

PATENT SPECIFICATION

(11) 1317514

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NO DRAWINGS

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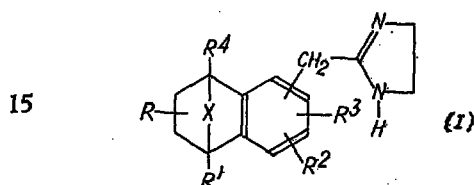
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(54) IMIDAZOLINE DERIVATIVES

(71) We, CARLO ERBA S.P.A., an Italian Body Corporate, of Via Carlo Imbonati 24, Milan 20159, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

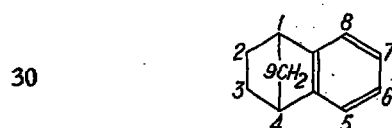
This invention relates to imidazolyl compounds having vasoconstrictor activity, to a process for making them and to pharmaceutical compositions containing them.

The compounds have the general formula (I)



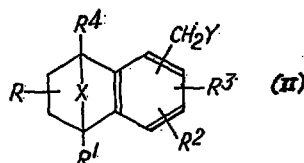
wherein X is an up to C_3 saturated or unsaturated divalent aliphatic hydrocarbon group; and each of R, R^1 , R^2 , R^3 and R^4 , which may be the same or different, is a hydrogen atom, a hydroxy group, or a C_{1-6} alkyl-substituted or unsubstituted amino group, or a C_{1-6} alkyl, C_{2-6} alkenyl or C_{1-6} alkoxy group; or a pharmaceutically acceptable acid addition salt thereof. The aliphatic hydrocarbon, alkyl, alkenyl and alkoxy groups can be straight or branched chain.

The benzonorbornanes are numbered in this specification according to the following system:



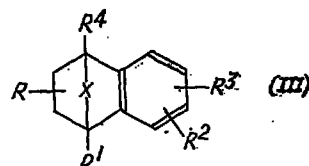
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The compounds can be prepared by reacting ethylenediamine with a compound of general formula (II)



wherein X and R to R^4 are as defined above, and Y is a cyano or carboxy group, and if desired converting the reaction product to an acid addition salt by reaction with the appropriate acid. When Y is a carboxy group, the reaction is preferably performed in the presence of concentrated hydrochloric acid.

Starting materials wherein Y is a cyano group can be prepared either by chloromethylation of a compound of general formula (III)



wherein R to R^4 are as defined above, and then replacing the halogen atom with a cyano group; or by replacing the tertiary amino group of a Mannich base with a cyano group by reaction with a cyanide.

The pharmaceutically acceptable salts can be derived from organic or inorganic acids; a suitable acid is hydrochloric acid.

The compounds have been tested for vaso-pressor activity on rat tail arteries, following

the method of Nicholas, J. Pharm. Pharmac., 1969, 21, 826. This test shows, for example, that 6 - (imidazolin - 2' - ylmethyl) - 1,4-ethano - 1,2,3,4 - tetrahydronaphthalene (A), 6 - (imidazolin - 2' - ylmethyl) - 7 - methyl-1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene (B) are more active than noradrenalin and naphazoline:

	Compound	Concentration ^o
10	Noradrenalin	2×10^{-7}
	Naphazoline	2.5×10^{-8}
	A	2×10^{-8}
	B	2×10^{-9}

^oFinal concentration of the compound in g./ml. to obtain the same vasopressor effect (20 mm. Hg increase in perfusion pressure).

The invention also provides pharmaceutical compositions comprising a compound of general formula (I) and a pharmaceutically acceptable carrier or diluent.

The invention is illustrated by the following Examples.

