1219 176

PATENT SPECIFICATION (11) 1219 176

NO DRAWINGS

(21) Application No. 16480/68 (22) Filed 5 April 1968

(45) Complete Specification published 13 Jan. 1971

(51) International Classification A 61 k 27/00

(52) Index at acceptance

A5B 330 33Y 382 384 38Y 420 42Y 446 44Y 480 482 48Y 501 502 50Y 510 513 51Y 541 54Y 566 56Y 585 586 58Y 595 596 59Y 650 651 65Y 77Y

C2C 173—197—288 1E1K4 215 247 250 251 25Y 30Y 342 34Y 574 579 62X 790 79Y KF



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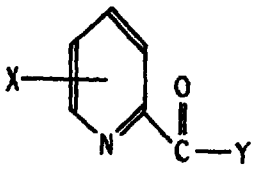
(54) ANTIHYPERTENSIVE COMPOSITIONS AND THEIR PREPARATION

(71) We, SCHERICO LTD., a Body Corporate constituted the laws of Switzerland, of Topferstrasse 5, Lucerne, 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:—

This invention relates to pharmaceutical compositions which may be used to elicit an anti-hypertensive effect in warm-blooded animals, and to processes for making them. More particularly, the invention is concerned with pharmaceutical compositions containing as an active hypotensive agent at least one compound of the general formula (I)



wherein X is hydrogen, lower alkyl, lower cycloalkyl, lower alkenyl, lower cycloalkenyl, lower alkoxy, lower cycloalkoxy phenyl, substituted phenyl, substituted or unsubstituted phenyl-lower alkyl, any substituent or substituents of the phenyl groups being halogen, trifluoromethyl, hydroxy, or lower alkoxy or lower cycloalkoxy and Y represents NHOH, OH, lower alkoxy, lower cycloalkoxy or, when X is other than hydrogen, then Y may also be $N<^{R_2}_{R_3}$ with R_2 and R_3 independently being hydrogen, lower alkyl or lower cycloalkyl and/or at least one salt of such a compound in admixture with a pharmaceutically acceptable carrier, provided that, when the carrier includes as the sole liquid solvent for the active ingredient a common solvent such as water or ethanol, the said solvent is sterile. Preferably R_2 and R_3 are independently hydrogen, *n*-lower alkyl or lower cycloalkyl.

Preferred, as active ingredients of the pharmaceutical compositions, are those compounds in which X is located at the 3-, 4- or 5-position. By the terms "lower alkyl", "lower alkoxy", "lower cycloalkyl" and "lower cycloalkoxy" as used herein and in the appended claims in connection with the X-substituent are meant straight or branched chain alkyl radicals, straight or branched chain alkoxy radicals, cycloalkyl radicals and cycloalkoxy radicals containing from 1 to 8 carbon atoms. Examples of such radicals include methyl, ethyl, n-butyl, isobutyl, isopropyl, cyclopropyl, cyclohexyl, cyclohexylmethyl, cyclopentyl, methoxy, ethoxy, propoxy, cyclopropoxy and n-butoxy.

By the terms "lower alkenyl" and "lower cycloalkenyl" as used herein and in the appended claims in connection with the X-substituent are meant straight or branched chain unsaturated radicals and cyclized unsaturated radicals containing from 3 to 6 carbon atoms, and, for purposes of illustration, embrace such radicals as allyl, butenyl and cyclopentyl. The preferred halogen substituents are chloro and bromo.

By the terms "lower alkyl" and "lower cycloalkyl" as used herein and in the claims in connection with the R_2- and R_3-substituents are meant alkyl and cycloalkyl groups containing from 1 to 8 carbon atoms such as, for example methyl, ethyl, propyl, cyclopropyl, n-butyl, iso-butyl and n-hexyl. Methyl and ethyl are the preferred substituents.

By the terms "lower alkoxy" and "lower cycloalkoxy" as used herein and in the claims in connection with the Y-substituent are meant alkoxy and cycloalkoxy groups, derived from aliphatic or cycloaliphatic alco-

hols containing from 1 to 8, generally 1 to 6, carbon atoms such, for example, as methanol, ethanol and propanol.

