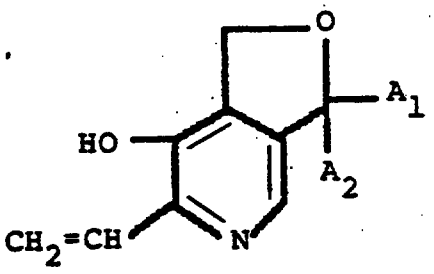
6-Vinyl-Furo-(3,4-c)-Pyridine Derivatives

The invention relates to 6-vinyl-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-vinyl-7-hydroxy--furo-(3,4-c)-pyridine derivatives of the general formula I



I

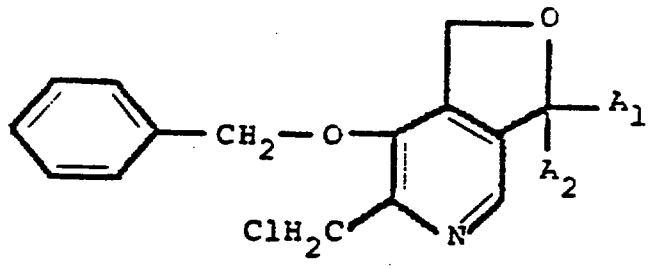
wherein each of A_1 and A_2 independently represents a hydrogen atom, a straight chain saturated or unsaturated hydrocarbon group having from 1 to 5 carbon atoms, a heterocyclic group having up to 6 ring atoms, a carbomonocyclic group, a phenylalkyl group or a phenylalkenyl group, each of the groups 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

B4

1 to 5 carbon atoms, dialkylaminoalkoxy groups in which each of the two alkyl groups and the alkoxy groups has from 1 to 5 carbon atoms or α- or β-(N-pyrrolidinyl)-alkoxy groups in which the alkoxy group has from 1 to 5 carbon atoms; and further provides pharmaceutically acceptable salts of such compounds.

The compounds according to the invention are of interest for their therapeutical activity, principally in the field of selective diuresis: their administration leads to a low K^+ elimination associated with a high Na^+ elimination and a uricosuric action.

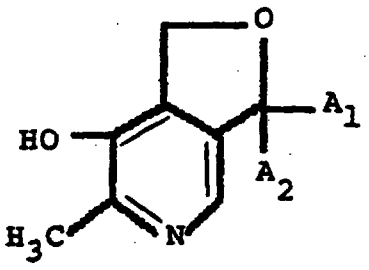
The invention also provides a process for the preparation of the compounds according to the invention, the process comprising reacting one mol of a 6-chloromethyl-7-benzoxy-furo-(3,4-c)-pyridine derivative of the general formula II



II

wherein A_1 and A_2 have the above meanings with one mol of triphenyl phosphine and two mol of formaldehyde at the boil in a polar solvent such as an alkanol which leads to the desired substitution in position 6, followed by an acidic treatment to cleave the benzyl group.

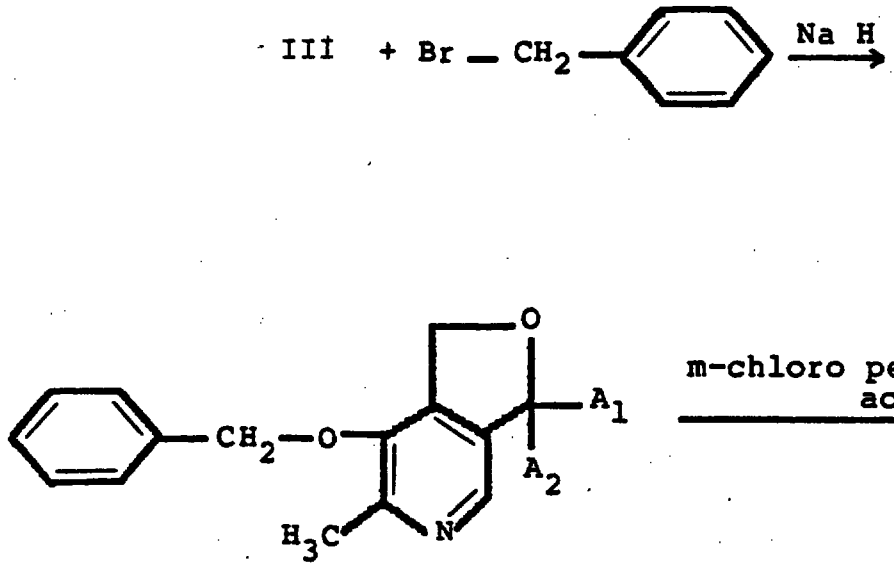
The 6-chloromethyl-7-benzoxy derivatives II may be obtained from corresponding 6-methyl-7-hydroxy derivatives of the general formula III



