unsubstituted or substituted by halogen,

R^5 has the meaning given for R^4 and is identical to R^4 or differs therefrom,

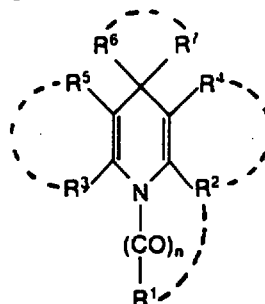
R^6 stands for hydrogen or alkyl having 1 to 4 C atoms and

R^7 has the abovementioned meaning,

the substituents R^I to R^{VIII} marked with Roman numerals in the abovementioned definitions having the meaning given in Claim 4.

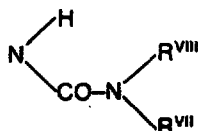
11. Use according to Claims 1 to 7 of compounds of the general formula (I) according to Claim 1, in which at least one of the substituents R^4 and R^5 stands for NO_2 and/or in which R^2 and R^4 together or R^3 and R^5 together form a lactone ring.

12. Compounds of the general formula (I)



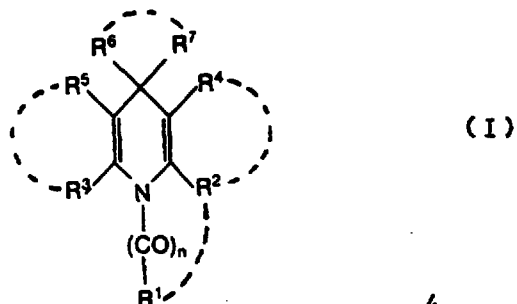
(I)

in which at least one of the substituents R^4 and R^5 stands for the group



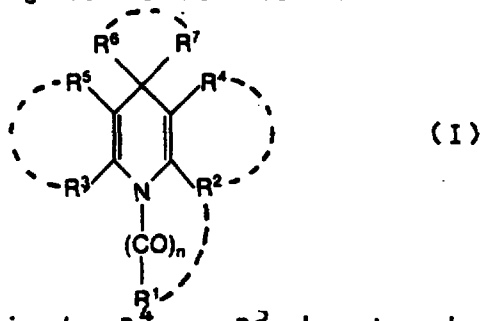
in which R^{VIII} and R^{VII} and the substituents R^1 , R^2 , R^3 , R^6 , R^7 and n and the remaining radical of R^4 and R^5 have the meaning given in Claims 1 and 8 to 11.

13. Compounds of the general formula (I)



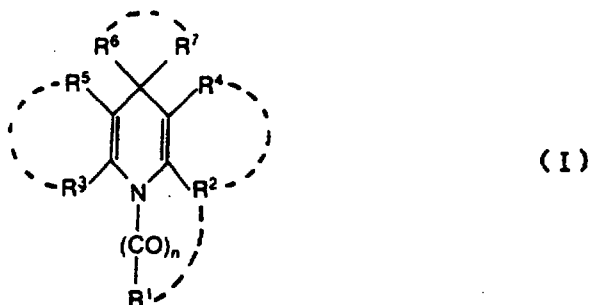
in which at least one of the substituents R^4 and R^5 stands for methyl, in which R^1 , R^2 , R^3 , R^6 , R^7 and n and the remaining radical of R^4 and R^5 have the meaning given in Claims 1 and 8 to 11.

14. Compounds of the general formula (I)



in which one of the radicals R^4 or R^5 denotes hydrogen, R^1 stands for hydrogen and n stands for 0 and R^2 , R^3 , R^6 and R^7 and the other radical of R^4 and R^5 have the meaning given in Claims 1 and 8 to 11.

15. Compounds of the general formula (I)



in which one of the radicals R^4 and R^5 denotes halogen and R^1 , R^2 , R^3 , R^6 and R^7 and n and the other radical of R^4



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and R^5 have the meaning given in Claim 1 and 8 to 11.

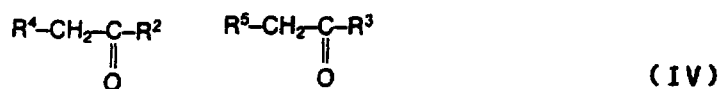
16. Compounds according to Claim 15, in which one of the radicals R^4 or R^5 stands for fluorine or chlorine.

17. Process for the preparation of compounds according to Claims 12 to 16, characterized in that

a) carbonyl compounds of the general formula (II)



are reacted with ketones of the formula (III) and (IV)



and primary amines of the formula (V)



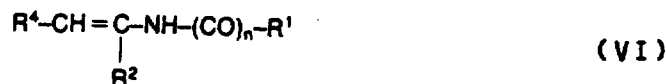
in which $n = 0$,

in the presence or absence of inert solvents, or

b) carbonyl compounds of the formula (II)



are reacted with enamines of the formula (VI)



and ketones of the formula (IV)



in the presence or absence of inert solvents or

c) enamines of the formula (VI)



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are reacted with ylidene compounds of the formula (VIII)



in the presence or absence of inert solvents, or

d) one or more functional groups of dihydropyridines are modified by customary methods of hydrolysis, esterification, transesterification, lactonization, condensation, acylation, reduction or cyclization.

18. Medicaments containing at least one compound according to Claims 12 to 16.

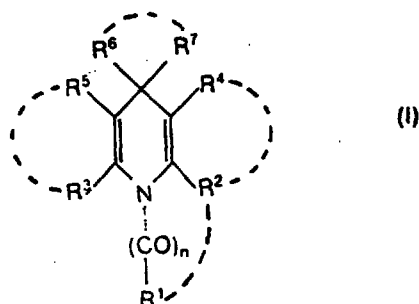
19. Process for the preparation of medicaments, characterized in that at least one compound according to Claims 12 to 16 is converted into a suitable form of administration, with or without using inert auxiliaries and vehicles.

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Claims

1. Use of 1,4-dihydropyridines of the general formula (I)



in which

n represents 0, 1 or 2,

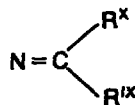
R^1 a) represents hydrogen, a straight-chain, branched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical which optionally contains 1 to 3 identical or different hetero chain members from the group comprising O, CO, SO_m ($m = 0, 1$ or 2), $=N-$, NR^I and $SiR^I R^{III}$, this hydrocarbon radical optionally being substituted by halogen, NO_2 , CN, N_3 , hydroxyl, aryl or heteroaryl or

b) represents an aryl or heteroaryl radical, these radicals optionally carrying 1 to 5 identical or different substituents from the group comprising aryl, alkyl, alkenyl, alkynyl, alkenoxy, alkinoxy, aralkyl, acyl, alkylene, dioxyalkylene, halogen, CF_3 , OCF_3 , SCF_3 , NO_2 , NO, CN, N_3 , COR^{IV} , $COOR^V$, OR^VI , NR^I or $NR^{VII} R^{VIII}$, it being possible for the alkyl, alkoxy and aryl radicals of the abovementioned substituents in their turn also to be substituted by halogen, $COOR^V$ or $NR^{VII} R^{VIII}$ or

c) represents the radical $NR^{VII} R^I$, the radicals R^I , R^{II} , R^{III} , R^{IV} , R^V , R^VI , R^{VII} and R^{VIII} mentioned under a), b) and c) having the meaning given below,

R^2
a) represents one of the substituents mentioned under R^1 but does not have to be identical thereto, or

b) represents the radicals NHR^I or



R^I , R^{IX} and R^X having the meaning given below, or the substituents R^1 and R^2 together form a 5- to 8-membered, saturated or unsaturated ring which optionally contains 1, 2 or 3 identical or different ring members from the group comprising O, S, NR^I and CO and which optionally contains 1 to 3 identical or different substituents from the group comprising halogen, hydroxyl, alkyl, alkoxy, aryl or aralkyl,

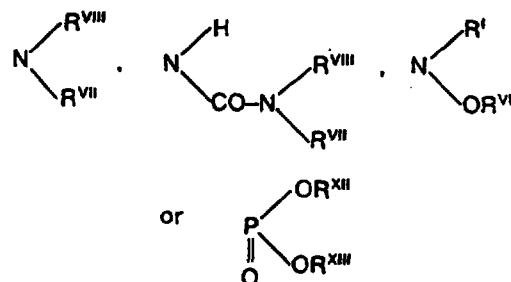
R^3 represents one of the substituents mentioned under R^2 and is identical thereto or differs therefrom, only one of the two substituents R^2 or R^3 in each case representing alkoxy, alkylthio or NHR^I ,

R^4

a) represents hydrogen, NO_2 , NO, CN, $SO_m R^{XI}$ ($m = 0, 1$ or 2), halogen

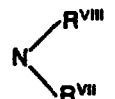


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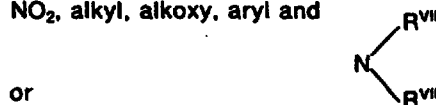
$R^I R^{VII}$, R^{VIII} , R^{XI} and R^{XIII} having the meaning given below, or

b) represents a branched or unbranched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical which is optionally substituted by halogen, OH, CN, alkoxy, alkylthio, aryloxy, $COOR^V$ or



R^V , R^{VI} and R^{VIII} having the meaning given below, or

c) represents an aromatic hydrocarbon radical or a 5- to 7-membered saturated or unsaturated hetero ring with 1 to 4 identical or different hetero members from the group comprising O, S, $=N-$ and NR^I , this hetero ring being linked to the dihydropyridine ring either via a carbon atom or a nitrogen atom, the aromatic hydrocarbon radical and the hetero rings optionally carrying 1 to 3 identical or different substituents from the group comprising halogen, OH, CN, CF_3 , OCF_3 , SCF_3 , NO_2 , alkyl, alkoxy, aryl and



