(12) UK Patent Application (19) GB (11) 2 050 375 A

(21) Application No **8015511**
(22) Date of filing **9 May 1980**
(30) Priority data
(31) **79/16505**
(32) **11 May 1979**
(33) **United Kingdom (GB)**
(43) Application published
7 Jan 1981
(51) **INT CL**^{3}
C07D 211/90
A61K 31/44 //
C07C 121/76
(52) Domestic classification
C2C 1531 200 215 220 227 22Y 250 251 25Y 305 30Y 326 350 351 355 360 361 364 366 368 36Y 376 623 62Y 634 638 63Y 652 65X 666 676 678 802 80Y AA MB MC
(56) Documents cited
GB 2026471
GB 1436289
(58) Field of search
C2C
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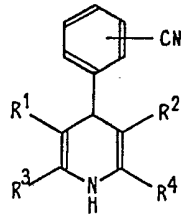
(54) **4-Cyanophenyl-1,4-dihydropyridine compound, processes for preparation thereof and pharmaceutical composition comprising the same**

(57) The 4-cyanophenyl-1,4-dihydropyridine compounds have the formula:-



(I)

wherein
R^1 is n-propoxycarbonyl, isobutoxycarbonyl or neopentyloxycarbonyl,
R^2 is lower alkoxycarbonyl,
R^3 is lower alkyl, and
R^4 is di(lower)alkoxymethyl, formyl hydroxyiminomethyl, cyano or hydroxymethyl.

These compounds and their pharmaceutically acceptable salts thereof have vasodilating and hypotensive activity making them useful in the therapeutic treatment of cardiovascular diseases and hypertension.

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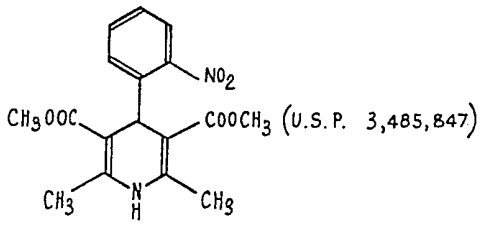
SPECIFICATION

4-cyanophenyl-1,4-dihydropyridine compound, processes for preparation thereof and pharmaceutical composition comprising the same

This invention relates to 4-cyanophenyl-1,4-dihydropyridine compound and a salt thereof. More particularly, it relates to new 4-cyanophenyl-1,4-dihydropyridine compound and a pharmaceutically acceptable salt thereof which have vasodilating and hypotensive acitivity, to processes for the preparation thereof, and to pharmaceutical composition comprising the same for therapeutical treatment in cardiovascular diseases and hypertension in human beings.

With regard to the states of the arts in this field, the following compound (Nifedipine) is known and used as a vasodilating agent.



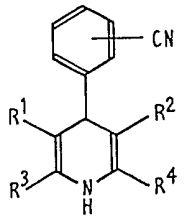
(U.S.P. 3,485,847)

One object of this invention is to provide new and useful 4-cyanophenyl-1, 4-dihydropyridine compound and a pharmaceutically acceptable salt thereof.

Another object of this invention is to provide processes for the preparation of 4-cyanophenyl-1,4-dihydropyridine compound and a salt thereof.

A further object of this invention is to provide useful pharmaceutical composition comprising, as an active ingredient, said 4-cyanophenyl-1, 4-dihydropyridine compound and a pharmaceutically acceptable salt thereof as a vasodilator and hypotensor.

The 4-cyanophenyl-1, 4-dihydropyridine compound of this invention can be represented by the formula:



(I)

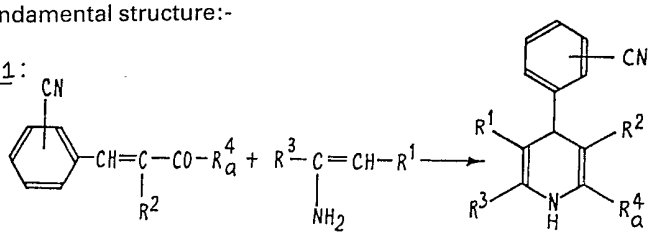
wherein R^1 is n-propoxycarbonyl, isobutoxycarbonyl or neopentyloxycarbonyl,
R^2 is lower alkoxycarbonyl,
R^3 is lower alkyl, and
R^4 is di(lower)alkoxymethyl, formyl hydroxyiminomethyl, cyano or hydroxymethyl.

With regard to the object compound of the above formula (I), it is to be understood that there may be one or more optical isomers, which are due to the presence of asymmetric carbon atom(s) in the molecule of the compound (I), and these isomers are also included within the scope of this invention.

According to this invention, the object compound (I) can be prepared by the processes as illustrated by the following schemes.

