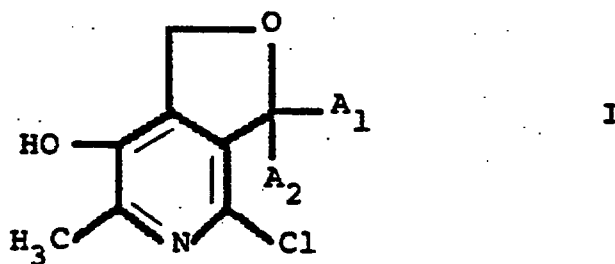


4-Chloro-Furo-(3,4-c)-pyridine DerivativesDESCRIPTION

The invention relates to new 4-chloro substituted furo-(3,4-c)-pyridine derivatives, to a process for their preparation and to pharmaceutical compositions containing them.

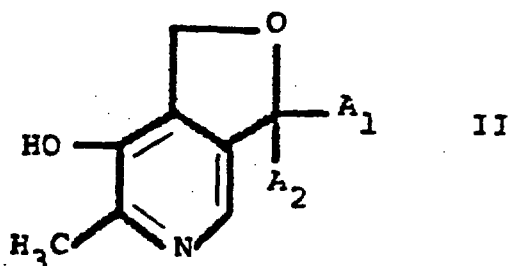
The invention provides 1,3-dihydro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine derivatives of the general formula I



wherein each of A_1 and A_2 independently represents a hydrogen atom, a straight chain saturated or unsaturated hydrocarbon group having from 1 to 5 carbon atoms, a heterocyclic group having up to 6 ring atoms, a carbomonocyclic group, a phenylalkyl group or a phenylalkenyl group, each of the groups represented by A_1 and A_2 being unsubstituted or being substituted by one or more chlorine or fluorine atoms, trifluoromethyl groups, alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms, alkylthio groups having from 1 to 5 carbon atoms, dialkylamino groups in which each alkyl group has from 1 to 5 carbon atoms, dialkylaminoalkoxy groups in which each of the two alkyl groups and the alkoxy group has from 1 to 5 carbon atoms or an α - or β -(N-pyrrolidinyl)-alkoxy group in which the alkoxy group has from 1 to 5 carbon atoms.

The compounds according to the invention are of interest for their therapeutical activity, principally in the fields of selective diuresis and lowering of blood pressure. The diuresis induced by these compounds leads to a high elimination rate of Na^+ and a low elimination rate of K^+ .

The invention further provides a process for the preparation of 1,3-dihydro-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine derivatives of the general formula I as above defined, the process comprising treating a compound of the general formula II



wherein A_1 and A_2 have the meanings ascribed to them above, with at least a molar equivalent of N-chlorosuccinimide, to obtain the corresponding 4-chloroderivative of the general formula I; the reaction is performed between 0° and 15°C in a non polar solvent such as dichloromethane or tetrahydrofuran.

The invention further provides a pharmaceutical composition comprising a 1,3-dihydro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine derivative having the general formula I as herein defined in admixture with a

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pharmaceutically acceptable diluent or carrier.

The starting compounds II may be prepared as described in our Patent Applications Nos 2092586 and 2137618. The invention is illustrated by the following

5 Examples.

Example 11,3-dihydro-3,6-dimethyl-4-chloro-7-hydroxy-furo-(3,4-c)-pyridine

5 The starting material being the hydrochloride of 1,3-dihydro-3,6-dimethyl-7-hydroxy-furo-(3,4-c)-pyridine, it was first necessary to eliminate the hydrochloric acid before performing the reaction.

10 Into a two litre reactor fitted with warming, cooling and stirring means, there were poured 22.15 g (0.11 mol) of the starting material and 500 ml of water. After stirring, there was added a sufficient amount of a 10 % aqueous solution of sodium bicarbonate to reach pH 7 ; a white precipitate appeared, and was separated, washed and dried (16.5 g or 0.1 mol).

15 16.5 g of the base were then treated in a similar reactor with 200 ml of dichloromethane, under stirring, leading to a suspension. This was cooled to 5°C ; there was then slowly added 14.7 g (0.11 mol) of N-chlorosuccinimide and the mixture was stirred for two hours. A white precipitate formed, and was
20 separated, washed, dried and recrystallized from ethanol at 40°C. Yield 16.8 g (84 %) of a white crystalline product, elemental analysis of which showed good correspondence with the formula $C_9H_{10}ClNO_2$. Melting point 248°C.

