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(72) Inventor ROLAND SALZMANN

(54) PHARMACEUTICAL PREPARATIONS

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, 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 present invention relates to new pharmaceutical compositions.

The present invention provides a pharmaceutical composition incorporating as active agents

(a) a 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine or a 3 - hydrazino - cycloalkane[c]pyridazine; and

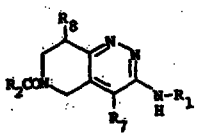
(b) a β - blocker.

The present invention also provides a process for the production of the above composition, including the step of bringing together active agents a) and b) in a purity sufficient for pharmaceutical acceptability.

Active agent a) may be separate from or admixed with active agent b).

The present invention provides a pack containing separately active agents a) and b) until required for concomitant administration as the above composition. Conveniently said pack may be together with, or in physical relation to, instructions for the concomitant administration of a predetermined anti-hypertensive amount of active agent a) and active agent b).

Especially suitable 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine derivatives are those of formula I,



I

wherein

R_1 is amino or

$$-N=C-R_3R_4,$$

wherein each of R_3 and R_4 is, independently, alkyl,

R_2 is alkyl of 1 to 6 carbon atoms, alkenyl of 3 to 6 carbon atoms, or $-OR_5$ or $-(CH_2)_nR_6$

wherein

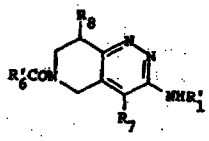
R_5 is alkyl of 1 to 4 carbon atoms, allyl, phenyl, or phenylalkyl (of 1 to 5 carbon atoms) which may be substituted in the phenyl radical by chlorine, methyl or methoxy,

n is 0, 1 or 2, and

R_6 is phenyl, or phenyl monosubstituted by fluorine, chlorine, bromine, alkyl of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms or alkyl (of 1 to 5 carbon atoms)thio, and

R_7 and R_8 are hydrogen or methyl.

Especially interesting antihypertensive compounds of formula I are compounds of formula Ia,



Ia

wherein

R_7 and R_8 are as defined above,

R_1' is amino or isopropylidenamino, and

R_6' is ethoxy, phenylethyl, phenyl, or phenyl substituted by fluorine or alkoxy of 1 to 5 carbon atoms.

Especially indicated for use in the combination of the invention are the following compounds:

3 - hydrazino - 5,6,7,8 - tetrahydro - 6 - (3 - phenylpropionyl) - pyrido[4,3 - c]-pyridazine, 6 - *p* - ethoxybenzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine, 3 - hydrazino - 5,6,7,8 - tetrahydro - 8 - methylpyrido[4,3 - c]pyridazine -

6 - carboxylic acid ethyl ester, 5,6,7,8 - tetrahydro - 3 - isopropylidenehydrazino - 6 - (3 - phenylpropionyl)pyrido - [4,3 - c]pyridazine, 6 - (*o* - fluorobenzoyl) - 5,6,7,8 - tetrahydro - 3 - isopropylidenehydrazino - pyrido[4,3 - c]-pyridazine, 5,6,7,8 - tetrahydro - 3 - isopropylidene - hydrazino - 8 - methylpyrido-[4,3 - c]pyridazine - 6 - carboxylic acid ethyl ester, 6 - (*o* - fluorobenzoyl) - 5,6,7,8 - tetrahydro - 3 - hydrazino - pyrido[4,3 - c]-pyridazine, and especially 5,6,7,8 - tetrahydro - 3 - isopropylidene - hydrazino - pyrido[4,3 - c]pyridazine - 6 - carboxylic acid ethyl ester, 5,6,7,8 - tetrahydro - 3 - isopropylidene - hydrazino - 4,8 - dimethylpyrido[4,3 - c]pyridazine - 6 - carboxylic acid ethyl ester, 3 - hydrazino - 5,6,7,8 - tetrahydro - 4,8 - dimethylpyrido[4,3 - c]-pyridazine carboxylic acid ethyl ester and 6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]pyridazine.