[I] Construction of fundamental structure:-

(1) Process 1:

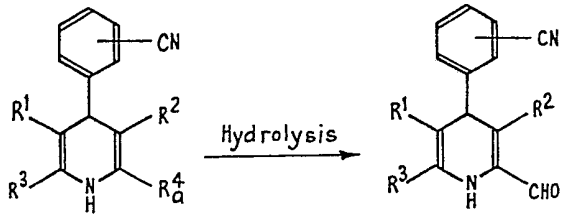


(II) (III) (I-1)

wherein R^1, R^2 and R^3 are each as defined above and
R^4_a is di(lower) alkoxymethyl.

[II] Transformations of a functional group:-

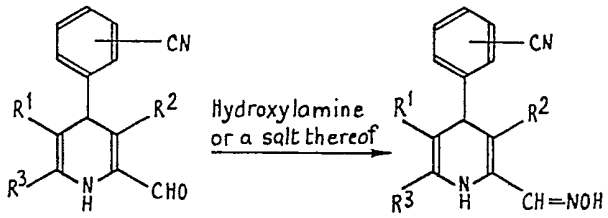
(2) Process 2:



(I-1) (I-2)

wherein R^1, R^2, R^3 and R_a^4 are each as defined above.

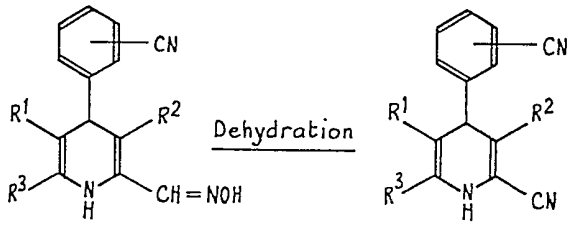
(3) Process 3:



(I-2) (I-3)

wherein R^1, R^2 and R^3 are each as defined above.

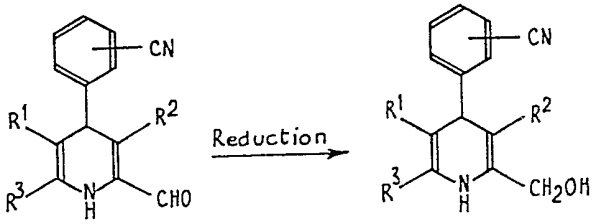
(4) Process 4:



(I-3) (I-4)

wherein R^1, R^2 and R^3 are each as defined above.

(5) Process 5:



(I-2) (I-5)

wherein R^1, R^2 and R^3 are each as defined above.

Detailed explanation for the definitions used throughout this specification will be made and the suitable examples thereof will be illustrated in the following.

The term "lower" used in connection with all of the alkane moieties is intended to mean 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms, and more preferably 1 to 4 carbon atoms.

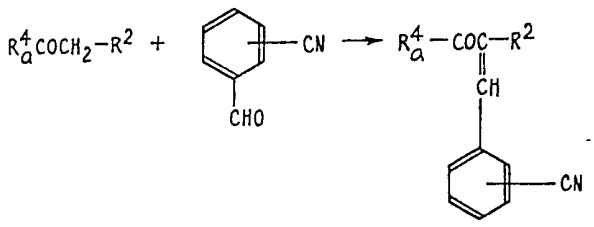
"Lower alkoxycarbonyl" for R^2 can be also represented by the formula: -co-o-(lower)alkyl, wherein the lower alkyl group includes monovalent radical of straight- and branched-chain(lower)alkanes. Suitable lower alkoxycarbonyl group may be methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl and the like, and the most preferred one is methoxycarbonyl.

"Lower alkyl" for R^3 may include a monovalent radical of straight- and branched-chain (lower) alkanes, and suitable lower alkyl group may be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, neopentyl, hexyl, heptyl, octyl and the like, more preferred one is C_1-C_4 alkyl group, and the most preferred one is methyl.

"Di-(lower)alkoxymethyl" for R^4 and R_a^4 may include dimethoxymethyl, diethoxymethyl, dipropoxymethyl and the like, and the most preferred one is dimethoxymethyl.

The starting compounds of this invention include known and new compounds, and they were prepared as follows.

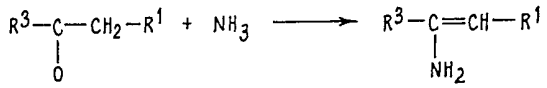
The starting compounds (II) used in Process 1 can be prepared by reacting 4-substituted-acetoacetate (II_A) and an aldehyde (II_B) as shown in the following reaction scheme.



(II_A) (II_B) (II)

wherein R^2 and R_a^4 are each as defined before.

The other starting compounds (III) used in Process 1 can be prepared from a 4-substituted acetoacetate compound (III_A) and ammonia or a salt thereof as shown in the following reaction schema.