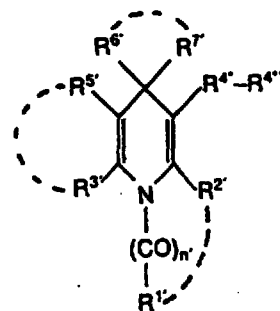
or

d) represents the radical



wherein X denotes oxygen, sulphur or NR^I , and Y represents a single bond, O, S or NR^I , and R^8 has the meaning given for R^1 and is identical to the substituent R^1 or differs therefrom, or

e) represents the radical



wherein

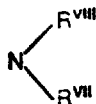
n' , R^I , R^2 , R^3 , R^5 , R^6 and R^7 have the meaning given for n , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 and are identical thereto or differ therefrom, and R^4 and $R^{4'''}$ are identical or different and each represent a radical, minus one hydrogen, of the substituents mentioned for R^4 under a) to d), or R^2 and R^4 together form a branched, unbranched, saturated or unsaturated 5- to 8-membered ring which optionally contains 1, 2 or 3 identical or different ring members from the group comprising



c85

O, CO, CS, C=NR^I, =N-, NR^I, SO_m (m = 0, 1 or 2) and SiR^{II}R^{III}, and which is optionally substituted by halogen, hydroxy, alkoxy, aryl, aralkyl

or



or disubstituted by a straight-chain or branched alkylene chain with 3 to 8 carbon atoms, it being possible for this common ring of R² and R⁴ also to be directly fused to the common ring of R¹ and R², the radicals R^I, R^{II}, R^{III}, R^{VII} and R^{VIII} having the meaning given below,

R⁵ has the meaning given for R⁴ and is identical to R⁴ or different therefrom, or

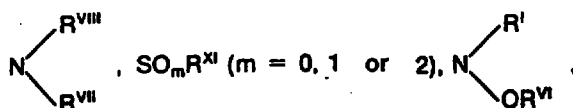
R⁵ and R³ together form a ring which is identical to the ring formed by R² and R⁴ or differs therefrom, or

R⁶ represents hydrogen, alkyl or halogenoalkyl, and

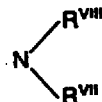
R⁷

a) represents a saturated, unsaturated, cyclic, straight-chain or branched aliphatic hydrocarbon radical which is optionally substituted by halogen, aryl or heteroaryl, or

b) represents an aryl or heteroaryl radical which optionally contains 1 to 5 identical or different substituents from the group comprising NO₂, CN, N₃, NO, CF₃, halogen, COR^{IV}, COR^V, OR^{VI},



alkyl, aryl, alkenyl, alkynyl, alkenoxy, alkinoxy, aralkyl, acyl, alkylene and dioxyalkylene, it being possible for the abovementioned alkyl and aryl substituents in their turn also to be substituted by halogen, COOR^V or



and in the abovementioned definitions of the substituents R¹ to R⁸

R^I represents hydrogen, alkyl, aryl, aralkyl, heteroaryl or acyl,

R^{II} and R^{III} are identical or different and each represent alkyl, aryl, aralkyl or heteroaryl, R^{IV}, R^V and R^{VI} are in each case identical or different and represent hydrogen, alkyl, aryl, aralkyl or heteroaryl, the alkyl and aryl radicals optionally being substituted by halogen, nitro, trifluoromethyl, alkoxy, alkylthio or alkyl,

R^{VII} and R^{VIII} are in each case identical or different and represent hydrogen, aryl or aralkyl, or represent alkyl which is optionally interrupted by O, S or NR^I, or, together with the nitrogen atom, form a 5- to 7-membered ring which can contain 1 or 2 identical or different hetero ring members from the group comprising O, S and NR^I, or

one of the radicals R^{VII} or R^{VIII} represents an aliphatic aryl group with up to 6 carbon atoms, R^X, R^{XI}, R^{XII} and R^{XIII} are in each case identical or different and represent alkyl, aryl or aralkyl, the alkyl, aryl, aralkyl, heteroaryl and acyl radicals mentioned under R¹ to R⁸ and under R¹ to R^{XIII}, and the hetero ring formed with R^{VII} and R^{VIII}, in their turn optionally being substituted by OH, CF₃,

OCF₃, CN, NO₂, halogen, lower thioalkyl, lower alkyl, lower alkoxy, aryl or aralkyl, and the following substituents being mentioned as heteroaryl:

thienyl, furyl, pyryl, pyridyl, quinolyl, isoquinolyl, pyrimidyl, pyrazolyl, pyridazyl, quinazolyl, quinoxalyl, benzothienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, oxydiazolyl, pyrazinyl, oxazinyl, thiazinyl, indolizyl, indolyl, benzofuranyl, indazolyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, benztriazolyl, benzoxadiazolyl, cinnolyl, phthalazyl, naphthyridyl, or benzotriazinyl,

in the form of isomers, isomer mixtures, racemates and optical antipodes, and of their pharmaceutically acceptable salts, which, from a concentration of 10⁻⁵ g/ml upwards, cause an at least 25% augmentation of the contraction of the isolated left atrium of the guinea pig heart, for the preparation of medicaments which increase the influx of Ca⁺⁺ into the cell.

2. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments with a positive inotropic action.

3. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments with a cardiotonic action.

4. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments with an antihypotonic action.

5. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments for reducing blood-sugar.

6. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments for decreasing the swelling of mucous membranes.

7. Use according to Claim 1 of compounds of the general formula (I) for the preparation of medicaments for influencing the salt and liquid balance.

8. Use according to Claims 1 to 7 of compounds of the general formula (I) according to Claim 1, in which

n represents 0, 1 or 2,

R¹-

a) represents hydrogen, a straight-chain, branched cyclic saturated or unsaturated aliphatic hydrocarbon radical with up to 10 C atoms which optionally contains 1 or 2 identical or different hetero chain members from the group comprising O, CO, S, SO₂, =N- and NR^I, this hydrocarbon radical optionally being substituted by halogen, NO₂, CN, N₃, hydroxyl, with 1 to 4 C atoms, phenyl, naphthyl or heteroaryl or

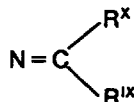
b) represents a phenyl, naphthyl or heteroaryl radical, these radicals optionally carrying 1 to 3 identical or different substituents from the group comprising phenyl, alkyl, alkenyl, alkynyl, alkenoxy, alkinoxy with in each case up to 4 C atoms, aralkyl with 7 to 14 C atoms, acyl with up to 6 C atoms, alkylene, dioxyalkylene with up to 4 carbon atoms in the alkylene chain, halogen, CF₃, OCF₃, SCF₃, NO₂, CN, N₃, COR^{IV}, COOR^V, OR^{VI}, NR^I or NR^{VII}R^{VIII}, it being possible for the alkyl, alkoxy and aryl radicals of the abovementioned substituents in their turn also to be substituted by halogen, COOR^V or NR^{VII}R^{VIII} or



c) represents the radical $\text{NR}^{\text{VIII}}\text{R}^{\text{I}}$, the radicals R^{I} , R^{II} , R^{III} , R^{IV} , R^{V} , R^{VI} , R^{VII} and R^{VIII} mentioned under a), b) and c) having the meaning given below, R^2 and

a) represents one of the substituents mentioned under R^1 but does not have to be identical thereto or

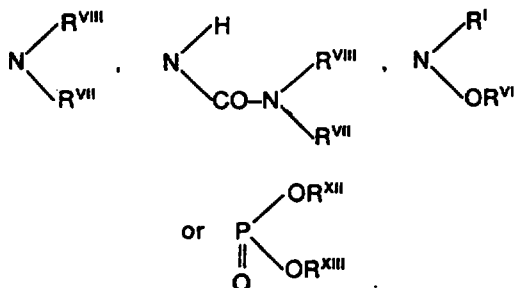
b) represents the radicals NHR^{I} or



R^{I} , R^{IX} and R^{X} having the meaning given below, or the substituents

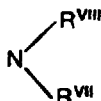
R^1 and R^2 together form a 5- to 7-membered saturated or unsaturated ring which optionally contains one or two identical or different ring members from the group comprising O, S, NR^{I} and CO and which optionally contains one to three identical or different substituents from the group comprising halogen, hydroxyl, alkyl, alkoxy with in each case 1 to 4 C atoms, phenyl, naphthyl or aralkyl with 7 to 14 C atoms, R^3 represents one of the substituents mentioned under R^2 and is identical thereto or differs therefrom, only one of the two substituents R^2 or R^3 in each case representing alkoxy, alkylthio or NHR^{I} ,

R^4 a) represents hydrogen, NO_2 , NO , CN , $\text{SO}_m-\text{R}^{\text{IX}}$ ($m = 0$ or 2), halogen,



R^{I} , R^{VI} , R^{VIII} , R^{XII} and R^{XIII} having the meaning given below, or

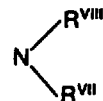
b) represents a branched or unbranched, cyclic, saturated or unsaturated aliphatic hydrocarbon radical with up to 10 C atoms, which is optionally substituted by halogen, OH, CN, alkoxy, alkylthio with in each case 1 to 4 carbon atoms, phenyloxy, naphthoxy, COOR^{V} or



R^{V} , R^{VII} and R^{VIII} having the meaning given below, or

c) represents an aromatic hydrocarbon radical with 6 to 10 C atoms or a 5- to 7-membered saturated or unsaturated hetero ring with 1 to 3 identical or different hetero members from the group comprising O, S, $-\text{N}=\text{}$ and NR^{I} , this hetero ring

being linked to the dihydropyridine ring either via a carbon atom or a nitrogen atom and the aromatic hydrocarbon radical and the hetero rings optionally carrying 1 to 3 identical or different substituents from the group comprising halogen, OH, CN, CF_3 , OCF_3 , SCF_3 , NO_2 , alkyl, alkoxy with in each case 1 to 4 C atoms, phenyl, naphthyl and



