United States Patent [19]

Pifferi

[11] **3,891,641**

[45] **June 24, 1975**

[54] **3-AMINOALCOXY-6-HYDRAZINO PYRIDAZINES**

[75] Inventor: **Giorgio Pifferi**, Milan, Italy

[73] Assignee: **I. S. F. S.p.A.**, Milan, Italy

[22] Filed: **Jan. 17, 1972**

[21] Appl. No.: **218,531**

[30] **Foreign Application Priority Data**

May 29, 1971 Italy 25230/71

[52] **U.S. Cl.**... **260/250 A**; 260/247.5 D; 260/268 H; 424/250

[51] **Int. Cl.** **C07d 51/04**

[58] **Field of Search** ..... 260/250 A

[56] **References Cited**

UNITED STATES PATENTS

2,858,311	10/1958	Steck	260/250 A
3,579,517	5/1971	Houlihan et al.	260/250 A
3,598,822	8/1971	Anderson et al.	260/250 A

OTHER PUBLICATIONS

Edgar A. Steck et al., J. Am. Chem. Soc., Vol. 76, 4454–57, (1954).

Primary Examiner—Donald G. Daus
Assistant Examiner—Jose Tovar
Attorney, Agent, or Firm—Harold L. Stowell; Dennis P. Clarke

[57] **ABSTRACT**

The invention provides new N-substituted 3-aminoalcoxy-6-hydrazinopyridazines which have a marked anti-hypertensive activity, and a LD_{50} much higher than that of the clinically used drug hydralazine. The compounds of the invention are prepared by reacting 3-aminoalcoxy-6-halogenopyridazines with hydrazine.

4 Claims, No Drawings

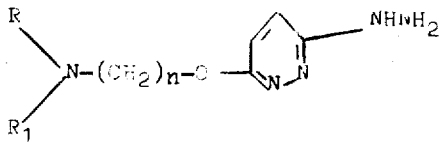
3-AMINOALCOXY-6-HYDRAZINO PYRIDAZINES

This invention relates to compounds having antihypertensive activity, and to their preparation.

It is known that some 6-substituted 3-hydrazinopyridazines have, in addition to a marked antihypertensive activity, also an appreciable toxicity which limits their usefulness, especially when they are used for a long time, as frequently necessary in the treatment of hypertension.

The invention provides N-substituted 3-aminoalcoxy-6-hydrazinopyridazines which have a marked antihypertensive activity and a LD_{50} much higher than that of the clinically used drug hydralazine.

The new compounds of this invention are the N-substituted 3-aminoalcoxy-6-hydrazinopyridazines, of general formula:



wherein *n* is an integer from 2 to 6, R is hydrogen, lower alkyl, or lower hydroxyalkyl, R_1 is lower alkyl, lower hydroxyalkyl, or phenyl, or R and R_1, together with the nitrogen atom to which they are bound represent a heterocyclic ring having 1 or 2 heteroatoms, preferably a 5- or 6 membered ring, e.g. pyrrolidino, piperidino, morpholino, or 4-lower alkylpiperazino. The compounds of formula (I) may be employed as such or in the form of acid addition salts, obtained from the bases by treatment with mineral acids, such as hydrochloric, hydrobromic, or sulfuric acid, or organic acids, such as acetic, succinic, benzoic, or p-toluenesulfonic acid.

The hypotensive effect of the compounds of formula (I) has been proved by administering them intravenously in aqueous solution to anaesthetized cats and measuring the decrease in their arterial blood pressure. The antihypertensive action of the new compounds has been measured by inducing renal hypertension in rats by the method of Grollman (Proc. Soc. Exptl. Biol. and Med., 57, 102, 1944) and observing the decrease in arterial blood pressure following oral administration of an aqueous solution of a compound of the invention as a salt, e.g. the hydrochloride.

The minimum effective dosages of certain compounds of formula (I) in the two aforesaid tests and their corresponding approximate intraperitoneal LD_{50} in the rat are grouped in the following Table together with the values for hydralazine.