Examples of picolinic acid compounds of Formula I which can be utilised as the active ingredient in the compositions of this invention include the following.—5 - n - butylpicolinic acid; 5 - t - butylpicolinic acid; 5-propylpicolinic acid; 5 - cyclopropylpicolinic acid; 5 - ethylpicolinic acid; 5 - butenylpicolinic acid; 5 - cyclopentenylpicolinic acid; 5-methoxypicolinic acid; 5 - ethoxypicolinic acid; 5 - propoxy - picolinic acid; 5 - hexylpicolinic acid; 5 - cyclopentylpicolinic acid; 5 - isopropoxypicolinic acid; 5 - pentylpicolinic acid; 5 - phenylpicolinic acid; 5 - 3,4-dimethoxy - phenyl - picolinic acid; 5 - *p* - n-butylphenylpicolinic acid; 5 - *p* - chlorophenylpicolinic acid; 5 - cyclohexylpicolinic acid; 3 - n - butylpicolinic acid; 3 - t - butylpicolinic acid; 3 - propylpicolinic acid; 3 - isopropylpicolinic acid; 3 - cyclopropylpicolinic acid; 3 - ethylpicolinic acid; 3 - butenylpicolinic acid; 3 - cyclopentenylpicolinic acid; 3-methoxypicolinic acid; ethoxypicolinic acid; 3 - propoxypicolinic acid; 3 - hexylpicolinic acid; 3 - cyclopentylpicolinic acid; 3 - isopropoxypicolinic acid; 3 - pentylpicolinic acid; 3-phenylpicolinic acid; 3 - 3,4 - dimethoxyphenylpicolinic acid; 3 - *p* - n - butylphenylpicolinic acid; 3 - *p* - chlorophenylpicolinic acid; 3 - cyclohexylpicolinic acid; 5 - n-butyl - N,N - dimethylpicolinamide; 5 - cyclopentyl - N,N - dimethylpicolinamide; 5-cyclohexyl - N,N - dimethylpicolinamide; 5-phenyl - N,N - dimethylpicolinamide; 5 - n-butyl - picolinamide; 5 - n - butyl - N,N-diethylpicolinamide; 5 - cyclopentyl - N,N-diethylpicolinamide; 5 - cyclohexyl - N,N-diethylpicolinamide: 5 - phenyl - N,N - diethylpicolinamide; 5 - n - butyl - N - methylpicolinamide; 5 - (n - butyl) - picolinoylhydroxamic acid; 5 - (cyclo - pentyl) - picolinoylhydroxamic acid; ethyl - 5 - n - butylpicolinate; 5 - n - butyl - N - ethylpicolinamide; 5 - n - butyl - N - cyclopropylpicolinamide; 3 - n - butyl - N,N - dimethylpicolinamide; 3 - cyclopenyl dimethylpicolinamide; 3-cyclohexyl - N,N - dimethylpicolinamide; 3-phenyl - N,N - dimethylpicolinamide; 3 - n-butylpicolinamide; 3 - n - butyl - N,N - diethylpicolinamide; 3 - cyclopentyl - N,N-diethylpicolinamide; 3 - cyclohexyl - N,N-diethylpicolinamide; 3 - phenyl - N,N - diethylpocilinamide; 3 - n - butyl - N - methylpicolinamide; 3 - (n - butyl) - picolinoylhydroxamic acid; 3 - (cyclopenyl) - picolinoylhydroxamic acid; ethyl - 3 - n - butyl picolinate; 3 - n - butyl - N - ethylpicolinamide and 3-n - butyl - N - cyclo - propylpicolinamide.

The picolinic acid compounds, and their non-toxic functional derivatives are either compounds which are well-known and readily available, or they may be prepared by procedures analogues to those described in the art. For example, to prepare 5 - *n* - butylpicolinamide, 25 g. of 5 - n - butylpicolinic acid and 25 ml. of thionyl chloride are mixed together; after all of the acid has dissolved, the mixture is concentrated *in vacuo* and then taken up in 500 ml. of anhydrous benzene; the mixture is then added to a solution of excess ammonia in one liter of benzene, and the resulting mixture concentrated *in vacuo;* water and potassium carbonate are added and the amide extracted with ether; thereafter, the ether extract is dried and concentrated; the residual solid is recrystallised from acetonitrile. Similarly, other X-substituted picolinamides and picolinic acid esters may be prepared by standard amidation and esterification procedures.

