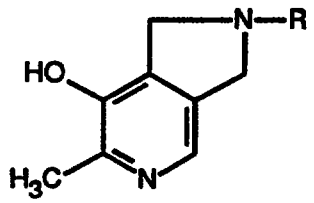
TITLE:

Pyrrolo-Pyridine Derivatives, Process and Compositions

DESCRIPTION:

The invention relates to pyrrolo-pyridine derivatives, to a process for their preparation and to therapeutic compositions containing them.

The invention provides pyrrolo-pyridine derivatives of the formula (1):



(1)

wherein R represents a phenyl group, optionally substituted by one or more substituents selected from chlorine and fluorine atoms; carboxy, hydroxy and cyano groups; straight chain and branched chain alkyl groups having up to 10 carbon atoms and being unsubsituted or substituted by one or more hydroxy and/or cyano and/or carboxy groups; alkoxy groups having up to 10 carbon atoms; alkylcarbonyl groups having up to 8 carbon atoms; and alkoxycarbonyl groups having up to 8 carbon atoms. The invention also provides therapeutically acceptable salts thereof.

The invention also provides a process for the preparation of pyrrolo-pyridine derivatives of the formula (1) as above defined, the process comprising reacting, in an inert atmosphere, 2-methyl-3-hydroxy--4,5-dibromomethyl-pyridine or an acid addition salt thereof, with a stoichiometric excess of a compound of the formula NH_2-R wherein R is as above defined, in a protic solvent, at a temperature of from room temperature to the boiling point of the reaction mixture.

The 2-methyl-3-hydroxy-4,5-dibromomethyl-pyridine, used as starting compound in the process of the invention, was readily prepared in the form of its hydrobromide as follows: 33g (0.16 mol) of pyridoxine hydrochloride and 460 ml of hydrobromic acid (47% by volume) was poured into a two-litre reactor maintained under nitrogen circulation. The mixture was slowly warmed to reflux temperature and reflux was maintained for about 15 min. After cooling to room temperature, the resulting compound was filtered off, washed three times with iced water then once with acetone, and dried under reduced pressure in a sulphuric acid atmosphere to yield 43.8 g (72.6%) of 2-methyl-3-hydroxy-4,5-dibromomethyl-pyridine hydrobromide.

6-methyl-2-(substituted phenyl)-pyrrolo[3,4-c]pyridines are known from Form Glas., 1983, 39(9). The compounds there disclosed have various substituents in the 7-position but have only the trifluoromethyl group as a substituent of 2-phenyl group. They have antimicrobial activities. By contrast, the compounds of the invention have a 7-hydroxy substituent and do not have a trifluoromethyl substituent on the 2-phenyl group. Moreover, they have anti-allergic activity but no antimicrobial activity.

To date, in the allergy field, two types of anti--allergic compounds may be found: symptomatic compounds and compounds blocking mechanisms in the first stages of the allergy reaction; the mainly used compounds of this category, are sodium cromoglycate (Lomusol ®) which may be administered only by aerosol and not P.O. in contrast with ketotifen (Zaditen ®) which may be administered P.O. but, due to its aspecificity, presents secondary effects which in some cases may not be accepted.

The compounds of the invention have shown anti-allergic activity: pharmacological experiments (such as the Passive Cutaneous Anaphylaxy -PCA- test as described below under the heading the "pharmacology") have shown that they inhibited the degranulation, and complementary studies have shown also that, in contradistinction to ketotifen, they had no significant effect as anti-PAF, anti-leukotriene, anti-histaminic or anti-cholinergic compounds, so they did not act on mediators; these results imply that they operate above mediators, at the beginning of the allergy reaction, and act at a stage prior to the stages at which the usual anti-allergics act.

The invention further provides a therapeutic composition comprising a pyrrolo-pyridine derivative of the formula (1) as above defined, or a therapeutically acceptable salt thereof, in admixture with a therapeutically acceptable diluent or carrier.

The invention will be better understood from the description of the following examples.

