995,398

PATENT SPECIFICATION

NO DRAWINGS

995,398

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Int. Cl.:—A 61 k 3/00 // C 07 c

COMPLETE SPECIFICATION

Novel Hypotensive Composition

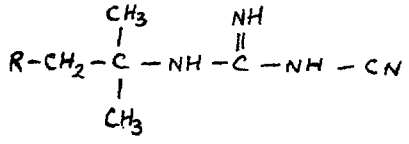
We, AMERICAN CYANAMID COMPANY, a corporation organised under the Laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel pharmaceutical compositions for the control of hypertension, and in particular to pharmaceutical compositions containing 1-substituted-3-cyanoguanidines which operate to reduce elevated blood pressures. The invention also relates to certain novel 1-substituted-3-cyanoguanidines.

Angiotensin is a polypeptide found naturally in the blood stream of the human body and is a potent pressor agent. In the field of hypertension, it is currently believed that angiotensinemia is involved in the genesis of the disease process and that a sustained elevation of mean blood pressure results in a poor prognosis for life. Furthermore, it is generally acknowledged that a drug which could antagonize the effects of angiotensin and reduce elevated blood pressure without producing untoward effects would be of value in the treatment of hypertension.

Our invention is based upon the discovery that certain 1-substituted-3-cyanoguanidines possess excellent activity as potent hypotensive agents coupled with antiangiotensin activity. The action of these 1-substituted-3-cyanoguanidines is that of long lasting vasodilation, rather than that of adrenergic or ganglionic blockade.

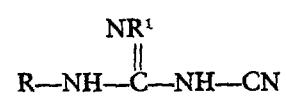
Thus, in accordance with one aspect of the invention, there is provided a pharmaceutical composition for the control of hypertension comprising a compound of the formula:



I

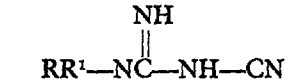
wherein R is hydrogen or an alkyl group having from 1 to 3 carbon atoms, or a non-toxic acid-addition salt thereof, and an edible pharmaceutically acceptable carrier. The non-toxic acid-addition salts of the cyanoguanidines formula I are formed with a variety of organic and inorganic salt-forming reagents. Thus, acid-addition salts, formed by admixture of the cyanoguanidine with an acid, suitably in a neutral solvent, are formed with such acids as sulfuric, phosphoric, hydrochloric, hydrobromic, citric, lactic, tartaric, acetic and benzoic acids. It will be understood that references in the description hereinafter to the cyanoguanidines of formula I include, unless the context otherwise requires, their non-toxic acid-addition salts.

Certain 1-substituted-3-cyanoguanidines have been discussed in the literature. Thus, British Patent Specification No. 599,713 discloses generally alkyl-substituted dicyandiamides of the formula:

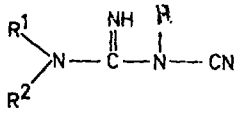


wherein R is an alkyl group and R^1 is hydrogen or an alkyl group. British patent specification No. 599,722 discloses, again generally, substituted dicyandiamides of the formula:

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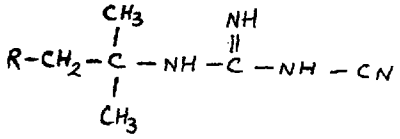


wherein R and R^1 may stand for hydrogen or for hydrocarbon radicals which may be substituted or not and may be the same or different provided that both are not at the same time hydrogen. Again, our own British patent specification No. 631,878 discloses generally 1 - substituted - 3 - cyanoguanidines having the general formula:



wherein R^1 is hydrogen or an aliphatic aromatic or heterocyclic radical and R^2 is an aliphatic aromatic or heterocyclic radical. However none of these prior-art disclosures specifically disclose cyanoguanidines of formula I above. Further none of the prior-art disclosures suggest that the cyanoguanidines of formula I above have excellent activity as potent hypotensive agents coupled with antiangiotensin activity, and it was not at all to be expected from the prior-art that the cyanoguanidines of formula I would possess these properties.

Apart from 1-t-butyl-3-cyanoguanidine, which is disclosed in J.C.S., 1958, page 3750, the cyanoguanidines of formula I above are believed to be novel compounds, and in accordance with a further aspect of the present invention there is provided a compound of the formula:



wherein R is an alkyl group having from 1 to 3 carbon atoms, and non-toxic acid addition salts thereof.

The 1-substituted-3-cyanoguanidines, the active ingredients of the novel composition of the present invention, may be readily prepared by the interaction of an amine such as, for example, *t*-butyl-amine, *t*-amylamine, *t*-hexylamine, 2 - amino - 2,4 - dimethylpentane, with sodium dicyanimide in a lower alkanol solvent in the presence of a mineral acid. Suitable lower alkanol solvents are, for example, *iso*-propanol, and *n*-butanol. Suitable mineral acids are sulfuric acid and phosphoric acid. The reaction is generally carried out at steam bath temperatures over a period of time of from 15 minutes to a dozen hours. The resultant 1-substituted-3-cyano-guanidine may be isolated by procedures well-known to those skilled in the art.