The anti-hypertensive effect of the picolinic acid compounds was ascertained, and the therapeutically effective dosage determined, by standard pharmacological procedures. One such laboratory procedure is the Desoxycorticosterone Acetate Hypertension Test in the rat (DOCA - Hypertension - Rat) which may be described as follows:

Rats become hypertensive if a 25 mg. pellet of desoxycorticosterone acetate is subcutaneously implanted at the same time as 1 percent NaCl is substituted for normal drinking water. This hypertension passes through two phases. The first is that induced solely by the salt retaining effect of the mineralocorticoid and persists until the DOCA pellet is totally absorbed. This phase lasts some 6—10 weeks after implantation.

The second phase is a post-metacorticoid hypertension which is self-sustaining for as much as a year. This hypertension resembles human essential hypertension in several respects. Pathological changes observed in kidneys and heart are similar to those seen at post-mortem in untreated human essential hypertension. Furthermore, drugs which effect human hypertension also are similarly active in the rat.

The hypertensive rat is minimally restrained in a plastic chamber and a sphygmomanometer cuff is placed at the base of the tail. A sensitive condenser-microphone pickup is then taped to the tail. This device permits the electronic sensing and recording of the arterial pulse exactly as in classical sphygmomanometry.

The picolinic acid compounds were administered orally. Readings of systolic pressure were taken on an oscilloscope using an aneroid pressure sensor hourly after oral administration.

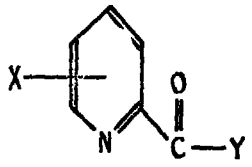
The hypotensive effect of a few of the picolinic acid compounds is indicated in the following table:—

Compound	Dose mg./kg.	No. of Rats	Pre-treatment Average Systolic Pressure	Maximal Post-treatment Systolic Pressure (mm Hg)	Percent Change
5-n-Butyl-N-methylpicolinamide	30	5	215	173	−19*
5-n-Butyl-N-methylpicolinamide	100	5	193	145	−25*
5-Ethylpicolinamide	30	10	179	162	−10*
5-Ethylpicolinamide	100	5	174	110	−37*
5-n-Butylpicolinamide	200	10	208	126	−40*
5-n-Butyl-N,N-dimethylpicolinamide	25	5	189	180	−11*
5-n-Butyl-N,N-dimethylpicolinamide	50	10	204	170	−17*
5-n-Butyl-N,N-dimethylpicolinamide	200	10	190	126	−39*

*Statistically significant effect (paired t-test; p 0.05).

From the foregoing test procedure, as well as by other standard laboratory techniques, the anti-hypertensive activity of the picolinic acid compounds is demonstrated.

Accordingly, this invention in another of its aspects, resides in a method of elliciting an anti-hypertensive response in a non-human animal which comprises the administration of dosage units of an anti-hypertensive composition comprising, as an active ingredient, a compound of the general formula



wherein X and Y are as hereinbefore defined, and/or a salt of such compounds.

The therapeutically effective dosage, as determined by procedures such as the one described hereinabove and also by comparison with other well-known hypotensive agents, is usually about 15—250 mg./kg. of body weight. Although it is expected that a therapeutically effective dosage will be administered about three times daily, the actual total daily dosage will depend upon the degree of severity of the hypertension, its cause and other health factors of the hypertensive warm-blooded mammal. Thus, in each specific instance the attending diagnostician will determine the dosage frequency and degree of lowering the high blood pressure.

The use of anti-hypertensive agents to reduce elevated blood pressure has gained wide

acceptance of recent years. The spectrum of drug types ranges from the very potent ganglionic blocking drugs to the mild diuretics of the benzothiadiazine type.