Example 2

25 1,3-dihydro-3-propyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3-propyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 79 % of a product, elemental
30 analysis of which showed good correspondence with the formula $C_{11}H_{14}ClNO_2$. Melting point 242°C.

Example 3

1,3-dihydro-3-phenyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

5 This compound has been prepared by the method described in Example 1 from 1,3-dihydro-3-phenyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 69 % of a crystalline product, elemental analysis of which showed good correspondence with the formula $C_{14}H_{12}ClNO_2$. Melting point 230°C.

Example 4

10 1,3-dihydro-3-p.chlorophenyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3-p.chlorophenyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 76 % of a crystalline
15 product, elemental analysis of which showed good correspondence with the formula $C_{14}H_{11}Cl_2NO_2$. Melting point 218°C.

Example 5

1,3-dihydro-3-p.methoxyphenyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

20 This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3-p.methoxyphenyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 73 % of a crystalline product, elemental analysis of which showed good correspondence with the formula $C_{15}H_{14}ClNO_3$. Melting point 204°C.

25 Example 6

1,3-dihydro-3-p.methylthiophenyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3-p.thiomethylphenyl-6-methyl-
30 7-hydroxy-furo-(3,4-c)-pyridine. Yield 72 % of a crystalline

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product, elemental analysis of which showed good correspondence with the formula $C_{15}H_{14}ClNO_2S$. Melting point $193^{\circ}C$.

Example 7

5 1,3-dihydro-3-p.trifluoromethylphenyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3-p.trifluoromethylphenyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 81 % of a crystalline product, elemental analysis of which showed good
10 correspondence with the formula $C_{15}H_{11}ClF_3NO_2$. Melting point $221^{\circ}C$.

Example 8

1,3-dihydro-3- α -furyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

15 This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3- α -furyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 71 % of a white crystalline product, elemental analysis of which showed good correspondence with the formula $C_{12}H_{10}ClNO_3$. Melting point $187^{\circ}C$.

20 Example 9

1,3-dihydro-3- α -thienyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3- α -thienyl-6-methyl-7-hydroxy-
25 furo-(3,4-c)-pyridine. Yield 70 % of a white crystalline product, elemental analysis of which showed good correspondence with the formula $C_{12}H_{10}ClNO_2S$. Melting point $168^{\circ}C$.

Example 10

30 1,3-dihydro-3-phenylethyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

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This compound has been prepared by the method described in Example 1 from 1,3-dihydro-3-phenylethyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 79 % of a yellowish crystalline product, elemental analysis of which showed good correspondence with the formula $C_{16}H_{16}ClNO_2$. Melting point 193°C.

Example 11

1,3-dihydro-3,3,6-trimethyl-4-chloro-7-hydroxy-furo-(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3,3,6-trimethyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 89 % of a white crystalline product, elemental analysis of which showed good correspondence with the formula $C_{10}H_{12}ClNO_2$. Melting point 251°C.

Example 12

1,3-dihydro-3-phenyl-3,6-dimethyl-4-chloro-7-hydroxy-furo-(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3-phenyl-3,6-dimethyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 84 % of a white crystalline product, elemental analysis of which showed good correspondence with the formula $C_{15}H_{14}ClNO_2$. Melting point 246°C.

Example 13

1,3-dihydro-3-p.chlorophenyl-3,6-dimethyl-4-chloro-7-hydroxy-furo-(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3-p.chlorophenyl-3,6-dimethyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 87 % of a white crystalline product, elemental analysis of which showed good correspondence with the formula $C_{15}H_{13}Cl_2NO_2$. Melting point 233°C.

Example 14

1,3-dihydro-3- α -thienyl-3,6-dimethyl-4-chloro-7-hydroxy-furo-
(3,4-c)-pyridine

5 This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3- α -thienyl-3,6-dimethyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 68 % of a white crystalline product, elemental analysis of which showed good correspondence with the formula $C_{13}H_{12}ClNO_2S$. Melting point 209°C.

10 Example 15

1,3-dihydro-3-n-pentyl-3-p-tolyl-4-chloro-6-methyl-7-hydroxy-
furo-(3,4-c)-pyridine

15 This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3-n-pentyl-3-p-tolyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 66 % of a product, elemental analysis of which showed good correspondence with the formula $C_{20}H_{24}ClNO_2$. Melting point 180°C.