(III_A) (III)

wherein R^1 and R^3 are each as defined before.

Processes for preparation of the 4-cyanophenyl-1,4-dihydropyridine compound (I) will be explained in detail below.

(1) Process 1:

This process related to a method for preparing a compound (I-1) by reacting a compound (II) with an amino compound (III).

Each of the starting compounds (II) and (III) includes cis and trans isomers due to the double bond in their molecules, and both of such cis and trans isomers are equivalent in view of the compound (I-1), and therefore, each isomer and optional mixtures of the isomers of these starting compounds (II) and (III) are to be included within the scope of this process.

The reaction can be carried out at ambient temperature or under warming or heating. The reaction can be conducted in the absence of a solvent, but may be conducted in a suitable solvent such as benzene, toluene, xylene, chloroform, carbon tetrachloride, methylene chloride, ethylene chloride, methanol, propanol, butanol, water or other conventional solvents. The reaction can preferably be accelerated in the presence of an agent such as an acid (e.g. acetic acid), a base (e.g. pyridine or picoline) or in a conventional buffer solution. These agents act as a reaction accelerator and may also be used as a solvent when they are in liquid. The reaction can also be accelerated by warming or heating. The reaction condition may vary according to the kind of the reactants, solvent and/or other agent as mentioned above to be used.

As to the reaction mode of this Process, the process can also be conducted, for example, by reacting a

mixture of the 4-substituted acetoacetate compound (II_A), the aldehyde (II_B) and the amino compound (III).

(2) Process 2:

This process relates to a method for preparing a compound (I-2) by hydrolysing a compound (I-1).

The compound (I-1) can be prepared as illustrated in the above Process 1.

In this process, the di(lower)alkoxymethyl group for R_a^4 of the compound (I-1) is transformed by hydrolysis into a formyl group.

Hydrolysis may be carried out in a conventional manner which is conventionally applied for cleavage of so-called an acetal function into the corresponding carbonyl function and preferably, for example, hydrolysis is carried out by an acidic hydrolysis, i.e. in the presence of an acid such as an inorganic acid (e.g. hydrochloric acid, sulfuric acid, etc.) or an organic acid (e.g. formic acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, etc.).

This hydrolysis may be carried out in a suitable conventional solvent such as water, acetone, methyl ethyl ketone, dioxane, ethanol, methanol, N,N-dimethylformamide, N-methylmorpholine or dimethylsulfoxide, an optional mixture thereof or a buffer solution thereof. The reaction temperature is not restrictive, and the reaction is usually conducted under cooling, at room temperature or under somewhat elevated temperature.

(3) Process 3:

This process relates to a method for preparing a compound (I-3) by reacting the compound (I-2) with hydroxylamine or a salt thereof.

According to this process, the formyl group of the starting compound (I-2) is transformed into the hydroxyiminomethyl group.

The compound (I-2) can be obtained by the above Process 2.

Preferable salt of hydroxylamine may be a salt with an acid such as an inorganic acid (e.g. hydrochloric acid, sulfuric acid, etc.) or an organic acid (e.g. acetic acid, etc.)

The reaction is carried out in a usual manner, for example, in the presence of a catalyst such as an acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, formic acid, acetic acid, p-toluenesulfonic acid, boron trifluoride, silicon tetrachloride or titanium tetrachloride); in a basic condition brought about by a base, for example free hydroxylamine; or in an acidic or basic conventional buffer solution. The reaction is usually conducted in a suitable conventional solvent such as water, dioxane, ethanol, methanol or dimethylformamide or an optional mixture thereof.

The reaction temperature is not restrictive, and the reaction is usually carried out under cooling, at room temperature or under somewhat elevated temperature.

(4) Process 4:

This process relates to a method for preparing a compound (I-4) by reacting the compound (I-3) with a dehydrating agent.

The oxime compound (I-3) can be obtained by the above Process 3.

Suitable example of the dehydrating agent includes conventional organic or inorganic ones such as an inorganic acid (e.g. sulfuric acid, phosphoric acid, polyphosphoric acid, etc.), an organic acid (e.g. formic acid, acetic acid, ethanesulfonic acid, p-toluenesulfonic acid, etc.), an organic acid anhydride (e.g. acetic anhydride, benzoic anhydride, phthalic anhydride, etc.), an organic acid halide (e.g. acetyl chloride, benzoyl chloride, trichloroacetyl chloride, mesyl chloride, tosyl chloride, ethyl chloroformate, phenylchloroformate, etc.); an inorganic halogen compound (e.g. thionyl chloride, phosphorus pentachloride, phosphorus oxychloride, phosphorus tribromide, stannic chloride, titanium tetrachloride, etc.); a carbodiimide (e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethyl-carbodiimide, etc.), N,N'-carbonyldiimidazole; pentamethyleneketene-N-cyclohexylimine; ethoxy-acetylene; 2-ethyl-7-hydroxyisoxazolium salt; other phosphorus compound (e.g. phosporus pentoxide, polyphosphoric acid ethyl ester, triethylphosphate or phenylphosphate) and the like or a mixture thereof. When an acid is used as the dehydrating agent, the reaction can also be conducted in the presence of its salt such as an alkali metal salt (e.g. sodium salt or potassium salt), or the like.