It is not known how the 1-substituted-3-cyanoguanidines of formula I above operate to reduce elevated blood pressure and no theory of why these compounds so operate is advanced. It is not intended that the present invention should be limited to any theory as to mechanism.

The method of administering the 1-substituted-3-cyanoguanidines of formula I above is limited to oral administration. They may be orally administered, for example, with an inert diluent or with an assimilable edible pharmaceutically acceptable carrier, or they may be enclosed in hard or soft gelatin capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. It is an advantage of the present invention that the 1-substituted-3-cyanoguanidines may be orally administered in any convenient manner.

The amount of a single dose or of a daily dose to be given will vary with the size of the individual to be treated, but should be such as to give a proportionate dosage of from about 5 mg. to about 25 mg. per kg. of body weight per day. In terms of total weight of active ingredient, this is usually from about 0.2 g. to about 2.0 g. per daily dosage. This dosage regimen may be adjusted to provide the optimum therapeutic response; for example, several divided doses may be administered daily or the dose may be proportionately reduced as indicated by the exigencies of the therapeutic situation. As indicated previously in one embodiment of our invention, it is preferred to incorporate the 1-substituted-3-cyanoguanidines directly in the food of the diet. Any suitable method for dispersing the active ingredient uniformly throughout the food can be used. The amount of active ingredient added to the diet may be varied, but it is ordinarily found that an amount of 1-substituted-3-cyanoguanidine within the range of from about 0.2 g. to about 2.0 g. per kilogram of diet promotes the maximum lowering of vascular blood pressure.

The following examples illustrate methods of preparation and the hypotensive effect of the novel compositions of the present invention and the method of administering them.

Example 1.

1-*t*-butyl-3-cyanoguanidine.

A solution of 111 g. of *t*-butylamine hydrochloride and 90 g. of sodium dicyanimide in 600 ml. of butanol is refluxed for 24 hours. Filtration, followed by evaporation of the filtrate *in vacuo* gives the product which is crystallized from aqueous ethanol as waxy crystals, m.p. 188—189° C. (dec.).

EXAMPLE 2.

1-*t*-amyl-3-cyanoguanidine.

In 125 ml. of butanol is dissolved 19.2 g. of tertiary amyl amine. To this is added 5.85 ml. of sulfuric acid and 2.5 ml. of water. The white solid which precipitates upon the addition of the sulfuric acid dissolves when the flask is swirled. This solution is then concentrated to ½ its volume and 24.0 g. of sodium dicyanimide is then added. The mixture is heated over steam for ½ hour at which time the pH of the mixture is 7.8—8.2. The mixture is then heated over steam overnight, about 17 hours. The resultant white solid is then filtered off and washed with ethanol. The filtrate is then evaporated to near dryness and the residue is triturated with 155 ml. of water and cooled. The white solid is filtered off, and washed thoroughly with water; m.p. 155.5—157° C.

EXAMPLE 3.

Hypotensive and anti-angiotensin activities of *t*-butyl-dicyandiamide and *t*-amyldicyandiamide in normo-tensive rats.

Conscious male albino Sherman strain rats were fastened to rat boards in a supine position by means of canvas vests and limb ties. The femoral areas were anesthetized by subcutaneous infiltration of lidocaine. The left or right common iliac arteries were exposed and clamped off proximally by an artery clamp and distally with thread. Incisions were made near the tie and short nylon catheters were inserted and tied in place. The other end of the catheters were fitted with 24 gauge hubless needles attached to thick-walled polyethylene tubes. The cyanoguanidines were administered to the animals orally by gavage. The compounds were suspended in 2% aqueous starch solution at a concentration such that 1 ml. per 100 g. of body weight gave the animal the desired dose. Volume was usually 2 ml. since the rats averaged 200 g. The vasopressor agents, angiotensin and epinephrine, were injected into the femoral vein. Mean arterial blood pressure was measured 2 hours after administration of the compounds. Blood pressure measurements were made with four Statham P23 Db strain gauges attached to a Sanborn Polyviso Recorder. The recorder is equipped with four strain gauge preamplifiers with averageing circuits for measuring mean arterial pressure. Table I summarized the effects on mean blood pressure (MBP) and on the vasopressor response to intravenous injections of angiotensin (angio), 0.25 mcg./kg. and epinephrine (epi), 2 mcg./kg., two hours after administering *t*- butyldicyandiamide and *t*-amyldicyandiamide to a series of rats. The tabulation shows the maximum rise in MBP produced by the two pressor agents. Under the conditions of this experiment, the two cyanoguanidines demonstrated hypotensive and antiangiotensin activity. Responses to epinephrine was essentially unaltered.

TABLE I

Treatment	Oral Dose, mg./kg.	No. of Rats	Cardiovascular Effects 2 Hours after Treatment		
			MBP*	Angio hypertension	Epi hypertension
			mm. Hg.	mm. Hg	mm. Hg.
Controls		50	113 ± 5	33 ± 10	39 ± 6
t-butyldicyandiamide	100	5	82 ± 7	11 ± 2	30 ± 10
t-amyldicyandiamide	100	6	75 ± 12	5 ± 3	39 ± 8
	10	4	102 ± 7	10 ± 2	49 ± 6

* Data expressed as the mean ± the standard deviation.

