United States Patent Office 3,585,196
Patented June 15, 1971

3,585,196

MERCAPTO PYRIDAZINEDIONES

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No Drawing. Filed Feb. 1, 1968, Ser. No. 702,182
Int. Cl. C07d 51/04
U.S. Cl. 260—247.1 5 Claims

ABSTRACT OF THE DISCLOSURE

4,5 - dimercapto - 1,2 - dihydropyridazinediones having substituents attached to each of the nitrogen atoms of the pyridazine nucleus which are prepared by treating the corresponding N,N'-substituted 4,5-dihalopyridazinedione with a hydrosulfide. The substituted 4,5-dimercapto-1,2-dihydropyridazinediones are useful as inhibitors of gastric acid secretion.

BACKGROUND OF THE INVENTION

(1) Field of the invention

Gastric acid secretion inhibitors.

SUMMARY OF THE INVENTION

This invention is concerned with novel pyridazinedione compounds useful as gastric acid secretion inhibitors.

More specifically, this invention is concerned with 4,5-dimercapto-1,2-dihydropyridazinediones having substituents attached to each of the nitrogens of the pyridazine nucleus.

This invention is also concerned with methods for preparing the novel compounds of this invention which comprises treating the corresponding 4,5-dihalopyridazinedione with an alkali hydrosulfide or a compound capable of being converted to an alkali hydrosulfide. The invention is concerned also with pharmaceutical compositions containing the novel pyridazinediones of this invention.

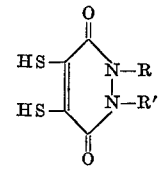
DESCRIPTION OF THE PREFERRED EMBODIMENTS

While certain pyridazinedione compounds are known, particularly those that have been used as dyes, fungicides, and bacteriacides, it has been found that a select group of heretofore unknown pyridazinedione compounds possess the unique property of inhibiting gastric acid secretion in mammals. The preferred products now used to control gastric acidity are mainly either anticholinergic agents or antacids. The anticholinergic agents have the disadvantage in that they act by or through the nervous system by blocking the nerve impulses to the cells of the gastric mucosa responsible for secretion of acid. Because of their effect on the nervous system, the anticholinergic agents are non-specific, additionally affecting other secretory mechanisms of the body as well as other body functions dependent in whole or in part on stimulation by the nervous system. The antacid compounds, on the other hand, have limited effectiveness as they act only to neutralize the acid after it has been secreted into the stomach, and furthermore, have a very short duration of activity.

The pyridazinedione compounds of this invention do not act by either of the above mechanisms and thus afford a new approach to acid inhibition as they control acid production at the gastric mucosa cellular level. Pharmacological studies indicate that the pyridazinediones of this invention effect inhibition at the enzyme level and in addition are effective in inhibiting histamine stimulated gastric secretion, an important property not shared with other types of gastric acid inhibitors.

The novel compounds of this invention having this

property of inhibiting the production of gastric acids can be illustrated by the structural formula



wherein R and R' can be the same or dissimilar substituents and each represents

(1) loweralkyl
(2) substituted loweralkyl wherein the substituents can be
  (a) hydroxy
  (b) diloweralkylaminoacetoxy
  (c) loweralkanoyloxy
  (d) morpholinyl
  (e) dioxothiomorpholinyl
  (f) diloweralkylamino
  (g) carboxy
  (h) phenyl
  (i) piperidino
  (j) loweralkylpiperazinyl
  (k) loweralkylphenylamino
  (l) loweralkylbenzylamino
  (m) loweralkylpiperidyl
  (n) thiomorpholinyl
(3) cyclohexyl and loweralkylaminocyclohexyl
(4) phenyl
(5) substituted phenyl wherein the substituents may be loweralkoxy or halo; carboxy or dialkylamino
(6) loweralkylpiperidyl

The loweralkyl referred to in (1) and (2) above advantageously contains from 1–5 carbon atoms. When the loweralkyl radical is substituted as in (2a–m) above, R and/or R' may be respectively

