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ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ **CY1321**
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ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ
ΓΡΑΦΕΙΟΥ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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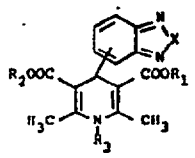
(54) **1,4-dihydropyridines, their preparation and pharmaceutical compositions containing them**

(57) Compounds of formula I,



I

where X is oxygen or sulphur; R_1 and R_2 are various esterifying radicals; and R_3 is H or C_{1-3} alkyl. The compounds are useful for treating coronary insufficiency, intermittent claudication, cerebrovascular insults, spasms in muscles and hypertension.

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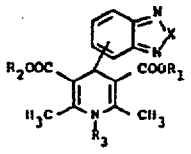
SPECIFICATION

1,4-Dihydropyridines, their preparation and pharmaceutical compositions containing them

The present invention relates to 1,4-dihydropyridine derivatives.

The present invention provides compounds of formula I,



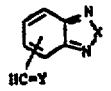
I

wherein R_1, R_2, R_3 and X are as defined as follows, and y indicates the ring position of the dihydropyridine moiety:-

Compound	R_1	R_2	R_3	y	X
1	CH_3	$CH_2CH(CH_3)_2$	H	4	O
2	CH_3	CH_3	H	4	O
3	C_2H_5	C_2H_5	H	5	O
4	$CH_2CH(CH_3)_2$	C_2H_5	H	4	S
5	$CH_2CH(CH_3)_2$	C_2H_5	H	4	O
6	$C(CH_3)_3$	$C(CH_3)_3$	H	4	O
7	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	H	4	O
8	$(CH_2)_2OC_2H_5$	C_2H_5	H	4	O
9	$(CH_2)_2OC_2H_5$	C_2H_5	H	4	S
10	$(CH_2)_2OC_2H_5$	C_2H_5	H	5	S
11	$CH(CH_3)_2$	CH_3	H	4	O
12	$(CH_2)_2OCH_3$	CH_3	H	4	O
13	$(CH_2)_2OCH(CH_3)_2$	CH_3	H	4	O
14	$(CH_2)_2OC_2H_5$	CH_3	H	4	O
15		CH_3	H	4	O
16	$(CH_2)_2OCH_3$	$CH(CH_3)_2$	H	4	O
17	CH_3	C_2H_5	H	4	O
18	C_2H_5	C_2H_5	CH_3	4	O
19	C_2H_5	C_2H_5	$n\text{-}C_3H_7$	4	O

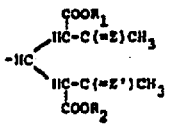
The compounds of formula I fall under the scope of European Patent Application No. 78100165.6, but are not specifically disclosed therein. It has now been found that the compounds of formula I have particularly valuable pharmacological properties, e.g. their coronary activity is particularly long lasting and potent. Their calcium antagonistic activity is particularly potent. They also possess a good tolerability.

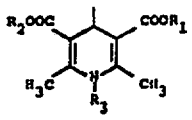
The present invention also provides a process for the production of a compound of formula I as defined above, comprising replacing the moiety -HC=Y in a compound of formula II,



II

wherein X is as defined above and -HC=Y is i) formyl, ii) a radical of formula

or iii) a radial of formula  wherein Z and Z' are independently oxygen or NR_3, and R_1, R_2 and R_3 are as defined above, by a moiety of formula III,



III

wherein R_1, R_2 and R_3 are as defined above.

The process may be effected in conventional manner for analogous dihydropyridine syntheses, e.g. according to Hantzsch. When the moiety -HC=Y is formyl and when it is desired to produce a compound of formula I, wherein R_1 is identical to R_2, it is convenient to react a compound of formula II with a compound of formula IV,

$$CH_3\text{-}CO\text{-}CH_2\text{-}COOR_2 \qquad \text{IV}$$

wherein R_2 is as defined above, in the presence of a compound of formula V,

$$H_2NR_3 \qquad \text{V}$$

wherein R_3 is as defined above.

Preferably at least 2 moles of a compound of formula IV per mole of a compound of formula II are present.

