

PATENT SPECIFICATION

NO DRAWINGS

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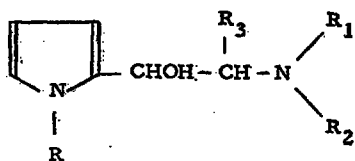
COMPLETE SPECIFICATION

Disubstituted Aminoethanols

We, WHITEFIN HOLDING S.A., of Viale C. Cattaneo 9, Lugano, Switzerland a company organised under the laws of the republic of Switzerland 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:—

The invention relates to N,N - disubstituted pyrrol - aminoethanols and methods for their preparation.

The N,N - disubstituted pyrrol - aminoethanols of the invention have the formula:



I

wherein R is an alkyl, aryl or arylalkyl group which may be substituted by one or more halogen atoms, alkyl, hydroxy, alkoxy, tri-fluoromethyl, nitro, amino, mono- or dialkylamino radicals;

R₁ is an alkyl or cycloalkyl radical;

R₂ is an alkyl, or arylalkyl group, or R₁ and R₂ taken together with the nitrogen atom to which they are attached represent a heterocyclic ring which may include a further hetero atom; and

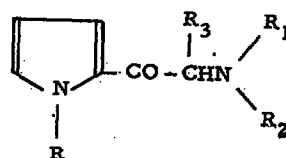
R₃ is a hydrogen atom or an alkyl radical and their salts with organic and inorganic acids and alkyl halides.

The invention includes pharmaceutical

[Price 4s. 6d.]

preparations containing the N,N - disubstituted pyrrol - aminoethanols of the invention or their physiologically tolerable salts with acids or alkyl halides in admixture or conjunction with a solid or liquid pharmaceutically acceptable carrier or diluent.

The N,N - disubstituted pyrrol - aminoethanols of the invention can be prepared according to the invention by reducing a compound of the formula:



II

wherein R, R₁, R₂ and R₃ have the meanings given above. The reduction is preferably carried out in the presence of an inert solvent with a reducing agent such as lithium aluminium hydride, sodium borohydride or aluminium isopropoxide at a temperature of from 0° to 90°C for a period of from 2 to 60 hours. This method is particularly useful for reducing the keto-group when there are present in the molecule other groups which may be affected by hydrogenation.

The starting materials of the formula II may be prepared according to the processes disclosed in our Patent Specification 21777/66 Serial No. 1,154,742.

The acid addition salts of the new compounds of the invention can be prepared in

the usual manner, that is by reacting the N,N - disubstituted pyrrol - aminoethanols with either the chemically equivalent amount of organic or inorganic acid in water or in a water - miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling, or an excess of the acid in a water - immiscible solvent, such as diethyl ether or chloroform, with the desired salt separating directly. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, methanesulphonic, benzenesulphonic and hydroxy - benzoic acids. The preferred salts of the invention are those with aromatic hydroxy - carboxylic acids—such as *p* - hydroxybenzoic, gentisic, gallic, protocatechuic, and β - resorcylic acid. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic and sulphuric acids. The quaternary ammonium salts of the invention can be prepared by reacting a N,N - disubstituted pyrrol - amino - ethanol of the general formula I with a lower alkyl halide, such as methyl bromide or methyl iodide.

The new compounds of the invention exhibit significant properties on the Central or Peripheral Nervous System. Particularly marked are the sedative and analgetic effects on the CNS. The analgetic activity has been tested in mice by the hot-plate test and by stretching by injection of acetic acid. With regard to last test the ED₅₀ values in mice of 1 - [α - (N - *o* - chloro - benzyl) - pyrrol] - 2 - disec. butylaminoethanol are 0.7 mg/100 g. subcutaneously and 1.5 mg/100 g. orally. By the oral route 1 - [α - (N - *o* - chloro - benzyl) - pyrrol] - 2 - disec. butylaminoethanol is three times more potent than codeine, nine times more than aminopyrine and twelve times more than acetylsalicylic acid. The peak analgetic effect occurs in 60 minutes, but the effect is marked also four hours after drug administration.

