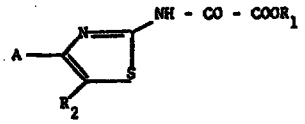
SPECIFICATION

4-Substituted thiazole oxamic acids and salts and esters thereof

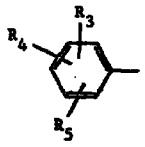
The invention is concerned with novel 4-substituted thiazole-2-oxamic acids and esters and salts thereof having interesting pharmacological properties.

According to one feature of the invention there are provided compounds of general formula



(I)

[wherein R_1 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms;
R_2 represents a hydrogen atom or a methyl or —COOH group;
A represents a pyridyl or benzodioxanyl group or a group of the formula



(in which R_3, R_4 and R_5, which may be the same or different, each represents a hydrogen or halogen atom or a hydroxy, alkoxy, alkyl, alkoxycarbonyl, dialkylamino, carboxamido, nitro or cyano group; or one of R_3, R_4 and R_5 represents a morpholino, piperidino, hydroxypiperidino or phenyl group and the remaining two symbols from R_3, R_4 and R_5 are as defined above), subject to the proviso that when R_2 represents a hydrogen atom then A represents other than an unsubstituted phenyl group or a phenyl group substituted only by one halogen atom or one alkyl or alkoxy group] and salts thereof.

When R_1 is an alkyl group having 1 to 4 carbon atoms, the group may be selected from methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl and tert.-butyl groups.

When A is a pyridyl group this may be lined via the 2-, 3- or 4-position, referred to the nitrogen atom, to the thiazole nucleus.

When R_3, R_4 and R_5 include alkyl groups, i.e. in alkoxy, alkoxycarbonyl and dialkylamino groups, as well as alkyl groups *per se*, the alkyl group preferably has 1 or 2 carbon atoms.

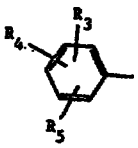
The term "halogen" used herein is intended to mean fluorine, chlorine, bromine and iodine.

The novel compounds according to the invention exhibit interesting pharmacological properties. In particular, our tests have shown that they possess superior antiallergic properties compared to known antiallergic compounds. The compounds show particular advantage in that they may be readily administered orally and in low doses.

It will be appreciated that salts of the compounds for use in medicine should be physiologically acceptable.

However, other salts may be useful in the preparation of the compounds of general formula I or physiologically acceptable salts thereof.

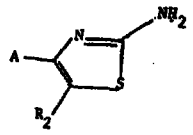
Preferred compounds of general formula I, by virtue of their favourable physiological properties, are compounds wherein R_1 represents a hydrogen atom or an ethyl group, R_2 represents a hydrogen atom, and A represents a pyridyl or benzodioxanyl group or a group of the formula:



(wherein R_3 represents a hydrogen atom or a hydroxy group, R_4 represents a hydrogen atom or a methyl or methoxy group, and R_5 represents a methyl, methoxy or dimethylamino group), and salts thereof.

The following compounds have proved to be especially effective:— 4-(3,4-dimethoxyphenyl)-thiazole oxamic acid, 4-(4-dimethylaminophenyl)-thiazole oxamic acid and 4-(benzodioxan-6-yl)thiazole oxamic acid. Further examples of preferred compounds are 4-(pyrid-2-yl)-thiazole-ethyl oxamate, 4-(3,5-dimethoxyphenyl)-thiazole-oxamic acid, 4-(3-hydroxyphenyl)-thiazole-oxamic acid, 4-(4-hydroxyphenyl)-thiazole oxamic acid, 4-(2-hydroxy-4-methoxyphenyl)-thiazole ethyl oxamate, 4-(4-dimethylaminophenyl)-thiazole ethyl oxamate and 4-(2-hydroxy-4,6-dimethylphenyl)-thiazole ethyl oxamate.

According to a further feature of the invention there is provided a process for the preparation of compounds according to the invention, which process comprises reacting a substituted 2-aminothiazole of formula



(II)

(wherein R_2 and A are as hereinbefore defined) with an oxalic acid ester halide, preferably a chloride, or a dialkyl oxalate and, if desired, subsequently saponifying the ester produced.

If desired, the starting compound of formula II may be reacted in the form of an acid addition salt. The reaction may be conveniently effected by dissolving or suspending the compound of formula II in an inert solvent, and admixing dropwise with the oxalic acid derivative. Examples of solvents and/or suspension agents which are inert under the reaction conditions and which may be used for this purpose include benzene, toluene, xylene, or alcohol and tetrahydrofuran. It may also be advantageous to add an organic base, for example pyridine or triethylamine, to the reaction mixture to act as an acid binder for the acid which is formed. As the reaction tends to be strongly exothermic, the oxalic acid derivative is preferably added slowly and if required, with cooling. In general the reaction will be finished after a period of from 30 to 180 minutes.

