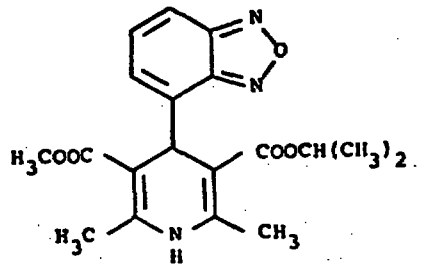
SPECIFICATION

A 1,4-Dihydropyridine derivative, its preparation and pharmaceutical compositions containing it

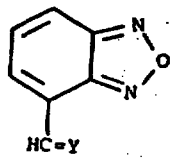
The present invention provides 4-(2,1,3-benzoxadiazolyl)-4)-2,6-dimethyl-1,4-dihydro-3-methoxy-carbonyl-pyridine-5-carboxylic acid isopropyl ester of formula I,



I

The compound of formula I falls under the scope of European Patent Application No. 78100165.6, but is not specifically disclosed therein. It has now been found that the compound of formula I has particularly valuable pharmacological properties, e.g. its coronary activity is particularly long lasting and potent. Its calcium antagonistic activity is particularly potent. It also possesses a good tolerability.

A process for the production of the compound of formula I may comprise replacing the moiety $-HC=Y$ in a compound of formula II,



II

wherein

$-HC=Y$ is

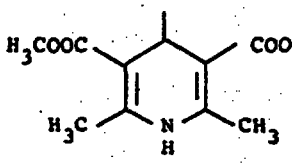
i) formyl,

ii) a radical of formula $-CH=C(COOCH(CH_3)_2)-C(=Z)CH_3$

or

iii) a radical of formula $-HC(HC(COOCH(CH_3)_2)-C(=Z)CH_3)-HC(COOCH_3)-C(=Z')CH_3$

wherein Z and Z' are independently oxygen or NH, by a moiety of formula III,



III

The process may be effected in conventional manner for analogous dihydropyridine syntheses, e.g. according to Hantzsch. When the moiety $-HC=Y$ is formyl it is possible to react such a compound of formula II with the compound of formula IV

$$CH_3-CO-CH_2-COOCH_3 \qquad IV$$

and the compound of formula VII,

$CH_3-C(NH_2)=CH-COOCH(CH_3)_2$ VII

A compound of formula II, wherein $-HC=Y$ is a radical ii) or iii), may be formed as an intermediate in the above reactions. It may however be produced by different processes.

Alternatively it is convenient to react a compound of formula II, wherein the moiety $-HC=Y$ is a radical ii) with the compound of formula IV or VI,

$CH_3-C(NH_2)=CH-COOCH_3$ VI

and, where appropriate, with ammonia. A compound of formula II, wherein the moiety $-HC=Y$ is a radical iii) may be an intermediate.

In the above reactions it is possible in certain instances that a mixture of dihydropyridines may be formed. If so these may be separated in conventional manner, e.g. by column or thin layer chromatography.

When the starting material is a compound of formula II, wherein $-HC=Y$ is a radical iii), the reaction is a ring cyclisation. When Z and Z' are both oxygen, then ammonia should be present.

However, all the above reactions may be effected under the same conditions.

The reaction may be effected conveniently in solution. A suitable solvent is water, ethanol, dioxane, dimethyl formamide, dimethyl sulphoxide, pyridine or glacial acetic acid. Suitable reaction temperatures may be from 20 to 160°, preferably from 60 to 120°C.

Insofar as the production of starting materials is not particularly described these compounds are known or may be produced in analogous manner to known compounds.

In the following Examples the temperatures are given in degrees Centigrade and are uncorrected. The title compound of Example 1 forms no part of the present invention. It is present to illustrate the production process of the presently claimed compound.

EXAMPLE 1

4-(2,1,3-Benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydro-3-methoxy-carbonyl-pyridine-5-carboxylic acid isobutyl ester

3 g of 2,1,3-benzoxadiazole-4-aldehyde, 3.2 g of aceto-acetic acid isobutyl ester, 2.3 g β-aminocrotonic acid methyl ester and 10 ml of ethanol are stirred under reflux for 3 hours. The mixture is subsequently evaporated and the residue is chromatographed on silica gel with chloroform/acetic acid ethyl ester (8:1) to yield the title compound. The product is recrystallised from diisopropyl ether and methylcyclohexane, m.pt. 148-158°.