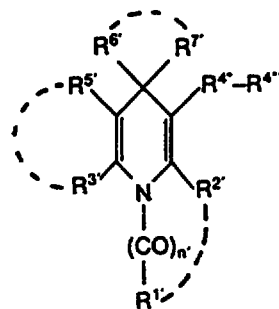
or

d) represents the radical



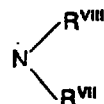
wherein X denotes oxygen, sulphur or NR^{I} , and Y represents a single bond, O, S or NR^{I} , and R^6 has the meaning given for R^1 and is identical to the substituent R^1 or differs therefrom, or

e) represents the radical



wherein

n , R^{I} , R^2 , R^3 , R^5 , R^6 and R^7 have the meaning given for n , R^{I} , R^2 , R^3 , R^5 , R^6 and R^7 and are identical thereto or differ therefrom, and R^4 and $\text{R}^{4''}$ are identical or different and each represent a radical, minus one hydrogen, of the substituents mentioned for R^4 under a) to d), or R^2 and R^4 together form a branched, unbranched, saturated or unsaturated 5- to 7-membered ring which optionally contains 1, 2 or 3 identical or different ring members from the group comprising O, CO, CS, $\text{C}=\text{NR}^{\text{I}}$, $=\text{N}-$, NR^{I} and SO_m ($m = 0$ or 2) and which is optionally substituted by halogen, hydroxyl, alkoxy with 1 to 4 C atoms, phenyl, naphthyl, aralkyl with 7 to 14 C atoms, or

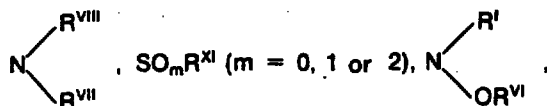


or disubstituted by a straight-chain or branched alkylene chain with 3 to 6 carbon atoms, it being possible for this common ring of R^2 and R^4 also to be directly fused to the common ring of R^1 and R^2 , the radicals R^{I} , R^{II} , R^{III} , R^{VII} and R^{VIII} having the meaning given below, R^5 has the meaning given for R^4 and is identical to R^4 or differs therefrom, R^6 represents hydrogen, alkyl or halogenoalkyl with in each case 1 to 4 C atoms and

R⁷

a) represents a saturated, unsaturated cyclic, straight-chain or branched aliphatic hydrocarbon radical with up to 10 C atoms, which is optionally substituted by halogen, phenyl, naphthyl or heteroaryl or

b) represents a phenyl, naphthyl or heteroaryl radical which optionally contains 1 to 3 identical or different substituents from the group comprising NO₂, halogen, CN, N₃, NO, CF₃, COR^{IV}, COOR^V, OR^{VI},



alkyl with 1 to 4 C atoms, phenyl, naphthyl, alkenyl, alkynyl, alkenoxy, alkinyloxy with in each case up to 4 C atoms, aralkyl with 7 to 14 C atoms, acyl with 1 to 4 C atoms, alkylene and dioxyalkylene with in each case up to 4 C atoms, it being possible for the abovementioned alkyl and aryl substituents in their turn also to be substituted by halogen, COOR^V or



and in the abovementioned definitions of the substituents R¹ to R⁷

R¹ represents hydrogen, alkyl with 1 to 6 C atoms, phenyl, naphthyl, aralkyl with 7 to 12 C atoms, heteroaryl or acyl with up to 7 C atoms, R^{II} and R^{III} are identical or different and each represent alkyl with 1 to 6 C atoms, phenyl, naphthyl, aralkyl with 7 to 12 C atoms or heteroaryl,

R^{VII}, R^V and R^{VI} are in each case identical or different and represent hydrogen, alkyl with 1 to 6 C atoms, phenyl, naphthyl, aralkyl with 7 to 12 C atoms or heteroaryl, the alkyl and aryl radicals optionally being substituted by halogen, nitro, trifluoromethyl, alkoxy, alkylthio and alkyl with in each case 1 to 4 C atoms,

R^{VII} and R^{VIII} are in each case identical or different and represent hydrogen, phenyl, naphthyl or aralkyl with 7 to 12 C atoms or represent alkyl with 1 to 6 C atoms which is optionally interrupted by O, S or NR^I, or, together with the nitrogen atom, from a 5- to 7-membered ring which can contain 1 or 2 identical or different hetero ring members from the group comprising O, S and NR^I, or one of the radicals R^{VII} and R^{VIII} represents an aliphatic acyl group with up to 6 carbon atoms, R^{IX}, R^X, R^{XII} and R^{XIII} are in each case identical or different and represent alkyl with 1 to 6 C atoms, phenyl, naphthyl or aralkyl with 7 to 12 C atoms, the alkyl, aryl, aralkyl, heteroaryl and acyl radicals mentioned under R¹ to R⁸ and under R¹ to R^{VIII} and the hetero ring formed with R⁶ and R⁷ in their turn optionally being substituted by OH, CF₃, OCF₃, CN, NO₂, halogen, alkyl with 1 to 4 C atoms, alkoxy, alkylthio with in each case 1 to 4 C atoms, phenyl or benzyl,

and the following substituents being mentioned as heteroaryl:

thienyl, furyl, pyryl, pyridyl, quinolyl, isoquinolyl, pyrimidyl, pyridazinyl, quinazolyl, quinoxalyl, benzothienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, oxydiazolyl, pyrazinyl, oxazinyl, thiazinyl, indolizynyl, indolyl, benzofuranyl, indazolyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, benztriazolyl, benzoxadiazolyl, cinnolyl, phthalazinyl, naphthyridinyl or benzotriazinyl,

in the form of isomers, isomer mixtures, racemates and optical antipodes and of their pharmaceutically acceptable salts.

9. Use according to Claims 1 to 7 of compounds of the general formula (I) according to Claim 1, in which n represents 0 or 1,

R¹

a) represents hydrogen, a straight-chain, branched cyclic saturated or unsaturated aliphatic hydrocarbon radical with up to 10 C atoms which optionally contains by one or two identical or different hetero chain members from the group comprising O, CO, S, =N- and NR^I, this hydrocarbon radical optionally being substituted by F, Cl, Br, NO₂, CN, OH, phenyl or pyridyl or

b) represents a phenyl, naphthyl or pyridyl radical, these radicals optionally carrying 1 or 2 identical or different substituents from the group comprising phenyl, alkyl, alkenyl, alkoxy, alkenoxy with in each case up to 4 C atoms, benzyl, acetyl, alkylene, dioxyalkylene with 2 to 4 C atoms, fluorine, chlorine, bromine, CF₃, OCF₃, SCF₃, NO₂, CN, COOR^V, OR^{VI}, NR^I and NR^{VII}R^{VIII}, it being possible for the alkyl, alkoxy and aryl radicals of the abovementioned substituents in their turn also to be halogen substituted or

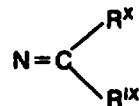
c) represents the radical NR^{VII}R^{VIII}, the radicals R¹ to R^{VIII} mentioned under a), b) and

c) having the meaning given below,

R²

a) represents one of the substituents mentioned under R¹ but does not have to be identical thereto or

b) represents the radicals NHR^I or



R¹, R^{IX} and R^X having the meaning given below, or the substituents,

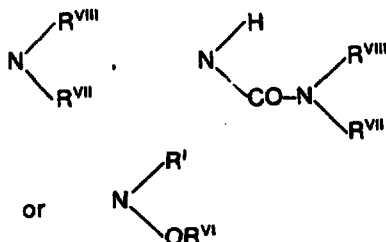
R¹ and R² together form a 5- to 7-membered saturated or unsaturated ring which optionally contains 1 or 2 identical or different ring members from the group comprising O, S, NR^I and CO and which optionally contains 1 or 2 identical or different substituents from the group comprising halogen, hydroxyl, alkyl, alkoxy each with 1 to 4 C atoms, phenyl and benzyl,



R^3 represents one of the substituents mentioned under

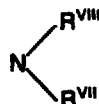
R^2 and is identical thereto or differs therefrom, only one of the two substituents R^2 or R^3 in each case representing alkoxy, alkylthio or NHR^1 , R^4

a) represents hydrogen, NO_2 , CN , SR^{XI} , SO_2R^{XI} ,



R^I , R^{VI} , R^{VII} , R^{VIII} and R^{IX} having the meaning given below,

b) represents a branched or unbranched alkyl or cycloalkyl radical with up to 8 C atoms, which is optionally substituted by halogen, hydroxyl, cyano, alkoxy with 1 to 4 C atoms, phenyloxy, $COOR^V$ or



R^V , R^{VII} and R^{VIII} having the meaning given below or

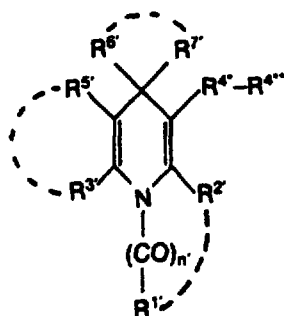
c) represents an aromatic hydrocarbon radical with 6 to 10 C atoms or a 5- to 7-membered saturated or unsaturated hetero ring with 1 to 3 identical or different hetero members from the group comprising O, S, =N- and NR^I , this hetero ring being linked to the dihydropyridine ring either via a carbon atom or a nitrogen atom, and the aromatic hydrocarbon radical and the hetero rings optionally carrying 1 or 2 identical or different substituents from the group comprising halogen, hydroxyl, cyano, CF_3 , NO_2 , phenyl, alkyl and alkoxy each with 1 to 4 C atoms, or

d) represents the radical



wherein X represents oxygen or NR^I and Y represents a single bond, oxygen or NR^I and R^8 has for meaning given for R^1 and is identical to the substituent or differs therefrom, or

e) represents the radical



wherein n' , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 have the meaning given for n , R^1 , R^2 , R^3 , R^5 , R^6 and R^7 and are identical thereto or differ therefrom, and $R^{4'}$ and $R^{4''}$ are identical or different and each represent a radical, minus one hydrogen, of the substituents mentioned for R^4 under a) to d), or R^2 and R^4 together form a branched unbranched saturated or unsaturated 5- to 7-membered ring which optionally contains 1 or 2 identical or different ring members from the group comprising O, CO, CS, $C=NR^I$, =N- and NR^I and which is optionally substituted by halogen or hydroxyl

R^1 having the meaning given below,

R^5 has the meaning given for R^4 and is identical to R^4 or differs therefrom or

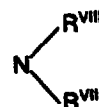
R^5 and R^3 together form a ring of the kind defined for R^2 and R^4 and is identical thereto or differs therefrom,

R^6 represents hydrogen or alkyl with 1 to 4 C atoms which is optionally substituted by fluorine, chlorine or bromine and