As most of the thiazole reaction products only dissolve with difficulty it is recommended to let the reaction mixture stand for a prolonged period of time, for example overnight, and if necessary while stirring, before further processing.

After completion of the reaction, the reaction mixture is preferably worked-up in a manner known *per se*, e.g. by evaporation of the solvent, extraction of the residue with a suitable solvent or solvent mixture (for example, ether, ethyl acetate, chloroform or hexane), purification of the extracts, evaporation of the solvent and recrystallization. In some cases, purification using column chromatography has proved to be suitable.

If a final product of formula I is desired in which R_1 is hydrogen, the ester group may be split off by saponification in the conventional way. This is conveniently done, for example, by hydrolysis in the presence of a catalyst, for example a basic or acidic agent such as a strong base (e.g. sodium or potassium hydroxide) or a mineral acid (e.g. hydrochloric acid, sulfuric acid or phosphoric acid).

Compounds of general formula I in which R_1 is hydrogen may optionally be converted into their corresponding salts by conventional methods. In order to do so the acid may be dissolved and/or suspended in water and the desired base added until a pH of 7 is attained.

Examples of compounds of general formula I which have been readily prepared by the above process are the following acids, and also their corresponding esters and salts:

4-(pyrid-4-yl)-thiazole-2-oxamic acid,
4-(pyrid-3-yl)-thiazole-2-oxamic acid,
4-(pyrid-2-yl)-thiazole-2-oxamic acid,
4-(4-morpholinophenyl)-thiazole-2-oxamic acid,
4-(4-nitrophenyl)-thiazole-2-oxamic acid,
4-(4-piperidinophenyl)-thiazole-2-oxamic acid,
4-(2-hydroxyphenyl)-thiazole-2-oxamic acid,
4-(3,5-dimethoxyphenyl)-thiazole-2-oxamic acid,
4-(3,4-dimethoxyphenyl)-thiazole-2-oxamic acid,
4-(2,4-dimethoxyphenyl)-thiazole-2-oxamic acid,
4-(4-hydroxyphenyl)-thiazole-2-oxamic acid,
4-(3-hydroxyphenyl)-thiazole-2-oxamic acid,
4-(2,5-dimethoxyphenyl)-thiazole-2-oxamic acid,
4-(3,5-dimethoxy-4-hydroxyphenyl)-thiazole-2-oxamic acid,
4-(2-hydroxy-4-methoxyphenyl)-thiazole-2-oxamic acid,
4-(2-hydroxybiphenylyl)-thiazole-2-oxamic acid,
4-(4-dimethylaminophenyl)-thiazole-2-oxamic acid,
4-(3,4,5-trimethoxyphenyl)-thiazole-2-oxamic acid,
4-(2-methyl-4-hydroxyphenyl)-thiazole-2-oxamic acid,
4-(benzodioxanyl)-thiazole-2-oxamic acid,
4-(3-methoxy-4-hydroxyphenyl)-thiazole-2-oxamic acid,
4-(2-methoxycarbonylphenyl)-thiazole-2-oxamic acid,
4-(3-ethoxycarbonylphenyl)-thiazole-2-oxamic acid,
4-(3-dimethylaminophenyl)-thiazole-2-oxamic acid,
4-(2-hydroxy-4,6-dimethylphenyl)-thiazole-2-oxamic acid,
4-(3-methyl-4-hydroxyphenyl)-thiazole-2-oxamic acid,
4-phenyl-5-methyl-thiazole-2-oxamic acid, and
4-(pyrid-3-yl)-5-carboxy-thiazole-2-oxamic acid.

The starting compounds of general formula II are known compounds and may be obtained, for example, by reacting thiourea with a correspondingly substituted acetophenone of formula

$$A—CO—CH_3 \qquad (III)$$

(wherein A is as defined above) according to the method of Orteleva-King. It is of advantage to effect the reaction according to the instructions in Chemische Berichte, volume 92, pages 35/36 (1959).

As stated above, our tests have shown that the compounds according to the invention possess excellent antiallergic properties, and are superior to known antiallergics such as 1,3-bis-(2-carboxychromone-5-yloxy)-2-hydroxypropane, in particular by the fact that they are also effective when administered orally.

In addition, we have found that the inhibiting action on allergic reactions which is exhibited by compounds according to the invention may be effective with lower doses and is maintained over a longer period than is the case with hitherto known compounds.

We have estimated the antiallergic action in rats by the so-called PCA-test (Passive Cutaneous Anaphylaxis test).

In this test, the skin of rats is sensitized by intradermal injections of various dilutions of egg-albumin antiserum (undiluted and in dilutions of 1:3, 1:9, 1:27, etc). On the day following sensitization, the animals receive egg-albumin in Evans-blue solution i.v. By measuring the extension of the blue staining the PCA-titer may be determined. The compounds to be tested are administered i.v. and/or p.o. in various concentrations together with Evans-blue solution. Each rat receives 5 mg of egg albumin dissolved in 1 ml of a solution of 0.25% Evans-blue in a sterile saline solution.