Further examples of suitable compounds of formula I are:

—3 - hydrazino - 5,6,7,8 - tetrahydro - 6 - (*o* - toluoyl)pyrido[4,3 - c]pyridazine, 3 - hydrazino - 5,6,7,8 - tetrahydro - 6 - pivaloyl - pyrido[4,3 - c]pyridazine, 3 - hydrazino - 5,6,7,8 - tetrahydro - 6 - (*p* - toluoyl)pyrido[4,3 - c]pyridazine, 6 - (*m* - chlorobenzoyl) - 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]-pyridazine, 6 - butyryl - 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]-pyridazine,

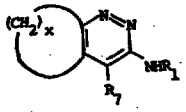
—as well as 5,6,7,8 - tetrahydro - pyrido-[4,3 - c]pyridazine carboxylic acid esters, such as

3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]pyridazine - 6 - carboxylic acid methyl ester, 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]-pyridazine - 6 - carboxylic acid benzyl ester, 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]pyridazine - 6 - carboxylic acid ethyl ester,

—and hydrazones, such as

3 - (2 - butylidenehydrazino) - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]pyridazine - 6 - carboxylic acid ethyl ester, and 6 - benzoyl - 3 - (2 - butylidenehydrazino) - 5,6,7,8 - tetrahydropyrido[4,3 - c]-pyridazine.

Especially suitable 3 - hydrazinocycloalkane[c]pyridazine derivatives are those of formula II,

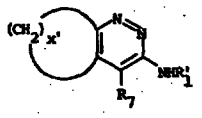


II

wherein

X is an integer from 4 to 6, and R_1 and R_7 are as defined above.

Especially interesting compounds of formula II are compounds of formula IIa,



IIa

wherein

R_1' and R_7 are as defined above, and X^1 is the integer 5 or 6.

Especially valuable representatives of this series are *inter alia*: 3 - hydrazino - 5,6,7,8,9,10 - hexahydrocycloocta[c]-pyridazine, 3 - hydrazino - 6,7,8,9 - tetrahydro(5H)cyclohepta[c]pyridazine, and especially 3 - hydrazino - 5,6,7,8,9,10 - hexahydro - 4 - methylcycloocta[c]pyridazine, and the 3 - isopropylidenehydrazino derivatives thereof.

Especially suitable β - blockers are compounds of formula III,



(III)

wherein

R is a homocyclic or heterocyclic radical containing at least one 6-membered aromatic radical, by which it is bound to the oxygen atom of the aminopropoxy radical, and

R_9 is alkyl of up to 5 carbon atoms, especially branched, alkyl radical.

R has preferably up to 13 carbon atoms, and may bear suitable substituents. Preferably R is fully unsaturated. Preferably the aminopropoxy group is bound through the oxygen atom thereof to a six-membered aromatic ring. Preferably the aminopropoxy group is ortho and meta to bonds forming any second ring joined to said aromatic ring. Preferably R_9 is isopropyl or tert. butyl. Preferably the hetero atom is nitrogen.

Especially suitable β - blockers in accordance with the invention are compounds of formula IIIa,



(IIIa)

wherein

R' is 4 - oxindolyl, 9 - fluorenon - 4 -yl, 1 - isoquinolinyl or 7 - chloro - 1 - isoquinolinyl, 4 - indolyl, 4 - (1 - methylindolyl), 4 - (3 - methylindolyl), 4 - (2 - acetylindolyl), 4 - (2 - A - 3 - B - indolyl),

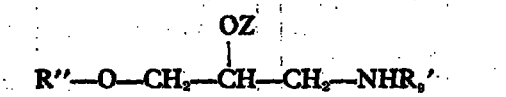
wherein

A is methyl, hydroxymethyl, carboxyl, carbalkoxy, carbamoyl, N - alkyl of 1 to 5 carbon atoms carbamoyl, N,N - dialkyl of 1 to 5 carbon atoms carbamoyl, carbazoyl or 3 - alkyl of 1 to 5 carbon atoms carbazoyl, and

B is hydrogen or methyl, and

R_9' is alkyl of 3 or 4 carbon atoms, branched on the α carbon atom.

In a preferred method of the invention β - blockers of formula IV,



wherein

R_9' is as defined above,

R'' is 4 - indolyl, 2 - methyl - 4 - indolyl, 4 - oxindolyl or 9 - fluorenon - 4 - yl, and

Z is hydrogen or the acyl radical of an aliphatic carboxylic acid,

are used.

Z in formula IV preferably is hydrogen or pivaloyl.

R_9' preferably is isopropyl or tert.butyl.

Examples of suitable compounds of formula IV are : 4 - (2 - hydroxy - 3 - isopropylaminopropoxy)indole, 4 - (2 - hydroxy - 3 - isopropylaminopropoxy) - 2 methylindole, 4 - (3 - tert.butylamino - 2 - pivaloyloxypropoxy) - 9 - fluorenone, and 4 - (3 - tert.butylamino - 2 - hydroxypropoxy) - 9 - fluorenone.