R^7

a) represents a saturated, unsaturated cyclic, straight-chain or branched aliphatic hydrocarbon radical with up to 8 C atoms, which is optionally substituted by halogen, or

b) represents a phenyl or heteroaryl radical which optionally contains 1 to 3 identical or different substituents from the group comprising NO_2 , CN , N_3 , CF_3 , halogen, COR^V , COR^V , OR^VI , SR^{XI} ,



phenyl, alkyl with 1 to 4 C atoms, benzyl

and acyl with 1 to 4 C atoms,

and in the abovementioned definitions of the substituents R^1 to R^8

R^1 represents hydrogen, alkyl with 1 to 6 C atoms, phenyl, naphthyl, benzyl, phenethyl, heteroaryl or acyl with up to 4 C atoms,

R^{II} and R^{III} are identical or different and in each case represent alkyl with 1 to 6 C atoms, phenyl, naphthyl, benzyl or heteroaryl,

R^{IV} , R^V and R^{VI} are in each case identical or different and represent hydrogen, alkyl with 1 to 6 C atoms, phenyl, naphthyl, benzyl or heteroaryl, the alkyl, phenyl and benzyl radicals optionally being substituted by fluorine, chlorine, nitro, CF_3 , methyl, methoxy and methylthio,

R^{VII} and R^{VIII} are in each case identical or different and represent hydrogen, phenyl or benzyl or represent alkyl with 1 to 6 carbon atoms, which is optionally interrupted by O or NR^I , or

together with the nitrogen atom, form a 5- to 7-membered ring which can contain 1 or 2

identical different hetero ring members from the group comprising O, S and NR^I ,

or

one of the radicals R^{VII} or R^{VIII} represents an aliphatic acyl group with up to 6 carbon atoms and R^{IX} , R^X , R^{XI} , R^{XII} and R^{XIII} are in each case identical



or different and represent alkyl with 1 to 6 C atoms, phenyl or benzyl, the following substituents being mentioned as heteroaryl:

thienyl, furyl, pyryl, pyridyl, quinolyl, isoquinolyl, pyrimidyl, pyridazinyl, quinazolyl, quinoxalyl, benzothienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, oxydiazolyl, pyrazinyl, oxazinyl, thiazinyl, indolyl, benzofuranyl, indazolyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, benztriazolyl or benzoxadiazolyl.

10. Use according to Claims 1 to 7 of compounds of the general formula (I) according to Claim 1 in which n represents O,

R¹

a) represents hydrogen, an aliphatic hydrocarbon radical with up to 6 C atoms, which optionally contains a hetero chain member from the group comprising O, CO, =N- and NR¹ and which is optionally substituted by halogen, nitro, hydroxyl or phenyl or

b) represents a phenyl or pyridyl radical which are optionally substituted by halogen, NO₂, CF₃, OCF₃, CN, COOR^V or NR^{VIII}R^{VIII},

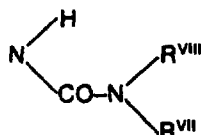
R² represents one of the substituents mentioned under

R¹ but does not have to be identical thereto or represents one of the radicals NHR¹ or N=CR^XR^{XI},

R³ represents one of the substituents mentioned under

R² and is identical thereto or differs therefrom,

R⁴ a) represents hydrogen, NO₂, NR^{VII}R^{VIII},



or halogen, or

b) represents an alkyl radical with 1 to 4 C atoms, which is optionally substituted by halogen, OH, CN, alkoxy with 1 to 4 C atoms, COOR^V or NR^{VII}R^{VIII} or

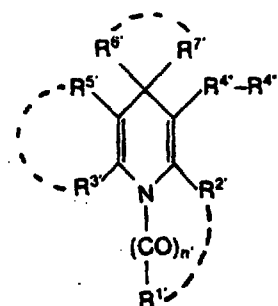
c) represents phenyl, pyridyl or thienyl, which are optionally substituted by halogen, OH, CN, alkyl or alkoxy with in each case 1 to 4 C atoms or by NR^{VII}R^{VIII} or

d) represents the radical



wherein X denotes oxygen and Y represents a single bond, oxygen or NR¹ and R⁸ has the meaning given for R¹ and is identical to the substituent R¹ or differs therefrom or

e) represents the radical



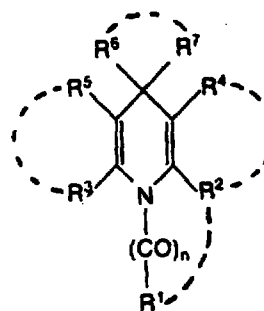
wherein n, R¹, R², R³, R⁵, R⁶ and R⁷ have the meaning given for n, R¹, R², R³, R⁵, R⁶ and R⁷ and are identical thereto or differ therefrom, and R⁴ and R^{4''} are identical or different and each represent a radical, minus one hydrogen, of the substituents mentioned for R⁴ under a) to d), or R² and R⁴ together form a 5- to 7-membered ring which optionally contains 1 to 2 different ring members from the group comprising O, CO, CS and C=NR¹ and which is optionally substituted by halogen,

R⁵ has the meaning given for R⁴ and is identical to R⁴ or differs therefrom,

R⁶ represents hydrogen or alkyl with 1 to 4 C atoms and R⁷ has the abovementioned meaning, the substituents R¹ to R^{VIII} marked with Roman numerals in the abovementioned definitions having the meaning given in Claim 4.

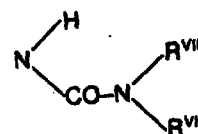
11. Use according to Claims 1 to 7 of compounds of the general formula (I) according to Claim 1, in which at least one of the substituents R⁴ and R⁵ represents NO₂ and/or in which R² and R⁴ together or R³ and R⁵ together form a lactone ring.

12. Compounds of the general formula (I)



(I)

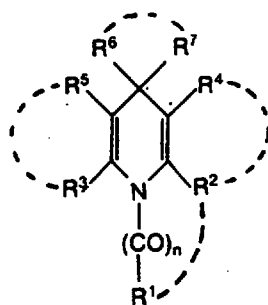
in which at least one of the substituents R⁴ and R⁵ represents the group



wherein R^{VIII} and R^{VII} and the substituents R¹, R², R³, R⁶, R⁷ and n and the remaining radical of R⁴ and R⁵ have the meaning given in Claims 1 and 8 to 11.

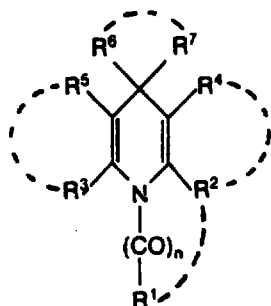


13. Compounds of the general formula (I)



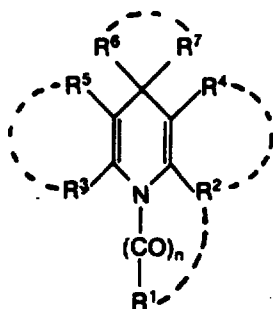
in which at least one of the substituents R^4 and R^5 represents methyl, wherein R^1 , R^2 , R^3 , R^6 , R^7 and n and the remaining radical of R^4 and R^5 have the meaning given in Claims 1 and 8 to 11.

14. Compounds of the general formula (I)



in which one of the radical R^4 or R^5 denotes hydrogen, R^1 represents hydrogen and n represents 0 and R^2 , R^3 , R^6 and R^7 and the other radical of R^4 and R^5 have the meaning given in Claims 1 and 8 to 11.

15. Compounds of the general formula (I)



in which one of the radicals R^4 and R^5 denotes halogen and R^1 , R^2 , R^3 , R^6 and R^7 and n and the other radical of R^4 or R^5 have the meaning given in Claim 1 and 8 to 11.

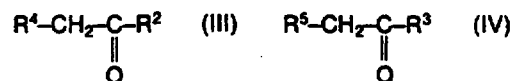
16. Compounds according to Claim 15, in which one of the radicals R^4 or R^5 represents fluorine or chlorine.

17. Process for the preparation of compounds according to Claims 12 to 16, characterised in that

a) carbonyl compounds of the general formula (II)



are reacted with ketones of the formulae (III) and (IV)



and primary amines of the formula (V)

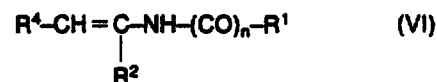


in which n is 0, if appropriate in the presence of inert solvents, or

b) carbonyl compounds of the formula (II)



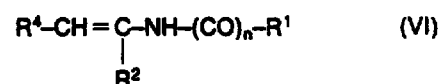
are reacted with enamines of the formula (VI)



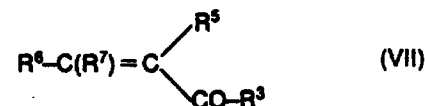
and ketones of the formula (IV)



if appropriate in the presence of inert solvents or c) enamines of the formula (VI)



are reacted with ylidene compounds of the formula (VII)



if appropriate in the presence of inert solvents, or d) one or more functional groups of dihydropyridines are modified by customary methods of hydrolysis, esterification, transesterification, lactonisation, condensation, acylation, reduction or cyclisation.

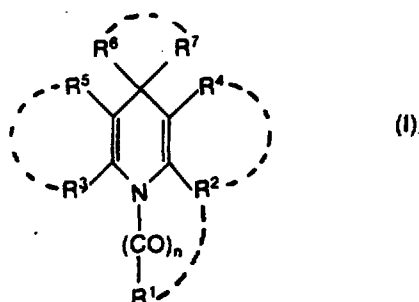
18. Medicaments containing at least one compound according to Claims 12 to 16.

19. Process for the preparation of medicaments, characterised in that at least one compound according to Claims 12 to 16 is converted into a suitable form of administration, if appropriate using inert auxiliaries and excipients.



