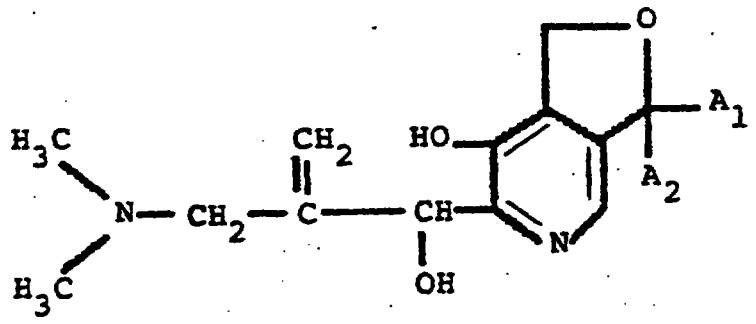
TITLE:

Preparation of 6-Substituted-Furo-(3,4-c)-Pyridine Derivatives

DESCRIPTION:

The invention relates to the preparation of 1,3--dihydro-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7--hydroxy-furo-(3,4-c)-pyridine derivatives of the general formula I



I

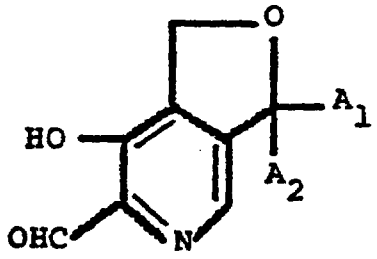
wherein each of A_1 and A_2 independently represents a hydrogen atom, a straight chain saturated or unsaturated hydrocarbon group having from 1 to 5 carbon atoms, a heterocyclic group having up to 6 ring atoms, a carbomonocyclic group, a phenylalkyl group or a phenylalkenyl group, each of the groups 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 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 α- or β-(N-pyrrolidinyl)-alkoxy groups in which the alkoxy group has from 1 to 5 carbon atoms.

These compounds have been described and claimed in our British Patent Application No. 2153824. They are of interest for their therapeutical activity, principally

in the fields of diuresis, lowering of blood pressure, kidney protection and also as antihistaminic agents.

It has surprisingly been found that in the process described in our aforesaid Patent Application the protection of the hydroxy group in position 7 might be omitted and nevertheless the product might be prepared with a better yield.

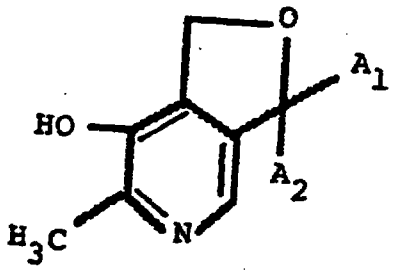
Accordingly, the invention provides a process for the preparation of 1,3-dihydro-6-(1-hydroxy-2-dimethylamino-methyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine derivatives of the general formula I as above defined, the process comprising reacting a 6-formyl-7-hydroxy-furo-(3,4-c)-pyridine derivative of the general formula II



II

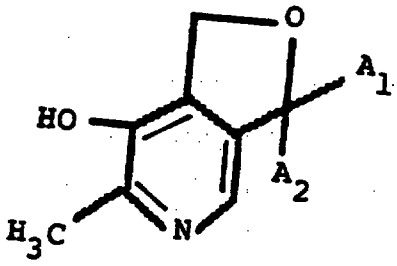
wherein A_1 and A_2 are as above defined with a slight excess of 1-dimethylaminomethyl-vinylmagnesium bromide at the boil, in a non polar solvent such as tetrahydrofuran.

The 6-formyl-7-hydroxy-furo-(3,4-c)-pyridine derivatives II may be obtained from corresponding 6-methyl--7-hydroxy derivatives of the general formula III