Examples of further suitable β - blockers in accordance with the invention are: 1 - (1 - isoquinolinyloxy) - 3 - (2 - methyl - 3 - butin - 2 - ylamino) - 2 - propanol, 1 - (4 - indolyloxy) - 3 - (2 - methyl - 3 - butin - 2 - ylamino) - 2 - propanol, 4 - [3 - (2 - methyl - 3 - butin - 2 - ylamino) - 2 - pivaloyloxypropoxy] - 9 - fluorenone, 4 - [2 - hydroxy - 3 - (2 - methyl - 3 - butin - 2 - ylamino)-propoxy]oxindole, and 4 - [3 - (2 - methyl - 3 - butin - 2 - ylamino) - 2 - pivaloyloxypropoxy]oxindole.

"Substituted" as used herein preferably means mono-substituted unless otherwise defined.

It will be appreciated that active agents a) and/or b) may be in free base form or in pharmaceutically acceptable acid addition salt form.

Examples of acids which form suitable physiologically tolerable acid addition salt forms with β - blockers are: hydrochloric, hydrobromic, sulphuric, fumaric malonic and maleic acid.

Examples of acids for pyridazines are: hydrochloric, fumaric methane sulphonic, and gentianic acid.

The pyridazines and the indicated β - blockers are known or may be produced in accordance with known processes.

The combination of active agent a) and active agent b) exhibits a synergistic increase in anti-hypertensive effect and a synergistic decrease in induced tachycordia, as indicated by standard tests in animals, e.g. in renal hypertonic dogs (Goldblatt method) and in renal hypertonic rats (Grollmann method) as concomitant administration of an anti-hypertensive pyridazine and a β - blocker.

The combination of active agents a) and b) is thereof indicated for use as an anti-hypertensive preparation. An indicated daily dose of active agent a) is from about 2 to about 200 mg conveniently administered 2 to 4 times a day in unit dosage form containing from about 0.5 to about 100 mg, or in sustained release form.

The indicated weight ratio of active agent a) to active agent b) is from about 200:1 to about 1:50, e.g. below 50:1 and above 1:10. For example said weight ratio may be from about 12:1 to about 1:6, or from about 10:1 to 1:10.

A preferred range of said weight ratio is from about 4:1 to 1:4, especially 1:1.

The condition to be treated will naturally also have to be taken into consideration when determining the dose. Thus, the dose of the β - blocker 4 - (2 - hydroxy - 3 -isopropylamino - propoxy)indole may vary, for example, from twice 2.5 mg to twice 15 mg/day, and that of the pyridazine - 6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido-[4,3 - c]pyridazine from twice 2.5 mg to approximately twice 30 mg/day.

Thus, particularly good results are obtained with the daily combined administration of 5 mg of 6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine together with 5 mg of 4 - (3 - tert.butylamino - 2 - pivaloyloxypropoxy) - 9 - fluorenone, i.e. at a ratio of 1:1. If desired, the dose of the pyridazine or the β - blocker in the latter combination may be increased to 20 mg daily, corresponding to a ratio between 4:1 and 1:4.

The combination of the invention may be used on its own or in the form of an appropriate preparation for enteral or parenteral administration. The active components may be combined in a single preparation or may be administered separately, e.g. in the form of a double pack.

The production of the combination of the invention may be effected by mixing the components in accordance with known methods, for example with reference to the Examples hereafter. The form suitable for enteral administration, e.g. tablets, mantle tablets containing two kernels, layer tablets, dragées,

capsules, suppositories, is of practical importance for administration of the combination of the invention.

Examples of suitable pharmacologically inert adjuvants are:

for tablets and dragées: lactose, starch, talc, stearic acid,
for injectable solutions: water, alcohols, glycerin, vegetable oils,
for suppositories: natural or hardened fats.

The preparations of the invention may further contain other therapeutically valuable compounds and preserving, stabilizing or wetting agents, solubilizers, sweetening or colouring substances and flavourings.