The study of the sedative activity has been carried out by testing:

- the behaviour of animals treated with the new compounds of the invention: reduction of motility and lessened reactivity was noted;
- the influence on the effects of subhypnotic and hypnotic doses of barbiturates;

c) the sedative effect on the cough centre previously excited by an ammoniacal aerosol in rat and by electrical stimulation of the superior laryngeal nerve in decerebrate cat. According to the last test the ED values are from 8 to 20 mg/kg in rat and from 5 to 10 mg/kg intraperitoneally in cat.

The new compounds of the invention have shown a very low toxicity: LD₅₀ values higher than 100 mg/kg by the intraperitoneal route in mice; higher than 400 mg/kg by the oral route in mouse and rat. A daily administration of 100 mg/kg by the oral route is acceptable in mouse and rat. A daily administration of 100 mg/kg for three months is well tolerated in rat. The examination of the tissues following slaughter did not reveal evidence of pathological changes and the hematologic values found were unaffected.

The new compounds of the invention can be administered orally, subcutaneously or intravenously in any pharmaceutical form suitable for these administration routes.

The following Examples illustrate the invention.

EXAMPLE I

5.4 g. (0.022 mol) of 1 - benzyl - 2 - dimethylaminoacetyl - pyrrole and 40 ml. of methyl alcohol are placed in a 100 ml. four-necked flask fitted with a stirrer, a dropping funnel, a reflux condenser and a thermometer. The solution is stirred and a mixture of 1.7 g. (0.044 mol) of sodium borohydride in 4 ml. of water is added slowly through the dropping funnel at such a rate that the solvent refluxes gently without external heating. When the addition is complete and the initial reaction subsides, the mixture is stirred and heated at gentle reflux for six hours. The solvents are distilled off under reduced pressure and the residue is suspended in water and shaken with diethyl ether. The ether extract is dried over anhydrous magnesium sulphate, the solvent is removed by evaporation under reduced pressure and the oily residue is fractionated. Yield of the desired 1 - [α - (N - benzyl) - pyrrol] - 2 - dimethylaminoethanol 4.9 g.; B.P. 120°C/0.4 mm Hg.

By analogous procedures the following compounds have been prepared:

- 1 - [α - (N - benzyl) - pyrrol] - 2 - diethyl - aminoethanol
- 1 - [α - (N - benzyl) - pyrrol] - 2 - dipropyl - aminoethanol
- 1 - [α - (N - benzyl) - pyrrol] - 2 - diisopropylaminoethanol
- 1 - [α - (N - benzyl) - pyrrol] - 2 - dibutyl - aminoethanol
- 1 - [α - (N - benzyl) - pyrrol] - 2 - diisobutylaminoethanol
- 1 - [α - (N - benzyl) - pyrrol] - 2 - disec. butylaminoethanol

B.P.=143°—145°C/0.5 mm Hg;

B.P.=160°—165°C/0.4 mm Hg;

B.P.=155°—160°C/0.4 mm Hg;

B.P.=158°—163°C/0.4 mm Hg;

B.P.=160°—165°C/0.4 mm Hg;

B.P.=150°—155°C/0.4 mm Hg;