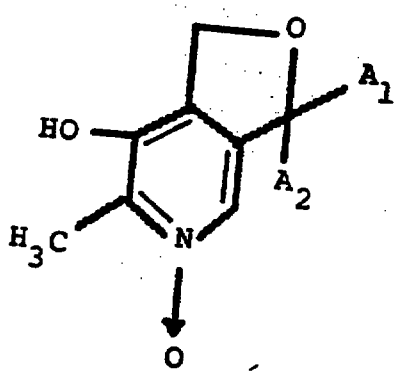


III

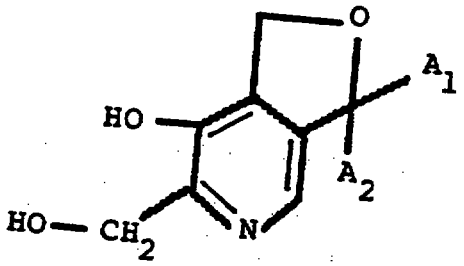
wherein A_1 and A_2 are as above defined by the following sequence of reactions:



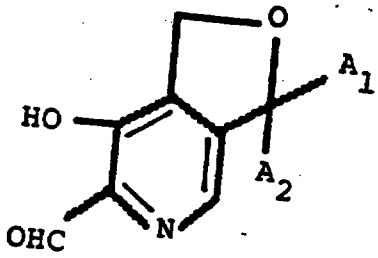
m-chloro peroxybenzoic acid



$(CF_3\ CO)_2\ O$



MnO_2



The compounds III are disclosed in our British Patent Application No. 2137618.

The preparation of one only of the starting compounds, 1,3-dihydro-3-p-chlorophenyl-6-formyl-7-hydroxy-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, 22.3 g of 1,3-dihydro-3-p-chlorophenyl-6-methyl-7-hydroxy-furo-(3,4-c)-pyridine were treated at 0°C, in the presence of 300 ml of methylene dichloride, with 18.2 g of m-peroxybenzoic acid, slowly added. After stirring overnight at room temperature, there were added 150 ml of 10 % sodium sulphate solution. After stirring and decantation, the methylene dichloride phase was washed with the same amount of sodium sulphate solution, twice with 150 ml of sodium bicarbonate solution and three times with 100 ml of water then dried over anhydrous sodium sulphate. By evaporation to dryness, there was obtained a beige precipitate which was washed with petroleum ether, filtered and dried. Yield 22.9 g (96 %) of 1,3-dihydro-3-p-chlorophenyl-6-methyl-7-hydroxy -furo-(3,4-c)-pyridine-N-oxide.

b) In the same reactor as above, the 22.9 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 21.3 g (93 %) of 1,3-dihydro-3-p-chlorophenyl-6-hydroxymethyl-7-hydroxy-furo-(3,4-c)-pyridine.

c) The 21.3 g of the compound obtained in the previous step were treated in a 2 litre reactor with 27 g of manganese dioxide in the presence of 0.9 litre of chloroform at 28-30°C, under stirring for 3 hours. After separation, filtration, washing with chloroform and then with ethyl acetate, the solution was evaporated to dryness and the paste treated with isopropyl oxide then with pentane. There was thus obtained 20.1 g (95 %) of 1,3-dihydro-3-p-chlorophenyl-6-formyl-7-hydroxy-furo-(3,4- c)-pyridine.

The following examples illustrate the invention.

Example 1

1,3-dihydro-3-methyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

a) Preparation of the organomagnesium reagent

In a two litre reactor fitted with warming, cooling and stirring means were poured, under nitrogen circulation, 19.4 g (0.8 mol) of magnesium, and 100 ml of tetrahydrofuran, preferably distilled on lithium aluminium hydride. The mixture was refluxed.

There was then slowly added 132 g (0.8 mol) of 3-dimethylamino-2-bromo-1-propylene. No external heating was applied, the reflux being maintained and controlled by the addition of this compound. At the end of the addition, one litre of distilled tetrahydrofuran was added. The mixture was refluxed for two hours and then cooled to 10°C.

b) Reaction

To the reaction mixture from the previous step was slowly added, under stirring, 89 g (0.5 mol) of 1,3-dihydro-3-methyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. The temperature reached about 25°C at the end of the addition. Stirring was maintained overnight at room temperature. The mixture was then cooled to 0°C and 250 ml of water saturated with ammonium chloride and 250 ml of diethyl ether were added to it. After stirring for 15 minutes at room temperature there was obtained a two-phase mixture with an oil supernatant.