EXAMPLE 1

2-phenyl -6-methyl-7-hydroxy-1,3-dihydro-pyrrolo[3,4-c]-pyridine

General formula 1; R=phenyl

Into a two litre reactor fitted with appropriate means to establish nitrogen circulation, there were poured 37.6 g (0.10 mol) of 2-methyl-3-hydroxy-4,5-dibromo-methyl-pyridine hydrobromide, 21.4 g (0.23 mol) of aniline and 500 ml of toluene. The mixture was slowly warmed to reflux temperature and reflux was maintained for two hours. Then the suspension was stirred overnight. The resulting compound was filtered off, washed with diethyl-ether, and then treated with 500 ml

of a mixture of water/diethyl-ether (80/20 by volume). Thereafter 100 ml of a 5M sodium hydroxide solution was added and the pH was adjusted to pH 5 by addition of acetic acid. After filtration, the recovered compound was successively washed with water, ethanol and diethyl--ether, and dried. The residue thus obtained was treated by 300 ml of a methanol/chloroform mixture (2/1) by volume) and the mixture was refluxed. After cooling, the resulting compound was filtered off and washed with diethyl-ether.

Yield was 16.6 g (73.4%) of a beige powder melting at 270°C (Tottoli). The elemental analysis showed a good correspondence with the formula $C_{14}H_{14}N_2O$ (molecular weight 226.28).
^{1}H-NMR (CF_3COOD/TMS) δ ;
2.90 (s. CH_3), 5.60 (s. CH_2), 5.68 (s. CH_2), 7.70 (s. 5H), 8.43 (s. 1H)

The following compounds have been prepared as described in Example 1, using the appropriate NH_2-R reagent.

EXAMPLE 2

2-(3-methylphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine
R=3-methylphenyl
Cream-white powder melting at 268-270°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{15}H_{16}N_2O$ (molecular weight 240.30).
^{1}H-NMR (CF_3COOD/TMS) δ :
2.8 (s. CH_3), 3.1 (s. CH_3), 5.7 (s. $2CH_2$), 7.6 (s. 4H), 8.2 (s. 1H)

EXAMPLE 3

2-(4-isopropylphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine
R=4-isopropylphenyl

Yellow powder melting at a temperature above 300°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{17}H_{20}N_2O$ (molecular weight 268.36).

^{1}H-NMR (DMSO/TMS) δ:

1.2 (d. $2CH_3$), 2.7 (s. CH_3), 3.4 (m. 1H), 5.4 (s. $2CH_2$), 7.4 (s. 4H), 8.2 (s. 1H)

EXAMPLE 4

2-(4-tert.butylphenyl)-6-methyl-7-hydroxy-1,3-dihydro-pyrrolo[3,4-c]pyridine

R=4-tert.butylphenyl. Prepared as the hydrochloride. Yellow powder melting at 270°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{18}H_{22}N_2O.HCl$ (molecular weight 318.85).

^{1}H-NMR (DMSO/TMS) δ:

1.26 (s. $3CH_3$), 2.43 (s. CH_3), 4.57 (s. $2CH_2$), 6.54-6.63 (d. 2H), 7.25-7.33 (d. 2H), 8.1 (s. 1H).

EXAMPLE 5

2-(3-hydroxyethylphenyl)-6-methyl-7-hydroxy-1,3-dihydro-pyrrolo[3,4-c]pyridine

R=3-hydroxyethylphenyl. Prepared as the hydrochloride. Pale, yellow powder melting at 256-257°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{16}H_{18}N_2O_2.HCl$ (molecular weight 306.80).