III

wherein A_1 and A_2 have the above meanings by the following sequence of reactions:

(36)


III + Br — CH2
Na H
m-chloro peroxybenzoic acid
(CF3 CO)2 O
SOCl2
II
CH2—O
A1
A2
H3C
N
O
HO - CH2

The compounds II are disclosed in our British Patent No. 2092586 and in our British Patent Application No. 2137618.

The preparation of one only of the starting compounds, 1,3-dihydro-3-p-chlorophenyl-6-chloromethyl-7-benzoxy--furo-(3,4-c)-pyridine, is now described in detail, other starting materials being obtained by the same way.

a) Into a one litre reactor fitted with stirring, warming and cooling means were poured 400 ml of dimethylformamide, 12.5 g of 50% sodium hydride and slowly, under stirring, 38 g of 1,3-dihydro-3-p-chlorophenyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine. After stirring for 90 minutes at room temperature there were added 16 ml of benzyl bromide and the resultant suspension was stirred overnight. After evaporation to dryness, the pasty product obtained was stirred with one litre of methylene dichloride, washed with water until complete elimination of chlorine and bromine and dried on anhydrous sodium sulphate. The methylene dichloride was evaporated off and the residue was dissolved in isopropanol at the boil, treated with carbon black and warm filtered, and then recrystallized. It was washed with petroleum ether and dried. Yield 33 g (74%) of 1,3-dihydro-3-p-chlorophenyl-6-methyl--7-benzoxy-furo-(3,4-c)-pyridine.

(38)

b) In the same reactor as above, 30 g of the product of the previous step were treated at 0°C, in the presence of 300 ml of methylene dichloride, with 18.2 g of m-chloroperoxybenzoic acid, slowly added. After stirring overnight at room temperature, there were added 150 ml of 10% sodium sulphite solution. After stirring and decantation, the product was washed with the same amount of sodium sulphite solution, twice with 150 ml of sodium bicarbonate solution and three times with 100 ml of water, and then dried over anhydrous sodium sulphate. On evaporation to dryness, there was obtained a beige precipitate which was washed with petroleum ether, filtered and dried. Yield 28 g (90%) of 1,3-dihydro-3-p-chlorophenyl-6-methyl-7-benzoxy-furo-(3,4-c)-pyridine-N-oxide.

c) In the same reactor as above, 28 g of the compound obtained in the previous step were treated at 0-5°C, in the presence of 175 ml of methylene dichloride, with 4.3 ml of trifluoroacetic anhydride added dropwise under stirring. The mixture was stirred overnight at room temperature, and then cooled and treated dropwise with 95 ml of methanol. After evaporation to dryness, the residue was taken up in 300 ml of chloroform, washed twice with 75 ml of 10% sodium bicarbonate solution and three times with 100 ml of water and dried on anhydrous sodium sulphate. The chloroform was

evaporated off and the residue was washed with diethyl ether and dried under reduced pressure. Yield 25 g (89%) of 1,3-dihydro-3-p-chlorophenyl-6-hydroxy-methyl--7-benzoxy-furo-(3,4-c)-pyridine.

d) In a two litre reactor fitted as above and under nitrogen circulation, 25 g of the previously obtained compound were stirred with 400 ml of dry benzene; there were slowly added 6.3 ml of thionyl chloride under stirring at room temperature. The resultant mixture was warmed at 70°C for one hour, leading to a yellow precipitate. This was separated off, washed with benzene and then with diethyl ether, and dissolved in 400 ml of methylene dichloride. The solution was washed with 10% sodium bicarbonate solution until pH 8, washed with water, treated with carbon black, filtered, and concentrated up to crystallization. The product was separated off, washed with diethyl ether and dried, giving 25 g (yield 92%) of 1,3-dihydro-3-p--chlorophenyl-6-chloromethyl-7-benzoxy-furo-(3,4-c)-pyridine.