The development of some compounds currently used for anti-hypertensive therapy recognizes the role of the adrenergic nervous system, particularly epinephrine and norepinephrine, the latter being the predominant adrenergic neuromediator, in maintaining arterial pressure. Thus, α - adrenergic blocking compounds (phentolamine or dibenzyline), amine depleters (reserpine or syrosingopine), false transmitter-depleters (α - methyl dopa), and post-ganglionic adrenergic neurone blockers (guaonethidine or bretylium) all decrease arterial pressure by modulating some component(s) of the adrenergic nervous system.

Without wishing to suggest that this necessarily is the mechanism by which the picolinic acid compounds exert these hypotensive effects, the anti-hypertensive therapy of these compounds could involve enzyme inhibition of neurotransmitter synthesis. Since norepinephrine is the sympathetic neurohumoral transmitter which plays a key role in the maintenance of blood pressure, inhibition of its synthesis might be expected to yield an effective anti-hypertensive agent. Suppression of norepinephrine synthesis from its immediate precursor, dopamine, can be achieved by an adequate inhibition of the enzyme, dopamine β - hydroxylase. In their action in warm blooded animals it is found that the picolinic acid compounds are inhibitors of dopamine β - hydroxylase.

Using standard laboratory techniques it has also been found that the toxic dosage livels (LD_{50}) of the picolinic acid compounds are significantly greater than the minimal effective dosage necessary to achieve a hypotensive effect.

As is true for all classes of compounds useful in the treatment of physiological disorders, not all the members have the same order of activity. From the abovedescribed, and other, laboratory procedures it is determined that, in general, those picolinic acid compounds which have an X-substituent located at either the 5 - position or the 3 - position exhibit a more potent hypotensive effect than at the 4-position, with the 5 - position often preferred. Although the X-substituted picolinic acids have, in general, about the same activity as the amides, the overall pharmacological effect of the amides indicates, in many instances a more favorable therapeutic profile. The preferred X-substituent is lower alkyl, with the *n* - butyl substituent being the most preferred. Specific picolinic acid compounds which are of particular interest for their anti-hypertensive effect in warm-blooded animals are: 5 - n - butylpicolinamide; 5 - n - butylpicolinic acid; 5-n-butyl-N,N-dimethylpicolinamide; 5 - cyclopentylpicolinic acid; 5 - cyclopentylpicolinamide; 5 - cyclohexylpicolinic acid; 5 - phenylpicolinic acid; 3 - n - butylpicolinamide; 3 - n - butylpicolinic acid and 3 - n - butyl - N,N - dimethylpicolinamide.

The pharmaceutical compositions of this invention may take a variety of forms, depending primarily upon the mode of administration. In the various pharmaceutical compositions, the concentration of the active ingredient is such that an amount of composition which can be conveniently administered during each treatment contains a sufficient quantity of the active ingredient to elicit an appropriate and proper anti-hypertensive response. Generally, the compositions contain from 1 per cent to 99 per cent by weight of the picolinic acid compound, and from 1 per cent to 99 per cent by weight of a suitable pharmaceutical carrier compatible with the active ingredient, with a picolinic acid content of from 1 per cent to 50 per cent constituting a preferred range.

The novel pharmaceutical compositions provided by this invention are prepared utilising procedures known generally for the preparation of pharmaceutical compositions, all of which involve the deliberate association of the picolinic acid compound, as the active ingredient, with a pharmaceutical carrier.

The word "known" as used in the specification and in the appended claims, in relation to procedures for making the pharmaceutical compositions, designates procedures in actual use or described in the literature.

Compositions suitable for oral administration which is a convenient mode of administration, may be in the form, for example of tablets, capsules, powders, solutions, aqueous or oily suspensions or syrups, all of which contain the picolinic acid as the active ingredient, and a solid or liquid carrier compatible with the active ingredient, and which itself may be inert or pharmaceutically active.

In tablets, the picolinic acid compound, is associated with a suitable solid carrier such, for example, as gelatin, lactose, talc, stearic acid, acacia or a cellulosic material, in a finely divided particulate form. Generally, any of the tableting materials conventionally used in pharmaceutical practice can be employed if there is no incompatibility with the active ingredient. The tablets often include disintegrating agents such as maize or starch, and lubricating or mould-release agents such as magnesium stearate.