This reaction is usually carried out in a conventional solvent such as diethyl ether, dimethylformamide, pyridine, acetic acid, formic acid, benzene, carbon tetrachloride, chloroform, methylene chloride, tetrahydrofuran, dioxane, and the like, and usually carried out at room temperature or under heating, and the reaction temperature is not restrictive to the above.

This dehydration process can also be conducted successively to the foregoing Process 3 without any isolation of the oxime compound (I-3). This case is also included in the scope of this invention.

(5) Process 5:

This process relates to a method for preparing a compound (I-5) by reducing the compound (I-2).

The compound (I-2) can be prepared by the above Process 2.

The reduction can be carried out in a conventional manner which can be applied for reduction of formyl group into hydroxy-methyl group, and particularly, the reduction is conducted by reduction using a reducing agent such as an alkali metal borohydride (e.g. lithium borohydride, sodium borohydride, potassium borohydride, sodium cyanoborohydride, etc.) or by catalytic reduction for which preferable catalyst may be palladium carbon, palladium chloride or rhodium carbon and the like. The reduction is usually carried out in a conventional solvent such as water, methanol, ethanol, isopropanol, dimethylformamide, tetrahydrofuran, etc., and the like. The reaction temperature is not restrictive, and the reaction is usually carried out under cooling, at room temperature or at somewhat elevated temperature. And, the method of reduction may be

optionally selected according to the kind of the compound (I-2).

In accordance with this invention, the reaction product can be separated and isolated from the reaction mixture and purified by methods commonly used for this purpose, for instance, extraction with suitable solvent, chromatography, precipitation, recrystallization and so on.

Suitable examples of a salt of the dihydropyridine compound include a pharmaceutically acceptable salt such as an inorganic acid salt (e.g. hydrochloride, hydrobromide, phosphate, sulfate, etc.) and an organic acid salt (e.g. formate, acetate, fumarate, maleate, aspartate, glutamate, etc.).

The compound (I) thus obtained frequently includes at least one pair of optical isomers due to the presence of an asymmetric carbon atom at the fourth position of the 1,4-dihydropyridine nucleus and can exist as each optical isomer or a mixture thereof. A racemic compound can be resolved into each optical isomer by a conventional method for racemic resolution, such as a chemical resolution of the salts of the diastereomer with a conventional optically active acid (e.g. tartaric acid or camphor-sulfonic acid, etc.).

The compound (I) according to this invention is structurally characterized in the third position (i.e. R^1 of its molecule, namely characterized in the specific radical (e.g. n-propoxycarbonyl, etc.) of the symbol R^1 of the compound (I).

As to utility of thus characterized compound, it is to be noted that the compound (I) and a pharmaceutically acceptable salt thereof are possessed of strong vasodilating and hypotensive activity and useful for therapeutical treatment in hypertension and cardiovascular diseases such as coronary insufficiency, angina pectoris or myocardial infarction.

Particularly, the compound (I), wherein R^2 is methoxycarbonyl, R^3 is methyl and R^4 is cyano or hydroxymethyl, is preferable as a compound having such therapeutical effects as mentioned above, and more particularly, said compound is possessed of stronger vasodilating activity than those of the prior Patent Application in United Kingdom No. 52720/1976 (filing date: December 17, 1976), and more useful for hypotensive agents.

In addition to the above utility, it is further to be noted that the compound (I), wherein R^2 is methoxycarbonyl, R^3 is methyl and R^4 is dimethoxymethyl, formyl or hydroxyiminomethyl, has vasodilating and hypotensive activities as well as can be used as an intermediate for preparing the more preferable vasodilating agent and hypotensor of this invention as illustrated hereinabove.

For therapeutical purpose, the 4-cyanophenyl-1,4-dihydropyridine compound (I) is administered in oral daily dose of 0.1 to 500 mg, preferably 1 to 50 mg.

The pharmaceutical composition of this invention comprises, as an active ingredient, the 4-cyanophenyl-1,4-dihydropyridine compound (I) or pharmaceutically acceptable salt thereof in an amount of about 0.01 mg. to about 500 mg, preferably about 0.1 mg to about 250 mg per dosage unit for oral and parenteral use.