The invention further provides a pharmaceutical composition comprising a 1,3-dihydro-6-vinyl-7-hydroxy--furo-(3,4-c)-pyridine derivative of the general formula I as above defined or a pharmaceutically acceptable salt thereof in admixture with a

pharmaceutically acceptable diluent or carrier.

The invention is illustrated by the following Examples.

Example 1

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

Using the same apparatus as above, 14.5 g (0.05 mol of 1,3-dihydro-3-methyl-6-chloromethyl-7-benzoxy-furo-(3,4-c)-pyridine dissolved in 300 ml of absolute ethanol were refluxed with 13.1 g (0.05 mol) of triphenyl phosphine for two hours. There were then added 3 g (0.1 mol) of trioxymethylene and, dropwise, a solution of 2.3 g of sodium in 100 ml of methanol. At the end of the addition, the mixture was refluxed for two hours, and then treated with 3 ml of acetic acid and evaporated to dryness. The dry residue was dissolved in benzene and passed through a silica gel column (eluent : benzene). The fractions containing the 1,3-dihydro-3-methyl-6-vinyl-7-benzoxy-furo-(3,4-c)--pyridine were gathered, evaporated to dryness and treated with isopentane. Yield 7.35 g (55%).

This product was then treated with 70 ml of hydrochloric acid (d 1.18) and 50 ml of ethanol under stirring at 70°C for 3 hours.

After cooling, separation and washing (ethanol, then water) there were obtained 5.1 g (87%) of 1,3-dihydro--3-methyl-6-vinyl-7-hydroxy-furo-(3,4-c)-pyridine melting at 237°C-238°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{10}H_{11}NO_2$.HCl. The overall yield of this sequence of reactions was 48%.

Example 2

1,3-dihydro-3-propyl-6-vinyl-7-hydroxy-furo-(3,4-c)--pyridine

The method of Example 1 was repeated, but starting with 0.1 mol of 1,3-dihydro-3-propyl-6-chloromethyl-7--benzoxy-furo-(3,4-c)-pyridine. Yield 11g (46%) of a product melting at 230-232°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{12}H_{15}NO_2$.HCl.

Example 3

1,3-dihydro-3-cyclohexyl-6-vinyl-7-hydroxy-furo-(3,4-c)--pyridine.

The method of Example 1 was repeated, but starting with 0.1 mol of 1,3-dihydro-3-cyclohexyl-6-chloromethyl-7--benzoxy-furo-(3,4-c)-pyridine. Yield 14.5 g (52%) of a product melting at 207°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{15}H_{19}NO_2$.HCl.

(42)

Example 4

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

The method of Example 1 was repeated, but starting with 0.1 mol of 1,3-dihydro-3-phenyl-6-chloromethyl-7-benzoxy--furo-(3,4-c)-pyridine. Yield 12.25 g (45%) of a product melting at 241-243°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{15}H_{13}NO_2.HCl$.

Example 5

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

The method of Example 1 was repeated, but starting with 0.1 mol of 1,3-dihydro-3-p-chlorophenyl-6-chloromethyl--7-benzoxy-furo-(3,4-c)-pyridine. Yield 16.6 g (54%) of a product melting at 218-221°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{15}H_{12}NO_2Cl.HCl$.

Example 6

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

The method of Example 1 was repeated, but starting with 0.1 mol of 1,3-dihydro-3-α-furyl-6-chloromethyl-7--benzoxy-furo-(3,4-c)-pyridine. Yield 12.15 g (47%) of a product melting at 210°C (Tottoli), elemental analysis

of which showed good correspondence with the formula $C_{13}H_{11}NO_3.HCl$.

Example 7

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

The method of Example 1 was repeated, but starting with 0.1 mol of 1,3-dihydro-3-p-methoxyphenyl-6-chloromethyl--7-benzoxy-furo-(3,4-c)-pyridine. Yield 13 g (43%) of a product melting at 189-191°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{16}H_{15}NO_3.HCl$.

Example 8

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

The method of Example 1 was repeated, but starting with 1,3-dihydro-3,3-dimethyl-6-chloromethyl-7-benzoxy-furo--(3,4-c)-pyridine. Yield 11.8 g (52%) of a product melting at 246-248°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{11}H_{13}NO_2.HCl$

Example 9

1,3-dihydro-3-methyl-3-n-pentyl-6-vinyl-7-hydroxy-furo-(3,4-c)-pyridine.