The tablets are typically made by admixing the active ingredient, a suitable carrier, a lubricant or mould -release agent, and a disintegrating agent, and compressing the mixture in a conventional tableting machine into tablets of a preselected size. Conveniently, each tablet contains from 50 to 250 milligrams of the active ingredient. The tablets can be scored so that they are easily broken. Optionally, the tablets can be coated with a tablet-

coating material in order to make them more attractive and palatable. They can also have an enteric coating so that they will release their ingredients slowly and over a longer period.

The capsules, which may be of hard or soft gelatin, are made by filling the shell with the proper amount of active ingredient and a solid filler, such as starch, gelatin, lactose, talc, stearic acid, or magnesium stearate. Such a capsule generally contains from 50 to 250 milligrams of active material, thus providing a minimum dose of active ingredient in a form convenient for oral administration.

In suspensions or syrups the pharmaceutical carrier is usually an aqueous vehicle such as an aromatic water, a syrup, or a pharmaceutical mucilage. Examples of suitable aromatic waters are the following: Anise water, N.F. (IX); Bitter Almond water, N.F. (VIII); Campher water, N.F.; Cinnamon water, U.S.P.; Fennel water, N.F.; Peppermint water, U.S.P. Spearmint water, N.F. (IX); Wintergreen water, N.F. (IX).

Examples of suitable syrups are the following: Syrup (simple syrup), U.S.P.; Acacia syrup, U.S.P.; Aromatic Eriodictyon syrup, N.F.; Aromatic Rhubarb syrup, N.F. (IX); Cacao syrup, U.S.P.; Cherry syrup, U.S.P.; Cinnamon syrup, N.F. (IX); Citric acid syrup, U.S.P.; Compound Sarsparilla syrup, N.F.; Compound White Pine syrup, N.F.; Ginger syrup, N.F. (IX).; Glycyrrhiza (Licorice) syrup, U.S.P.; Orange syrup, U.S.P.; Orange Flower syrup, N.F.; Raspberry syrup, U.S.P.; Tolu Balsam syrup, U.S.P.; Wild Cherry syrup, U.S.P.; Examples of suitable pharmaceutical mucilages include the following: Acacia (Gum Arabic), U.S.P.; Acacia mucilage, U.S.P.; Tragacanth, U.S.P.; Tragacanth mucilage, N.F. The pharmaceutical carrier in the suspensions or syrups can also be a hydroalcoholic vehicle, such as an elixir. Examples of suitable elixirs are the following: Aromatic elixir, U.S.P.; Red Aromatic elixir, N.F.! Glycyrrhiza elixir, N.F.; Iso-Alcoholic elixir (Iso-Elixir), N.F. Colouring agents, tinctures, spirits and other adjuvants can be admixed with the composition if desired. Normally, the suspension or syrups contain from about 1 per cent to about 6 per cent by weight of the picolinic acid compound, although lower or higher concentration can be employed.

Compositions suitable for parenteral administration, either instramuscularly or intravenously are typically sterile solutions and suspensions of the picolinic acid compound in aqueous or oily media. Usually these parenteral compositions are so proportioned as to afford from 1 to 125 gm. per liter of the steroid as the active ingredient. Particularly suitable picolinic acid compounds for use in these compositions are soluble alkali and alkaline earth metal derivatives, such as the sodium salt of the free acid.

A sterile solution suitable for injection may be prepared by admixing from 0.5 to 5 parts by weight of the active ingredient, preferably in the form of an alkali or alkaline earth metal salt, and from 95 to 99.5 parts by weight of water or isotonic saline solution at a temperature and for a time sufficient to dissolve the active ingredient. This solution is then sterilized by filtration or by the application of heat. The solution is preferably sterilized in an autoclave at a steam pressure of 15 pounds per square inch for from 5 to 15 minutes. The sterile solution may contain preservatives such as a mixture of methyl- and propylparaben benzoic acid, or other nontoxic antimicrobial agents.