EXAMPLE 1: Tablets

6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido-[4,3 - c]pyridazine	10 mg
4 - (2 - hydroxy - 3 - isopropylaminopropoxy)indole	10 mg
magnesium stearate	1 mg
polyvinylpyrrolidone	4 mg
talc	5 mg
maize starch	10 mg
lactose	158 mg
dimethylsilicone oil	0.5 mg
polyethylene glycol 6000	1.5 mg
for a tablet of	200.0 mg

The active ingredients are mixed with the magnesium stearate, polyethylene glycol 6000, polyvinylpyrrolidone, talc, maize starch and lactose.

The mixture is moistened with water and kneaded until it can be granulated. The resulting mixture is granulated with a suspension of dimethylsilicone oil in water, is dried, and the dried and sieved granulate is pressed into tablets.

EXAMPLE 2: Tablets

6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido-[4,3 - c]pyridazine	5 mg
4 - (3 - tert.butylamino - 2 - pivaloyloxypropoxy) - 9 - fluorenone	20 mg
lactose	62 mg
wheat starch	45 mg
colloidal silicic acid	5 mg
polyvinylpyrrolidone	5 mg
talc	7 mg
magnesium stearate	1 mg
for a tablet of	150 mg

The active ingredients are mixed with the lactose, the colloidal silicic acid and part of the wheat starch. The mixture is passed through a sieve and kneaded with an aqueous/alcoholic solution of polyvinylpyrrolidone until a plastic mass results. This is passed through a sieve, is dried, and the dry granulate is again sieved. The remaining wheat starch, talc and magnesium stearate are subsequently admixed, and the mixture is pressed into tablets.

EXAMPLE 3:

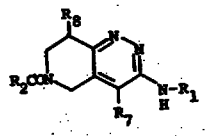
The β - blocker and/or the pyridazine used in Example 1 or 2 is replaced by a corresponding amount of a β - blocker and/or pyridazine listed in the description.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition incorporating as active agents
(a) a 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine or a 3 - hydrazino - cycloalkane[c]pyridazine; and
(b) a β - blocker.

2. A composition of claim 1 wherein active agent a) is a 3 - hydrazino - 5,6,7,8 - tetrahydro[4,3 - c]pyridazine.

3. A composition of claim 2, wherein active agent a) is of formula I,



I

wherein

R_1 is amino or

$$-N=C-R_3R_4,$$

wherein each of R_3 and R_4 is, independently, alkyl,

R_2 is alkyl of 1 to 6 carbon atoms, alkenyl of 3 to 6 carbon atoms, or $-OR_5$ or $-(CH_2)_nR_6$

wherein

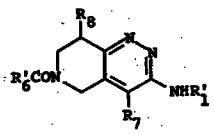
R_5 is alkyl of 1 to 4 carbon atoms, allyl, phenyl, or phenylalkyl (of 1 to 5 carbon atoms) which may be substituted in the phenyl radical by chlorine, methyl or methoxy,

n is 0, 1 or 2, and

R_6 is phenyl, or phenyl monosubstituted by fluorine, chlorine, bromine, alkyl of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms or alkyl (of 1 to 5 carbon atoms)thio, and

R_7 and R_8 are hydrogen or methyl.

4. A composition of claim 3, wherein active agent a) is of formula Ia,



Ia

capsules, suppositories, is of practical importance for administration of the combination of the invention.

Examples of suitable pharmacologically inert adjuvants are:

for tablets and dragées: lactose, starch, talc, stearic acid,
for injectable solutions: water, alcohols, glycerin, vegetable oils,
for suppositories: natural or hardened fats.

The preparations of the invention may further contain other therapeutically valuable compounds and preserving, stabilizing or wetting agents, solubilizers, sweetening or colouring substances and flavourings.

EXAMPLE 1: Tablets

6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido-[4,3 - c]pyridazine	10 mg
4 - (2 - hydroxy - 3 - isopropyl-aminopropoxy)indole	10 mg
magnesium stearate	1 mg
polyvinylpyrrolidone	4 mg
talc	5 mg
maize starch	10 mg
lactose	158 mg
dimethylsilicone oil	0.5 mg
polyethylene glycol 6000	1.5 mg
for a tablet of	200.0 mg

The active ingredients are mixed with the magnesium stearate, polyethylene glycol 6000, polyvinylpyrrolidone, talc, maize starch and lactose.

The mixture is moistened with water and kneaded until it can be granulated. The resulting mixture is granulated with a suspension of dimethylsilicone oil in water, is dried, and the dried and sieved granulate is pressed into tablets.