The method of Example 1 was repeated, but starting with 1,3-dihydro-3-methyl-3-n-pentyl-6-chloromethyl-7-benzoxy-

-furo-(3,4-c)-pyridine. Yield 14.40 g (51%) of a product melting at 245°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{15}H_{21}NO_2.HCl$.

Example 10

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

The method of Example 1 was repeated, but starting with 1,3-dihydro-3-methyl-3-p-chlorophenyl-6-chloromethyl-7--benzoxy-furo-(3,4-c)-pyridine. Yield 15.1 g (47%) of a product melting at 212°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{17}H_{14}NO_2Cl.HCl$.

Example 11

1,3-dihydro-3-methyl-3-p-fluorophenyl-6-vinyl-7-hydroxy--furo-(3,4-c)-pyridine

The method of Example 1 was repeated,but starting with 1,3-dihydro-3-methyl-3-p-fluorophenyl-6-chloromethyl-7--benzoxy-furo-(3,4-c)-pyridine. Yield 16.2 g (53%) of a product melting at 222°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{17}H_{14}NO_2F.HCl$.

Example 12

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

The method of Example 1 was repeated, but starting with 1,3-dihydro-3-ethyl-3-p-chlorophenyl-6-chloromethyl-7--benzoxy-furo-(3,4-c)-pyridine. Yield 14.8 g (44%) of a product melting at 199-201°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{18}H_{16}NO_2Cl.HCl$.

Example 13

1,3-dihydro-3,3-diphenyl-6-vinyl-7-hydroxy-furo-(3,4-c)-pyridine

The method of Example 1 was repeated, but starting with 1,3-dihydro-3,3-diphenyl-6-chloromethyl-7-benzoxy-furo-(3,4-c)-pyridine. Yield 17.15 g (49%) of a product melting at 206-208°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{21}H_{17}NO_2.HCl$.

Example 14

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

The method of Example 1 was repeated, but starting with 1,3-dihydro-3,3-di-α-furyl-6-chloromethyl-7-benzoxy-furo--(3,4-c)-pyridine. Yield 13.7 g (42%) of a product melting at 184-186°C (Tottoli), elemental analysis of

which showed good correspondence with the formula $C_{17}H_{21}NO_4.HCl$.

Example 15

1,3-dihydro-3-cyclohexyl-3-(2,3-dichlorophenyl)-6-vinyl--7-hydroxy-furo-(3,4-c)-pyridine.

The method of Example 1 was repeated, but starting with 1,3-dihydro-3-cyclohexyl-3-(2,3-dichlorophenyl)-6--chloromethyl-7-benzoxy-furo-(3,4-c)-pyridine. Yield 16.15 g (38%) of a product melting at 179-182°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{21}H_{21}NO_2Cl_2.HCl$.

Example 16

1,3-dihydro-3-p-fluorophenyl-6-vinyl-7-hydroxy-furo--(3,4-c)-pyridine

The method of Example 1 was repeated, but starting with 0.1 mol of 1,3-dihydro-3-p-fluorophenyl-6-chloromethyl--7-benzoxy-furo-(3,4-c)-pyridine. Yield 17.2 g (58%) of a product melting at 187°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{15}H_{12}NO_2FHCl$.

TOXICITY

Acute toxicity was determined by the usual routes per os and ip on mice. LD_{50} per os and ip were over 600 mg/kg for all compounds.

PHARMACOLOGY

Diuretic action has been appreciated on rats (male WISTAR) weighing 180-200 g by the following method.

Rats to be treated were submitted to a complete fast for 16 hours and placed in metabolic cages wherein the urine might be collected. The rats received 2.5 ml/kg of physiologic serum per os for controls or the same volume of serum containing, in solution or in suspension, about 10 mg/kg of the tested compounds. Urine was collected after 6 hours and Na^+, K^+ and uric acid dosed. Six compounds were tested (identified by the Example No.). For the experiments, seven batches of each eight rats were used, one for control and the six other for compounds. The results are reported in the following Table wherein the figures are, in each case, the average values of the corresponding batch. Each is accompanied by the percentage of increase with respect to control.