Example 16

20 1,3-dihydro-3,3-diphenyl-4-chloro-6-methyl-7-hydroxy-furo-
(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3,3-diphenyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 88 % of a white crystalline product, elemental analysis of which showed good correspondence
25 with the formula $C_{20}H_{16}ClNO_2$. Melting point 240°C.

Example 17

1,3-dihydro-3-(2,3-dichlorophenyl)-3-phenyl-4-chloro-6-methyl-
7-hydroxy-furo-(3,4-c)pyridine

This compound has been prepared by the method described

in Example 1, from 1,3-dihydro-3-(2,3-dichlorophenyl)-3-phenyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 81 % of a white crystalline product, elemental analysis of which showed good correspondence with the formula $C_{20}H_{14}Cl_3NO_2$. Melting point 221°C.

Example 18

1,3-dihydro-3-p.trifluoromethylphenyl-3-phenyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3-p.trifluoromethylphenyl-3-phenyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 84 % of a white crystalline product, elemental analysis of which showed good correspondence with the formula $C_{21}H_{15}ClF_3NO_2$. Melting point 259°C.

Example 19

1,3-dihydro-3-p-pyrrolidinylethoxyphenyl-3-p-chlorophenyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1, from 1,3-dihydro-3-pyrrolidinylethoxyphenyl-3-p-chlorophenyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 78 % of a white crystalline product, elemental analysis of which showed good correspondence with the formula $C_{26}H_{26}Cl_2NO_3$. Melting point 200°C.

Example 20

1,3-dihydro-3-(3,4,5-trimethoxyphenyl-ethyl)-3- α -furyl-4-chloro-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine

This compound has been prepared by the method described in Example 1 from 1,3-dihydro-3-(3,4,5-trimethoxyphenyl-ethyl)-3- α -furyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 58 % of a yellowish crystalline product, elemental analysis of which showed good correspondence with the formula $C_{23}H_{25}ClNO_6$. Melting point 197°C.

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TOXICITY

Toxicity has been researched on rats and mice, per oral route; no LD₅₀ could be determined on rats, whereas for mice it was not lower than 4 g/kg.

5 PHARMACOLOGY

The interest of the compounds of the invention has been evidenced by various pharmacologic tests.

1. Study of the urinary elimination in the rat.

10 This study was conducted on Wistar male rats weighing 270-280 g.

Ten batches each of twelve animals were used; eight batches were treated with compounds according to the invention and one batch was treated with tienilic acid as reference compound, all animals of these nine
15 batches receiving the same dose of 10 mg/kg/day; the tenth batch was a control.

The animals were treated for three days and placed in a metabolic cage fitted for the collection of urine; neither food nor drink was given during the treatment
20 in order to avoid any contamination. The collected volumes of urine were measured after six hours and twenty four hours. After six hours, each animal received 25 ml/kg of physiologic serum. On the fourth day, the animal received the last treatment. For all batches
25 Na⁺ and K⁺ were measured and the ratio Na⁺/K⁺ calculated. The results are reported in the following Table.

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T A B L E

ADMINISTRATION PER OS OF 10 mg/kg/day	VOLUMES (ml)			Na/K RATIO
	0 - 6 h	6 - 24 h	0 - 24 h	
Control	6.6	11.3	17.9	1.24
Tienilic acid	8.4	10.8	19.2	1.51
EX. 2	9.0	11.3	20.3	2.24
EX. 3	9.9	10.8	20.7	2.53
EX. 4	10.8	10.8	21.6	2.80
EX. 7	10.1	11.6	21.7	2.37
EX. 12	9.9	11.4	21.3	2.87
EX. 15	10.9	11.8	22.7	2.46
EX. 17	9.6	12.0	21.6	2.55
EX. 18	10.0	12.4	22.4	2.39

2. Action on blood pressure.

5 This study was conducted on rats suffering from high blood pressure induced by the method of GOLDBLATT in comparison with Indapamine. This method is not described here, for it is well known. The study showed, at the same therapeutic doses, that the compounds of the invention have a similar action on the lowering of blood pressure on the rats.

10 The major interest of the compounds of the invention lies in the high Na^+/K^+ ratio which is a very favourable factor. It is well known that a low elimination rate of K^+ is benefic to the patient in most cases.