EXAMPLE 4.

Antihypertensive activities of *t*-butyl dicyandiamide and *t*-amyldicyandiamide in conscious, hypertensive dogs.

Renal hypertension was produced in dogs by renal artery constriction with a Goldblatt clamp. A persistent elevation in blood pressure ensued as a consequence of kidney ischemia. Prior to constricting the renal artery, the mean blood pressure of one of the hypertensive animals, Dog 863, was 109 mm. Hg. as determined directly by means of a Statham pressure transducer—Sanborn recorder system. Several months postoperatively, the animal's mean blood pressure was elevated to 157 mm. Hg. Five minutes after this reading, the dog was given *t*-butyldicyandiamide, 25 mg./kg. orally. After dosage, the mean blood pressure values at different time periods were as follows: 70 minutes, 148 mm. Hg; 130 minutes, 125 mm. Hg; 185 minutes, 125 mm. Hg: 250 minutes, 120 mm. Hg. In another study with hypertensive Dog 863, mean blood pressure was 158 mm. Hg. prior to dosage. The animal was then given *t*-amyldicyandiamide, 25 mg./kg. orally. The mean blood pressure values at intervals after dosing were as follows: 105 minutes, 172 mm. Hg; 224 minutes, 135 mm. Hg; 332 minutes, 125 mm. Hg; 1384 minutes, 155 mm. Hg.

EXAMPLE 5.

Actions of *t*-amyldicyandiamide on arterial blood pressure and flow in an anesthetized, normotensive dog.

The effect of *t*-amyldicyandiamide on peri-

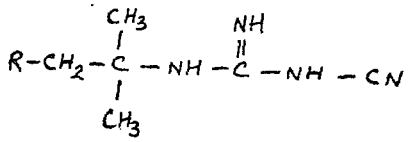
pheral vascular resistance and arterial pressure was studied in dogs anesthetized with pentobarbital. Using a retroperitioneal approach, the abdominal aorta was exposed and ligated. Blood was led from a cannula in the aorta proximal to the tie through a Sigmamotor pump to a cannula in the distal section of the divided vessel. The outflow of the pump was adjusted so that the perfusion pressure in the hindquarters was approximately equal to the systemic pressure. Any change in perfusion pressure thereafter represented a corresponding change in vascular resistance since blood flow through the bed was kept constant. Perfusion and arterial pressures were measured with pressure transducers attached to a polygraph. In Table II, the typical effects of *t*-amyldicyandiamide, 5 mg./kg. intraperitoneally, on the arterial and perfusion pressures of a dog are tabulated. The data indicate that the drug-induced hypotension was related to a decrease in peripheral vascular resistance.

TABLE II

Minutes after *t*-amyl-dicyandiamide 10 mg./kg. I.P.	Per cent change from the control	
	Perfusion Pressure	Systolic blood pressure
30	—39	—40
90	—42	—35
120	—45	—44

WHAT WE CLAIM IS:—

1. A compound of the formula

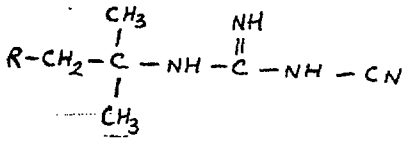


wherein R is an alkyl group having from 1 to 3 carbon atoms.

2. A non-toxic acid-addition salt of a compound according to claim 1.

3. A method of preparing a compound according to claim 1 or claim 2 substantially as hereinbefore described.

4. A pharmaceutical composition for the control of hypertension comprising a compound of the formula



wherein R is hydrogen or an alkyl group having from 1 to 3 carbon atoms, or a non-toxic acid addition salt thereof and an edible pharmaceutically acceptable carrier.

5. A composition according to claim 4 wherein the active compound is 1-t-butyl-3-cyanoguanidine, or a non-toxic acid addition salt thereof.

6. A composition according to claim 4, wherein the active compound is 1-t-amyl-3-cyanoguanidine, or a non-toxic acid addition salt thereof.

7. A composition according to any one of claims 4—6 containing from 0.2 gram to 2.0 grams per unit dosage form of the active ingredient.

8. A composition according to claim 4 substantially as hereinbefore described with reference to any one of the Examples.

9. An edible capsule containing a composition according to any one of claims 4—8.

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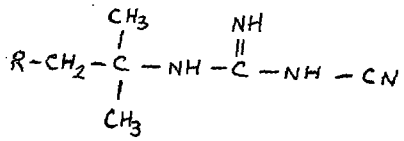
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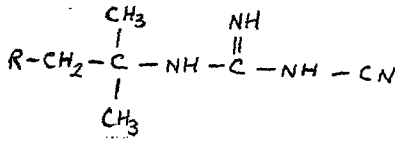


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