One skilled in the art will recognize that in determining the amount of the active ingredient in the dosage unit form, the activity of the ingredient as well as conditions of the patient must be considered. For administration purpose of this pharmaceutical composition, the active ingredient may usually be formulated in a solid form such as tablet, granule, powder, capsule, troche, lozenge or suppository, or a suspension or solution form such as syrup, injection, emulsion, lemonade etc. and the like.

A pharmaceutical carrier or diluent includes solid or liquid non-toxic pharmaceutically acceptable substances. Examples of solid or liquid carriers or diluents are lactose, magnesium stearate, terra alba, sucrose, corn starch, talc, stearic acid, gelatin, agar, pectin, acacia, peanut oil, olive oil or sesame oil, cacao butter, ethyleneglycol or other conventional ones. Similarly, the carrier or diluent may include a time delay material such as glyceryl monostearate, glyceryl distearate, a wax and the like.

For the purpose of showing the utility of the compound (I), the pharmaceutical tests were conducted on the represented compounds as follows.

HYPOTENSIVE EFFECT:

Test Method;

Five Wistar rats were used per group. Each animal was immobilized in a cage sized to the body. Blood pressure was measured at the femoral artery by means of a pressure transducer and recorded as electrically integrated values of mean arterial pressure, and heart rate was determined by a pulse wave detector. Operation for the catheterization was performed under light anesthesia with ether. The test compound was administered orally 3 hrs after completion of the operation.

Test compound.

Compound A : Nifedipine

Compound B : n-propyl 2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-6-cyano-1,4-dihydropyridine-3-carboxylate

Compound C : n-propyl 2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-6-hydroxymethyl-1,4-dihydropyridine-3-carboxylate

Compound D : isobutyl 2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-6-cyano-1,4-dihydropyridine-3-carboxylate

Test Result

Values of △ Maximum Decrease of blood pressure (mmHg) and Time (minutes) of Duration were shown in the following table.

TABLE

Dose Compound	1 mg/kg (Duration, minutes)	10 mg/kg (Duration, minutes)
A	−25.6 (60)	−44.6 (>360)
B	−37.4 (>360)	−50.6 (>360)
C	−12.2 (120)	−41.8 (>360)
D	−20.2 (>360)	−40.6 (>360)

The following Examples are given for the purpose of illustrating the syntheses of some specific object compounds of this invention.

PREPARATION OF THE STARTING COMPOUND

Preparation 1

A benzene solution (120 ml) of 2-cyanobenzaldehyde (30.97 g), methyl 4,4-dimethoxyacetoacetate (46.14 g), acetic acid (2.3 g) and piperidine (2.4 g) was refluxed under heating for 8 hours. After addition of benzene (80 ml) and washing with water, the solution was treated with an activated charcoal. The evaporated residue was chromatographed on silica gel (500 g) with methylene chloride as an eluent. The fractions containing a desired compound were collected and evaporated to give methyl 2-(2-cyanobenzylidene)-4,4-dimethoxy-acetoacetate (25.16 g).

N.M.R. δppm($CDCl_3$) : 3.41 (s), 3.50 (s) } (6H), 3.69 (s), 3.92 (s) } (3H),

4.83 (s), 5.10 (s) } (1H), 7.40-7.90 (4H, m),

8.04 (s), 8.17 (s) } (1H)

Example 1

A mixture of methyl 2-(2-cyanobenzylidene)-4,4-dimethoxyacetoacetate (11.12 g) and n-propyl 3-aminocrotonate (7.53 g) was stirred at 67°C for 4 hours, and the stirring was continued at 95.5°C for 14 hours and at 102°C for additional 15 hours. The reaction mixture (11.83 g) was dissolved in a proper quantity of diisopropyl ether, and chromatographed on silica gel (300 g) with methylene chloride as an eluent. Fractions containing a desired compound were collected. The solvent was distilled off from the eluate under reduced pressure to give pale yellowish crystals (1.45 g) of n-propyl 6-dimethoxy-methyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate, mp 139-141°C.

N.M.R.δppm ($CDCl_3$) : 1.78 (3H, t, J=7.3Hz).
1.64 (2H, sixtet, J=7.3Hz), 2.42 (3H, s),
3.47 (3H, s), 3.52 (3H, s), 3.73 (3H, s),
4.04 (2H, t, J=7.3Hz), 5.42 (1H, s),
6.08 (1H, s), 6.77 (1H, m), 7.13-7.38
(1H,m), 7.38-7.71 (3H, m)

Example 2

Isobutyl 6-dimethoxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (17.38 g) was obtained by heating a mixture of methyl 2-(2-cyanobenzylidene)-4,4-dimethoxyacetoacetate (10.82 g) and isobutyl 3-aminocrotonate (8.47 g) in substantially the same manner as that of Example 1, mp 126-128°C.