Revendications

1. Utilisation des 1,4-dihydropyridines de formule générale (I)



dans laquelle
n signifie 0, 1 ou 2
R¹

a) représente de l'hydrogène, un radical hydrocarbure cyclique à chaîne droite ou ramifiée, aliphatique saturé ou insaturé, qui comporte éventuellement 1 à 3 hétéroéléments de chaîne identiques ou différents appartenant au groupe O, CO, SO_m (m = 0, 1 ou 2), =N-, NR¹ ou SiR¹R¹¹, ce radical d'hydrocarbure étant éventuellement substitué par un halogène, NO₂, CN, N₃, un radical hydroxy, aryle ou hétéroaryle, ou bien

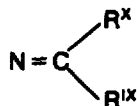
b) représente un radical aryle ou hétéroaryle où ces radicaux comportent éventuellement 1 à 5 produits de substitution identiques ou différents, provenant des groupes aryle, alkyle, alkényle, alkynyle, alkenoxy, alkinoxy, aralkyle, acyle, alkylène, dioxyalkylène, halogène, CF₃, OCF₃, SCF₃, NO₂, NO, CN, N₃, COR^{IV}, COOR^V, OR^{VI}, NR¹ ou NR^{VII}R^{VIII}, les radicaux alkyle, alkoxy et aryle des produits de substitution pouvant être, à leur tour, substitués par un halogène COOR^V ou NR^{VII}R^{VIII} ou

c) représente le radical NR^{VII}R¹, tandis que les radicaux mentionnés sous a), b) et c), R¹, R^{II}, R^{III}, R^{IV}, R^V, R^{VI}, R^{VII} et R^{VIII} ont la signification mentionnée ci-dessous.

R²

a) représente l'un des produits de substitution mentionnés sous R¹ mais ne doit pas être identique à celui-ci, ou

b) représente les radicaux NHR¹ ou



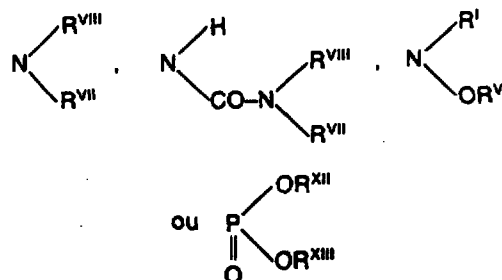
où R¹, R^{IX} et R^X ont les significations mentionnées ci-dessous,

les produits de substitution R¹ et R² forment ensemble un anneau saturé ou insaturé à 5 à 8 éléments, qui contient, éventuellement, 1, 2 ou 3 éléments d'anneau identiques ou différents parmi O, S, NR¹ ou CO et qui contient, éventuellement, 1 à 3 produits de substitution identiques ou différents des groupes halogène, hydroxy, alkyle, alkoxy, aryle ou aralkyle,

R³ représente l'un des groupes substituants mentionnés sous R² et est identique ou différent de celui-ci, tandis qu'un seulement des deux groupes substituants R² ou R³ représente, chaque fois, un alkoxy, un alkylthio ou un NHR¹,

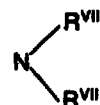
R⁴

a) représente de l'hydrogène, NO₂, NO, CN, SO_m-R^{XI} (m = 0, 1 ou 2), ou un halogène,



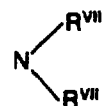
où R¹, R^{VII}, R^{VIII}, R^{XI} et R^{XIII} ont la signification mentionnée ci-dessous, ou

b) représente un radical d'hydrocarbure cyclique ramifié ou non ramifié, aliphatique saturé ou non saturé qui est éventuellement substitué par un halogène, OH, CN, un alkoxy, un alkylthio, un aryloxy, COOR^V, ou



tandis que R^V, R^{VII} et R^{VIII} ont la signification mentionnée ci-dessous, ou

c) représente un radical hydrocarbure aromatique ou un anneau hétérocyclique saturé ou insaturé à 5 à 7 atomes avec 1 à 4 hétéroéléments identiques ou différents des groupes O, S, -N=, NR¹, où cet anneau hétérocyclique est relié par un atome de carbone ou par un atome d'azote à l'anneau de la dihydropyridine et où le radical d'hydrocarbure aromatique et les anneaux hétérocycliques portent éventuellement 1 à 3 groupes substituants identiques ou différents des groupes halogène, OH, CN, CF₃, OCF₃, SCF₃, NO₂, alkyle, alkoxy, aryle et



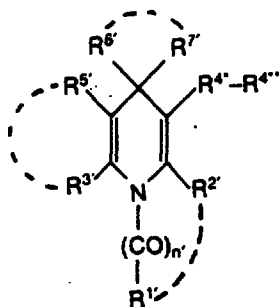
d) représente le radical



où X est de l'oxygène, du soufre ou NR¹ et où Y représente une liaison simple, O, S ou NR¹ et où R⁸ a la signification indiquée pour R¹ et est identique au groupe substituant R¹ ou est différent de celui-ci, ou



e) représente le radical



où n' , R^1 , R^2 , R^3 , R^5 , R^6 et R^7 ont les significations mentionnées pour n , R^1 , R^2 , R^3 , R^5 , R^6 et R^7 et sont identiques à ceux-ci ou différents de ceux-ci, et où $R^{4'}$ et $R^{4''}$ sont identiques ou différents et représentent chacun un radical diminué d'un atome d'hydrogène des groupes substituants mentionnés sous a) à d) pour R^4 , ou

R^2 et R^4 forment ensemble un anneau ramifié, non ramifié, saturé, non saturé, à 5 à 8 éléments, qui contient éventuellement 1, 2 ou 3 éléments d'anneaux différents ou identiques, parmi O, CO, CS, $C=NR^1$, $=N-$, NR^1 , SO_m ($m = 0, 1$ ou 2) ou $SiR^IV R^{III}$ et qui est éventuellement substitué par un halogène, un hydroxy, un alkoxy, un aryle, un aralkyle,



ou qui est disubstitué par une chaîne

alkylène droite ou ramifiée à 3 ou 8 atomes de carbone, où cet anneau commun de R^2 et R^4 peut être condensé directement avec l'anneau commun de R^1 et R^2

où les radicaux R^1 , R^II , R^{III} , R^{VII} , R^{VIII} ont la signification mentionnée ci-dessous.

R^5 possède la signification mentionnée pour R^4 et est identique à R^4 ou est différent de celui-ci, ou R^5 et R^3 constituent ensemble un anneau qui est identique à l'anneau formé par R^2 et R^4 ou est différent de celui-ci,

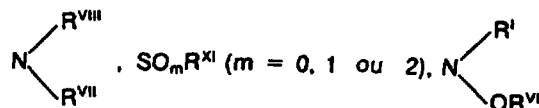
R^6 représente de l'hydrogène, un alkyle ou un alkyle halogéné,

et

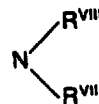
R^7

a) représente un radical d'hydrocarbure cyclique saturé ou insaturé ou aliphatique à chaîne droite ou ramifiée, qui est substitué éventuellement par un halogène, un aryle ou un hétéroaryle, ou

b) représente un radical aryle ou hétéroaryle qui contient éventuellement 1 à 5 groupes substituants identiques ou différents parmi NO_2 , CN , N_3 , NO , CF_3 , des halogènes, COR^{IV} , $COOR^V$, OR^VI .



alkyle, aryle, alkenyle, alkynyle, alkenoxy, alkin-oxy, aralkyle, acyle, alkylène ou dioxyalkylène, où les groupes substituants alkyle et aryle précités peuvent être substitués, à leur tour, par un halogène, $COOR^V$ ou par



et où, dans les définitions précitées des groupes substituants R^1 à R^8 , R^I représente de l'hydrogène, un alkyle, un aryle, un aralkyle, un hétéroaryle ou un acyle, R^{II} et R^{III} sont identiques ou différents et représentent chacun un alkyle, un aryle, un aralkyle ou un hétéroaryle, où R^{IV} , R^V et R^VI sont chacun identiques ou différents et représentent de l'hydrogène, un alkyle, un aryle, un aralkyle ou un hétéroaryle, où les radicaux alkyle et aryle sont substitués éventuellement par un halogène, un nitro, un trifluorométhyle, un alcoxy, un alkylthio ou un alkyle, R^{VII} et R^{VIII} sont chacun égaux ou différents et représentent de l'hydrogène, un aryle ou un aralkyle ou représentent un alkyle qui est éventuellement interrompu par O, S ou NR^I , ou forment avec l'atome d'azote, un anneau à 5-7 éléments qui peut contenir 1 ou 2 éléments d'anneaux hétérocycliques identiques ou différents des groupes O, S, NR^I , ou

où l'un des radicaux R^{VII} ou R^{VIII} représente un groupe acyle aliphatique à 6 atomes de carbone au maximum, où R^IX , R^X , R^{XI} , R^{XII} et R^{XIII} sont chacun identiques ou différents et représentent un alkyle, un aryle ou un aralkyle,

où les radicaux alkyle, aryle, aralkyle, hétéroalkyle et acyle mentionnées sous R^1 à R^8 sous R^I à R^{XIII} ainsi que l'anneau hétérocyclique formé avec R^{VII} et R^{VIII} sont éventuellement substitués, pour leur part, par OH, CF_3 , OCF_3 , CN , NO_2 , un halogène, un thioalkyle inférieur, un alkyle inférieur, un alkoxy inférieur, un aryle ou un aralkyle, et où les groupes substituants suivants peuvent être cités comme hétéroaryles:

thiényle, furyle, pyryle, pyridyle, quinoléyle, isoquinoléyle, pyrimidyle, pyridazinyle, quinazolyle, quinoxalyle, benzothiényle, pyrazolyle, imidazolyle, oxazolyle, isoxazolyle, thiazolyle, triazolyle, oxydiazolyle, pyrazinyle, oxazinyle, thiazinyle, indolizinyne, indolyne, benzofuranyne, indazolyle, benzothiényne, benzimidazolyle, benzoxazolyle, benzisoxazolyle, benzthiazolyle, benztriazolyle, benzoxadiazolyle, cinnolinyle, phtalazinyle, naphtyridinyle ou benzotriazinyle.

sous forme d'isomères, de mélanges d'isomères, de racémates et d'antipodes optique, ainsi que de leurs sels qui ne présentent pas d'inconvénients



en pharmacie et qui, dès une concentration de 10^{-5} g/ml provoquent dans l'oreille gauche isolée du cobaye un renforcement des contractions d'au moins 25%, en vue de la production de médicaments augmentant la pénétration de l'ion Ca^{++} dans les cellules.