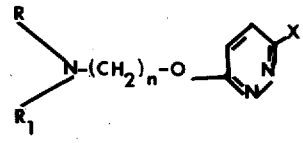
TABLE

Compound of Example No.	Mouse	Anaesthetized Cat		Awake hypertensive rat
	LD_{50} mg/kg intraperitoneal	Effective dosage mg/kg intravenous	Half effect time: minutes	Effective dosage mg/kg orally
1	300	0.01	120	0;5
2	800	0.2	150	1
3	900	0.1	130	1
Hydralazine	100	0.5	100	1

These results show that the compounds of this invention are less toxic and more active than hydralazine, in both tests and for both the animal species tested.

This invention therefore includes within its scope pharmaceutical compositions containing as an active principle one or more compounds of formula (I) or their non-toxic salts with organic or inorganic acids, in association with a compatible pharmaceutical vehicle.

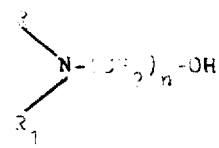
According to this invention, the compounds of formula (I) are prepared by reacting compounds of the formula:



II

wherein R, R_1 and n are as defined above and X is chlorine or bromine, with a hydrazine, which may be anhydrous or in the form of the monohydrate. The compounds of formula (II) are heated with hydrazine to a temperature from 20°C to the boiling point of the mixture, preferably between 70° and 115°C. The reaction can be conducted using an excess of hydrazine, or using an inert organic solvent, such as ethanol, propanol, or cyclohexanol. The excess of hydrazine is employed to promote the reaction, and to bind the hydrochloric or hydrobromic acid that forms during the reaction.

The intermediates of formula (II) are easily prepared by reacting 3,6-dichloropyridazine or 3,6-dibromopyridazine with an aminoalcohol of formula:



wherein R, R_1 and n are as defined above. The reaction can be accomplished, according to the nature of the aminoalcohol employed, either by heating the halogeno-pyridazine with the compound of formula (III) in the presence of anhydrous sodium or potassium carbonate in an aprotic high-boiling solvent, such as dimethylformamide, or else by heating the halogenopyridazine with an anhydrous alkali metal salt of the aminoalcohol of formula (III) in an inert organic solvent, such as benzene or toluene. The reaction temperature is not critical and may range from 50°C to the boiling point of the selected solvent. The so obtained compounds of formula (I) are separated from the reac-

tion mixture and purified by conventional methods for organic bases.

The following Examples illustrate the invention.

EXAMPLE 1

3-(2-Anilinoethoxy)-6-hydrazinopyridazine

a. 3-(2-anilinoethoxy)-6-chloropyridazine

3.76 Grams of N-(2-hydroxyethyl)-aniline and grams 2.98 of 3,6-dichloropyridazine are added to 40 ml of anhydrous dimethylformamide containing 10 grams of potassium carbonate and the mixture is heated to 100°C for 10 hours with stirring. The insoluble mineral salts are filtered off, and the filtrate is concentrated to dryness under vacuum. The residue is taken up with chloroform, washed with water, dried over Na_2SO_4. The solvent is removed by distillation and the remaining solid is recrystallized from ethyl acetate. 2.5 g (50% of theoretical) of 3-(2-anilinoethoxy)-6-chloropyridazine, m.p. 98°–101°C, are obtained.

b. 3-(2-anilinoethoxy)-6-hydrazinopyridazine

A mixture of 50 g of 3-(2-anilinoethoxy)-6-chloropyridazine in 500 ml of hydrazine monohydrate is refluxed for 3 hours. The reagent in excess is distilled off under vacuum and the residue is taken up with water and kept overnight in the refrigerator. The precipitate is collected by filtration and washed with warm ethanol. The residue is heated with an excess of boiling ethanol, the insoluble matter is filtered off over charcoal, and a solution of gaseous hydrogen chloride in diethyl ether is added to the filtrate, until the mixture is acid to Congo Red.

The precipitate is collected by vacuum filtration and recrystallized from ethanol, thus giving, in good yield, 3-(2-anilinoethoxy)-6-hydrazinopyridazine as the dihydrochloride, m.p. 189°–192°C (dec), IR spectrum (Nujol): 3300–2000 (NH^+), 1670 (δNH), 1610 (pyridazine ring), 1590 and 1500 (phenyl), 1055 (C—O), 760 cm^{-1} (monosubstituted phenyl).