N.M.R. δppm ($CDC\ell_3$) : 0.74 (3H, d, J=6.5Hz), 0.87 (3H, d, J=6.5Hz), 2.02 (1H, m), 2.41 (3H, s), 3.47 (3H, s), 3.52 (3H, s), 3.73 (3H, s), 3.87 (2H, d, J=6.5Hz), 5.42 (1H, s), 6.06 (1H, s), 6.76 (1H, m), 7.13-7.43 (1H, m), 7.43-7.68 (3H, m)

Example 3

Neopentyl 6-dimethoxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (8.53 g) was obtained by heating a mixture of methyl 2-(2-cyanobenzylidene)-4,4-dimethoxyacetoacetate (10.37 g) and neopentyl 3-aminocrotonate (8.60 g) in substantially the same manner as that of Example 1, mp 130-131°C.

N.M.R. δppm ($CDC\ell_3$) : 0.85 (9H, s), 2.36 (3H, s), 3.42 (3H, s), 3.46 (3H, s), 3.67 (3H, s), 3.80 (2H, s), 5.37 (1H, s), 6.00 (1H, s), 6.75 (1H, m), 7.00-7.35 (1H, m), 7.35-7.65 (3H, m)

Example 4

To a solution (132 ml) of n-propyl 6-dimethoxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (13.28 g) in acetone was added dropwise 6N hydrochloric acid (13.2 ml) at 12°C with stirring, and the stirring was continued for 5.5 hours. The resultant mixture was adjusted to about pH 7 with an aqueous sodium bicarbonate solution. The acetone was distilled off under reduced pressure. The precipitated crystals were collected by filtration and washed with an aqueous sodium chloride solution, water and petroleum ether, successively, and then recrystallized from a mixture of benzene and n-hexane. The crystals were collected by filtration and washed with diethyl ether to give n-propyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (3.37 g), mp 137.5-141.0°C.

The mother liquor of the above recrystallization was evaporated to dryness and the residue was chromotagraphed on silica gel (240 g) with methylene chloride as an eluent to recover the above same product (3.83 g). Total yield was 7.2 g.

N.M.R. δppm ($CDC\ell_3$) : 0.78 (3H, t, J=7Hz), 1.63 (2H, sixtet, J=7Hz), 2.43 (3H, s), 3.77 (3H, s), 4.02 (2H, t, J=7Hz), 5.45 (1H, s), 6.95 (1H, m), 7.2-7.8 (4H, m), 10.51 (1H, s)

Example 5

Isobutyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (6.82 g) was obtained by reacting isobutyl 6-dimethoxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (20.37 g) with 6N hydrochloric acid (14 ml) in substantially the same manner as that of Example 4, mp 152.5-154.5°C.

N.M.R. δppm ($CDC\ell_3$) : 0.76 (3H, d, J=6.5Hz), 0.82 (3H, d, J=6.5Hz), 2.02 (1H, m), 2.46 (3H, s), 3.83 (3H, s), 3.90 (2H, d, J=6.5Hz), 5.53 (1H, s), 7.0 (1H, m), 7.2-7.8 (4H, m), 10.55 (1H, s),

Example 6

Neopentyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (5.83 g) was obtained by reacting neopentyl 6-dimethoxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (15.56 g) with 6N hydrochloric acid (14.2 ml) in substantially the same manner as that of Example 4, mp 141.0-143.0°C.

N.M.R. δppm ($CDC\ell_3$) : 0.86 (9H, s), 2.43 (3H, s), 3.80 (3H, s), 3.85 (2H, s), 5.49 (1H, s), 7.00 (1H, m), 7.3-7.7 (4H, m), 10.50 (1H, s)

Example 7

A mixture of n-propyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (4.29 g), hydroxylamine hydrochloride (0.87 g), sodium acetate (1.13 g) and acetic acid (26 ml) was stirred at ambient temperature for 5 hours. To this mixture was added acetic anhydride (5 g), followed by stirring at ambient temperature for 80 minutes, at 85°C for 2.5 hours and at 93°C for additional 9.5 hours. After cooling, the solvent was removed from the reaction mixture under reduced pressure, and to the residue were added an aqueous solution of sodium bicarbonate and methylene chloride. The separated organic layer was washed with water, dried and then evaporated to dryness to give a residue (3.42 g), which was chromatographed on silica gel (100 g) with methylene chloride as an eluent and desired fractions were collected and evaporated. The resultant residue was recrystallized twice from a mixed solvent of methanol and water and then from methylene chloride to give pure crystals (2.29 g) of n-propyl 6-cyano-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate, mp 150.0 - 151.5°C.

N.M.R. δppm ($CDC\ell_3$) : 0.77 (3H, t, J=7Hz), 1.59 (2H, sixtet, J=7Hz), 2.37 (3H, s), 3.74 (3H, s), 3.98 (2H, t, J=7Hz), 5.38 (1H, s), 6.85 (1H, m), 7.0-7.7 (4H, m).