2. Utilisation, selon la revendication 1, des composés de la formule générale (I) pour la production de médicaments ayant un effet inotrope positif.

3. Utilisation, selon la revendication 1, de composés de la formule générale (I) pour la production de médicaments ayant un effet de tonique cardiaque.

4. Utilisation, selon la revendication 1, de composés de la formule générale (I) pour la production de médicaments ayant un effet anti-hypotonique.

5. Utilisation, selon la revendication 1, des composés de la formule générale (I) pour la production de médicaments, afin de diminuer la teneur en sucre dans le sang.

6. Utilisation, selon la revendication 1, des composés de la formule générale (I) pour la production de médicaments, en vue de la décongestion des muqueuses.

7. Utilisation, selon la revendication 1, de composés de la formule générale (I) pour la production de médicaments, afin d'influencer le métabolisme des sels et des liquides.

8. Utilisation, selon les revendications 1 à 7, des composés de la formule générale (I) et, selon la revendication 1, dans laquelle:

n représente 0, 1 ou 2

R^1

a) représente de l'hydrogène, un radical d'hydrocarbure aliphatique à chaîne droite ou ramifiée, cyclique saturé ou non saturé, avec au maximum 10 atomes de carbone qui contient éventuellement 1 ou 2 hétéroéléments de chaîne identiques ou différents des groupes O, CO, S, SO_2 , $=\text{N}-$, ou NR^1 et où ce radical d'hydrocarbure est substitué éventuellement par un halogène NO_2 , CN, N_3 , hydroxy, avec 1 à 4 atomes de carbone, du phényle, du naphthyle ou de l'hétéroaryle ou

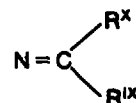
b) représente un radical phényle, naphthyle ou hétéroaryle où ces radicaux portent éventuellement 1 à 3 groupes substituants identiques ou différents des groupes phényle, alkyle, alkényle, alkynyle, alkénoxy, alkinoxy avec, chaque fois, un maximum de 4 atomes de carbone, aralkyle avec 7 à 14 atomes de carbone, acyle avec un maximum de 6 atomes de carbone, alkylène, dioxyalkylène, avec un maximum de 4 atomes de carbone dans la chaîne alkylène, un halogène, CF_3 , OCF_3 , SCF_3 , NO_2 , CN, N_3 , COR^{IV} , COOR^{V} , OR^{VI} , NR^1 ou $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$, où les radicaux alkyle, alkoxy et aryle des groupes substituants précités peuvent être substitués à leur tour à nouveau par un halogène, COOR^{V} ou $\text{NR}^{\text{VII}}\text{R}^{\text{VIII}}$, ou

c) représente le radical $\text{NR}^{\text{VII}}\text{R}^1$ et où les radicaux R^1 , R^{II} , R^{III} , R^{IV} , R^{V} , R^{VI} , R^{VII} et R^{VIII} mentionnés sous a), b) et c) ont la signification indiquée ci-dessous,

R^2

a) représente un groupe substituant indiqué sous R^1 , mais ne doit pas être identique à celui-ci, ou

b) représente le radical NHR^1 ou



où R^1 , R^{IX} et R^x possèdent la signification mentionnée ci-dessous,

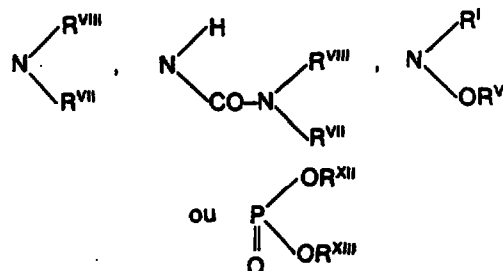
ou les groupes substituants

R^1 et R^2 forment ensemble un anneau saturé ou insaturé à 5 ou 7 éléments qui contient éventuellement 1 ou 2 éléments d'anneaux identiques ou différents des groupes O, S, NR^1 ou CO et qui contient éventuellement 1 à 3 groupes substituants identiques ou différents des groupes halogène, hydroxy, alkyle, alkoxy, avec chacun 1 à 4 atomes de carbone, phényle, naphthyle ou aralkyle avec 7 à 14 atomes de carbone,

R^3 représente un groupe substituant mentionné sous R^2 et est identique à celui-ci ou est différent de celui-ci, où un seul des deux groupes substituants R^2 ou R^3 représente chaque fois un alkoxy, un alkylthio ou NHR^1 ,

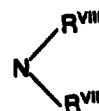
R^4

a) représente de l'hydrogène, NO_2 , NO, CN, $\text{SO}_m-\text{R}^{\text{IX}}$ ($m = 0$, ou 2), un halogène,



où R^1 , R^{VII} , R^{VIII} , R^{XI} et R^{XIII} ont la signification mentionnée ci-dessous, ou

b) représente un radical d'hydrocarbure cyclique ramifié ou non ramifié, aliphatique saturé ou non saturé, avec au maximum 10 atomes de carbone, qui est substitué éventuellement par un halogène, OH, CN, un alkoxy, un alkylthio, avec chaque fois 1 à 4 atomes de carbone, un phényloxy, un naphthoxy, COOR^{V} ou

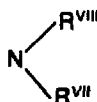


où R^{V} , R^{VII} et R^{VIII} ont la signification mentionnée ci-dessous, ou

c) représente un radical d'hydrocarbure aromatique avec de 6 à 10 atomes de carbone ou un anneau hétérocyclique saturé ou insaturé à 5 à 7 éléments, avec 1 à 3 hétéroéléments identiques ou différents du groupe O, S, $=\text{N}-$, NR^1 , où cet anneau hétérocyclique est relié soit par un atome



de carbone, soit par un atome d'azote, à l'anneau de la dihydropyridine et où le radical d'hydrocarbure aromatique et les anneaux hétérocycliques portent éventuellement 1 à 3 groupes substituants identiques ou différents du groupe des halogènes, OH, CN, CF₃, OCF₃, SCF₃, NO₂, alkyle, alkoxy avec chaque fois 1 à 4 atomes de carbone, phényle, naphthyle et



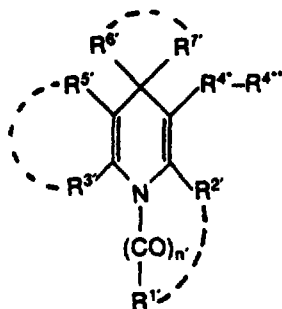
ou

d) représente un radical

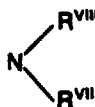


où X est de l'oxygène, du soufre ou NR^I et où Y représente une liaison simple, O, S ou NR^I et où R⁸ a la signification mentionnée pour R^I et est identique au substituant R^I ou est différent de celui-ci ou

e) représente le radical



où n', R^I, R², R³, R⁵, R⁶ et R⁷ ont la signification indiquée pour n, R^I, R², R³, R⁵, R⁶ et R⁷ et sont identiques à ceux-ci ou différents de ceux-ci et R⁴ et R^{4''} sont identiques ou différents et représentent, chaque fois, un radical réduit d'un atome d'hydrogène des groupes substituants mentionnés pour R⁴ sous a) à b), ou R² et R⁴ constituent ensemble un anneau ramifié, non ramifié, saturé ou insaturé à 5 à 7 éléments, qui contient éventuellement 1, 2 ou 3 éléments d'anneau identiques ou différents des groupes O, CO, CS, C=NR^I, =N-, NR^I ou SO_m (m = 0 ou 2) et qui est éventuellement substitué par un halogène, un hydroxy, un alkoxy, avec 1 à 4 atomes de carbone, un radical phényle, naphthyle, aralkyle avec 7 à 14 atomes de carbone,



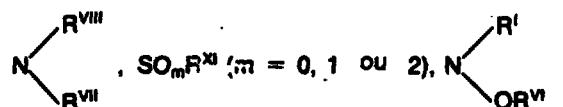
ou qui est disubstitué par une chaîne alkylène droite ou ramifiée, avec 3 à 8 atomes de carbone et où cet anneau commun de R² et R⁴ peut former aussi directement un anneau avec l'anneau com-

mun de R^I et R² et où les radicaux R^I, R^{II}, R^{III}, R^{VII}, R^{VIII} ont la signification mentionnée ci-dessous, R⁵ possède la signification mentionnée pour R⁴ et est identique à R⁴ ou est différent de celui-ci, R⁶ représente de l'hydrogène, un alkyle ou un alkyle halogéné, avec chaque fois 1 à 4 atomes de carbone et