EXAMPLE 1

Benzonorbornane (10.8 g.), glacial acetic acid (9.6 ml.), phosphoric acid (11.4 g.), 37% hydrochloric acid (15 ml.) and paraformaldehyde (4.2 g.) were stirred vigorously at 62 to 65°C for 26 hr., cooled, diluted with cold water and extracted with ether to give, after evaporation, an oil containing 6-chloromethylbenzonorbornane, b.p. 85—80°C/0.2 mm. This product (14.3 g.) was refluxed for 24 hr. with potassium cyanide (5.8 g.) in dry acetone (250 ml.) and potassium iodide (0.5 g.). The mixture was filtered and concentrated; the residue was extracted with ether, and the ethereal solution washed with water, dried and evaporated to give, as an oil, 6-cyanomethylbenzonorbornane, b.p. 108—110°C/0.2 mm.

The following were prepared in the same way:

- 7 - methyl - 6 - cyanomethylbenzonorbornane, m.p. 67—70°C.
- 5 - hydroxy - 6 - cyanomethylbenzonorbornane
- 8 - hydroxy - 6 - cyanomethylbenzonorbornane
- 5 - hydroxy - 8 - cyanomethylbenzonorbornane
- 5 - methoxy - 6 - cyanomethylbenzonorbornane
- 8 - methoxy - 6 - cyanomethylbenzonorbornane
- 5 - methoxy - 8 - cyanomethylbenzonorbornane
- 9 - methyl - 6 - cyanomethylbenzonorbornane
- 9 - isopropylidene - 6 - cyanomethylbenzonorbornane
- 9 - isopropyl - 6 - cyanomethylbenzonorbornane

1 - methyl - 4 - isopropyl - 6 - cyanomethylbenzonorbornane.

EXAMPLE 2

6-Cyanomethylbenzonorbornane (9 g.) and ethylenediamine mono p-toluene sulphonate (11.4 g.) were heated at 175°C for 4 hr., cooled, stirred with dilute sodium hydroxide and then extracted with ethyl acetate. The solvent was evaporated to give 6-(imidazolin-2'-ylmethyl)benzonorbornane, which was dissolved in alcohol containing excess hydrogen chloride, and precipitated with ether to give, after crystallisation from isopropanol-diethyl ether, the hydrochloride, m.p. 190—3°C.

The following free bases and respective hydrochlorides were prepared in the same way:

- 6 - (Imidazolin - 2' - ylmethyl) - 7-methylbenzonorbornane.
- 6 - (Imidazolin - 2' - ylmethyl) - 9-methylbenzonorbornane.
- 6 - (Imidazolin - 2' - ylmethyl) - 1-methyl - 4 - isopropylbenzonorbornane.
- 6 - (Imidazolin - 2' - ylmethyl) - 5-methoxybenzonorbornane.
- 6 - (Imidazolin - 2' - ylmethyl) - 8-methoxybenzonorbornane, (m.p. of the hydrochloride 250—254°C).
- 8 - (Imidazolin - 2' - ylmethyl) - 5-methoxybenzonorbornane.
- 6 - (Imidazolin - 2' - ylmethyl) - 5-hydroxybenzonorbornane.
- 6 - (Imidazolin - 2' - ylmethyl) - 8-hydroxybenzonorbornane.
- 8 - (Imidazolin - 2' - ylmethyl) - 5-hydroxybenzonorbornane.
- 6 - (Imidazolin - 2' - ylmethyl) - 9-isopropylidenebenzonorbornane.
- 6 - (Imidazolin - 2' - ylmethyl) - 9-isopropylbenzonorbornane, (m.p. of the hydrochloride 205—209°C).

EXAMPLE 3

1,4 - Ethano - 1,2,3,4 - tetrahydronaphthalene (13 g.), glacial acetic acid (10.65 ml.), phosphoric acid (12.5 g.), concentrated hydrochloric acid (16 ml.) and paraformaldehyde (4.6 g.) were stirred vigorously at 65°C for 36 hr., cooled, diluted with water, and extracted with diethyl ether, and the extract concentrated to give 6 - chloromethyl - 1,4 - ethano-1,2,3,4 - tetrahydronaphthalene, b.p. 95°C/0.05 mm. This product (19.2 g.), sodium cyanide (5.4 g.), ethanol (250 ml.) and water (36 ml.) were refluxed for 18 hr., concentrated to dryness, and partitioned between water and ether. The ethereal extract was evaporated to give, after crystallisation from hexane, 6-cyanomethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene, m.p. 65—70°C.