Example 8

Isobutyl 6-cyano-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (1.81 g) was obtained by reacting isobutyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (3.39 g) with hydroxylamine hydrochloride (0.89 g), sodium acetate (1.12 g), acetic acid (25 ml) and acetic anhydride (6.24 g) in substantially the same manner as that of Example 7, mp 196.0-197.5°C.

N.M.R. δppm ($CDC\ell_3$) : 0.75 (3H, d, J=7Hz), 0.81 (3H, d, J=7Hz), 1.97 (1H, m), 2.40 (3H, s), 3.78 (3H, s), 3.85 (2H, d, J=7Hz), 5.41 (1H, s), 7.02 (1H, m), 7.19-7.68 (4H, m).

Example 9

Neopentyl 6-cyano-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (1.69 g) was obtained by reacting neopentyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (3.78 g) with hydroxylamine hydrochloride (0.97 g), sodium acetate (1.19 g), acetic acid (25 ml) and acetic anhydride (6.4 g) in substantially the same manner as that of Example 7, mp 173.0-174.0°C.

N.M.R. δppm ($CDC\ell_3$) : 0.87 (9H, s), 2.41 (3H, s), 3.79 (3H, s), 3.84 (2H, s), 5.44 (1H, s), 6.85 (1H, m), 7.2-7.8 (4H, m).

Example 10

To a suspension of n-propyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropropyridine-3-carboxylate (2.00 g) in ethanol (40 ml) was added sodium borohydride (0.17 g) at −5 to −10°C over a period of 5 minutes with stirring, and the stirring was continued at the same temperature for 2 hours. To the reaction mixture was added 50% acetic acid (0.6 ml), followed by removal of the solvent under reduced pressure. The residue was dissolved in ethyl acetate, washed with an aqueous solution of sodium chloride and then dried. The solution was evaporated to give crude cyrstals (2.04 g), which were recrystallized from a mixed solvent of methanol and water to give pure product (1.34 g) of n-propyl 6-hydroxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate, mp 49.0-152.5°C.

N.M.R. δppm ($CDC\ell_3$) : 0.77 (3H, t, J=7Hz), 1.61 (2H, sixtet, J=7Hz), 2.38 (3H, s), 3.63 (3H, s), 3.99 (2H, t, J=7Hz), 4.79 (2H, s), 5.31 (1H, s), 7.32 (1H, m), 7.1-7.6 (4H, m).

Example 11

Isobutyl 6-hydroxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (1.49 g) was obtained by reacting isobutyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (2.00 g) with sodium borohydride (0.18 g) in substantially the same manner as that of Example 10, mp 134.5-137.0°C.

N.M.R. δppm ($CDC\ell_3$) : 0.75 (3H, d, J=7Hz), 0.81 (3H, d, J=7Hz), 1.97 (1H, m), 2.39 (3H, s), 2.8 (1H, m), 3.64 (3H, s), 3.86 (2H, d, J=7Hz), 4.81 (2H, s), 5.35 (1H, s), 7.1-7.7 (5H, m),.

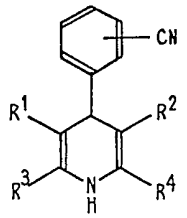
Example 12

Neopentyl 6-hydroxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (1.54 g) was obtained by reacting neopentyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate (2.00 g) with sodium borohydride (0.16 g) in substantially the same manner as that of Example 10, mp 178.0-179.5°C.

N.M.R. δppm ($CDC\ell_3$) : 0.87 (9H, s), 2.38 (3H, s), 3.63 (3H, s), 3.81 (2H, s), 4.78 (2H, s), 5.33 (1H, s), 7.37 (1H, m), 7.1-7.6 (4H, m).

CLAIMS

1. A compound of the formula:



(I)

wherein R^1 is n-propoxycarbonyl, isobutoxycarbonyl or neopentyloxycarbonyl,
R^2 is lower alkoxycarbonyl,
R^3 is lower alkyl, and
R^4 is di(lower) alkoxymethyl, formyl, hydroxyiminomethyl, cyano or hydroxymethyl.

2. The compound according to claim 1, wherein
R^1 is n-propoxycarbonyl, isobutoxycarbonyl or neopentyloxycarbonyl,
R^2 is methoxycarbonyl, R^3 is methyl and R^4 is dimethoxymethyl, formyl, hydroxyiminomethyl, cyano or hydroxymethyl.