	1 - [α - (N - benzyl) - pyrrol] - 2 - pyrrolidinoethanol	B.P.=148°—153°C/0.4 mm Hg;
	1 - [α - (N - benzyl) - pyrrol] - 2 - piperidinoethanol	M.P.=50°—52°C;
5	1 - [α - (N - benzyl) - pyrrol] - 2 - morpholinoethanol	M.P.=44°—47°C;
	1 - [α - (N - benzyl) - pyrrol] - 2 - (N' - benzyl - N' - methyl) - aminoethanol	B.P.=195°—200°C/0.2 mm Hg;
10	1 - [α - (N - benzyl) - pyrrol] - 2 - (N' - benzyl - N' - tert. - butyl) - aminoethanol	M.P.=123°—125°C;
	1 - [α - (N - methyl) - pyrrol] - 2 - pyrrolidinoethanol	M.P.=35°—46°C;
	1 - [α - (N - methyl) - pyrrol] - 2 - piperidinoethanol	M.P.=53°—54°C;
	1 - [α - (N - phenyl) - pyrrol] - 2 - diethyl - aminoethanol	B.P.=140°—145°C/0.3 mm Hg;
15	1 - [α - (N - phenyl) - pyrrol] - 2 - disec. - butylaminoethanol	B.P.=135°—140°C/0.3 mm Hg;
	1 - [α - (N - phenyl) - pyrrol] - 2 - pyrrolidinoethanol	B.P.=145°—150°C/0.1—0.2 mm Hg;
20	1 - [α - (N - phenyl) - pyrrol] - 2 - pyrrolidinoethanol hydrochloride	M.P.=119°—121°C;
	1 - [α - (N - phenyl) - pyrrol] - 2 - piperidinoethanol	B.P.=155°—160°C/0.1 mm Hg;
	1 - [α - (N - phenyl) - pyrrol] - 2 - piperidinoethanol hydrochloride	M.P.=140°—142°C (dec.);
25	1 - [α - (N - o - chlorobenzyl) - pyrrol] - 2 - diethylaminoethanol	B.P.=150°—155°C/0.2 mm Hg;
	1 - [α - (N - o - chlorobenzyl) - pyrrol] - 2 - disec.butylaminoethanol	B.P.=160°—165°C/0.1 mm Hg;
30	1 - [α - (N - o - chlorobenzyl) - pyrrol] - 2 - disec.butylaminoethanol <i>p</i> - hydroxy - benzoate	M.P.=128°—130°C (dec.);
	1 - [α - (N - o - chlorobenzyl) - pyrrol] - 2 - disec.butylaminoethanol α - resorcyate	M.P.=91°—94°C (dec);
35	1 - [α - (N - o - chlorobenzyl) - pyrrol] - 2 - disec.butylaminoethanol β - resorcyate	M.P.=72°—74°C (dec.);
	1 - [α - (N - o - chlorobenzyl) - pyrrol] - 2 - disec.butylaminoethanol protocate - chuate	M.P.=60°—70°C (dec.);
40	1 - [α - (N - o - chlorobenzyl) - pyrrol] - 2 - pyrrolidinoethanol	B.P.=150°—155°C/0.1 mm Hg;
	1 - [α - (N - o - chlorobenzyl) - pyrrol] - 2 - pyrrolidinoethanol hydrochloride	M.P.=137°—138°C;
	1 - [α - (N - benzyl) - pyrrol] - 2 - diethyl - aminopropanol hydrochloride	M.P.=140°—142°C (dec.);
45	1 - [α - (N - benzyl) - pyrrol] - 2 - pyrrolidinopropanol	B.P.=135°—140°C/0.1—0.2 mm Hg;
	1 - [α - (N - benzyl) - pyrrol] - 2 - pyrrolidinopropanol hydrochloride	M.P.=140°—142°C;
50	1 - [α - (N - benzyl) - pyrrol] - 2 - piperidinopropanol	B.P.=150°—155°C/0.1—0.2 mm Hg;
	1 - [α - (N - <i>p</i> - chlorobenzyl) - pyrrol] - 2 - diethylaminoethanol	B.P.=160°—165°C/0.1 mm Hg;
	1 - [α - (N - <i>p</i> - chlorobenzyl) - pyrrol] - 2 - disec.butylaminoethanol	B.P.=160°—165°C/0.3 mm Hg;
55	1 - [α - (N - chlorobenzyl) - pyrrol] - 2 - piperidinoethanol	B.P.=155°—160°C/0.1 mm Hg;
	1 - [α - (N - <i>p</i> - chlorobenzyl) - pyrrol] - 2 - piperidinoethanol hydrochloride	M.P.=134°—135°C;
60	1 - [α - (N - <i>p</i> - chlorobenzyl) - pyrrol] - 2 - pyrrolidinoethanol	B.P.=145°—155°C/0.1—0.2 mm Hg;
	1 - [α - (N - <i>p</i> - chlorobenzyl) - pyrrol] - 2 - pyrrolidinoethanol hydrochloride	M.P.=121°—122°C;

