United States Patent [19]

Campbell et al.

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[54] **2-(SECONDARY AMINOALKOXYMETHYL) DIHYDROPYRIDINE DERIVATIVES AS ANTI-ISCHAEMIC AND ANTIHYPERTENSIVE AGENTS**

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[73] Assignee: **Pfizer Inc.**, New York, N.Y.

[21] Appl. No.: **576,982**

[22] Filed: **Feb. 3, 1984**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 463,081, Feb. 2, 1983, abandoned.

[30] **Foreign Application Priority Data**

Mar. 11, 1982 [GB] United Kingdom 8207180

[51] **Int. Cl.**[4] **C07D 211/90**; A61K 31/455

[52] **U.S. Cl.** **514/356**; 546/321

[58] **Field of Search** 544/333; 546/321, 283, 546/274, 280, 257, 271, 167, 284, 270; 424/251, 258, 266; 514/356

[56] **References Cited**

U.S. PATENT DOCUMENTS

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Bossert, F. et al, "4–Aryldihydropyridines", Angew. Chem. Int. Ed. Engl. 20, pp. 762–769 (1981).

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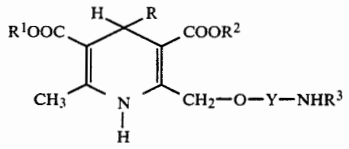
[57] **ABSTRACT**

A dihydropyridine compound of the formula



or a pharmaceutically acceptable acid addition salt thereof,

wherein

Y is $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2CH(CH_3)-$ or $-CH_2C(CH_3)_2-$;

R is aryl or heteroaryl;

R^1 and R^2 are each independently C_1–C_4 alkyl or 2-methoxyethyl; and

R^3 is hydrogen, C_1–C_4 alkyl, 2-(C_1–C_4 alkoxy)ethyl, cyclopropylmethyl, benzyl, or $-(CH_2)_mCOR^4$ where m is 1, 2 or 3 and

R^4 is hydroxy, C_1–C_4 alkoxy or $-NR^5R^6$ where R^5 and R^6 are each independently hydrogen or C_1–C_4 alkyl

can be employed for treating or preventing a heart condition or hypertension.

17 Claims, No Drawings

2-(SECONDARY AMINOALKOXYMETHYL) DIHYDROPYRIDINE DERIVATIVES AS ANTI-ISCHAEMIC AND ANTIHYPERTENSIVE AGENTS

This is a continuation-in-part of U.S. patent application Ser. No. 463,081, filed Feb. 2, 1983, abandoned.

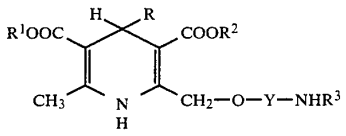
BACKGROUND OF THE INVENTION

This invention relates to certain dihydropyridines, specifically to certain 1,4-dihydropyridines having a substituted-amino containing group attached to the 2-position, which have utility as anti-ischaemic and antihypertensive agents.

The compounds of the invention reduce the movement of calcium into the cell and they are thus able to delay or prevent the cardiac contracture which is believed to be caused by an accumulation of intracellular calcium under ischaemic conditions. Excessive calcium influx during ischaemia can have a number of additional adverse effects which would further compromise the ischaemic myocardium. These include less efficient use of oxygen for ATP production, activation of mitochondrial fatty acid oxidation and possibly, promotion of cell necrosis. Thus the compounds are useful in the treatment or prevention of a variety of cardiac conditions, such as angina pectoris, cardiac arrythmias, heart attacks and cardiac hypertrophy. The compounds also have vasodilator activity since they can inhibit calcium influx in cells of vascular tissue and they are thus also useful as antihypertensive agents and for the treatment of coronary vasospasm.

SUMMARY OF THE INVENTION

According to the invention, there are provided novel 1,4-dihydropyridine derivatives of the formula:



(I)

wherein

Y is $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2CH(CH_3)-$ or $-CH_2C(CH_3)_2-$;

R is aryl or heteroaryl;

R^1 and R^2 are each independently C_1–C_4 alkyl or 2-methoxyethyl; and

R^3 is hydrogen, C_1–C_4 alkyl, 2-(C_1–C_4 alkoxy)ethyl, cyclopropylmethyl, benzyl, or $-(CH_2)_mCOR^4$ where m is 1, 2 or 3 and R^4 is hydroxy, C_1–C_4 alkoxy or $-NR^5R^6$ where R^5 and R^6 are each independently hydrogen or C_1–C_4 alkyl;

and their pharmaceutically acceptable acid addition salts.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the formula (I) containing one or more asymmetric centres will exist as one or more pairs of enantiomers, and such pairs or individual isomers may be separable by physical methods, e.g. by fractional crystallisation of the free bases or suitable salts or chromatography of the free bases. The invention includes the separated pairs as well as mixtures thereof, as racemic mixtures or as separated d- and l- optically-active isomeric forms.