3. The compound according to claim 2, which is n-propyl 6-dimethoxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

4. The compound according to claim 2, which is isobutyl 6-dimethoxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

5. The compound according to claim 2, which is neopentyl 6-dimethoxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

6. The compound according to claim 2, which is n-propyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

7. The compound according to claim 2, which is isobutyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

8. The compound according to claim 2, which is neopentyl 6-formyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

9. The compound according to claim 2, which is n-propyl 6-hydroxyiminomethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

10. The compound according to claim 2, which is isobutyl 6-hydroxyiminomethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

11. The compound according to claim 2, which is neopentyl 6-hydroxyiminomethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

12. The compound according to claim 2, which is n-propyl 6-cyano-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

13. The compound according to claim 2, which is isobutyl 6-cyano-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

14. The compound according to claim 2, which is neopentyl 6-cyano-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

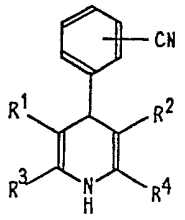
15. The compound according to claim 2, which is n-propyl 6-hydroxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

16. The compound according to claim 2, which is isobutyl 6-hydroxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

17. The compound according to claim 2, which is neopentyl 6-hydroxymethyl-2-methyl-4-(2-cyanophenyl)-5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylate.

18. A pharmaceutical composition which comprises, as an active ingredient, the compound claimed in claim 1 in association with a pharmaceutically acceptable carrier or diluent.

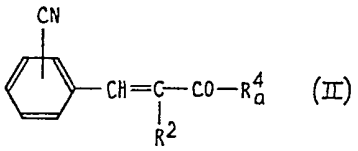
19. A process for preparation of a compound of the formula:



(I)

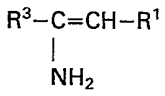
wherein R^1 is n-propoxycarbonyl, isobutoxycarbonyl or neopentyloxycarbonyl,
R^2 is lower alkoxycarbonyl,
R^3 is lower alkyl, and
R^4 is di(lower)alkoxymethyl, formyl, hydroxyiminomethyl, cyano or hydroxymethyl, which comprises

(1) reacting a compound of the formula:



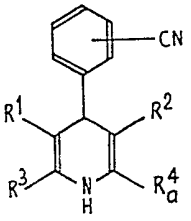
(II)

wherein R^2 is as defined above and R^4_a is di(lower)-alkoxymethyl, with an amino compound of the formula:



(III)

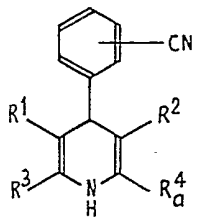
wherein R^1 and R^3 are each as defined above, to give a compound of the formula:



(I-1)

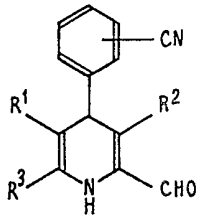
wherein R^1, R^2, R^3 and R^4_a are each as defined above; or

(2) hydrolyzing the compound of the formula:



(I-1)

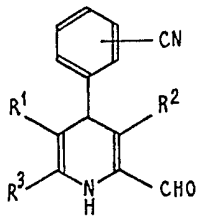
wherein R^1, R^2, R^3 and R_a^4 are each as defined above, to give a compound of the formula:



(I-2)

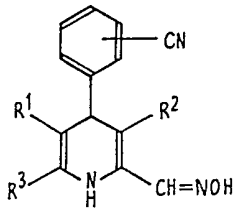
wherein R^1, R^2 and R^3 are each as defined above; or

(3) reacting the compound of the formula:



(I-2)

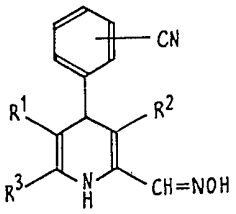
wherein R^1, R^2 and R^3 are each as defined above, with hydroxylamine or a salt thereof to give a compound of the formula:



(I-3)

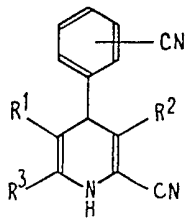
wherein R^1, R^2 and R^3 are each as defined above; or

(4) reacting the compound of the formula:



(I-3)

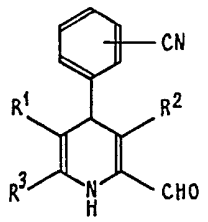
wherein R^1, R^2 and R^3 are each as defined above, with a dehydrating agent to give a compound of the formula:



(I-4)

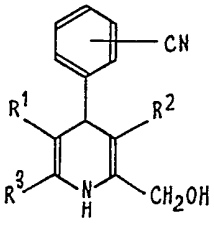
wherein R^1, R^2 and R^3 are each as defined above; or

(5) reducing the compound of the formula:



(I-2)

wherein R^1, R^2 and R^3 are each as defined above, to give a compound of the formula:



(I-5)

wherein R^1, R^2 and R^3 are each as defined above.

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon Surrey, 1980.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.