These injectable solutions can be prepared with a high concentration of active ingredient. The solution is then diluted to a desired concentration before use.

The pharmaceutical compositions generally described in the foregoing may also include other active ingredients such as diuretics, especially the thiazide diuretics, and other known hypotensive agents, so as to achieve enhanced hypotensive effects.

The following examples show, by way of illustration only, some of the pharmaceutical compositions provided by this invention.

EXAMPLE 1

The composition of this Example is in the form of tablets:

Components	Amount (gms. per 1000 tablets)
5-n-Butylpicolinamide	200.0
Lactose	90.0
Dicalcium Phosphate, Hydrous	122.5
Polyvinylpyrrolidone	25.0
Polyvinylglycol M.W. = 1500	7.5
Corn starch	50.0
Magnesium stearate	5.0
	500.0

Procedure:

The 5 - n - butylpicolinamide, the lactose and the dicalcium phosphate are mixed together. The polyethylene glycol 1500 and the polyvinylpyrrolidone are dissolved in approximately 20 ml. of water. The powder blend is granulated with the water solution, additional water is added if necessary, and the damp mass so-obtained passed through a 12 mesh screen. The granules are then spread on trays and air-dried at 35° C. Thereafter, the dry granules are blended with the starch and the magnesium stearate and compressed into 500 mg. tablets.

EXAMPLE 2

The composition of this Example is in the form of capsules

Components	Amount (gms. per 1500 capsules)
5-n-Butylpicolinamide	200.0
Lactose	198.0
Magnesium stearate	2.0
	400.0

Procedure:

The ingredients are blended and then introduced into hard gelatin capsules.

EXAMPLE 3

The composition of this Example is in the form of an elixir.

Components		Amount (gms. per 1000/ml)
5-n-Butyl-N,N-dimethylpicolinamide		40.0
Sugar		500.0
Glycerin		200.0
Compound Orange spirit		10.0 ml.
Alcohol		100.0 ml.
Amaranth		0.1 ml.
Water	q.s.	1000.0 ml.

Procedure:

The 5 - n - butyl - N,N - dimethylpicolinamide, the sugar, the glycerin and the amaranth are successively dissolved in approximately 400 ml. of water with the aid of heat. The solution is cooled to room temperature, and the compound orange spirit dissolved in the alcohol and the alcoholic solution added to the elixir base. Sufficient water is added to make the product up to 1000 ml. The elixir is agitated until homogeneous, and then clarified by passing it through an asbestos pad, using a filter aid if necessary.

EXAMPLE 4

The composition of this Example is in the form of a sterile injectable.

Components		Amount (gms. per 1000 ampoules)
5-n-Butyl-N,N-dimethylpicolinamide		110.0
Water for Injection	q.s.	1100.0 ml.

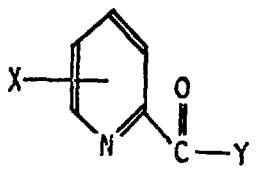
Procedure:

The 5 - n - butyl - N,N - dimethylpicolinamide is dissolved in the water for injection and the resulting solution passed through a sterile 0.45 micron membrane filter. It is then aseptically introduced into ampoules (1.1 ml. per ampoule). The sealed ampoules are autoclaved for 30 minutes under 20 p.s.i.g. steam pressure.

In order to achieve a satisfactory antihypertensive response, usually no more than 1 to 3 tablets or capsules as described above need be administered daily. The elixir described is usually administered in the amount of 1 to 3 teaspoons (5 cc.) per day while the usual injection dosage is 1 to 3 cc. per day. In severe or aggravated conditions, additional medication may be administered.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition useful in eliciting an anti-hypertensive effect which comprises, as an active ingredient, at least one compound of the general formula



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Water	q.s.	1000.0 ml.