The pharmaceutically acceptable acid addition salts of the compounds of the formula (I) are those formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts. The preferred salts are maleates.

The term "aryl" as used in this specification, includes, for example, phenyl optionally substituted by one or two substituents selected from nitro, halo, C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, trifluoromethyl, and cyano. It also includes 1- and 2-naphthyl.

The term "heteroaryl" as used in this specification includes, for example, benzofuranyl; benzothienyl; pyridyl optionally monosubstituted by methyl or cyano; quinolyl; benzoxazolyl; benzthiazolyl; furyl; pyrimidinyl; thiazolyl; 2,1,3-benzoxadiazol-4-yl; 2,1,3-benzthiadiazol-4-yl; and thienyl optionally monosubstituted by halo or C_1–C_4 alkyl.

"Halo" means fluoro, chloro, bromo or iodo.

C_3 and C_4 alkyl and alkoxy groups can be straight or branched chain.

R^3 is preferably H, CH_3, benzyl, 2-methoxyethyl, $-CH_2COOCH_3$, $-CH_2COOC_2H_5$, $-CH_2CONH_2$, $-CH_2CONHCH_3$, or $-CH_2COOH$.

R^3 is most preferably H or CH_3.

R is preferably 2-chlorophenyl, 2-fluorophenyl, 2-methoxyphenyl, 3-chlorophenyl, 2-chloro-3-hydroxyphenyl, 2-chloro-6-fluorophenyl, unsubstituted phenyl or 2,3-dichlorophenyl.

R^1 is preferably CH_3.

R^2 is preferably C_2H_5.

Y is preferably $-(CH_2)_2-$ or $-CH_2CH(CH_3)-$.

"m" is preferably 1.

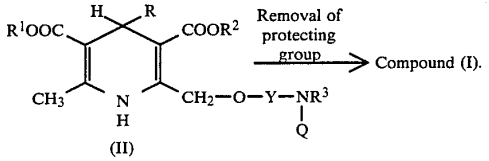
Most preferably, R is 2-chlorophenyl.

Most preferably, Y is $-(CH_2)_2$.

The most preferred compounds have the formula (I) wherein R is 2-chlorophenyl, R^1 is CH_3, R^2 is C_2H_5, R^3 is H or CH_3, and Y is $-(CH_2)_2-$.

The compounds of the formula (I) are primary or secondary amines and in one method they can be prepared by the removal of the amino-protecting group from the corresponding amino-protected dihydropyridines.

This general method can be illustrated in more detail as follows:

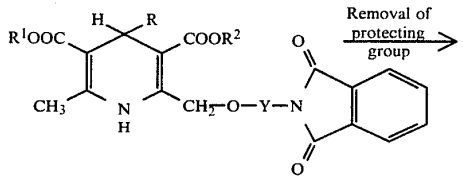


(II)

(Q=an amino-protecting group and R, R^1, R^2, R^3 and Y are as defined for formula [I]);

OR

-continued



Compound (I) [R^3 = H].

[R, R^1, R^2 and Y are as defined for formula (I)].

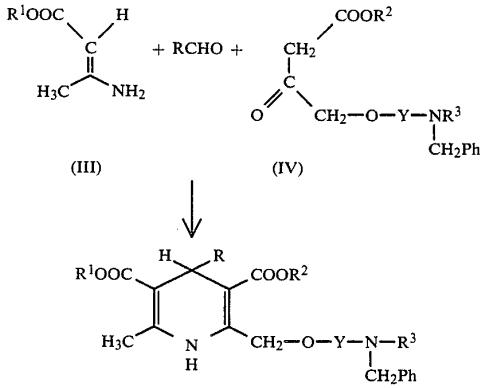
One preferred amino-protecting group is benzyl. It is typically removed by hydrogenation, using e.g. H_2/Pd on charcoal under acidic conditions in a suitable organic solvent, e.g. methanol. The acidic conditions are preferably obtained by using compound (II) in the form of an organic acid addition salt, e.g. as an oxalate or acetate salt.