^{1}H-NMR (CF_3COOD/TMS) δ:

2.8 (s. CH_3), 3.1 (d. CH_2), 4.1 (t. CH_2), 5.3 (s. $2CH_2$), 7.2-7.5 (m. 4H), 8.3 (s. 1H)

EXAMPLE 6

2-(4-cyanomethylphenyl-6-methyl-7-hydroxy-1,3-dihydro-pyrrolo[3,4-c]pyridine

R=4-cyanomethylphenyl

Yellow powder melting at 211-212°C (Tottoli). Elemental analysis showed a good correspondence with the formula

$C_{16}H_{15}N_3O$ (molecular weight 265.32).
^{1}H-NMR (DMSO/TMS) δ :
2.8 (s. CH_3), 3.9 (s. CH_2), 5.2 (s. $2CH_2$), 7.3 (s. 4H), 8.3 (s. 1H)

EXAMPLE 7

2-(4-carboxymethylphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine
R=4-carboxymethylphenyl
Beige powder melting at 261-264°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{16}H_{16}N_2O_3$(molecular weight 284.32).
^{1}H-NMR (DMSO/TMS) δ :
2.4 (s. CH_3), 3.9 (s. CH_2), 5.1 (s. $2CH_2$), 7.2-7.3 (m. 4H), 8.2 (s. 1H)

EXAMPLE 8

2-(3-methoxyphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine
R=3-methoxyphenyl
Pale yellow powder melting at 251-252°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{15}H_{16}N_2O_2$ (molecular weight 256.31).
^{1}H-NMR (DMSO/TMS) δ:
2.8 (s. CH_3), 4.1 (s. OCH_3), 6.2 (s. $2CH_2$), 7.1-7.5 (m. 4H), 8.0 (s. 1H).

EXAMPLE 9

2-(4-ethoxyphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine
R=4-ethoxyphenyl. Prepared as the hydrochloride.
Pale beige powder melting at 243-244°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{16}H_{18}N_2O_2$.HCl (molecular weight 306.79).
^{1}H-NMR (DMSO/TMS) δ :
1.2 (t. CH_3), 2.5 (s. CH_3), 4.1 (q. CH_2), 5.6 (s. $2CH_2$), 7.6 (s. 4H), 8.22 (s. 1H)

EXAMPLE 10

2-(2,4-dimethoxyphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine

R=2,4-dimethoxyphenyl

Beige powder melting at 216°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{16}H_{18}N_2O_3$ (molecular weight 286.33).

^{1}H-NMR (DMSO/TMS) δ :

2.35 (s. CH_3), 3.7 (s. OCH_3), 3.8 (s. OCH_3), 4.48 (s. $2CH_2$), 6.3-6.8 (m. 3H), 7.93 (s, 1H).

EXAMPLE 11

2-(3,4-dimethoxyphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine

R=3,4-dimethoxyphenyl. Prepared as the hydrobromide.

Yellow powder melting at 265°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{16}H_{18}N_2O_3 \cdot HBr$ (molecular weight 367.24).

^{1}H-HMR (CF_3COOD/TMS) δ :

2.9 (s. CH_3), 4.0 (s. $2OCH_3$), 5.5-6.5 (d. $2CH_2$), 7.15-7.55 (m. 3H), 8.45 (s. 1H)

EXAMPLE 12

2-(3,4,5-trimethoxyphenyl)-6-methyl-7-hydroxy-1,3--dihydro-pyrrolo[3,4-c]pyridine

R=3,4,5-trimethoxyphenyl

Yellow powder melting at 220°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{17}H_{20}N_2O_4$ (molecular weight 316.36).

^{1}H-NMR ($CDCl_3$/TMS) δ :

2.4 (s. CH_3), 3.67 (s. OCH_3), 3.73 (s. $2OCH_3$), 4.55 (s. $2CH_2$), 5.72 (s. 3H), 8.0 (s. 1H).

EXAMPLE 13

2-(4-chlorophenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine

R=4-chlorophenyl

Cream-white powder melting at 256-258°C (Tottoli).

Elemental analysis showed a good correspondence with the formula $C_{14}H_{13}ClN_2O$ (molecular weight 260.72).
^{1}H-NMR (DMSO/TMS) δ :
2.8 (s. CH_3), 5.2 (s. $2CH_2$), 7.3 (s. 4H), 8.3 (s. 1H).