Procedure:

The 5 - n - butyl - N,N - dimethylpicolinamide, the sugar, the glycerin and the amaranth are successively dissolved in approximately 400 ml. of water with the aid of heat. The solution is cooled to room temperature, and the compound orange spirit dissolved in the alcohol and the alcoholic solution added to the elixir base. Sufficient water is added to make the product up to 1000 ml. The elixir is agitated until homogeneous, and then clarified by passing it through an asbestos pad, using a filter aid if necessary.

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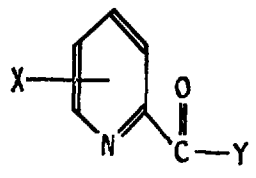


wherein X is hydrogen, lower alkyl, lower cyclo-alkyl, lower alkenyl, lower cycloalkenyl, lower alkoxy, lower cycloalkoxy, phenyl, substituted phenyl, substituted or unsubstituted

phenyl - lower - alkyl, any substituent or substituents of the phenyl groups being halogen, trifluoromethyl, hydroxy, lower alkoxy or lower cycloalkoxy and Y represents NHOH, OH, lower alkoxy, lower cycloalkoxy or, when X is other than hydrogen, then Y may also be $N<^{R_2}_{R_3}$ with R_2 and R_3 independently being hydrogen, lower alkyl or lower cycloalkyl, and/or at least one salt of such a compound, in admixture with a pharmaceutically acceptable carrier, provided that, when the carrier includes as the sole liquid solvent for the active ingredient a common solvent such as water or ethanol, the said solvent is sterile.

2. A composition according to Claim 1 in which R_2 and R_3 are independently hydrogen, *n* - lower alkyl or lower cycloalkyl.

3. A composition as claimed in claim 1 or claim 2 in which the substituent X is n-butyl.

4. A composition as claimed in any one of claims 1 to 3 in which the substituent X is located at the 3-position.

5. A composition as claimed in any one of claims 1 to 3 in which the substituent X is located at the 4-position.

6. A composition as claimed in any one of claims 1 to 3, in which the substituent X is located at the 5-position.

7. A composition as claimed in any one of claims 1 to 6, in which one of R_1 and R_3 is methyl, ethyl or cyclopropyl the other being hydrogen.

8. A composition as claimed in any one of claims 1 to 6, in which R_2 and R_3, which may be the same or different, are methyl or ethyl.

9. A composition as claimed in any one of claims 1 to 8, in which Y is methoxy or ethoxy.

10. A composition as claimed in claim 1, in which the active ingredient is 5 - n - butylpicolinamide.

11. A composition as claimed in claim 1 in which the active ingredient is 5 - n - butylpicolinic acid.

12. A composition as claimed in claim 1 in which the active ingredient is 5 - n - butyl-N,N - dimethylpicolinamide.

13. A composition as claimed in claim 1 in which the active ingredient is 5 - cyclopentylpicolinic acid.

14. A composition as claimed in any one of the preceding claims wherein the carrier comprises at least one ingredient selected from gelatin, lactose, talc, stearic acid, acacia or a cellulosic material, disintegrating agents such as maize or starch, lubricating or mould-release agents such as magnesium stearate, aromatic water, syrup, pharmaceutical mucilage, an elixir, colouring agents, tinctures, spirits, oily media, sterile water or isotonic saline solution, preservatives such as methylparaben, propylparaben, benzoic acid, and nontoxic antimicrobial agents.

15. A composition as claimed in any one of the preceding claims which comprises from 1 per cent to 50 per cent by weight of the said active compound and from 99 to 50 per cent by weight of the carrier.

16. A composition as claimed in claim 15 which comprises about 40 per cent by weight of the said active compound.

17. A composition as claimed in any one of the preceding claims which is in the form of dosage units.

18. A composition as claimed in claim 17, wherein the composition is in the form of a tablet, a pill or a capsule.

19. A composition as claimed in claim 17, wherein the composition is in the form of a solution, including an injectable solution, a suspension or a syrup.

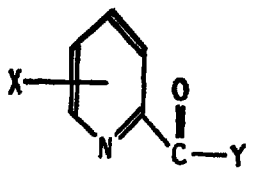
20. A composition as claimed in any of the preceding claims which contains one or more other active compounds displaying useful complementary effects, such as for example diuretics and other hypotensive agents.