The following were prepared in the same way:

- 6 - cyanomethyl - 7 - methyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene, m.p. 89—91°C.
- 5 5 - cyanomethyl - 6,7 - dimethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene, m.p. 131—4°C.
- 5 - methoxy - 6 - cyanomethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene, m.p. 135—140°C.
- 10 5 - methoxy - 8 - cyanomethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene, m.p. 95—97°C.
- 8 - methoxy - 6 - cyanomethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene
- 15 5 - hydroxy - 6 - cyanomethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene
- 5 - hydroxy - 8 - cyanomethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene
- 20 8 - hydroxy - 6 - cyanomethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene
- 9 - isopropyl - 6 - cyanomethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene
- 1 - isopropyl - 4 - methyl - 6 - cyano - methyl - 1,4 - ethano - 1,2,3,4 - tetra - hydronaphthalene.
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EXAMPLE 4

- 6 - Cyanomethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene (31.4 g.) and ethylenediamine mono p-toluene sulphonate (37 g.) were heated at 175°C for 4 hr., cooled and stirred with dilute sodium hydroxide, and then extracted with ethyl acetate. Evaporation of the solvent gave, 6 - (imidazolin - 2' - ylmethyl) - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene free base which was converted, in alcohol, to the hydrochloride, and precipitated with ether to give, after crystallisation from isopropanol-hexane, the solid hydrochloride, m.p. 250°C.
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EXAMPLE 5

- 6 - Cyanomethyl - 7 - methyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene (37 g.) and ethylenediamine mono p-toluene sulphonate (40.7 g.) were heated for 5 hours at 180—185°C, cooled to room temperature and stirred vigorously with 5% sodium hydroxide (1 litre) to give a solid which was filtered, washed with water and dried, then crystallised with isopropyl ether to give 6 - (imidazolin - 2' - ylmethyl) - 7 - methyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene free base (39.5 g.), m.p. 154—6°C. The hydrochloride prepared in the usual way had m.p. 282—3°C. (methanol).
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- The following free bases and respective hydrochlorides were prepared in the same way:
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- 6 - (Imidazolin - 2' - ylmethyl) - 5 - methoxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.
- 60 6 - (Imidazolin - 2' - ylmethyl) - 8 - methoxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

- 8 - (Imidazolin - 2' - ylmethyl) - 5 - methoxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene. 65
- 6 - (Imidazolin - 2' - ylmethyl) - 5 - hydroxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.
- 6 - (Imidazolin - 2' - ylmethyl) - 8 - hydroxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene. 70
- 8 - (Imidazolin - 2' - ylmethyl) - 5 - hydroxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.
- 5 - (Imidazolin - 2' - ylmethyl) - 6,7 - dimethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene, (m.p. of the hydrochloride 233—235°C). 75
- 6 - (Imidazolin - 2' - ylmethyl) - 1 - isopropyl - 4 - methyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene. 80
- 6 - (Imidazolin - 2' - ylmethyl) - 9 - isopropyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

EXAMPLE 6

- Potassium cyanide (4.37 g.) in water (30 ml.) was added to 6 - dimethylaminomethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene methylodide (20 g.) in dioxan (150 ml.), and the mixture refluxed for two hours. After evaporation, the residue was extracted with ether, and the solvent removed to give, after crystallisation from hexane, solid 6 - cyano - methyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene, m.p. 65—70°C. The same method was used to prepare also the other nitriles mentioned in Examples 1 and 3. By reacting the nitriles with ethylenediamine mono p-toluene sulphonate, as described in Examples 2, 4 and 5, all the compounds mentioned in Examples 2, 4 and 5 could be obtained.
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EXAMPLE 7

