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ASPERGILLIC ACID AS AN ANTI-HYPERTENSIVE AGENT

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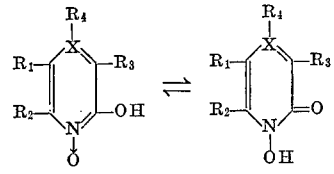
U.S. Cl. 424—250 1 Claim

ABSTRACT OF THE DISCLOSURE

Method of treating hypertension by administering to a hypertensive patient a therapeutically effective amount of a compound of the Formula



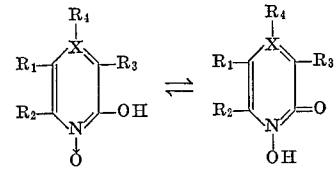
wherein X is C or N; and R_1, R_2, R_3 and R_4 each are hydrogen, alkyl, cycloalkyl or aryl, with the limitation that R_4 is present only when X is C.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a method of treating hypertension using cyclic hydroxamic acids as the antihypertensive agents.

Aspergillic acid and a number of its derivatives have been previously reported as anti-bacterial agents and some of the compounds have additionally been reported to possess anti-inflammatory activity. It has now unexpectedly been found that the compounds are useful as antihypertensive agents.

The compounds useful in the practice of this invention are represented by the formula



wherein X is C or N; and R_1, R_2, R_3 and R_4 each are hydrogen, alkyl, cycloalkyl or aryl with the limitation that R_4 is present only when X is C.

Representative compounds which are represented by the above formula include:

3-n-pentyl-1-hydroxy-2-(1H)-pyrazinone
5-n-pentyl-1-hydroxy-2-(1H)-pyrazinone
6-n-pentyl-1-hydroxy-2-(1H)-pyrazinone
3,6-diethyl-1-hydroxy-2-(1H)-pyrazinone
3-ethyl-6-n-butyl-2-(1H)-pyrazinone
5-ethyl-6-propyl-2-(1H)-pyrazinone
5-ethyl-6-isopropyl-2-(1H)-pyrazinone
3,5,6-triethyl-2-(1H)-pyrazinone
3,5-diethyl-6-propyl-2-(1H)-pyrazinone

5-phenyl-6-methyl-2-(1H)-pyrazinone
5-cyclohexyl-3-methyl-2-(1H)-pyrazinone
5-n-butyl-1-hydroxy-2-(1H)-pyridone
3-n-butyl-1-hydroxy-2-(1H)-pyridone
4-n-butyl-1-hydroxy-2-(1H)-pyridone
6-n-butyl-1-hydroxy-2-(1H)-pyridone
6-ethyl-3-propyl-2-(1H)-pyridone
6-ethyl-3-isopropyl-2-(1H)-pyridone
4-isobutyl-1-hydroxy-2-(1H)-pyridone
3-isobutyl-6-sec-butyl-2-(1H)-pyridone
5-cyclohexyl-3-methyl-2-(1H)-pyridone
4-cyclopentyl-6-ethyl-2-(1H)-pyridone
5-phenyl-3-ethyl-2-(1H)-pyridone
3-phenyl-6-ethyl-2-(1H)-pyridone

The compounds useful in the practice of this invention can be prepared by methods well known in the art. See, for example, Dunn et al., "Pyrazine Derivatives XI Synthesis of Cyclic Hydroxamic Acids Related to Aspergillic Acid" J. Chem. Soc., 1949, 2707–12; U.S. 2,666,054; France 2,022,146 and G.B. 1,238,106.

The antihypertensive activity of the compounds useful in the practice of this invention was first established in the spontaneously hypertensive rate using standard procedures. The compounds are effective as antihypertensive agents at dosages of from 60 to 200 mg./kg. of body weight daily.

In the practice of this invention, the compounds are administered to hypertensive patients, preferably by the oral route, in divided dosages, i.e., three to four times daily. They may also be co-administered with, for example, diuretics or tranquilizers in treating hypertension.

While the compounds can be administered alone, that is, as the sole component of a filled capsule, it is preferred to formulate the compound in various dosage forms for oral or parenteral administration such as tablets, syrups, sterile aqueous or non-aqueous suspension and the like. The oral dosage forms are prepared by methods well known in the art (as are the parenteral) and generally in clude a pharmaceutically acceptable carrier or diluent such as lactose, starch or sucrose along with lubricating agents such as magnesium stearate and flavoring and sweetening agents and the like.

We claim:

1. A method of reducing blood pressure in hypertensive patients which comprises administering to said patients an antihypertensively effective amount of aspergillic acid.

References Cited

UNITED STATES PATENTS

2,666,054	1/1954	Safir	260—250

FOREIGN PATENTS

2,022,146	7/1970	France.
1,238,106	7/1971	Great Britain.

OTHER REFERENCES

Dunn et al. J. Chem. Soc. (1949) pp. 2707–2712.

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U.S. Cl. X.R.
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