EXAMPLE 14

2-(2,4-difluorophenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine
R=2,4-difluorophenyl
Pale beige powder melting at 279°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{14}H_{12}F_2N_2O$ (molecular weight 262.26).
^{1}H-NMR (DMSO/TMS) δ:
2.6 (s. CH_3), 4.83 (s. $2CH_2$), 6.8-7.2 (m. 3H), 8.45 (s. 1H).

EXAMPLE 15

2-(2,6-dichlorophenyl-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine
R=2,6-dichlorophenyl
Cream white powder melting at 262°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{14}H_{12}Cl_2N_2O$ (molecular weight 295.17).
^{1}H-NMR (CF_3COOD/TMS) δ :
2.92 (s. CH_3), 5.9 (s. $2CH_2$), 7.72 (s. 3H), 8.45 (s. 1H).

EXAMPLE 16

2-(3-hydroxyphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine
R=3-hydroxyphenyl. Preapred as the hydrobromide.
Yellow powder melting at 306°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{14}H_{14}N_2O_2$.HBr (molecular weight 323.19).
^{1}H-NMR(DMSO/TMS) δ :
2.65 (s. CH_3), 4.72 (s. $2CH_2$), 6.0-6.4 (m. 3H), 6.9-7.3 (m. 1H), 8.51 (s. 1H)

EXAMPLE 17

2-(4-hydroxyphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine

R=4-hydroxyphenyl. Prepared as the hydrobromide.

Yellow powder melting at a temperature above 260°C. Elemental analysis showed a good correspondence with the formula $C_{14}H_{14}N_2O_2$. HBr (molecular weight 323.19).

^{1}H-NMR(DMSO/TMS) δ :

2.57 (s. CH_3), 4.68 (s. $2CH_2$), 6.3-6.8 (m. 4H), 8.38 (s.1H)

EXAMPLE 18

2-(2,4-dihydroxyphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine

R=2,4-dihydroxyphenyl

Green-yellow powder melting at a temperature above 260°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{14}H_{14}N_2O_3$ (molecular weight 258.27)

^{1}H-NMR (DMSO/TMS) δ:

2.38 (s. CH_3), 4.43 (s. $2CH_2$), 6.1-6.8 (m. 3H), 7.92 (s. 1H)

EXAMPLE 19

2-(2,4,6-trihydroxyphenyl)-6-methyl-7-hydroxy-1,3--dihydro-pyrrolo[3,4-c]pyridine

R=2,4,6-trihydroxyphenyl

Yellow powder melting at 290-291°C. Elemental analysis showed a good correspondence with the formula $C_{14}H_{14}N_2O_4$ (molecular weight 274.27).

^{1}H-NMR (DMSO/TMS) δ:

2.2 (s. CH_3), 5.1 (s. $2CH_2$), 6.2 (s. 1H), 6.7 (s. 1H), 8.1 (s. 1H)

EXAMPLE 20

2-[(4-hydroxy-2-methoxy)-phenyl]-6-methyl-7-hydroxy-1,3-

-dihydro-pyrrolo[3,4-c]pyridine
R=(4-hydroxy-2-methoxy)-phenyl. Prepared as the hydrochloride.
Yellow powder melting at a temperature above 260°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{15}H_{16}N_2O_{10}.HCl$ (molecular weight 308.76).
^{1}H-NMR (DMSO/TMS) δ:
2.62 (s. CH_3), 3.7 (s. OCH_3), 4.1-4.3 (m. $2CH_2$), 6.3-6.9 (m. 3H), 8.27 (s. 1H)