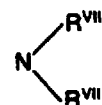
R⁷

a) représente un radical d'hydrocarbure cyclique saturé ou insaturé aliphatique à chaîne droite ou ramifiée, avec 10 atomes de carbone au maximum, qui est substitué éventuellement par un halogène, un groupe phényle, naphthyle ou hétéro-aryle, ou

b) représente un radical phényle, naphthyle ou hétéroaryle qui contient éventuellement 1 à 3 groupes substituants identiques ou différents parmi les groupes NO₂, halogène, CN, N₃, NO, CF₃, COR^{IV}, COOR^V, OR^{VI},



alkyle avec 1 à 4 atomes de carbone, phényle, naphthyle, alkenyle, alkynyle, alkenoxy, alkinoxyle avec chaque fois 4 atomes de carbone au maximum, aralkyle avec 7 à 14 atomes de carbone, acyle avec 1 à 4 atomes de carbone, alkylène ou dioxyalkylène avec chaque fois 4 atomes de carbone au maximum, où les groupes substituants alkyle et aryle précités peuvent être substitués à nouveau à leur tour par un halogène, COOR^V ou



et où, dans les définitions précitées des groupes substituants R^I à R⁷,

R^I représente de l'hydrogène, un alkyle à 1 à 6 atomes de carbone, un phényle, un naphthyle, un aralkyle à 7 à 12 atomes de carbone, un hétéroaryle ou un acyle à 7 atomes de carbone au maximum, où R^{II} et R^{III} sont identiques ou différents et représentent chacun un alkyle à 1 à 6 atomes de carbone, un phényle, un naphthyle, un aralkyle avec 7 à 12 atomes de carbone ou un hétéroaryle, R^{VII}, R^V et R^{VI} sont chaque fois identiques ou différents et représentent de l'hydrogène, un alkyle avec 1 à 6 atomes de carbone, un phényle, un naphthyle, un aralkyle avec 7 à 12 atomes de carbone ou un hétéroaryle, les radicaux alkyle et aryle étant éventuellement substitués par halogène, nitro, trifluoro-méthyle, alkoxy, alkylthio et alkyle avec chaque fois 1 à 4 atomes de carbone, R^{VII} et R^{VIII} sont chaque fois identiques ou différents et représentent de l'hydrogène, un phényle, un naphthyle ou un aralkyle à 7 à 12 atomes de carbone, ou un alkyle à 1 à 6 atomes de carbone



qui est interrompue éventuellement par O, S ou NR^I ou constituant, avec l'atome d'azote, un anneau à 5 à 7 éléments qui peut contenir 1 ou 2 éléments d'anneaux hétérocycliques identiques ou différents des groupes O, S ou NR^I ou où l'un des radicaux R^{VII} et R^{VIII} représente un groupe acyle aliphatique avec 6 atomes de carbone au maximum, R^X , R^Y , R^{XI} et R^{XII} sont chaque fois identiques ou différents et représentent un alkyle avec 1 à 6 atomes de carbone, un phényle, un naphtyle ou un aralkyle à 7 à 12 atomes, où les radicaux alkyle, aryle, aralkyle, hétéroaryle et acyle mentionnés sous R^I à R^8 , ainsi que l'anneau hétérocyclique formé avec R^6 et R^7 sont substituées éventuellement, pour leur part, par OH, CF_3 , OCF_3 , CN, NO_2 , un halogène, un alkyle à 1 à 4 atomes de carbone, un alkoxy, un alkylthio à 1 à 4 atomes de carbone, un radical phényle ou benzyle, et où les groupes substituants suivants peuvent être mentionnés comme hétéroaryles:

thiényle, furyle, pyryle, pyridyle, quinoléyle, isoquinoléyle, pyrimidyle, pyridazinyle, quinazolyle, quinoxalyle, benzothiényle, pyrazolyle, imidazolyle, oxazolyle, isoxazolyle, thiazolyle, triazolyle, oxydiazolyle, pyrazinyle, oxazinyle, thiazinyle, indolizinyne, indolyle, benzofuranyle, indazolyle, benzothiényle, benzimidazolyle, benzoxazolyle, benzisoxazolyle, benzthiazolyle, benztriazolyle, benzoxadiazolyle, cinnolinyle, phtalazinyle, naphtyridinyle ou benzotriazinyle,

sous forme d'isomères, de mélanges d'isomères, de racémates et d'antipodes optiques, ainsi que de leurs sels ne présentant pas de contre-indications pharmaceutiques.

9. Utilisation, selon les revendications 1 à 7, des composés de la formule générale (I) selon la revendication 1, dans laquelle n représente 0 ou 1,

R^I

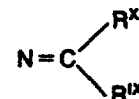
a) représente un radical d'hydrocarbure cyclique à chaîne droite ou ramifiée, aliphatique saturé ou non saturé, avec 10 atomes de carbone au maximum, qui contient éventuellement 1 ou 2 éléments de chaîne hétérocyclique identiques ou différents parmi O, CO, S, =N- ou NR^I et où ce radical d'hydrocarbure est substitué éventuellement par F, Cl, Br, NO_2 , CN, OH, un phényle ou un pyridyle ou

b) représente un radical phényle, naphtyle ou pyridyle où ces radicaux portent éventuellement 1 ou 2 groupes substituants identiques ou différents faisant partie des groupes phényle, alkyle, alkényle, alkoxy, alkénoxy avec chaque fois 4 atomes de carbone au maximum, benzyle, acétyle, alkylène, dioxyalkylène avec 2 à 4 atomes de carbone, fluor, chlore, brome, CF_3 , OCF_3 , SCF_3 , NO_2 , CN, COOR^V , OR^V , NR^I ou $\text{NR}^{VII}\text{R}^{VIII}$, où les radicaux alkyle, alkoxy et aryle des groupes substituants précités peuvent être substitués à leur tour à nouveau par un halogène ou

c) représente le radical $\text{NR}^{VII}\text{R}^{VIII}$, et où les radicaux R^I à R^{VIII} mentionnés sous a), b) et c) ont la signification mentionnée ci-dessous.

R^2
a) représente l'un des groupes substituants mentionnés sous R^I mais ne doit pas être identique à celui-ci ou

b) représente le radical NHR^I ou



où R^I , R^X et R^X possèdent la signification mentionnée ci-dessous

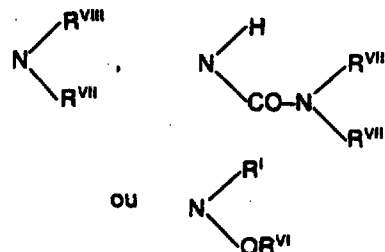
ou les groupes substituants

R^I et R^2 forment ensemble un anneau saturé ou insaturé à 5 à 7 éléments, qui contient éventuellement un ou 2 éléments d'anneau identiques ou différents faisant partie des groupes O, S, NR^I ou CO et qui contient éventuellement 1 ou 2 groupes substituants identiques ou différents faisant partie des groupes halogène, hydroxy, alkyle, alkoxy, avec de 1 à 4 atomes de carbone, phényle ou benzyle,

R^3 représente l'un des groupes substituants mentionnés sous R^2 et est identique à celui-ci ou différent de celui-ci, tandis qu'un seul des deux groupes substituants R^2 ou R^3 représente chaque fois un alkoxy, un alkylthio ou NHR^I ,

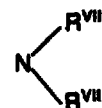
R^4

a) représente de l'hydrogène, NO_2 , CN, SR^{XI} , SO_2R^{XI} ,



où R^I , R^V , R^{VII} , R^{VIII} et R^X ont la signification mentionnée ci-dessous,

b) représente un radical alkyle ou cycloalkyle ramifié ou non ramifié, avec 8 atomes de carbone au maximum qui est substitué éventuellement par un halogène, un hydroxy, un cyano, un alkoxy à 1 à 4 atomes de carbone, un phényloxy, COOR^V ou



où R^V , R^{VII} et R^{VIII} ont la signification mentionnée ci-dessous, ou

c) représente un radical d'hydrocarbure aromatique à 6 à 10 atomes de carbone, ou un anneau hétérocyclique saturé ou insaturé à 5 à 7 éléments, avec 1 à 3 éléments hétérocycliques identiques ou différents, choisis dans les groupes O, S, =N-, NR^I , où cet anneau hétérocyclique est relié

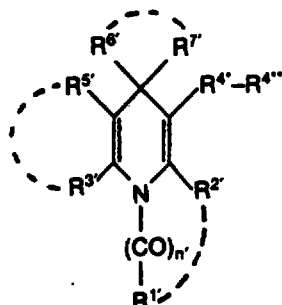


soit par un atome de carbone, soit par un atome d'azote, à l'anneau de la dihydropyridine et où le radical d'hydrocarbure aromatique et les anneaux hétérocycliques portent éventuellement un ou deux groupes substituants identiques ou différents, choisis parmi les groupes des halogènes, hydroxy, cyano, CF_3 , NO_2 , phényle, alkyle et alkoxy avec, chacun, 1 à 4 atomes de carbone, ou d) représente le radical



où X représente de l'oxygène ou NR^1 et où Y représente une liaison simple, de l'oxygène ou NR^1 et où R^8 a la signification mentionnée pour R^1 et est identique au groupe substituant ou est différent de celui-ci ou

e) représente le radical



où n' , R^1 , R^2 , R^3 , R^5 , R^6 et R^7 ont la signification indiquée pour n , R^1 , R^2 , R^3 , R^5 , R^6 et R^7 et sont identiques à ceux-ci ou différents de ceux-ci et R^4 et R^4'' sont identiques ou différents et représentent chacun un radical diminué d'un atome d'hydrogène des groupes substituants mentionnés pour R^4 sous a) à d), ou

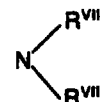
R^2 et R^4 forment ensemble un anneau ramifié ou non ramifié, saturé ou non saturé, à 5 ou 7 éléments, qui contient éventuellement un ou deux éléments d'anneau identiques ou différents, choisis dans les groupes O, CO, CS, $\text{C}=\text{NR}^1$, $=\text{N}-$ ou NR^1 et qui est éventuellement substitué par un halogène ou un hydroxy,

où R^1 a la signification mentionnée ci-dessous, R^5 possède la signification mentionnée pour R^4 et est identique à R^4 ou différent de celui-ci, ou R^5 et R^3 forment ensemble un anneau qui est défini comme pour R^2 et R^4 et qui est identique à celui-ci ou différent de celui-ci,

R^6 représente de l'hydrogène ou un radical alkyle à 1 à 4 atomes de carbone, qui est substitué éventuellement par le fluor, le chlore, le brome et R^7

a) représente un radical d'hydrocarbure cyclique saturé ou insaturé, aliphatique à chaîne droite ou ramifiée, à 8 atomes de carbone au maximum, qui est substitué éventuellement par un halogène, ou

b) représente un radical phényle ou hétéroaryle qui contient éventuellement 1 à 3 groupes substituants identiques ou différents, choisis parmi les groupes NO_2 , CN, N_3 , un halogène, COR^{IV} , COR^{V} , OR^{VI} , SR^{XI} ,



phényle, alkyle, avec 1 à 4 atomes de carbone, benzyle ou acyle à 1 à 4 atomes de carbone, où, dans les définitions précitées des groupes substituants

R^1 à R^8

R^1 représente de l'hydrogène, un alkyle à 1 à 6 atomes de carbone, un phényle, un naphthyle, un benzyle, un phénéthyle, un hétéroaryle ou un acyle à 4 atomes de carbone au maximum,