A typical procedure involving the removal of a benzyl group is as follows. Compound (II) as an oxalate salt in methanol is added to a suspension of 10% prehydrogenated palladium on charcoal in methanol, and the mixture is then stirred under hydrogen at 50 p.s.i. for up to about 18 hours, e.g. overnight, and at room temperature. If necessary, heating at up to about 60° C. can be provided. The product can then be isolated and purified by conventional procedures.

When both Q and R^3 are benzyl, hydrogenation under the above conditions normally only removes one of the benzyl groups. Further hydrogenation of the resulting monobenzyl product under the above conditions with fresh catalyst can then be used to remove the remaining benzyl group.

Many of the starting materials of the formula (II) in which Q is benzyl are described and claimed in our European patent application publication No. 0060674. Typical methods to the N-benzyl starting materials of the formula (II) are as follows:

(a) The benzyl-protected intermediates (II) can be prepared by the Hantzsch synthesis, as follows:

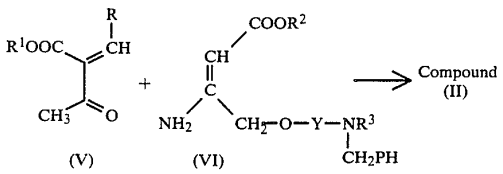


(III) (IV)

In a typical procedure, the ketoester (IV) and aldehyde are heated under reflux in a suitable organic solvent, e.g. a C_1–C_4 alkanol solvent such as ethanol, for about 15 minutes, and then the aminocrotonate (III) is added. Alternatively the aminocrotonate (III), ketoester (IV) and aldehyde can be heated together in the solvent. Preferably a small amount of a lower alkanoic acid such as acetic acid is added to neutralise the solution. The resulting solution can then be heated at 60°–130° C., preferably under reflux, until the reaction is essentially complete, typically in 24 hours or less. The product of the formula (II) can then be isolated and purified by conventional procedures.

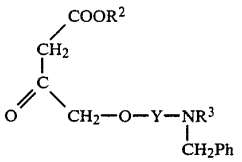
The ketoesters (IV) are either known compounds or can be prepared by methods analogous to those of the prior art, such as the method illustrated in the Preparations hereinafter, which are essentially the method of Troostwijk and Kellogg, *J.C.S. Chem. Comm.*, 1977, page 932. Similarly the amino-crotonates (III) are either known compounds or can be prepared by conventional procedures. Also the aldehydes are either known or can be prepared by known methods.

(b) The benzyl-containing intermediates (II) can also be prepared by the following process:



(V) (VI)

The crotonate (VI) is typically prepared in situ by reaction of the corresponding acetoacetate (IV):

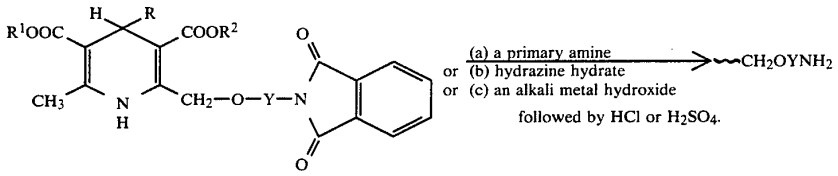


(IV)

with ammonium acetate, e.g. by refluxing in a suitable organic solvent, e.g. a C_1–C_4 alkanol such as ethanol, for, say, up to an hour. The crotonate (VI) is then reacted with compound (V), typically by heating in the solvent for up to about 5 hours at 60° C.–130° C., e.g. under reflux. The product (II) can then be isolated and purified by conventional procedures.

The starting materials (V) are either known compounds or may be prepared by methods analogous to those of the prior art, see e.g. *Can. J. Chem.*, 1967, 45, 1001.

The compounds of the formula (I) in which R^3 is H can be prepared from the corresponding phthalimido derivatives according to conventional procedures, e.g.:

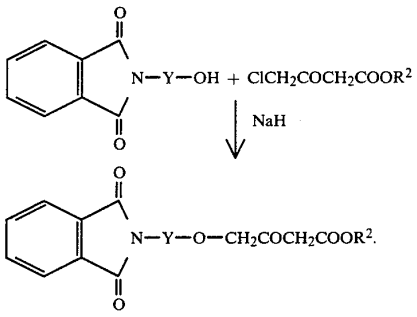


The prefered primary amine is methylamine. The preferred alkali metal hydroxide is potassium hydroxide.