TABLE

	Control	EX 1	EX 5	EX 6	EX 14	EX 15	EX 16
Per os dose mg/kg	-	9.7	10.1	9.9	9.8	10.3	10.0
V ml (6 h)	0.56	1.33 + 137%	1.60 + 185%	1.58 + 172%	1.18 + 111%	1.02 + 82%	1.92 + 243%
Na^+ 10^{-3}mEq (6 h)	93	253.0 + 172%	298.5 + 221%	330.0 + 255%	246.5 + 165%	298.0 + 220%	285.0 + 206%
K^+ 10^{-3}mEq (6 h)	76	83.0 + 8.5%	86.5 + 14%	90.5 + 19%	83.5 + 11%	77.5 + 2%	77.0 + 1.3%
Na^+/K^+	1.24	3.05	3.45	3.65	2.95	3.85	3.70
Uric acid 10^{-3}mM (6 h)	1.77	3.12 + 76%	3.33 + 88%	2.66 + 50%	3.15 + 78%	2.90 + 64%	2.81 +59%

PRESENTATION - POSOLOGY

Preferred oral forms for human use include tablets and gelatine capsules each containing 50 mg of active ingredient in admixture with appropriate excipient and/or carrier. Daily doses in human therapy are from 50 to 200 mg.

CLAIMS:

1. A 1,3-dihydro-6-vinyl-7-hydroxy-furo-(3,4-c)--pyridine derivative of the general formula I as herein defined, or a pharmaceutically acceptable salt of such a compound.

2. 1,3-Dihydro-3-methyl-6-vinyl-7-hydroxy-furo--(3,4-c)-pyridine.

3. 1,3-Dihydro-3-propyl-6-vinyl-7-hydroxy-furo-(3,4-c)-pyridine.

4. 1,3-Dihydro-3-cyclohexyl-6-vinyl-7-hydroxy-furo--(3,4-c)-pyridine.

5. 1,3-Dihydro-3-phenyl-6-vinyl-7-hydroxy-furo-(3,4-c)--pyridine.

6. 1,3-Dihydro-3-p-chlorophenyl-6-vinyl-7-hydroxy--furo-(3,4-c)-pyridine.

7. 1,3-Dihydro-3-α-furyl-6-vinyl-7-hydroxy-furo--(3,4-c)-pyridine.

8. 1,3-dihydro-3-p-methoxyphenyl-6-vinyl-7-hydroxy--furo-(3,4-c)-pyridine.

9. 1,3-Dihydro-3,3-dimethyl-6-vinyl-7-hydroxy-furo-(3,4-c)-pyridine.

10. 1,3-Dihydro-3-methyl-3-n-pentyl-6-vinyl-7-hydroxy--furo-(3,4-c)-pyridine.

11. 1,3-Dihydro-3-methyl-3-p-chlorophenyl-6-vinyl-7--hydroxy-furo-(3,4-c)-pyridine.

12. 1,3-Dihydro-3-methyl-3-p-fluorophenyl-6-vinyl-7-

-hydroxy-furo-(3,4-c)-pyridine.

13. 1,3-Dihydro-3-ethyl-3-p-chlorophenyl-6-vinyl-7--hydroxy-furo-(3,4-c)-pyridine.

14. 1,3-Dihydro-3,3-diphenyl-6-vinyl-7-hydroxy-furo--(3,4-c)-pyridine.

15. 1,3-Dihydro-3,3-di-α-furyl-6-vinyl-7-hydroxy-furo--(3,4-c)-pyridine.

16. 1,3-Dihydro-3-cyclohexyl-3-(2,3-dichlorophenyl)--6-vinyl-7-hydroxy-furo-(3,4-c)-pyridine.

17. 1,3-Dihydro-3-p-fluorophenyl-6-vinyl-7-hydroxy--furo-(3,4-c)-pyridine.

18. A process for the preparation of a compound according to claim 1, the process comprising reacting one mol of a 6-chloromethyl-7-benzoxy-furo-(3,4-c)--pyridine derivative of the general formula II as herein defined with one mol of triphenyl phosphine and two mol of formaldehyde at the boil in a polar solvent, and treating the resultant compound with an acid to cleave the benzyl group.

19. A pharmaceutical composition comprising a 1,3--dihydro-6-vinyl-7-hydroxy-furo-(3,4-c)-pyridine derivative according to any of claims 1 to 17 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.