- 1 - [α - (N - ¹³ - chlorobenzyl) - pyrrol] -
2 - piperidinoethanol B.P.=140°—142°C/0.1 mm Hg;
1 - [α - (N - o - chlorobenzyl) - pyrrol] -
2 - piperidinoethanol hydrochloride M.P.=125°—126°C;
5 1 - [α - (N - o - chlorobenzyl) - pyrrol] - 2 -
disec.butylaminoethanol β - resorcylate M.P.=72°—74°C (dec.);
1 - [α - (N - ethyl)pyrrol] - 2 - diethylamino-
ethanol B.P.=94—96°C/0.4 mm Hg;
10 1 - [α - (N - benzyl) - pyrrol] - 2 - (N' -
benzyl - N' - ethyl) - aminoethanol B.P.=195°—200°C/0.2 mm Hg;
1 - [α - (N - ethyl) - pyrrol] - 2 - piperidino-
ethanol B.P.=105°—110°C/0.15 mm Hg;
1 - [α - (N - ethyl) - pyrrol] - 2 - disec. -
butylaminoethanol B.P.=100°—105°C/0.2 mm Hg;
15 1 - [α - (N - methyl) - pyrrol] - 2 - diethyl -
aminoethanol B.P.=90°—95°C/0.3 mm Hg;
1 - [α - (N - methyl) - pyrrol] - 2 - diethyl -
aminoethanol *p* - hydroxybenzoate M.P.=136°—137°C/ (dec.);
20 1 - [α - (N - *p* - methoxybenzyl) - pyrrol] -
2 - piperidinoethanol B.P.=175°—185°C/0.3 mm Hg;
1 - [α - (N - *p* - methoxybenzyl) - pyrrol] -
2 - piperidinoethanol oxalate M.P.=114°—115°C (dec.);
1 - [α - (N - 2,6 - xylyl) - pyrrol] - 2 -
pyrrolidinoethanol M.P.=150°—160°C/0.2 mm Hg;
25 1 - [α - (N - 2,6 - xylyl) - pyrrol] - 2 -
pyrrolidinoethanol oxalate M.P.=174°—175°C;
1 - [α - (N - *p* - bromobenzyl) - pyrrol] -
2 - pyrrolidinoethanol B.P.=160°—170°C/0.4 mm Hg;
30 1 - [α - (N - *p* - bromobenzyl) - pyrrol] -
2 - pyrrolidinoethanol picrate M.P.=131°—132°C;
1 - [α - (N - 2,6 - xylyl - pyrrol] - 2 -
piperidinoethanol B.P.=165°—170°C/2 mm Hg;
1 - [α - (N - 2,6 - xylyl - pyrrol] - 2 -
piperidinoethanol oxalate M.P.=163°—164°C (dec.);
35 1 - [α - (N - ethyl) - pyrrol] - 2 - pyrrolidino-
ethanol B.P.=115°—125°C/0.5 mm Hg;
1 - [α - (N - ethyl) - pyrrol] - 2 - pyrrolidino-
ethanol *p* - hydroxybenzoate M.P.=145°—147°C (dec.).

EXAMPLE II

- 40 10 g. (0.0278 mol) of 1 - (o - chloro) -
benzyl - 2 - disec. - butylaminoacetyl -
pyrrole and 300 ml. of anhydrous diethyl
ether are placed in a 500 ml. four-necked
45 flask fitted with a mercury-sealed stirrer, a
thermometer, a dropping funnel and a re-
flux condenser topped with a tube contain-
ing anhydrous calcium chloride. The solu-
tion is stirred and a mixture of 1g. (0.0264
50 mol) of lithium aluminium hydride in 20 ml.
of diethyl ether is added slowly through the
dropping funnel at such a rate that the sol-
vent refluxes gently without external heat-
ing. When the addition is complete and the
55 initial reaction subsides, the mixture is stirred
and heated at gentle reflux for two hours.
The mixture is cooled and the excess of
lithium aluminium hydride is decomposed
with cracked ice. The water layer is separ-
60 ated and washed with diethyl ether. The
combined ether extracts are dried over
anhydrous magnesium sulphate and the sol-
vent is removed by distillation under re-
duced pressure. The oily residue is fraction-

ated under reduced pressure. Yield of the
desired 1 - [α - (N - o - chlorobenzyl) -
pyrrol] - 2 - di - sec - butyl - amino -
ethanol 8.8 g.; B.P.=160°—165°C/0.1
mm Hg.