EXAMPLE 21

2-[(4-hydroxy-2-ethoxy)-phenyl]-6-methyl-7-hydroxy-1,3--dihydro-pyrrolo[3,4-c]pyridine
R=(4-hydroxy-2-ethoxy)phenyl. Prepared as the hydrochloride.
White powder melting at 269-270°C (Tottoli). Elemental analysis of which showed a good correspondence with the formula $C_{16}H_{18}N_2O_3.HCl$ (molecular weight 322.79).
^{1}H-NMR (DMSO)/TMS) δ :
1.3 (t. CH_3), 2.5 (s. CH_3), 4.1 (q. CH_2), 5.6 (s. CH_2), 7.2-7.6 (m. 3H), 8.2 (s. 1H)

EXAMPLE 22

2-(3-carboxyphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine
R=3-carboxyphenyl. Prepared as the hydrochloride.
Yellow powder melting at 286°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{15}H_{14}N_2O_3.HCl_{0.5}H_2O$ (molecular weight 315.75).
^{1}H-NMR (DMSO/TMS) δ :
2.61 (s. CH_3), 4.3-4.6 (m. COOH), 4.73 (m. $2CH_2$), 6.8-7.4 (m. 4H), 8.3 (s. 1H)

EXAMPLE 23

2-(4-carboxyphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine

R=4-carboxyphenyl. Prepared as the hydrochloride.
Yellow powder melting at a temperature above 300°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{15}H_{14}N_2O_3$.HCl (molecular weight 306.75).
^{1}H-NMR (CF_3COOD/TMS) δ:
2.9 (s. CH_3), 5.35 (m. $2CH_2$), 7.4 (s. 1H), 8.2-8.5 (m. 4H)

EXAMPLE 24

2-[(2-methoxy-5-carboxy)-phenyl]-6-methyl-7-hydroxy-1,3--dihydro-pyrrolo[3,4-c]pyridine
R=(2-methoxy-5-carboxy)phenyl. Prepared as the hydrobromide.
Yellow powder melting at 277°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{16}H_{16}N_2O_4$.HBr (molecular weight 381.22).
^{1}H-NMR (DMSO/TMS) :
2.62 (s. CH_3), 3.93 (s. OCH_3), 4.74 (s. $2CH_2$), 7.0-7.5 (m. 3H), 8.4 (s. 1H)

EXAMPLE 25

2-(3-cyanophenyl)-6-methyl-7-hydroxy-1,3-dihydro-pyrrolo-[3,4-c]pyridine
R=3-cyanophenyl
Cream-white powder melting at a temperature above 310°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{15}H_{13}N_3O$ (molecular weight 251.29).
^{1}H-NMR (CF_3COOD/TMS) δ:
2.87 (s. CH_3), 5.1-5.3 (m. $2CH_2$), 7.2-7.6 (m. 4H), 8.32 (s. 1H)

EXAMPLE 26

2-(4-cyanophenyl)-6-methyl-7-hydroxy-1,3-dihydro-pyrrolo-[3,4-c]pyridine
R=4-cyanophenyl

Pale beige powder melting at a temperature above 310°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{15}H_{13}N_3O$ (molecular weight 251.29).

^{1}H-NMR (CF_3COOD)/TMS)δ :

2.9 (s. CH_3), 5.2 (m. $2CH_2$), 7.3-7.6 (m. 4H), 8.2 (s. 1H)

EXAMPLE 27

2-(4-methylcarbonylphenyl)-6-methyl-7-hydroxy-1,3--dihydro-pyrrolo[3,4-c]pyridine

R=4-methylcarbonylphenyl. Prepared as the hydrochloride. Pale yellow powder melting at 247-249°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{16}H_{16}N_2O_2$.HCl (molecular weight 304.78).

^{1}H-NMR (DMSO/TMS) δ:

2.7 (s. CH_3), 3.8 (s. CH_3), 5.1 (s. $2CH_2$), 7.1-7.4 (m. 4H), 8.1 (s. 1H)

EXAMPLE 28

2-(4-ethylcarbonylphenyl)-6-methyl-7-hydroxy-1,3-dihydro--pyrrolo[3,4-c]pyridine

R=4-ethylcarbonylphenyl

Yellow powder melting at 288-289°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{17}H_{18}N_2O_2$ (molecular weight 282.34).