By using the process described in Example 1, and corresponding starting compounds, e.g. a compound of formula II, wherein $-HC=Y$ is a radical ii), wherein Z is oxygen and a compound of formula VI, 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydro-3-methoxy carbonyl-pyridine-5-carboxylic acid isopropyl ester, may be obtained. m.pt. 131-153°C.

The compound of formula I exhibits pharmacological activity. In particular, the compound leads to a dilation of coronary vessels as demonstrated by the results of tests measuring the blood flow to the myocardium of an anaesthetised cat by means of the microsphere method (Rudolph A.M. and Heymann M.S.: Circulation Research 21, 163, 1967) upon administration of from 30 to 50 µg/kg i.v. or of from 50 to 150 µg/kg i.d. of the compound.

The compound of formula I also possesses a favourable effect against angina pectoris, as shown by the increase of the coronary flow of an anaesthetised cat upon administration of the compound.

The compound of formula I is therefore indicated for use in the treatment of coronary insufficiency.

The compound of formula I increases the blood flow to limbs, e.g. leg musculature, as can be shown by means of the microsphere method on the anaesthetised cat upon administration of from 30 to 50 µg/kg i.v. or from 50 to 150 µg/kg i.d. of the compound.

The compound of formula I is therefore indicated for use in the treatment of intermittent claudication and other periopheral disturbances of blood flow to limb muscle.

The compound of formula I increases cerebral blood flow, as can be shown by means of the microsphere method on the anaesthetised cat upon administration of from 30 to 50 µg/kg i.v. of from 50 to 150 µg/kg i.d. of the compound.

The compound of formula I is therefore indicated for use in the treatment of cerebrovascular insults.

The compound of formula I posseses calcium-antagonistic activity as indicated in standard tests, for example by an inhibition of a calcium induced contraction of isolated dog coronary arteries suspended in a depolarizing solution at concentration of 10^{-10} to 10^{-8} M of the compound according to the principles of Godfraind and Kaba, Brit. J. Pharm. *36*, 549-560, 1969.

The compound of formula I is therefore indicated for use as a spasmolytic agent for the treatment of spasms of muscles. For the above indications an indicated daily dose is from 5 to 100 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 1.25 mg to 50 mg, or in sustained release form.

Additionally, the compound of formula I exhibits antihypertensive activity, as indicated in standard tests, e.g. in the Grollman rat test [see A. Grollman, Proc. Soc. Expt. Biol. and Med. *57*, 104 (1944)] on s.c. administration of from 0.1 to 10 mg/kg animal body weight of the compound.

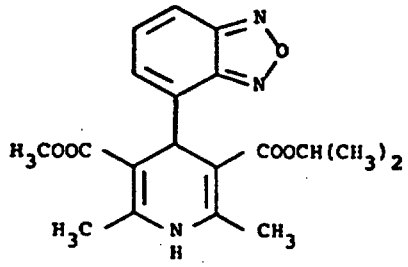
The compound of formula I is therefore further indicated for use as an antihypertensive agent. For this use an indicated daily dose is from 5 to 1000 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing 1.25 mg to 500 mg, or in sustained release form.

The compound of formula I may be administered in the form of a pharmaceutical composition. The present invention accordingly provides a pharmaceutical composition comprising the compound of formula I in association with a pharmaceutical carrier or diluent. Such compositions may be formulated by conventional techniques to be in conventional forms, for example capsules or tablets.

The coronary insufficiency, the intermittent claudication, the cerebrovascular insufficiency and the spasmolytic activities are preferred indications for the compound of formula I.

CLAIMS

1. A compound of formula I



I

which is 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydro-3-methoxy-carbonyl-pyridine-5-carboxylic acid isopropyl ester.

2. A pharmaceutical composition comprising the compound of claim 1 in association with a pharmaceutical carrier or diluent.
3. A compound of claim 1 for use as a pharmaceutical.
4. A compound of claim 1 for use in the treatment of coronary insufficiency.
5. A compound of claim 1 for use in the treatment of intermittent claudication.
6. A compound of claim 1 for use in the treatment of cerebral insults.
7. A compound of claim 1 for use in the treatment of hypertension.
8. A compound of claim 1 for use in the treatment of muscle spasms.

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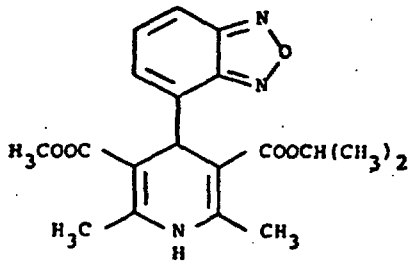
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