EXAMPLE 2: Tablets

6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido-[4,3 - c]pyridazine	5 mg
4 - (3 - tert.butylamino - 2 - pivaloyloxypropoxy) - 9 - fluorenone	20 mg
lactose	62 mg
wheat starch	45 mg
colloidal silicic acid	5 mg
polyvinylpyrrolidone	5 mg
talc	7 mg
magnesium stearate	1 mg
for a tablet of	150 mg

The active ingredients are mixed with the lactose, the colloidal silicic acid and part of the wheat starch. The mixture is passed through a sieve and kneaded with an aqueous/alcoholic solution of polyvinylpyrrolidone until a plastic mass results. This is passed through a sieve, is dried, and the dry granulate is again sieved. The remaining wheat starch, talc and magnesium stearate are subsequently admixed, and the mixture is pressed into tablets.

EXAMPLE 3:

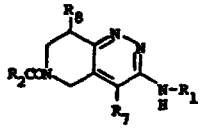
The β - blocker and/or the pyridazine used in Example 1 or 2 is replaced by a corresponding amount of a β - blocker and/or pyridazine listed in the description.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition incorporating as active agents
(a) a 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine or a 3 - hydrazino - cycloalkane[c]pyridazine; and
(b) a β - blocker.

2. A composition of claim 1 wherein active agent a) is a 3 - hydrazino - 5,6,7,8 - tetrahydro[4,3 - c]pyridazine.

3. A composition of claim 2, wherein active agent a) is of formula I,



I

wherein

R_1 is amino or

$$—N=C—R_3R_4,$$

wherein each of R_3 and R_4 is, independently, alkyl,

R_2 is alkyl of 1 to 6 carbon atoms, alkenyl of 3 to 6 carbon atoms, or $—OR_5$ or $—(CH_2)_nR_6$

wherein

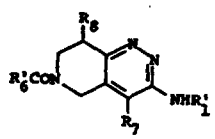
R_5 is alkyl of 1 to 4 carbon atoms, allyl, phenyl, or phenylalkyl (of 1 to 5 carbon atoms) which may be substituted in the phenyl radical by chlorine, methyl or methoxy,

n is 0, 1 or 2, and

R_6 is phenyl, or phenyl monosubstituted by fluorine, chlorine, bromine, alkyl of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms or alkyl (of 1 to 5 carbon atoms)thio, and

R_7 and R_8 are hydrogen or methyl.

4. A composition of claim 3, wherein active agent a) is of formula I*a*,



Ia

wherein

R_7 and R_8 are as defined in claim 3,
R_1' is amino or isopropylidenamino, and
R_6' is ethoxy, phenylethyl, phenyl, or phenyl substituted by fluorine or alkoxy of 1 to 5 carbon atoms.

5. A composition of claim 3 or 4, wherein R_7 and R_8 are both hydrogen.

6. A composition of claim 4, wherein active agent a) is 6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine.

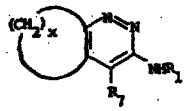
7. A composition of claim 4, wherein active agent a) is 5,6,7,8 - tetrahydro - 3 - isopropylidene - hydrazinopyrido[4,3 - c]-pyridazine - 6 - carboxylic acid ethyl ester.

8. A composition of claim 1, wherein active agent a) is chosen from the following:— 3 - hydrazino - 5,6,7,8 - tetrahydro - 6 - (*o* - toluoyl)pyrido[4,3 - c]pyridazine, 3 - hydrazino - 5,6,7,8 - tetrahydro - 6 - pivaloyl - pyrido[4,3 - c]pyridazine, 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]-pyridazine - 6 - carboxylic acid ethyl ester, 3 - (2 - butylidenehydrazino) - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]pyridazine - 6 - carboxylic acid ethyl ester, 6 - benzoyl - 3 - (2 - butylidenehydrazino) - 5,6,7,8 - tetrahydro-pyrido[4,3 - c]pyridazine, 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]-pyridazine - 6 - carboxylic acid methyl ester, 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido-[4,3 - c]pyridazine - 6 - carboxylic acid benzyl ester, 6 - butyryl - 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]-pyridazine, 3 - hydrazino - 5,6,7,8 - tetrahydro - 6 - (*p* - toluoyl)pyrido[4,3 - c]-pyridazine, 6 - (*m* - chlorobenzoyl) - 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido-[4,3 - c]pyridazine, 3 - hydrazino - 5,6,7,8 - tetrahydro - 6 - (3 - phenylpropionyl) - pyrido[4,3 - c]pyridazine.