- Ethylenediamine mono p-toluene sulphonate (16.5 g.) was added to 6 - carboxymethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene in ethanol (150 ml.) containing concentrated hydrochloric acid (10 ml.). The mixture was boiled for 15 hours, and evaporated to dryness, the residue was taken up in 5% sodium hydroxide and ether. Purification of the product and evaporation of the ether gave 6 - (imidazolin - 2' - ylmethyl) - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene free base, which in ethanol was converted to the hydrochloride, m.p. 250°C. Also the compounds mentioned in Example 2 and 5 could be obtained by using the same method, starting from the appropriate carboxymethylbenzo - norbornanes and carboxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalenes.
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WHAT WE CLAIM IS:—

1. A compound of general formula (I)



* C L M S *

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1,317,514

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- 6 - cyanomethyl - 7 - methyl - 1,4 - ethano-
1,2,3,4 - tetrahydronaphthalene, m.p.
89—91°C.
- 5 5 - cyanomethyl - 6,7 - dimethyl - 1,4-
ethano - 1,2,3,4 - tetrahydronaphthalene,
m.p. 131—4°C.
- 5 - methoxy - 6 - cyanomethyl - 1,4-
ethano - 1,2,3,4 - tetrahydronaphthalene,
m.p. 135—140°C.
- 10 5 - methoxy - 8 - cyanomethyl - 1,4-
ethano - 1,2,3,4 - tetrahydronaphthalene,
m.p. 95—97°C.
- 8 - methoxy - 6 - cyanomethyl - 1,4-
ethano - 1,2,3,4 - tetrahydronaphthalene
- 15 5 - hydroxy - 6 - cyanomethyl - 1,4-
ethano - 1,2,3,4 - tetrahydronaphthalene
- 5 - hydroxy - 8 - cyanomethyl - 1,4-
ethano - 1,2,3,4 - tetrahydronaphthalene
- 8 - hydroxy - 6 - cyanomethyl - 1,4-
ethano - 1,2,3,4 - tetrahydronaphthalene
- 20 9 - isopropyl - 6 - cyanomethyl - 1,4-
ethano - 1,2,3,4 - tetrahydronaphthalene
- 1 - isopropyl - 4 - methyl - 6 - cyano-
methyl - 1,4 - ethano - 1,2,3,4 - tetra-
hydronaphthalene.
- 25

EXAMPLE 4

- 6 - Cyanomethyl - 1,4 - ethano - 1,2,3,4-
tetrahydronaphthalene (31.4 g.) and ethylene-
diamine mono p-toluene sulphonate (37 g.)
30 were heated at 175°C for 4 hr., cooled and
stirred with dilute sodium hydroxide, and then
extracted with ethyl acetate. Evaporation of
the solvent gave, 6 - (imidazolin - 2' - yl-
methyl) - 1,4 - ethano - 1,2,3,4 - tetrahydro-
35 naphthalene free base which was converted, in
alcohol, to the hydrochloride, and precipitated
with ether to give, after crystallisation from
isopropanol-hexane, the solid hydrochloride,
m.p. 250°C.

EXAMPLE 5

- 6 - Cyanomethyl - 7 - methyl - 1,4 - ethano-
1,2,3,4 - tetrahydronaphthalene (37 g.) and
ethylenediamine mono p-toluene sulphonate
(40.7 g.) were heated for 5 hours at 180—
45 185°C, cooled to room temperature and stirred
vigorously with 5% sodium hydroxide (1 litre)
to give a solid which was filtered, washed
with water and dried, then crystallised with
isopropyl ether to give 6 - (imidazolin - 2'-
ylmethyl) - 7 - methyl - 1,4 - ethano - 1,2,3,4-
50 tetrahydronaphthalene free base (39.5 g.), m.p.
154—6°C. The hydrochloride prepared in the
usual way had m.p. 282—3°C. (methanol).