Analysis:	
Calculated for $C_{12}H_{13}N_3O.2HCl$:	C 45.30; H 5.38; N 22.09; Cl 22.26 %
Found:	Cl 44.88; H 5.44; N 22.50 Cl 21;89 %

EXAMPLE 2

3-(3-Dimethylaminopropoxy-6-hydrazinopyridazine

a. 3-(3-dimethylaminopropoxy)-6-chloropyridazine

9.2 Grams of sodium metal are finely subdivided in 140 ml of boiling anhydrous xylene, and 45.5 g of 3-dimethylaminopropanol are added to the heated mixture. When the sodium has entirely dissolved, the mixture is cooled to 60°C, and a solution of 59.6 g of 3,6-dichloropyridazine in 100 ml of anhydrous xylene is added dropwise. After heating for 10 hours to 60°C, the mixture is cooled and acidified with 20% hydrochloric acid. The aqueous phase is separated and rendered alkaline while cold with a 30% aqueous sodium hydroxide solution. The oil that separates is extracted with diethyl ether. The extract is dried over anhydrous K_2CO_3, and the solvent is removed by distillation. The residue is fractionally distilled under vacuum, thus giving 60 g (70% of theoretical) of 3-(3-dimethylaminopropoxy)-6-chloropyridazine, b.p. 109°–111°C/0.4 mm Hg.

b. 3-(3-dimethylaminopropoxy)-6-hydrazinopyridazine

11.4 Grams of 3-(3-dimethylaminopropoxy)-6-chloropyridazine are added to a solution of 100 ml of hydrazine monohydrate in 40 ml of ethanol, and the mixture is refluxed for 4 hours. The solution obtained is concentrated to dryness under a high vacuum. The residue is taken up with 150 ml of anhydrous methanol and acidified to Congo Red with a solution of gaseous hydrogen chloride in anhydrous methanol. The mixture is concentrated to approximately half its volume, and cooled, and the hydrazine dihydrochloride that separates is removed by filtration. The alcoholic filtrate is further concentrated and cooled, and the precipitate is collected by vacuum filtration. It is then purified by recrystallization from methanol, thus giving, in a good yield, 3-(3-dimethylaminopropoxy)-6-hydrazinopyridazine dihydrochloride, m.p. 210°–212°C (dec). IR spectrum (Nujol): 3300–2000 (NH^+), 1675 (δNH), 1625 (pyridazine ring), 1030 cm^{-1} (C—O).

Analysis:	
Calculated for $C_9H_{17}N_5O.2HCl$:	C 38.00; H 6.74 N 24.92; Cl 24.62 %
Found:	C 37.34; H 6.88; N 24.60; Cl 24.82 %

EXAMPLES 3 – 5

The following compounds are prepared by operating as in Example 2:

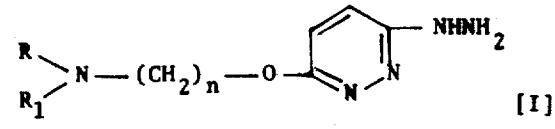
3. 3-(2-diethylaminoethoxy)-6-hydrazinopyridazone dihydrochloride, m.p. 201°–203°C (dec).

4. 3-(2-morpholinoethoxy)-6-hydrazinopyridazine dihydrochloride, m.p. 215°–218°C (dec).

5. 3-(2-N-methylpiperazinoethoxy)-6-hydrazinopyridazine trihydrochloride, m.p. 165°–168°C (dec).

What we claim is:

1. A compound of the formula:



[I]

wherein *n* is an integer from 2 to 3, R is hydrogen, methyl or ethyl and R_1 is methyl, ethyl or phenyl or its pharmaceutically acceptable acid addition salts.

2. 3-(2-Anilinoethoxy)-6-hydrazinopyridazine or its pharmaceutically acceptable acid addition salts.

3. 3-(3-Dimethylaminopropoxy)-6-hydrazinopyridazine or its pharmaceutically acceptable acid addition salts.

4. 3-(2-Diethylaminoethoxy)-6-hydrazinopyridazine or its pharmaceutically acceptable acid addition salts.

* * * * *