^{1}H-NMR (DMSO/TMS) δ:

1.2 (t. CH_3), 2.7 (s. CH_3), 4.1 (q. CH_2), 5.2 (s. $2CH_2$), 7.3 (s. 4H), 8.1 (s. 1H)

EXAMPLE 29

2-(4-methoxycarbonylphenyl)-6-methyl-7-hydroxy-1,3--dihydro-pyrrolo[3,4-c]pyridine

R=4-methoxycarbonylphenyl

Beige powder melting at 233-235°C (Tottoli). Elemental

analysis showed a good correspondence with the formula $C_{16}H_{16}N_2O_3$ (molecular weight 284.31).
^{1}H-NMR (DMSO/TMS) δ:
2.8 (s. CH_3), 3.6 (s. CH_3), 5.1 (s. $2CH_2$), 7.1-7.5 (m. 4H), 8.2 (s. 1H)

EXAMPLE 30

2-(4-ethoxycarbonylphenyl)-6-methyl-7-hydroxy-1,3--dihydro -pyrrolo[3,4-c]pyridine
R=4-ethoxycarbonylphenyl
Pale beige powder melting at 226-227°C (Tottoli). Elemental analysis showed a good correspondence with the formula $C_{17}H_{18}N_2O_3$ (molecular weight 298.34).
^{1}H-NMR (DMSO/TMS) δ:
1.3 (t. CH_3), 2.8 (s. CH_3), 4.3 (q. CH_2), 5.2 (s. $2CH_2$), 7.1-7.4 (m. 4H), 8.4 (s. 1H)

TOXICITY

For none of the compounds of the invention did per os administration of 1000 mg/kg to mice result in any death.

PHARMACOLOGY

The pharmaceutical interest of the compounds of the invention has been established, with ketotifen as reference compound, by the following pharmaceutical experiments: test of Passive Cutaneous Anaphylaxy (PCA) on the rat associated with hyperpermeability to histamine:

This experiment was conducted as described in 'Fiche Technique' No. 48 of J. Pharm. Paris, 1979, 10, (1) pages 69-72 (adaptation of the method of BITTEAU E. and HERTZ F.). The method is summarized as follows:

Twelve batches, each of 8 male Sprague Dawley rats (180-200 g) - one for the control, one for the reference

compound, at the dose of 1 mg/kg, and one for each of the following example compounds, at the dose of 50 mg/kg - have been used.

In two sites of the back, previously shaved, were made two injections of a homologous immune-serum (0.1 ml) diluted for a quater.

48 hours later, the rats received an intravenous injection of 1 ml of a mixture of ovalbumine (0.5%) and Evans blue (0.5%), in physiologic serum. As a consequence, the formation of the antigen-antibody complex induced the exudation of plasmatic proteins and the formation of cutaneous weals, this phenomen being quantified measuring their surface and their coloration, (after extracting for 24 hours in a formamide solution at 65°C): the optical density of the supernatant was determined at 620 nm by a spectrophotometer.

The animals were kept fasting for 18 hours before injection of antigen. The products were administered PO one hour before the administration of colorant.

Just before the IV injection of colorant, all animals received two intradermal injections, in two sites of the back, of histamine chlorhydrate (50 mcg/0.1 ml), opposed to the injections of the immune-serum.

30 minutes later, the induced weals were treated as the weals obtained with immune-serum.