Alternatively a compound of formula II may be reacted with a compound of formula VI,

$$CH_3\text{-}C(NHR_3)=CH\text{-}COOR_2 \qquad \text{VI}$$

wherein R_2 and R_3 are as defined above.

Preferably at least 2 moles of a compound of formula VI per mole of a compound of formula II are present.

When the moiety -HC=Y is formyl and preferably when it is desired to produce a compound of formula I wherein R_1 is different to R_2, it is also possible to react such a compound of formula II with a compound of formula IV and a compound of formula VII,

$$CH_3\text{-}C(NHR_3)=CH\text{-}COOR_1 \qquad \text{VII}$$

wherein R_1 and R_3 are as defined above.

It will be appreciated that a compound of formula VI may be formed as an intermediate during the reaction of a compound of formula IV and a compound of formula V. A compound of formula II, wherein -HC=Y is a radical ii) or iii), may be formed as an intermediate in the above reactions. They may however be produced by different processes.

Alternatively or particularly for the production of a compound of formula I, wherein R_1 is different to R_2, it is convenient to react a compound of formula II, wherein the moiety -HC=Y is a radical ii) with a compound of formula IV or VI, and where appropriate, with a compound of formula V. 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 when R_1 and R_2 are not identical that more than one isomer of formula I 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 an amine of formula V 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° C, 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 given are in degrees Centigrade and are uncorrected.

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 acetoacetic 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.p. 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 i) and compounds of formula IV and V, and for Examples 4, 5 and 8-17 a compound of formula II, wherein -HC=Y is a radical ii), wherein Z is oxygen and a compound of formula VI, the following compounds of formula I may be obtained, wherein y indicates the position of the dihydropyridine moiety:

Comp.	R_1	R_2	R_3	y	X	m.p.
2	CH_3	CH_3	H	4	O	215-221
3	C_2H_5	C_2H_5	H	5	O	173-174
4	$CH_2CH(CH_3)_2$	C_2H_5	H	4	S	85-95
5	$CH_2CH(CH_3)_2$	C_2H_5	H	4	O	145-146.5
6	$C(CH_3)_3$	$C(CH_3)_3$	H	4	O	207-210
7	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	H	4	O	135.5-137
8	$(CH_2)_2OC_2H_5$	C_2H_5	H	4	O	126-128
9	$(CH_2)_2OC_2H_5$	C_2H_5	H	4	S	Oel
10	$(CH_2)_2OC_2H_5$	C_2H_5	H	5	S	72-78
11	$CH(CH_3)_2$	CH_3	H	4	O	131-153
12	$(CH_2)_2OCH_3$	CH_3	H	4	O	151-153
13	$(CH_2)_2OCH(CH_3)_2$	CH_3	H	4	O	114-120
14	$(CH_2)_2OC_2H_5$	CH_3	H	4	O	140-147
15		CH_3	H	4	O	156-163
16	$(CH_2)_2OCH_3$	$CH(CH_3)_2$	H	4	O	119
17	CH_3	C_2H_5	H	4	O	159
18	C_2H_5	C_2H_5	CH_3	4	O	106
19	C_2H_5	C_2H_5	$n\text{-}C_3H_7$	4	O	99

The compounds of formula I exhibit pharmacological activity. In particular, they lead to a dilation of the 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 active substance.

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

The compounds of formula I are therefore indicated for use in the treatment of coronary insufficiency.

The compounds of formula I increase 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 compounds.

The compounds of formula I are therefore indicated for use in the treatment of intermittent claudication and other peripheral disturbances of blood flow to limb muscles.

The compounds of formula I increase 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. or from 50 to 150 µg/kg i.d. of the compounds.

The compounds of formula I are therefore indicated for use in the treatment of cerebrovascular insults.

The compounds of formula I possess 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 compounds according to the principles of Godfraind and Kaba, Brit, J. Pharm. *36*, 549-560, 1969.

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

Additionally, the compounds of formula I exhibit 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 compounds.