21. A composition as claimed in any one of the preceding claims, which comprises 50 to 250 mg. of the compound of general formula I or a functional derivative thereof per dosage unit.

22. A composition as claimed in any one of the preceding claims, which comprises 110 to 200 mg. of the compound of general formula I or a functional derivative thereof per dosage unit.

23. A composition for use in eliciting an anti-hypertensive effect substantially as herein described, with particular reference to any of the foregoing Examples.

24. A process for preparing a pharmaceutical composition as claimed in any one of claims 1 and 3 to 23, useful in eliciting an anti-hypertensive effect, which comprises bringing an active ingredient of the general formula



(I)

wherein X is hydrogen, lower alkyl, lower cycloalkyl, lower alkenyl, lower cycloalkenyl, lower alkoxy, lower cycloalkoxy, phenyl, substituted phenyl, substituted or unsubstituted phenyl - lower - alkyl, any substitutents of the phenyl groups being halogen, trifluoromethyl, hydroxy, lower alkoxy or lower cycloalkoxy, and Y represents NHOH, OH, lower alkoxy, lower cycloalkoxy or, when X is other than hydrogen, then Y may also be $N<^{R_2}_{R_3}$

with R_2 and/or R_3 independently being hydrogen, lower alkyl or lower cycloalkyl, and/or a salt of such compounds into a form suitable for pharmaceutical administration.

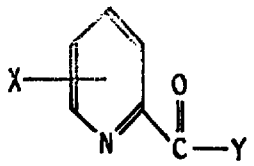
25. A process as claimed in claim 24 in which R_2 and R_3 are independently hydrogen, *n* - lower - alkyl or lower cycloalkyl.

26. A process as claimed in claim 24 or 25 which comprises admixing the active ingredient with a pharmaceutically acceptable carrier compatible therewith provided that, when the carrier includes as the sole liquid solvent for the active ingredient a common solvent such as water or ethanol, the said solvent is sterile.

27. A process as claimed in any one of claims 24 to 26 substantially as herein described with particular reference to any one of the Examples.

28. A method of eliciting an anti-hypertensive response in a non-human animal which comprises the administration of dosage units of an anti-hypertensive composition comprising, as an active ingredient, a compound of the general formula

(I)



wherein X is hydrogen, lower alkyl, lower cycloalkyl, lower alkenyl, lower cycloalkenyl, lower alkoxy, lower cycloalkoxy, phenyl, substituted phenyl, substituted or unsubstituted phenyl - lower - alkyl, any substituents of the concerned phenyl groups being halogen, trifluoromethyl, hydroxy, lower alkoxy or lower cycloalkoxy and Y represents NHOH, OH, lower alkoxy or, when X is other than hydrogen, then Y may also be $N<^{R_2}_{R_3}$ with R_2 and/R_3 independently being hydrogen, lower alkyl or lower cycloalkyl, and/or a salt of such compounds.

29. A method as claimed in claim 28 in which R_2 and R_3 are independently hydrogen, *n* - lower alkyl or lower cycloalkyl.

30. A method as claimed in claim 28 or 29, in which the composition is administered orally.

31. A method as claimed in claim 28 or 29, in which the composition is injected.

32. A method as claimed in any one of claims 28 to 31 wherein the active ingredient administered is 5 - n - butylpicolinamide.

33. A method as claimed in any one of claims 28 to 31 wherein the active ingredient administered is 5 - n - butylpicolinic acid.

34. A method as claimed in any one of claims 28 to 31 wherein the active ingredient administered is 5 - n - butyl - N,N - dimethylpocilinamide.

35. A method as claimed in any one of claims 28 to 31 wherein the active ingredient administered is 5 - cyclopentylpicolinic acid.

36. A method as claimed in any one of claims 28 to 35 in which the dosage unit contains from 50 to 250 mg. of said active ingredient.

37. A method as claimed in any one of claims 28 to 35 in which the dosage unit contains from 110 to 200 mg. of said active ingredient.

38. A method of eliciting an anti-hypertensive effect when treating non-human animals substantially as herein described.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1971.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