The mixture was separated and the aqueous phase was extracted twice with 250 ml aliquots of diethyl ether. The extracts were added to the oily phase, which had been washed with water three times. The oily phase was then dried on magnesium sulphate, treated with carbon black, concentrated to dryness and extracted twice with 250 ml of diisopropyl ether. The extracts were filtered, concentrated (reduction to 1/4 of initial volume) and cooled overnight, leading to a precipitate, which was separated and washed with diisopropyl ether. Yield 105 g (80 %).

The preparation of the other compounds of the invention follows the same process except that, in step (b), the starting material is different ; the following examples will, accordingly refer to example 1 and only mention the new starting material, the overall yield and the characteristics of the compound obtained.

Example 2

1,3-dihydro-3-propyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 83 g (0.4 mol) of 1,3-dihydro-3-propyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 66% of a product melting

at 187-194°C (Tottoli), with decomposition, the analysis of which showed a good correspondence with the formula $C_{16}H_{24}N_2O_3$, 2HCl.

Example 3

1,3-dihydro-3-cyclohexyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 99 g (0.4 mol) of 1,3-dihydro-3-cyclohexyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 59% of product melting at 180-184°C (Tottoli), with decomposition, the analysis of which showed a good correspondence with the formula $C_{19}H_{28}N_2O_3$, 2HCl.

Example 4

1,3-dihydro-3-phenyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 99 g (0.4 mol) of 1,3-dihydro-3-phenyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 49% of a product melting at 210-215°C (Tottoli), with decomposition, the analysis of which showed a good correspondence with the formula $C_{19}H_{22}N_2O_3$, 2HCl.

Example 5

1,3-dihydro-3-p-chlorophenyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 110 g (0.4 mol) of 1,3-dihydro-3-p-chlorophenyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 57% of a product melting at 195-200°C (Tottoli), with decomposition, the analysis of which showed a good correspondence with the formula $C_{19}H_{21}ClN_2O_3$. 2HCl.

(16)

Example 6

1,3-dihydro-3-(2,3-dichlorophenyl)-6-(1-hydroxy-2-dimethyl-aminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 124 g (0.4 mol) of 1,3-dihydro-3-(2,3-dichloro-phenyl)-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 62% of a product melting at 180-184°C (Tottoli), with decomposition, the analysis of which showed a good correspondence with the formula $C_{19}H_{20}Cl_2N_2O_3 \cdot 2HCl$.

Example 7

1,3-dihydro-3-p-fluorophenyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 104g (0.4 mol) of 1,3-dihydro-3-p-fluorophenyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 62% of a product melting at 198°C (Tottoli), with decomposition, the analysis of which showed a good correspondence with the formula $C_{19}H_{21}FN_2O_3 \cdot 2HCl$.

Example 8

1,3-dihydro-3-p-toluyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 103 g (0.4 mol) of 1,3-dihydro-3-p-toluyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 66% of a product melting at 203-207°C (Tottoli), with decomposition, the analysis of which showed a good correspondence with the formula $C_{20}H_{24}N_2O_3 \cdot 2HCl$.

(19)

Example 9

1,3-dihydro-3-p-methoxyphenyl-6-(1-hydroxy-2-dimethylamino-methyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 110 g (0.4 mol) of 1,3-dihydro-3-p-methoxyphenyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 63% of a product melting at 169-170°C (Tottoli), the analysis of which showed a good correspondence with the formula $C_{20}H_{24}N_2O_4 \cdot 2HCl$.

Example 10

1,3-dihydro-3-m-trifluoromethylphenyl-6-(1-hydroxy-2-dimethyl-aminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 124 g (0.4 mol) of 1,3-dihydro-3-m-trifluoromethylphenyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 58% of a product melting at 217-223°C (Tottoli), with decomposition, the analysis of which showed a good correspondence with the formula $C_{20}H_{21}F_3N_2O_3 \cdot 2HCl$.

Example 11

1,3-dihydro-3-p-(diethylaminoethoxy-phenyl)-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 142 g (0.4 mol) of 1,3-dihydro-3-p-(diethylaminoethoxy-phenyl)-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 51% of a product melting at 158-160°C (Tottoli), the analysis of which showed a good correspondence with the formula $C_{25}H_{35}N_3O_4 \cdot 2HCl$.