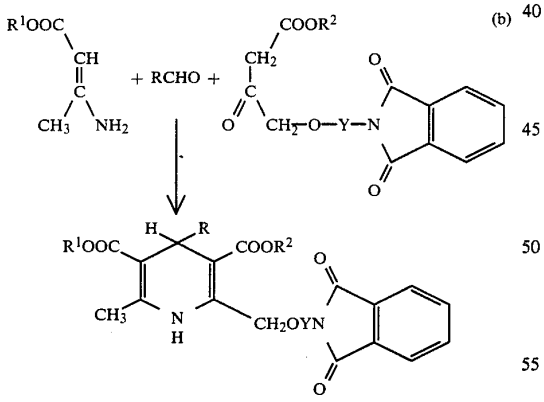
The reaction using methylamine is typically carried out in ethanol at room temperature, with heating if necessary. The reaction using hydrazine hydrate is typically carried out in ethanol at the reflux temperature or below. The reaction using potassium hydroxide is typically carried out at room temperature (although with heating if necessary) in tetrahydrofuran, following by the addition of the acid and heating at the reflux temperature or below. In all cases the product can be isolated conventionally.

The phthalimido starting materials can again be obtained conventionally, e.g.:

(a)



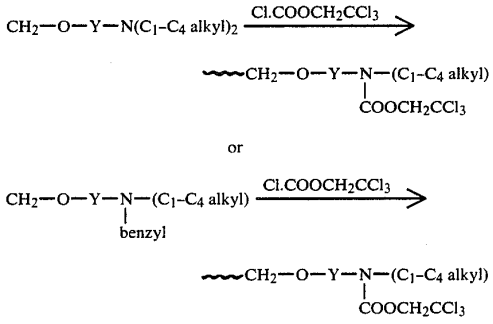
(b)



This is again the Hantzsch reaction.

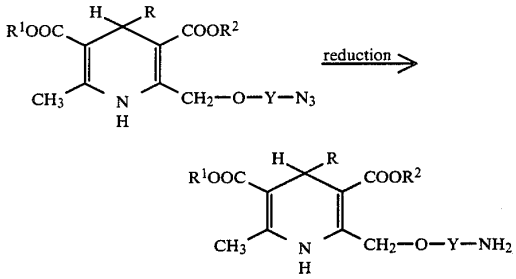
Compounds of the formula (I) in which R^3 is H can also be purified to very high levels by reacting them with phthalic anhydride to form the phthalimido derivatives which can then be converted back to the compounds in which R^3 is H by the methods previously described.

To prepare compounds in which R^3 is C_1–C_4 alkyl, —$COOCH_2CCl_3$ can be used as the amino-protecting group. This can be removed in a conventional manner using zinc and either formic or acetic acid. The N-protected starting materials necessary for this process can be prepared as follows:



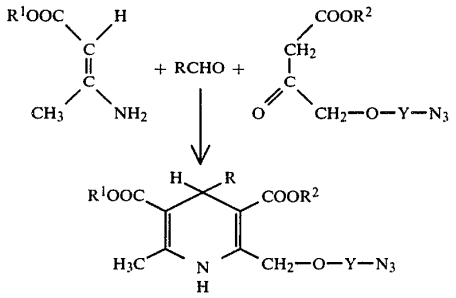
Typically the reaction with 2,2,2-trichloroethyl chloroformate is carried by heating the reactants at up to reflux temperature in e.g. toluene. Many of the dialkylamino and N-alkyl-N-benzylamino starting materials needed to prepared these N-protected intermediates are described and claimed in our corresponding European patent application publication No. 0060674, and others can be prepared analogously.

The compounds of the formula (I) where R^3=H can also be obtained from the corresponding azido compounds, the azido group being convertable to —NH_2 by reduction, e.g. with triphenylphosphine, or zinc and hydrochloric acid, or H_2/Pd, under conventional conditions.