9. A composition of claim 1, wherein active agent a) is chosen from the following:— 6 - *p* - ethoxybenzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine, 3 - hydrazino - 5,6,7,8 - tetrahydro - 8 - methylpyrido[4,3 - c]pyridazine - 6 - carboxylic acid ethyl ester, 5,6,7,8 - tetrahydro - 3 - isopropylidenehydrazino - 6 - (3 - phenylpropionyl)pyrido[4,3 - c]pyridazine, 6 - (*o* - fluorobenzoyl) - 5,6,7,8 - tetrahydro - 3 - isopropylidenehydrazino - pyrido[4,3 - c]-pyridazine, 5,6,7,8 - tetrahydro - 3 - isopropylidene - hydrazino - 8 - methylpyrido-[4,3 - c]pyridazine - 6 - carboxylic acid ethyl ester, 6 - (*o* - fluorobenzoyl) - 5,6,7,8 - tetrahydro - 3 - hydrazino - pyrido[4,3 - c]-pyridazine, 5,6,7,8 - tetrahydro - 3 - isopropylidene - hydrazino - 4,8 - dimethyl-pyrido[4,3 - c]pyridazine - 6 - carboxylic acid ethyl ester, 3 - hydrazino - 5,6,7,8 - tetrahydro - 4,8 - dimethylpyrido[4,3 - c]-pyridazine - 6 - carboxylic acid ethyl ester and 6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]pyridazine.

10. A composition of claim 1, wherein active agent a) is a 3 - hydrazino - cycloalkane[c]pyridazine.

11. A composition of claim 10, wherein active agent a) is of formula II,



II

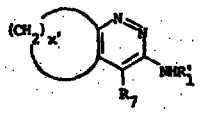
wherein

X is an integer from 4 to 6,
R_1 is amino or

$$-N=C-R_3R_4,$$

wherein each of R_3 and R_4 is, independently, alkyl, and
R_7 is hydrogen or methyl.

12. A composition of claim 11, wherein active agent a) is of formula II*a*,



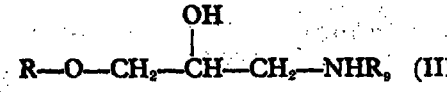
II*a*

wherein

R_1' is amino or isopropylidenamino,
R_7 is as defined in claim 11, and
X' is 5 or 6.

13. A composition of claim 12, wherein active agent b) is chosen from 3 - hydrazino - 5,6,7,8,9,10 - hexahydrocycloocta[c]pyridazine, 3 - hydrazino - 6,7,8,9 - tetrahydro(5H)-cyclohepta[c]pyridazine, 3 - hydrazino - 5,6,7,8,9,10 - hexahydro - 4 - methylcycloocta[c]pyridazine, and the 3 - isopropylidene - hydrazino derivatives thereof.

14. A composition according to any preceding claims, wherein active agent b) is of formula III,



$$R-O-CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-NHR_9 \quad \text{(III)}$$

wherein

R is a homocyclic or heterocyclic radical containing at least one 6 - membered aromatic radical, by which it is bound to the oxygen atom of the aminopropoxy radical, and
R_9 is an alkyl of 1 to 5 carbon atoms.

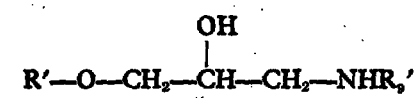
15. A composition according to claim 14, wherein in formula III

i) R has up to 13 carbon atoms, and is fully unsaturated, and

ii) the aminopropoxy group is bound through the oxygen atom thereof to a six-membered aromatic ring and is ortho and meta to bonds forming any second ring joined to said aromatic ring,

iii) R_9 is isopropyl or tert. - butyl.

16. A composition according to claim 15, wherein the active agent b) is of formula III*a*,



$$R'—O—CH_2—CH(OH)—CH_2—NHR_9' \quad (III a)$$

wherein

R' is 4 - oxindolyl, 9 - fluorenon - 4 - yl, 1 - isoquinolinyl or 7 - chloro - 1 - isoquinoninyl, 4 - indolyl, 4 - (1 - methylindolyl), 4 - (3 - methylindolyl), 4 - (2 - acetylindolyl), 4 - (2 - A - 3 - B - indolyl),

wherein

A is methyl, hydroxymethyl, carboxyl, carbalkoxy, carbamoyl, N - alkyl of 1 to 5 carbon atoms carbamoyl, N,N - di - alkyl of 1 to 5 carbon atoms carbamoyl, carbazoyl or 3 - alkyl of 1 to 5 carbon atoms carbazoyl, and

B is hydrogen or methyl, and

R_9' is alkyl of 3 or 4 carbon atoms, branched on the α carbon atom.