(a) 2-hydroxyethyl or 2(or 3)-hydroxypropyl
(b) 2-(diethylaminoacetoxy)ethyl, 2-(diethylaminoacetoxy)propyl, or 3(or 4)-(diethylaminoacetoxy)butyl
(c) 2-acetoxyethyl or 3-acetoxypropyl, 2-propionyloxyethyl, 3-butyryloxypropyl
(d) 2-(4-morpholinyl)ethyl
(e) 2-(1,1-dioxo-4-thiomorpholinyl)ethyl
(f) 3-(dimethylamino)-2-methylpropyl
  2-(dimethylamino)ethyl
  2-(diisopropylamino)ethyl
  2-(dibutylamino)ethyl
  3-(dimethylamino)propyl
  3-(diethylamino)propyl
  2-(dimethylamino)-2-methylpropyl
  3-(dimethylamino)-2,2-dimethylpropyl
  2-(diethylamino)propyl
  2-(diethylamino)-1-methylethyl
  4-(dimethylamino)-1-methylbutyl
(g) carboxymethyl, carboxypropyl
(h) phenylethyl, phenylpropyl
(i) 2-(piperidino)ethyl or 2-(piperidino)propyl
(j) 2-(4-methyl-1-piperazinyl)ethyl, 3-(4-methyl-1-piperazinyl)propyl, 2-(4-ethyl-1-piperazinyl)ethyl or 2-(4-ethyl-1-piperazinyl)ethyl
(k) 2-(methylphenylamino)ethyl or 2-(ethylphenyl-amino)ethyl
(l) methylbenzylaminoethyl, methylbenzylaminopropyl, ethylbenzylaminoethyl, or ethylbenzylaminopropyl
(m) (1-methyl-3-piperidyl)methyl or (1-ethyl-3-piperidyl)methyl
(n) 2-(4-thiomorpholinyl)ethyl

When the loweralkyl radical is substituted as in (3) above, then R and/or R' may be respectively 2-dimethyl-

aminocyclohexyl, 2-diethylaminocyclohexyl or 2-ethylmethylaminocyclohexyl. In addition, R and/or R' may be chlorophenyl, fluorophenyl, methoxyphenyl, ethoxyphenyl, or diethylaminophenyl, when the phenyl radical is substituted as in (5) above or methylpiperidyl, ethylpiperidyl or propylpiperidyl when the alkyl radical is substituted as in (6) above.

While R and R' may be the same, it is preferable that when R represents one of the groups stated above, R' represents loweralkyl.

The novel compounds of this invention advantageously can be prepared by treating the corresponding 4,5-dihalopyridazinedione with a compound capable of replacing the halogen atoms of the 4,5-dihalo pyridazinedione with a sulfhydryl group. Compounds which will satisfactorily effect this replacement include ammonium hydrosulfide, the alkali metal hydrosulfides such as sodium or potassium hydrosulfide, or sulfides that may on hydrolysis be converted to a hydrosulfide such as sodium sulfide or hydrogen sulfide plus an alkali hydroxide.

Although a solvent is not necessary to effect the above-stated reaction, it is deemed desirable for maximum yields. Suitable solvents that may be used to satisfactorily prepare the mercaptopyridazinediones of this invention include in addition to the preferred loweralkanols such as ethanol, isopropanol, or butanol, the glycols such as ethylene or propylene.

The temperature at which the reaction is effected is not particularly important, being limited by the boiling point of the solvent employed and the replacement of the halogen atom satisfactorily occurs when the reactants are heated under reflux conditions for about 1–4 hours, after which time the desired 4,5-dimercapto pyridazinedione may be separated from the reaction mixture by diluting the reaction mixture with water and then neutralizing it with 6 N hydrochloric acid.

It is obvious to those skilled in the art that the 1,2-dihydro-4,5-dimercapto-3,6-pyridazinedione products having a basic amino group in the R and/or R' substituent may also be obtained as the non-toxic acid addition salt, such as the hydrochloride, sulfate, phosphate or citrate, as shown in Example 2 below.

EXAMPLE 1

1,2-dicyclohexyl-1,2-dihydro-4,5-dimercapto-3,6-pyridazinedione

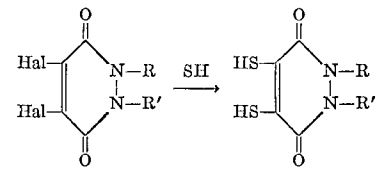
Sodium hydrosulfide dihydrate (0.92 g., 0.01 mole) and 4,5 - dihcloro-1,2-dicyclohexyl-1,2-dihydro-3,6-pyridazinedione (0.86 g., 0.0025 mole) are dissolved in 25 ml. of ethyl alcohol and the solution is heated under reflux. After two hours the reaction mixture is allowed to cool and the solvent is then removed by concentration under reduced pressure. The residue remaining is then treated by the addition of 45 ml. of water. Acidification of the aqueous mixture with 6 N HCl yields an oily material containing 1,2 - dicyclohexyl-1,2-dihydro-4,5-dimercapto-3,6-pyridazinedione which after recrystallization from absolute alcohol has a M.P. of 162–164.5° C.