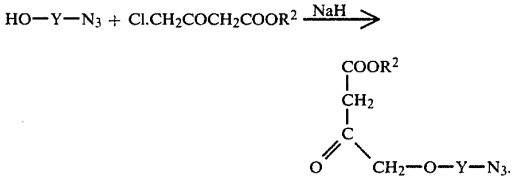


In a typical procedure using zinc dust, the reaction is carried out in methanol/aqueous hydrochloric acid. Heating is possible but is not generally necessary. Similarly hydrogenation can be carried out in e.g. methanol or ethanol in the presence of a catalyst such as $Pd/CaCO_3$ at room temperature.

Again the azido starting materials can be prepared by the Hantzsch synthesis under conditions similar to those previously described:

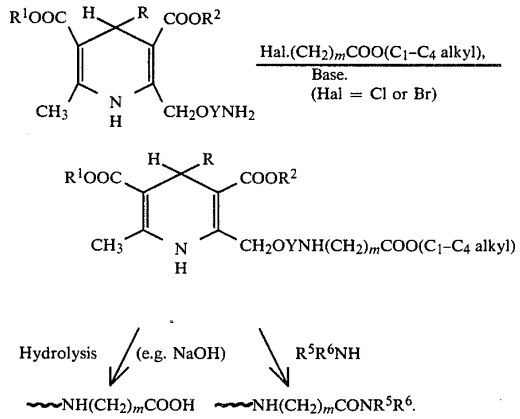


The azido-containing acetoacetates can also be obtained by conventional procedures:



Similarly the azido starting materials can also be prepared analogously to route (b) above for preparing the N-benzyl starting materials.

Some of the compounds of the invention can be prepared from other compounds of the invention by conventional techniques, e.g.:



The ability of the compounds to inhibit the movement of calcium into the cell is shown by their effectiveness in reducing the response of isolated heart tissue to an increase in calcium ion concentration in vitro. The test is performed by mounting spirally cut strips of rat aorta with one end fixed and the other attached to a force transducer. The tissue is immersed in a bath of physiological saline solution containing potassium ions at a concentration of 45 millimolar and no calcium. Calcium chloride is added to the bath with a pipette to give a final calcium ion concentration of 2 millimolar. The change in tension caused by the resulting contraction of the tissue is noted. The bath is drained and replaced with fresh saline solution and, after 45 minutes, the test is repeated with the particular compound under test present in the saline solution. The concentration of compound required to reduce the response by 50% is recorded.

The antihypertensive activity of the compounds is also evaluated after oral administration by measuring the fall in blood pressure in spontaneously hypertensive rats or renally hypertensive dogs.

For administration to man in the curative or prophylactic treatment of cardiac conditions and hypertension, oral dosages of the compounds will be in the range of from 2–50 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules are likely to contain from 1 to 10 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration would be within the range 1 to 10 mg per single dose as required.

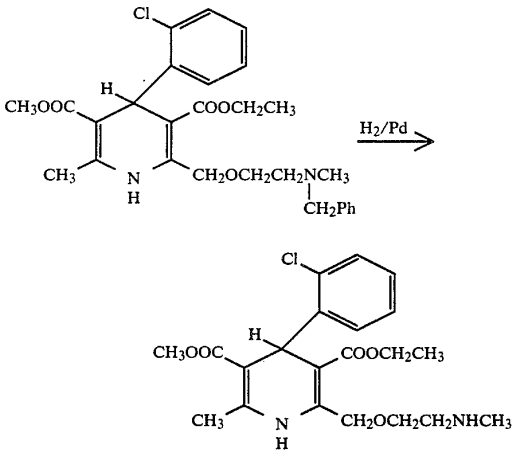
In a further aspect the invention provides a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also provides a compound of the formula (I), or a pharmaceutically acceptable acid addition salt thereof, for use in treating ischaemic heart disease, especially angina, or hypertension, in a human being.

The following Examples illustrate the invention: all temperatures are in °C.:

EXAMPLE 1

Preparation of 4-(2-chlorophenyl)-2-[2-(methylamino)ethoxymethyl]-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine, oxalate salt



A solution of 2-[2-(N-benzyl-N-methylamino)ethoxymethyl]-4-[2-chlorophenyl]-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine, oxalate salt (4.3 g) in methanol (220 ml) was added to a suspension of 10% (by weight) palladium on charcoal (0.4 g) pre-hydrogenated in methanol (50 ml). Stirring under hydrogen at 50 p.s.i. and room temperature overnight resulted in complete removal of the benzyl group. After removal of the catalyst by filtration, the methanol was removed by evaporation and the residue crystal-

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