17. A composition of claim 1, wherein active agent b) is of formula IV,



$$R''—O—CH_2—CH(OZ)—CH_2—NHR_9'$$

wherein

R_9' is alkyl of 1 to 5 carbon atoms,

R'' is 4 - indolyl, 2 - methyl - 4 - indolyl, 4 - oxindolyl or 9 - fluorenon - 4 - yl, and

Z is hydrogen or the acyl radical of an aliphatic carboxylic acid.

18. A composition according to any preceding claim wherein active agent b) is 4 - (2 - hydroxy - 3 - isopropylaminopropoxy)indole.

19. A composition according to any one of claims 1 to 17, wherein active agent b) is 4 - (3 - tert.butylamino - 2 - pivaloyloxypropoxy) - 9 - fluorenone.

20. A composition according to any one of claims 1 to 17, wherein active agent b) is chosen from the following : 4 - (2 - hydroxy - 3 - isopropylaminopropoxy) - 2 - methylindole, 4 - (3 - tert.butylamino - 2 - hydroxypropoxy) - 9 - fluorenone.

21. A composition according to any one of claims 1 to 17, wherein active agent b) is chosen from the following: 1 - (1 - isoquinolinyloxy) - 3 - (2 - methyl - 3 - butin - 2 - ylamino) - 2 - propanol, 1 - (4 - indolyloxy) - 3 - (2 - methyl - 3 -butin - 2 - ylamino) - 2 - propanol, 4 - [3 - (2 - methyl - 3 - butin - 2 - ylamino) - 2 - pivaloyloxypropoxy] - 9 - fluorenone, 4 - [2 - hydroxy - 3 - (2 - methyl - 3 - butin - 2 - ylamino)propoxy]oxindole, and 4 - [3 - (2 - methyl - 3 - butin - 2 - ylamino) - 2 - pivaloyloxypropoxy]oxindole.

22. A composition according to any preceding claim wherein the weight ratio of active agent a) to active agent b) is from 200:1 to 1:50.

23. A composition according to claim 22, wherein the said weight of active agent a) is less than 50 times the weight of active agent b).

24. A composition according to claim 22 or 23, wherein the said weight of active agent a) is more than one tenth the weight of active agent b).

25. A composition according to claim 22, wherein the said weight ratio is from 12:1 to 1:6.

26. A composition according to claim 22 wherein the said weight ratio is from 10:1 to 1:10.

27. A composition according to claim 26, wherein the said weight ratio is from 4:1 to 1:4.

28. A composition according to claim 22, wherein the said weight ratio is substantially 1:1.

29. A composition according to claim 27 containing as active agent a):—

6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]pyridazine

and as active agent b):—

4 - (3 - tert.butylamino - 2 - pivaloyloxypropoxy) - 9 - fluorenone.

30. A composition according to claim 28 containing as active agent a):

6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydro - pyrido[4,3 - c]pyridazine

and as active agent b):

4 - (2 - hydroxy - 3 - isopropylaminopropoxy)indole.

31. A composition according to any preceding claim in unit dosage form.

32. A composition according to claim 31, wherein active agent a) is present in an amount of from 2.5 mg to 30 mg per dosage unit.

33. A composition according to any one preceding claim, wherein active agent a) is admixed with active agent b).

34. A pack containing separately active agent a) and b) until required for concomitant administration as a composition as claimed in any one of claims 1 to 32.

35. A pack according to claim 34 together with instructions for the concomitant administration of a predetermined anti-hypertensive amount of active agent a) and active agent b).

36. A process for the production of a composition according to any one preceding claim, including the step of bringing together active agents a) and b) in a purity sufficient for pharmaceutical acceptability.

37. A process for the production of a composition according to claim 1 substantially as hereinbefore described with reference to the Examples.

38. A composition whenever produced by the process claimed in claim 36 or 37.

B. A. YORKE & CO.,
Chartered Patent Agents,
98, The Centre,
Feltham,
Middlesex, TW13 4EP.
Agents for the Applicants.

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