EXAMPLE 2

1 - methyl-2-[2-(4-morpholinyl)ethyl]-1,2-dihydro-4,5-dimercapto-3,6-pyridazinedione and its hydrochloride salt

1 - methyl-2-[2-(4-morpholinyl)ethyl]-1,2-dihydro-4,5-dichloro-3,6-pyridazinedione is treated with sodium hydrosulfide as described in Example 1. After removal of the solvent from the reaction mixture under reduced pressure the residue is mixed with water and made just faintly acid with 6 N HCl. The 1-methyl-2-[2-(4-morpholinyl)ethyl]-1,2 - dihydro - 4,5 - dimercapto-3,6-pyridazinedione which precipitates is collected and washed with water. Treatment with methanolic HCl and ether yields the hydrochloride salt which is crystallized from glacial acetic acid by addition of ether. It has a M.P. of 189–191° C.

1-R-2R'-4,5-dimercaptopyridazinediones that can be prepared by reacting known 1R-2R'-4,5-dihalopyridazinediones with sodium hydrosulfide according to the procedure set forth in Examples 1 and 2 are as follows.



Ex.	R	R'
3	Methyl	Methyl.
4	Isopropyl	Phenyl.
5	do	2-hydroxyethyl.
6	do	2-(diethylamino)acetoxyethyl.
7	do	2-acetoxyethyl.
8	Benzyl	Methyl.
9	2-(4-morpholinyl)-ethyl	2-(4-morpholinyl)-ethyl.
10	Methyl	2-(1,1-dioxo-4-thiomorpholinyl)-ethyl.
11	do	3-(dimethylamino)-2-methylpropyl.
12	do	Heptyl.
13	do	Carboxymethyl.
14	do	Cyclohexyl.
15	do	Phenyl.
16	do	p-Chlorobenzyl.
17	do	p-Carboxybenzyl.
18	do	Phenylethyl.
19	Isopropyl	Isopropyl.
20	do	m-Methoxyphenyl.
21	do	p-Carboxyphenyl.
22	Cyclohexyl	Phenyl.
23	Methyl	2-(dimethylamino)ethyl.
24	do	2-(diethylamino)ethyl.
25	do	2-(diisopropylamino)ethyl.
26	do	2-(dibutylamino)ethyl.
27	do	3-(dimethylamino)propyl.
28	do	3-(diethylamino)propyl.
29	do	2-(dimethylamino)-2-methylpropyl.
30	do	3-(dimethylamino)-2,2-dimethylpropyl.
31	do	2-(diethylamino)-1-methylethyl.
32	do	2-(diethylamino)-2-methylethyl.
33	do	4-(dimethylamino)-1-methylbutyl.
34	do	2-(piperidino)ethyl.
35	do	2-(4-thiomorpholinyl)ethyl.
36	do	2-(4-methyl-1-piperazinyl)ethyl.
37	do	3-(4-methyl-1-piperazinyl)-propyl.
38	do	3-(4-morpholinyl)propyl.
39	do	2-(methylphenylamino)ethyl.
40	do	Methylbenzylaminoethyl.
41	do	Methylbenzylaminopropyl.
42	do	3-(1-methylpiperidyl).
43	do	3-(1-methylpiperidyl)methyl.
44	do	2-(dimethylamino)cyclohexyl.
45	Phenyl	2-(diethylamino)ethyl.
46	do	2-(4-morpholinyl)ethyl.
47	m-Chlorophenyl	Do.
48	p-Fluorophenyl	Do.
49	m-Methoxyphenyl	Do.
50	Isopropyl	p-Dimethylaminomethylphenyl.
51	Methyl	Methoxycarbonymethyl.
52	Isopropyl	4-(β-diethylaminoethoxycarbonyl) phenyl.