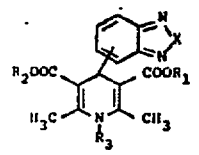
The compounds of formula I are therefore further indicated for use as antihypertensive agents. For this use an indicated daily dose is from about 5 to about 1000 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing about 1.25 mg to about 500 mg, or in sustained release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

The compounds of formula I may be administered in the form of a pharmaceutical composition. The present invention accordingly provides pharmaceutical composition comprising a 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.

Compounds 1, 5, 11, 12, 13, 14, 15, 16, 17, 18 and 19 are particularly interesting. Compounds 1 and 11 are especially interesting. The coronary insuffiency, the intermittent claudication, the cerebrovascular insufficiency and the spasmolytic activities are the preferred utilities for compounds of formula I.

CLAIMS

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

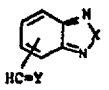


I

wherein R_1, R_2, R_3 and X are as defined as follows, and y indicates the ring position of the dihydropyridine moiety:-

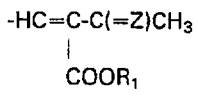
Compound	R_1	R_2	R_3	y	X
1	CH_3	$CH_2CH(CH_3)_2$	H	4	O
2	CH_3	CH_3	H	4	O
3	C_2H_5	C_2H_5	H	5	O
4	$CH_2CH(CH_3)_2$	C_2H_5	H	4	S
5	$CH_2CH(CH_3)_2$	C_2H_5	H	4	O
6	$C(CH_3)_3$	$C(CH_3)_3$	H	4	O
7	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	H	4	O
8	$(CH_2)_2OC_2H_5$	C_2H_5	H	4	O
9	$(CH_2)_2OC_2H_5$	C_2H_5	H	4	S
10	$(CH_2)_2OC_2H_5$	C_2H_5	H	5	S
11	$CH(CH_3)_2$	CH_3	H	4	O
12	$(CH_2)_2OCH_3$	CH_3	H	4	O
13	$(CH_2)_2OCH(CH_3)_2$	CH_3	H	4	O
14	$(CH_2)_2OC_2H_5$	CH_3	H	4	O
15		CH_3	H	4	O
16	$(CH_2)_2OCH_3$	$CH(CH_3)_2$	H	4	O
17	CH_3	C_2H_5	H	4	O
18	C_2H_5	C_2H_5	CH_3	4	O
19	C_2H_5	C_2H_5	$n\text{-}C_3H_7$	4	O

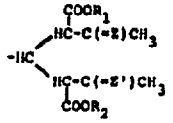
which comprises replacing the moiety -HC=Y in a compound of formula II,



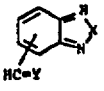
II

wherein X is as defined above and -HC=Y is i) formyl, ii) a radical of formula



or iii) a radical of formula 

wherein Z and Z' are independently oxygen or NR_3, and R_1, R_2 and R_3 are as defined above, by a moiety of formula III,



II

wherein R_1, R_2 and R_3 are as defined above.

2. A process for the production of a compound of formula I, as stated in claim 1 substantially as hereinbefore described with reference to any of the Examples.

3. A compound of formula I, whenever produced by a process according to claim 1 or 2.

4. Compound 1, stated in claim 1.

5. Compound 2, stated in claim 1.

6. Compound 3, stated in claim 1.

7. Compound 4, stated in claim 1.

8. Compound 5, stated in claim 1.

9. Compound 6, stated in claim 1.

10. Compound 7, stated in claim 1.

11. Compound 8, stated in claim 1.

12. Compound 9, stated in claim 1.

13. Compound 10, stated in claim 1.

14. Compound 11, stated in claim 1.

15. Compound 12, stated in claim 1.

16. Compound 13, stated in claim 1.

17. Compound 14, stated in claim 1.

18. Compound 15, stated in claim 1.

19. Compound 16, stated in claim 1.

20. Compound 17, stated in claim 1.

21. Compound 18, stated in claim 1.

22. Compound 19, stated in claim 1.

23. A pharmaceutical composition comprising a compound of any one of claims 3 to 22 in association with a pharmaceutical carrier or diluent.

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