- The following free bases and respective
55 hydrochlorides were prepared in the same
way:

- 6 - (Imidazolin - 2' - ylmethyl) - 5-
methoxy - 1,4 - ethano - 1,2,3,4 - tetra-
hydronaphthalene.
- 60 6 - (Imidazolin - 2' - ylmethyl) - 8-
methoxy - 1,4 - ethano - 1,2,3,4 - tetra-
hydronaphthalene.

- 8 - (Imidazolin - 2' - ylmethyl) - 5-
methoxy - 1,4 - ethano - 1,2,3,4 - tetra-
hydronaphthalene. 65
- 6 - (Imidazolin - 2' - ylmethyl) - 5-
hydroxy - 1,4 - ethano - 1,2,3,4 - tetra-
hydronaphthalene.
- 6 - (Imidazolin - 2' - ylmethyl) - 8-
hydroxy - 1,4 - ethano - 1,2,3,4 - tetra-
70 hydronaphthalene.
- 8 - (Imidazolin - 2' - ylmethyl) - 5-
hydroxy - 1,4 - ethano - 1,2,3,4 - tetra-
hydronaphthalene.
- 5 - (Imidazolin - 2' - ylmethyl) - 6,7 - di-
methyl - 1,4 - ethano - 1,2,3,4 - tetra-
hydronaphthalene, (m.p. of the hydro-
chloride 233—235°C). 75
- 6 - (Imidazolin - 2' - ylmethyl) - 1 - iso-
propyl - 4 - methyl - 1,4 - ethano - 1,2,
3,4 - tetrahydronaphthalene. 80
- 6 - (Imidazolin - 2' - ylmethyl) - 9 - iso-
propyl - 1,4 - ethano - 1,2,3,4 - tetra-
hydronaphthalene.

EXAMPLE 6

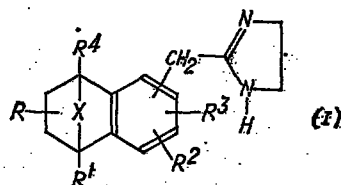
Potassium cyanide (4.37 g.) in water (30
ml.) was added to 6 - dimethylaminomethyl-
1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene
methyl iodide (20 g.) in dioxan (150 ml.), and
the mixture refluxed for two hours. After
evaporation, the residue was extracted with
ether, and the solvent removed to give, after
crystallisation from hexane, solid 6 - cyano-
methyl - 1,4 - ethano - 1,2,3,4 - tetrahydro-
90 naphthalene, m.p. 65—70°C. The same
method was used to prepare also the other
nitriles mentioned in Examples 1 and 3. By
reacting the nitriles with ethylenediamine
mono p-toluene sulphonate, as described in
Examples 2, 4 and 5, all the compounds men-
100 tioned in Examples 2, 4 and 5 could be
obtained.

EXAMPLE 7

Ethylenediamine mono p-toluene sulphonate
(16.5 g.) was added to 6 - carboxymethyl-
1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene
in ethanol (150 ml.) containing concentrated
hydrochloric acid (10 ml.). The mixture was
boiled for 15 hours, and evaporated to dryness,
the residue was taken up in 5% sodium
110 hydroxide and ether. Purification of the
product and evaporation of the ether gave 6-
(imidazolin - 2' - ylmethyl) - 1,4 - ethano-
1,2,3,4 - tetrahydronaphthalene free base,
which in ethanol was converted to the
115 hydrochloride, m.p. 250°C. Also the com-
pounds mentioned in Example 2 and 5 could
be obtained by using the same method, start-
ing from the appropriate carboxymethylbenzo-
norbornanes and carboxy - 1,4 - ethano - 1,2,
120 3,4 - tetrahydronaphthalenes.