PRESENTATION - POSOLOGY

15 Although any oral form is suitable, tablets and gelatine capsules each containing from 25 to 100 mg of active ingredient are preferred. Usual posology in human therapy is 50 to 250 mg/day.



CLAIMS

1. A 1,3-dihydro-4-chloro-6-methyl-7-hydroxy-
-furo[3,4-c]pyridine derivative having the general
formula I as herein defined.
2. 1,3-Dihydro-3,6-dimethyl-4-chloro-7-hydroxy-
-furo[3,4-c]pyridine.
3. 1,3-Dihydro-3-propyl-4-chloro-6-methyl-7-hydroxy-
-furo[3,4-c]pyridine.
4. 1,3-Dihydro-3-phenyl-4-chloro-6-methyl-7-hydroxy-
-furo[3,4-c]pyridine.
5. 1,3-Dihydro-3-p.chlorophenyl-4-chloro-6-methyl-7-hydroxy-
-furo[3,4-c]pyridine.
6. 1,3-Dihydro-3-p.methoxyphenyl-4-chloro-6-methyl-7-hydroxy-
-furo[3,4-c]pyridine.
7. 1,3-Dihydro-3-p.methylthiophenyl-4-chloro-6-methyl-
-7-hydroxy-furo[3,4-c]pyridine.
8. 1,3-Dihydro-3-p.trifluoromethylphenyl-4-chloro-6-methyl-
-7-hydroxy-furo[3,4-c]pyridine.
9. 1,3-Dihydro-3- κ -furyl-4-chloro-6-methyl-7-hydroxy-
-furo[3,4-c]pyridine.
10. 1,3-Dihydro-3- κ -thienyl-4-chloro-6-methyl-7-hydroxy-
-furo[3,4-c]pyridine.
11. 1,3-Dihydro-3-phenylethyl-4-chloro-6-methyl-7-hydroxy-
-furo[3,4-c]pyridine.
12. 1,3-Dihydro-3,3,6-trimethyl-4-chloro-7-hydroxy-
-furo[3,4-c]pyridine.
13. 1,3-Dihydro-3-phenyl-3,6-dimethyl-4-chloro-7-hydroxy-
-furo[3,4-c]pyridine.
14. 1,3-Dihydro-3-p.chlorophenyl-3,6-dimethyl-4-chloro-



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- 7-hydroxy-furo[3,4-c]pyridine.
15. 1,3-Dihydro-3-~~X~~-thienyl-3,6-dimethyl-4-chloro-7-hydroxy-furo[3,4-c]pyridine.
 16. 1,3-Dihydro-3-n.pentyl-3-p.tolyl-4-chloro-6-methyl-7-hydroxy-furo[3,4-c]pyridine.
 17. 1,3-Dihydro-3,3-diphenyl-4-chloro-6-methyl-7-hydroxy-furo[3,4-c]pyridine.
 18. 1,3-Dihydro-3-(2,3-dichlorophenyl)-3-phenyl-4-chloro-6-methyl-7-hydroxy-furo[3,4-c]pyridine.
 19. 1,3-Dihydro-3-p.trifluoromethylphenyl-3-phenyl-4-chloro-6-methyl-7-hydroxy-furo[3,4-c]pyridine.
 20. 1,3-Dihydro-3-p.pyrrolidinylethoxyphenyl-3-p.chlorophenyl-4-chloro-6-methyl-7-hydroxy-furo[3,4-c]pyridine.
 21. 1,3-Dihydro-3-(3,4,5-trimethoxyphenyl-ethyl)-3-~~X~~-furyl-4-chloro-6-methyl-7-hydroxy-furo[3,4-c]pyridine.
 22. A process for the preparation of a 1,3-dihydro-4-chloro-6-methyl-7-hydroxy-furo[3,4-c]pyridine derivative having the general formula I as herein defined, the process comprising treating a compound having the general formula II as herein defined with at least a molar equivalent of N-chlorosuccinimide at from 0 to 15°C in a non-polar solvent.
 23. A process according to claim 22 in which the non-polar solvent is dichloromethane or tetrahydrofuran.
 24. A pharmaceutical composition comprising a 1,3-dihydro-4-chloro-6-methyl-7-hydroxy-furo[3,4-c]pyridine derivative according to any of claims 1 to 21 in admixture with a pharmaceutically acceptable diluent or carrier.
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