The experimental results are summarized in the following table.

	immune-serum wheals		histamine wheals	
	area mm^2	coloration (DO)	area mm^2	coloration (DO)
control	113.2 ± 8 .47	0.634 ± 0.0774	125.2 ± 6.87	0.959 ± 0.0858
Ketotifen	73.8 ± 7.51 - 34.8 ***	0.347 ± 0.0646 - 45.3 ***	78.6 ± 6.67 - 37.2 ***	0.333 ± 0.0672 - 65.3 ***
ex 1	58.6 ± 4.15 - 48.2 ***	0.314 ± 0.0348 - 50.5 ***	103.2 ± 4.18 - 17.6 NS	0.777 ± 0.0677 - 19 NS
ex 4	70.2 ± 8.9 - 38 ***	0.353 ± 0.0694 - 44.3 ***	110 ± 5.75 - 12.1 NS	0.975 ± 0.1151 + 1.7 NS
ex 9	58.8 ± 6.2 - 48.1 ***	0.304 ± 0.0436 - 52 ***	116.2 ± 5.66 - 7 NS	0.868 ± 0.0884 - 9.5 NS
ex 11	53.8 ± 3.3 - 52.5 ***	0.284 ± 0.0421 - 55.2 ***	117.7 ± 6.23 - 6 NS	0.826 ± 0.0912 - 13.9 NS
ex 15	79.3 ± 7.54 - 30 **	0.391 ± 0.059 - 38.3 ***	118.8 ± 9.35 - 5 NS	0.791 ± 0.093 - 18 NS
ex 17	62.2 ± 5.77 - 45 **	0.337 ± 0.0412 - 47 **	109.8 ± 6.39 - 12 NS	0.820 ± 0.095 - 14.5 NS
ex 20	67.8 ± 7.38 - 40 **	0.391 ± 0.0723 - 38.3 **	125.1 ± 6.95 0 NS	0.912 ± 0.078 - 5 NS
ex 22	71.3 ± 4.91 - 37 ***	0.398 ± 0.0269 - 37.2 ***	121.2 ± 7.17 - 3 NS	0.854 ± 0.092 - 11 NS
ex 26	64.7 ± 5.6 - 43 **	0.384 ± 0.065 - 39 **	119.2 ± 5.53 - 5 NS	0.803 ± 0.106 - 16 NS
ex 29	73.6 ± 7.1 - 35 **	0.398 ± 0.044 - 37 **	112.7 ± 7.26 - 10 NS	0.896 ± 0.835 - 6.5 NS

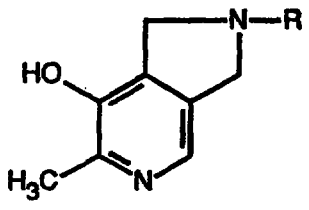
NS : not significant
* : significant
** : very significant
*** : highly significant

POSOLOGY

In human therapy usual doses per os administration, are 1 to 10 mg per diem, in tablets, gelatine capsules or in suspension, for at least a month. For IV route, the usual doses are from 0.5 to 2 mg per diem.

CLAIMS:

1. A pyrrolo-pyridine derivative of the general formula (1):



(1)

wherein R represents a phenyl group, optionally substituted by one or more substituents selected from chlorine and fluorine atoms; carboxy, hydroxy and cyano groups; straight chain and branched chain alkyl groups having up to 10 carbon atoms and being unsubstituted or substituted by one or more hydroxy and/or cyano and/or carboxy groups; alkoxy groups having up to 10 carbon atoms; alkylcarbonyl groups having up to 8 carbon atoms; and alkoxycarbonyl groups having up to 8 carbon atoms, or a therapeutically acceptable salt thereof.

2. A pyrrolo-pyridine derivative according to claim 1, as disclosed in any of the Examples herein.

3. A process for the preparation of a pyrrolo--pyridine derivative according to claim 1, the process comprising reacting, in an inert atmosphere, 2-methyl-3--hydroxy-4,5-dibromomethyl pyridine, or an acid addition salt thereo, with a stoichiometric excess of a compound of the formula NH_2-R wherein R is as defined in claim 1, in a protic solvent, at a temperature of from room temperature to the boiling point of the reaction mixture.

4. A process according to claim 3, substantially as disclosed in any of the Examples herein.

5. A therapeutic composition comprising a pyrrolo-

-pyridine derivative according to claim 1, or a therapeutically acceptable salt thereof, in admixture with a therapeutically acceptable diluent or carrier.