An exemplary capsule suitable for oral
administration has the following composi-
tion:

1 - [α - (N - o - chlorobenzyl) - pyrrol] - 2 - disec.butylamino - ethanol <i>p</i> - hydroxybenzoate	41.5 mg.	
Talcum	3 mg.	75
Dibasic calcium phosphate	63.5 mg.	
Magnesium stearate	2 mg.	
124.5 g. of 1 - [α - (N - o - chlorobenzyl) - pyrrol] - 2 - disec. - butylaminoethanol <i>p</i> - hydroxybenzoate, 9 g. of talcum, 190.5 g. of dibasic calcium phosphate and 6 g. of magnesium stearate are mixed and sieved twice through an 80 mesh sieve. The mixture is transferred into a mixer and allowed to turn for 15 minutes. With this mixture are filled 3000 No. 4 natural hard gelatin cap- sules.		80 85



WHAT WE CLAIM IS:—

1. A N,N - disubstituted pyrrol - amino - ethanol of the formula I hereinafter wherein R₁ is an alkyl, aryl or arylalkyl group which may be substituted by one or more halogen atoms, alkyl, hydroxy, alkoxy, tri - fluoromethyl, nitro, amino, mono - or di - alkylamino radicals.
2. R₁ is an alkyl or cycloalkyl radical.
3. R₁ is an alkyl or arylalkyl group, or R₁ and R₂ taken together with the nitrogen atom to which they are attached represent a heterocyclic ring which may include a further hetero atom; and
4. R₂ is a hydrogen atom or an alkyl radical or a salt thereof with an organic or inorganic acid or an alkyl halide.
5. 1 - [α - (N - benzyl) - pyrrol] - 2 - dimethylaminoethanol.
6. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
7. 1 - [α - (N - benzyl) - pyrrol] - 2 - dipropylaminoethanol.
8. 1 - [α - (N - benzyl) - pyrrol] - 2 - diisopropylaminoethanol.
9. 1 - [α - (N - benzyl) - pyrrol] - 2 - dibutylaminoethanol.
10. 1 - [α - (N - benzyl) - pyrrol] - 2 - diisobutylaminoethanol.
11. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
12. 1 - [α - (N - benzyl) - pyrrol] - 2 - diisobutylaminoethanol.
13. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
14. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
15. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
16. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
17. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
18. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
19. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
20. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
21. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
22. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
23. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
24. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
25. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
26. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
27. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
28. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
29. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
30. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
31. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
32. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
33. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
34. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
35. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
36. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
37. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
38. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
39. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
40. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
41. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
42. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
43. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
44. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
45. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
46. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
47. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
48. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
49. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
50. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
51. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
52. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
53. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
54. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
55. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
56. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
57. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
58. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
59. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
60. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
61. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
62. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
63. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
64. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.
65. 1 - [α - (N - benzyl) - pyrrol] - 2 - diethylaminoethanol.

55. 1 - [α - (N - 2,6 - xylyl - pyrrol) - 2 - piperidinoethanol oxalate.

56. 1 - [α - (N - ethyl) - pyrrol] - 2 - pyrrolidinoethanol.

57. 1 - [α - (N - ethyl) - pyrrol] - 2 - pyrrolidinoethanol *p* - hydroxybenzoate.

58. A process for the preparation of a N,N - disubstituted pyrrol - aminoethanol according to claim 1 which comprises reducing a compound of the formula II hereinbefore wherein R₁, R₂, R₃ and R₄ have the meanings given in claim 1 and where appropriate forming a salt with an organic or inorganic acid or an alkyl halide.

59. A process according to claim 58 in which the reduction is carried out in the presence of an inert solvent with lithium aluminium hydride, sodium borohydride or aluminium isopropoxide at a temperature of

from 0°—90°C for a period of from 2 to 60 hours.

60. A process for the preparation of a N,N - disubstituted pyrrol - aminoethanol substantially as hereinbefore described in any of the Examples.

61. A N,N - disubstituted pyrrol - aminoethanol prepared by a process according to any of claims 58, 59 or 60.

62. A pharmaceutical composition containing a N,N - disubstituted pyrrol - aminoethanol according to any of claims 1 to 57 and 61 in conjunction with a solid or liquid pharmaceutically acceptable diluent or carrier.

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