(18)

Example 12

1,3-dihydro-3-[p-[β-(N-pyrrolidinyl)-ethoxy]-phenyl]-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 142 g (0.4 mol) of 1,3-dihydro-3-[p-[β-(N-pyrrolidinyl)-ethoxy]-phenyl]-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 53% of a product melting at 173°C (Tottoli), the analysis of which showed a good correspondence with the formula $C_{25}H_{33}N_3O_4$. 2HCl.

Example 13

1,3-dihydro-3-methyl-3-n-pentyl-6-(1-hydroxy-2-dimethylamino-methyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 99 g (0.4 mol) of 1,3-dihydro-3-methyl-3-n-pentyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 59% of a product melting at 187-191°C (Tottoli), with decomposition, the analysis of which showed a good correspondence with the formula $C_{19}H_{30}N_2O_3$. 2HCl.

Example 14

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

The method of example 1 was repeated, but starting with 103 g (0.4 mol) of 1,3-dihydro-3-methyl-3-phenyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 69% of a product melting at 178-179°C (Tottoli), the analysis of which showed a good correspondence with the formula $C_{20}H_{24}N_2O_3$. 2HCl.

Example 15

1,3-dihydro-3-methyl-3-α-thienyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 103 g (0.4 mol) of 1,3-dihydro-3-methyl-3-α-thienyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 67% of a product melting at 169-175°C (Tottoli), with decompostion, the analysis of which showed a good correspondence with the formula $C_{18}H_{22}SN_2O_3 \cdot 2HCl$.

Example 16

1,3-dihydro-3-ethyl-3-m-trifluoromethylphenyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 136 g (0.4 mol) of 1,3-dihydro-3-ethyl-3-m-trifluoromethyl-phenyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 72% of a product melting at 185°C (Tottoli), the analysis of which showed a good correspondence with the formula $C_{22}H_{25}F_3N_2O_3 \cdot 2HCl$.

Example 17

1,3-dihydro-3-ethyl-3-α-furyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 104 g (0.4 mol) of 1,3-dihydro-3-ethyl-3-α-furyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 58% of a product melting at 164-169°C (Tottoli), with decomposition, the analysis of which showed a good correspondence with the formula $C_{19}H_{24}N_2O_4 \cdot 2HCl$.

Example 18

1,3-dihydro-3-phenyl-3-p-ethoxyphenyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 144 g (0.4 mol) of 1,3-dihydro-3-phenyl-3-p-ethoxyphenyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 64% of a product melting at 148-149°C (Tottoli), the analysis of which showed a good correspondence with the formula $C_{27}H_{30}N_2O_4 \cdot 2HCl$.

Example 19

1,3-dihydro-3,3-di-p-fluorophenyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 142 g (0,4 mol) of 1,3-dihydro-3,3-di-p-fluorophenyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 70% of a product melting at 175°C (Tottoli), the analysis of which showed a good correspondence with the formula $C_{25}H_{24}F_2N_2O_3 \cdot 2HCl$.

Example 20

1,3-dihydro-3-α-furyl-3-p-thiomethylphenyl-6-(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo-(3,4-c)-pyridine

The method of example 1 was repeated, but starting with 141 g (0.4 mol) of 1,3-dihydro-3-α-furyl-3-p-thiomethyl-phenyl-6-formyl-7-hydroxy-furo-(3,4-c)-pyridine. Yield 48% of a product melting at 143-151°C (Tottoli), with decomposition, the analysis of which showed a good correspondence with the formula $C_{24}H_{26}SN_2O_4 \cdot 2HCl$.

CLAIMS:

1. A process for the preparation of a 1,3-dihydro-6--(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo--(3,4-c)-pyridine derivative having the general formula I as herein defined, the process comprising reacting a 6-formyl-7-hydroxy-furo-(3,4-c)-pyridine derivative having the general formula II as herein defined with a slight excess of 1-dimethylaminomethyl-vinylmagnesium bromide at the boil in a non polar solvent.

2. A process according to claim 1 in which the non-polar solvent is tetrahydrofuran.

3. A process for the preparation of a 1,3-dihydro-6--(1-hydroxy-2-dimethylaminomethyl-allyl)-7-hydroxy-furo--(3,4-c)-pyridine derivative having the general formula I as herein defined, the process being substantially as described herein with reference to any of the Examples.