The novel compounds of this invention effectively inhibit acid secretion for a period of hours. For this reason the mercaptopyridazinedione compounds of this invention have special value in the prophylaxis and treatment of peptic ulcers. While the preferred dose is a function of the specific compound used and the individual requirements, generally the compounds of this invention are administered in a total daily dose of from about 0.5–500 mg., the preferred dose level being from about 1–100 mg. At the recommended doses these compounds have a very favorable therapeutic ratio.

As the compounds contemplated within the scope of this invention are effective upon oral administration, they can be compounded in any suitable oral dosage form, as in tablet, capsule, suspension, or other liquid or solid form that can be prepared by procedures well known in the art. Thus, these novel compounds may be admixed with a suitable diluent such as lactose, and encapsulated; or they may be combined with suitable binding agents and expanding agents and compressed into tablet form. In addition, a liquid pharmaceutical may be obtained by dissolving or suspending the novel compounds of this invention in a suitable flavored vehicle. While the com-

pounds are also active upon parenteral administration, the oral route is generally preferred.

Typical formulations for preparing tablets, capsules, and liquids containing the novel mercaptopyridazinediones are described below. It should be recognized by one skilled in the art that the formulations represent only one method for making the desired pharmaceutical composition. Factors such as the desired size of the tablet or capsule will be a determining factor as to the amount of diluent required. The type of diluent will be determined by the hardness of the tablet desired, or whether it is to be made by the wet, dry, or direct compression method. Also to be considered is whether other active ingredients are to be included in the formulation, which may be of benefit in controlling hypergastric acidity in a secondary manner, such as the barbiturates and tranquilizers and the like.

Table containing 25 mg. of 1-R-2R'-4,5-dimercaptopyridazinedione

	Each tablet (mg.)	1,000 tablets (gm.)
1-R-2-R'-4,5-dimercaptopyridazinedione	25	25
Starch	20	20
Lactose (powder)	20	20
Talc	5	5
Weight of granulation	70	70

Mix all of the ingredients and then compress into slugs. The slugs should then be ground to form granules that will pass through a 14–16 mesh screen. The granules may then be re-compressed into tablets, using a suitable compression mold to form tablets, each weighing 70 mg.

Capsule containing 50 mg. of 1-R-2-R'-4,5-dimercaptopyrididazinedione

	Mg.
1-R-2-R'-4,5-dimercaptopyridazinedione	50
Lactose	150
	200

Mix the ingrredients so as to evenly distribute the active ingredient throughout the lactose. Pack the powder into No. 2 empty gelatin capsules. Each capsule should have a net weight of 200 mg.

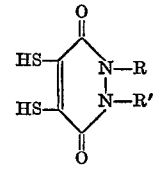
Suspension containing 5 mg. per 5 cc. of 1-R-2-R'-4,5-dimercaptopyridazinedione 1,000 ml.

1-R-2-R'-4,5-dimercaptopyridazinedione—1 gm.
Tragacanth—30 gm.
Amaranth—10 gm.
Syrup wild cherry U.S.P.—600 ml.
Distilled water q.s. ad—1,000 ml.

Hydrate the tragacanth with sufficient water to form a smooth paste and to this add the 1-R-2-R'-4,5-dimercaptopyridazinedione, followed by the Amaranth, which has previously been dissolved in distilled water and the syrup of wild cherry. The suspension is then brought to a volume of 1,000 ml. with distilled water and stirred well to suspend the added materials. Each 5 ml. will contain 5 mg. of 1-R-2-R'-4,5-dimercaptopyridazinedione.

What is claimed is:

1. A compound of formula



wherein R represents loweralkyl and R' represents loweralkyl or loweralkyl substituted with a 4 - morpholinyl radical and the non-toxic acid addition salts thereof wherein R' contains a 4-morpholinyl radical.

2. A compound of claim **1** wherein R represents loweralkyl and R' represents loweralkyl substituted with a 4-morpholinyl radical.

3. A compound of claim **2** wherein R is methyl and R' is 2-(4-morpholinyl)ethyl and the nontoxic acid addition salts thereof.

4. A compound of claim **1** wherein R and R' represent methyl.

5. A compound of claim **1** wherein R and R' represent loweralkyl.

References Cited

Wagner and Zook. Synthetic Organic Chemistry, Wiley and Son Inc. New York, 1953, (pp. 778 and 782 relied on).

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U.S. Cl. X.R.
260—243, 250, 247.2; 424—200, 248, 250