WHAT WE CLAIM IS:—

1. A compound of general formula (I)



wherein X is an up to C₃ saturated or unsaturated divalent aliphatic hydrocarbon group; and each of R, R¹, R², R³ and R⁴, which may be the same or different, is a hydrogen atom, a hydroxy group, or a C₁₋₆ alkyl substituted or unsubstituted amino group, or a C₁₋₆ alkyl, C₂₋₆ alkenyl or C₁₋₆ alkoxy group, the aliphatic hydrocarbon, alkyl, alkenyl and alkoxy groups being either straight or branched chain; or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1 wherein X is a methylene or ethylene group, and each of R, R¹, R², R³ and R⁴, which may be the same or different, is a hydrogen atom, a hydroxy group, an unsubstituted amino group, or an alkyl, alkenyl or alkoxy group, or a pharmaceutically acceptable acid addition salt thereof.

3. A compound according to claim 1 or 2 in the form of a hydrochloride salt.

4. 6 - (Imidazolin - 2' - ylmethyl)benzonorbornane.

5. 6 - (Imidazolin - 2' - ylmethyl) - 7-methylbenzonorbornane.

6. 6 - (Imidazolin - 2' - ylmethyl) - 9-methylbenzonorbornane.

7. 6 - (Imidazolin - 2' - ylmethyl) - 1-methyl - 4 - isopropylbenzonorbornane.

8. 6 - (Imidazolin - 2' - ylmethyl) - 5-methoxybenzonorbornane.

9. 6 - (Imidazolin - 2' - ylmethyl) - 8-methoxybenzonorbornane.

10. 8 - (Imidazolin - 2' - ylmethyl) - 5-methoxybenzonorbornane.

11. 6 - (Imidazolin - 2' - ylmethyl) - 5-hydroxybenzonorbornane.

12. 6 - (Imidazolin - 2' - ylmethyl) - 8-hydroxybenzonorbornane.

13. 8 - (Imidazolin - 2' - ylmethyl) - 5-hydroxybenzonorbornane.

14. 6 - (Imidazolin - 2' - ylmethyl) - 9-isopropylidenebenzonorbornane.

15. 6 - (Imidazolin - 2' - ylmethyl) - 9 - isopropylbenzonorbornane.

16. 6 - (Imidazolin - 2' - ylmethyl) - 1,4-ethano - 1,2,3,4 - tetrahydronaphthalene.

17. 6 - (Imidazolin - 2' - ylmethyl) - 5-methoxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

18. 6 - (Imidazolin - 2' - ylmethyl) - 8-methoxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

19. 8 - (Imidazolin - 2' - ylmethyl) - 5-

methoxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

20. 6 - (Imidazolin - 2' - ylmethyl) - 5-hydroxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

21. 6 - (Imidazolin - 2' - ylmethyl) - 8-hydroxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

22. 8 - (Imidazolin - 2' - ylmethyl) - 5-hydroxy - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

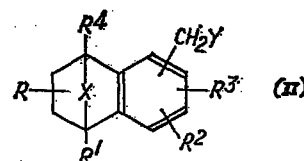
23. 6 - Imidazolin - 2' - ylmethyl) - 7-methyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

24. 5 - (Imidazolin - 2' - ylmethyl) - 6,7-dimethyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

25. 6 - (Imidazolin - 2' - ylmethyl) - 1-isopropyl - 4 - methyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

26. 6 - (Imidazolin - 2' - ylmethyl) - 9-isopropyl - 1,4 - ethano - 1,2,3,4 - tetrahydronaphthalene.

27. A process for preparing a compound according to any one of the preceding claims, the process comprising reacting ethylenediamine with a compound of general formula (II)



wherein X and R to R⁴ are as defined in claim 1, and Y is a cyano or carboxy group, and if desired converting the reaction product to an acid additional salt by reaction with the appropriate acid.

28. A process according to claim 27 substantially as described in any one of Examples 2, 4, 5 and 7.

29. A compound of general formula (I) prepared by a process according to claim 27 or 28.

30. A pharmaceutical composition comprising a compound according to any one of claims 1, 3, 9, 10, 12, 15, 19, 21 and 29, and a pharmaceutically acceptable carrier or diluent.

31. A pharmaceutical composition comprising a compound according to any one of claims 2, 4 to 8, 11, 13, 14, 16 to 18, 20 and 22 to 26, and a pharmaceutically acceptable carrier or diluent.

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