R^{II} et R^{III} sont identiques ou différents et représentent chacun un alkyle à 1 à 6 atomes de carbone, un phényle, un naphthyle, un benzyle ou un hétéroaryle,

R^{IV} , R^{V} et R^{VI} sont chaque fois identiques ou différents et représentent de l'hydrogène, un alkyle à 1 à 6 atomes de carbone, un phényle, un naphthyle, un benzyle ou un hétéroaryle, où les radicaux alkyle, phényle et benzyle sont éventuellement substitués par fluor, chlore, nitro, CF_3 , méthyle, méthoxy et méthylthio,

R^{VII} et R^{VIII} sont chaque fois identiques ou différents et représentent de l'hydrogène, un phényle ou un benzyle ou un alkyle à 1 à 6 atomes de carbone, qui est interrompu éventuellement par O ou par NR^1 , ou

forment avec l'atome d'azote, un anneau à 5 à 7 éléments qui peut contenir 1 ou 2 éléments d'anneau hétérocycliques identiques ou différents, choisis dans les groupes O, S ou NR^1 ,

ou

où l'un des radicaux R^{VII} ou R^{VIII} représente un groupe acyle aliphatique avec 6 atomes de carbone au maximum et

R^{IX} , R^{X} , R^{XI} , R^{XII} et R^{XIII} sont chaque fois identiques ou différents et représentent un groupe alkyle à 1 à 6 atomes de carbone, un phényle ou un benzyle, où les groupes substituants suivants peuvent être mentionnés comme hétéroaryles:

thiényl, furyl, pyryl, pyridyl, quinoléyl, isoquinoléyl, pyrimidyl, pyridazinyl, quinazolyl, quinoxalyl, benzothiényl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, oxydiazolyl, pyrazinyl, oxazinyl, thiazinyl, indolyl, benzofuranyl, indazolyl, benzothiényl, benzimisazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, benztriazolyl et benzoxadiazolyl.

10) Utilisation, selon les revendications 1 à 7, des composés de la formule générale (I) selon la revendication 1, dans laquelle

n représente 0

R^1

a) représente de l'hydrogène, un radical d'hydrocarbure aliphatique avec 6 atomes de carbone au maximum, qui contient éventuellement un élément de chaîne hétérocyclique choisi dans les groupes O, CO, $=\text{N}-$ ou NR^1 et qui est substitué éventuellement par un halogène, un groupe nitro, hydroxy ou phényle, ou



b) représente un radical phényle ou pyridyle qui est substitué éventuellement par un halogène, NO_2 , CF_3 , OCF_3 , CN , COOR^V ou $\text{NR}^{VII}\text{R}^{VIII}$, R^2 représente l'un des groupes substituants mentionnés sous R^1 mais ne doit pas être identique à celui-ci ou représente l'un des radicaux NHR^I ou $\text{N}=\text{CR}^X\text{R}^{XI}$.

R^3 représente l'un des groupes substituants mentionnés sous R^2 et est identiques à celui-ci ou différent de celui-ci,

R^4

a) représente de l'hydrogène, NO_2 , $\text{NR}^{VII}\text{R}^{VIII}$, $\text{NH-CO-NR}^{VII}\text{R}^{VIII}$ ou un halogène, ou

b) représente un radical alkyle à 1 à 4 atomes de carbone, qui est substitué éventuellement par un halogène, OH , CN , un groupe alkoxy à 1 à 4 atomes de carbone, COOR^V ou $\text{NR}^{VII}\text{R}^{VIII}$, ou

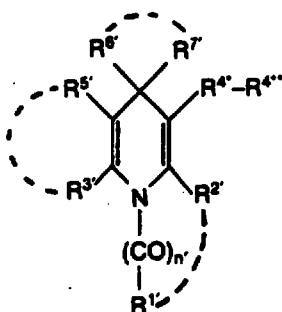
c) représente un groupe phényle, pyridyle ou thiényl qui est substitué éventuellement par un halogène, OH , CN , un alkyle ou un alkoxy, avec chaque fois 1 à 4 atomes de carbone ou par $\text{NR}^{VII}\text{R}^{VIII}$ ou

d) représente le radical



où X représente de l'oxygène et Y représente une liaison simple, l'oxygène ou NR^I et où R^8 a la signification mentionnée pour R^1 et est identique au groupe substituant R^1 ou différent de celui-ci ou

e) représente le radical



où n , R^1 , R^2 , R^3 , R^5 , R^6 et R^7 ont la signification mentionnée pour n , R^1 , R^2 , R^3 , R^5 , R^6 et R^7 et sont identiques à ceux-ci ou différents de ceux-ci, et R^4 et $\text{R}^{4''}$ sont identiques ou différents et représentent chacun un radical diminué d'un atome d'hydrogène des groupes substituants mentionnés pour R^4 sous a) à d), ou

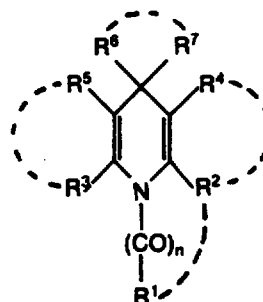
R^2 et R^4 forment ensemble un anneau, à 5-7 éléments, qui contient éventuellement un ou deux éléments d'anneau identiques ou différents, choisis dans les groupes O , CO , CS , $\text{C}=\text{NR}^I$, et qui est éventuellement substitué par un halogène, R^5 possède la signification mentionnée pour R^4 et est identique à R^4 ou différent de celui-ci,

R^6 représente de l'hydrogène ou un radical alkyle à 1 à 4 atomes de carbone, et R^7 possède la signification mentionnée ci-dessus,

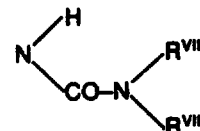
où, dans les définitions précitées, les groupes substituants désignés par des chiffres romains R^I à R^{VIII} possèdent la signification mentionnée à la revendication 4.

11) Utilisation, selon les revendications 1 à 7, des composés de la formule générale 1 selon la revendication 1, dans laquelle au moins l'un des groupes substituants R^4 et R^5 représente NO_2 et/ou dans laquelle R^2 et R^4 forment ensemble ou bien dans laquelle R^3 et R^5 forment ensemble un anneau de lactone.

12) Composés de la formule générale (I)

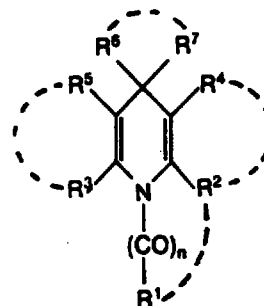


dans laquelle au moins l'un des groupes substituants R^4 et R^5 représente les groupes



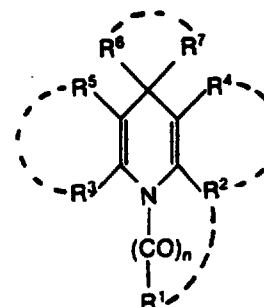
où R^{VIII} et R^{VII} et les groupes substituants R^1 , R^2 , R^3 , R^5 , R^7 et n , ainsi que le radical restant de R^4 et R^5 ont les significations mentionnées aux revendications 1 et 8 à 11.

13) Composés de la formule générale (I)



dans laquelle au moins l'un des groupes substituants R^4 et R^5 représente un radical méthyle, tandis que R^1 , R^2 , R^3 , R^6 , R^7 n , ainsi que le radical restant de R^4 et R^5 ont la signification mentionnée aux revendications 1 et 8 à 11.

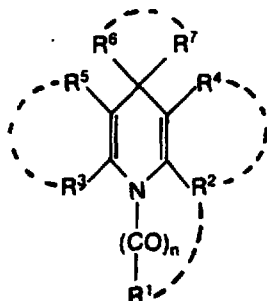
14) Composés de la formule générale (I)





dans laquelle l'un des radicaux R^4 ou R^5 représente de l'hydrogène, R^1 représente de l'hydrogène et n représente 0 et R^2 , R^3 , R^6 et R^7 , ainsi que l'autre radical de R^4 et R^5 ont la signification mentionnée dans les revendications 1 et 8 à 11.

15) Composés de la formule générale (I)



dans laquelle l'un des radicaux R^4 ou R^5 représente un halogène et où R^1 , R^2 , R^3 , R^6 et R^7 et n , ainsi que l'autre radical de R^4 ou R^5 ont la signification mentionnée aux revendications 1 et 8 à 11.

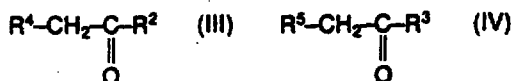
16) Composés selon la revendication 15, dans lesquels les radicaux R^4 ou R^5 représentent du fluor ou du chlore.

17) Procédé pour la production de composés selon les revendications 12 à 16, caractérisé en ce que l'on fait réagir

a) des composés carbonyles de la formule générale (II)



avec des cétones des formules (III) et (IV)



et des amines primaires de la formule (V)

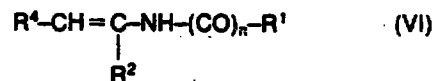


dans lesquels $n = 0$, éventuellement en présence de solvants inertes, ou

b) des composés carbonyles de la formule (II)



avec des énamines de la formule (VI)

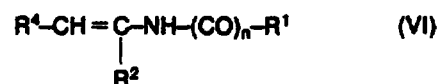


et des cétones de la formule (IV)



éventuellement en présence de solvants inertes ou

c) des énamines de la formule (VI)



avec des composés ylidiènes de la formule (VIII) éventuellement en présence de solvants inertes, ou

d) ou que l'on transforme un ou plusieurs groupes fonctionnels des dihydropyridines suivant les procédés classiques de l'hydrolyse, de l'estérification, de la transestérification, de la lactonisation, de la condensation, de l'acylation, de la réduction ou de la cyclisation.

18) Médicaments contenant au moins un composé selon les revendications 12 à 16.

19) Procédé de préparation de médicaments, caractérisé en ce que l'on introduit au moins un composé selon les revendications 11 à 16, éventuellement avec utilisation de substances de support ou d'adjuvants dans une formulation d'application appropriée.