25 to 30 minutes after administration of the dye and the test substance, the animals are killed and the degree of blue staining of the interior surface of the skin is measured in mm^2.

The PCA-titer is expressed as the reciprocal value of those serum dilutions, at which a blue staining with a diameter of at least 5 mm can just be perceived. Reduction of the PCA-titer is a measurement of the inhibition of allergic reactions, in the present case of egg albumin.

The following Table indicates the oral and/or intravenous action of several of the novel compounds:

Compound	ED_{50} mg/kg i.v.	ED_{50} mg/kg p.o.
4-(4-dimethylaminophenyl)-thiazole-2-oxamic acid	0.02	0.34
4-(benzodioxanyl)-thiazole-2-oxamic acid, ethanolamine salt	0.02	0.7
4-(pyrid-4-yl)-thiazole-2-oxamic acid, ethanolamine salt	0.05	–
4-(3,4-dimethoxyphenyl)-thiazole-2-ethyl oxamate	0.12	–
4-(3,4-dimethoxyphenyl)-thiazole-2-oxamic acid	0.13	–
4-(pyrid-3-yl)-thiazole-2-oxamic acid, ethanolamine salt	0.16	–
4-phenyl-5-methyl-thiazole-2-oxamic acid, ethanolamine salt	0.19	2.04
4-(3-dimethylaminophenyl)-thiazole-2-oxamic acid, ethanolamine salt	0.34	1.06
4-(2,4-dimethoxyphenyl)-thiazole-2-oxamic acid	0.39	–
4-(2,5-dimethoxyphenyl)-thiazole-2-oxamic acid, ethanolamine salt	0.4	–
4-(pyrid-4-yl)-thiazole-2-ethyl oxamate	–	1.2
4-(3,4-dimethoxyphenyl)-thiazole-2-methyl oxamate	–	1.2
4-(3-methyl-4-hydroxyphenyl)-thiazole-2-ethyl oxamate	–	2.1

The tests indicate that the compounds according to the invention may be used in the treatment of allergic diseases, e.g. asthma, hay fever, nettle rash, eczema and atopic dermatitides.

Thus, according to a further feature of the invention there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I or a physiologically acceptable salt thereof in association with a pharmaceutical carrier or excipient.

The compositions according to the invention may conveniently be in forms suitable for oral, rectal or parenteral administration, such as, for example, in the form of tablets, coated tablets, pills, capsules, solutions, suspensions, ointments, powders, tinctures, injection solutions or aerosols. Such forms of administration may be prepared by methods conventional to the pharmaceutical art.

For example, the active ingredients according to the invention may be admixed with conventional pharmaceutical fillers or carriers, disintegrants, binders, lubricants, thickeners or diluents, solvents and/or solubilizing agents or agents for obtaining a sustained release of active ingredient. The active ingredient may be formulated with preservatives, stabilizers, emulsifiers, buffers and the like.

The compositions of the invention may, if desired, be in the form of dosage units, such dosage units preferably containing from 5 to 50 mg of active ingredient for parenteral or inhalation administration, or 50 to 500 mg of active ingredient for oral administration.

The following Examples serve to illustrate the preparation of compounds according to the invention, and pharmaceutical compositions containing them. Examples A and B are provided for illustrative purposes only and describe the preparation of compounds of structures similar to formula I.

EXAMPLE A

4-(2-Methoxyphenyl)-thiazole-2-ethyl oxamate

To a suspension of 6 g of 2-amino-4-(2-methoxyphenyl)-thiazole hydroiodide in pyridine are added dropwise 2.9 g of ethyl oxalyl chloride, and the mixture is stirred overnight at room temperature. After evaporation to dryness, the residue is dissolved in sodium bicarbonate solution and extracted with diethyl ether several times. The combined extracts are washed three times with water and once with a saturated salt solution, and subsequently dried over $MgSO_4$. After evaporation to dryness and recrystallization from ethanol, the *title compound* is obtained in a yield of 4.2 g (78% of theory), m.p. 118—122°C.

The 2-amino-4-(2-methoxyphenyl)-thiazole hydriodide starting material is obtained as follows:

15 g of *o*-methoxyacetophenone and 15.2 g of thiourea are mixed well in a synthetic resin flask. To this mixture are added 27.7 g of iodine in small portions. When the addition of iodine is finished the reaction mixture is heated overnight on an oil bath to 100°C. After cooling, 50 ml of methanol are added and thereafter 400 to 500 ml of water; the solid mass is crushed in a mortar, the suspension is filtered, washed with water, some ethanol and ether and dried.

27.7 g (83%) of the desired compound are obtained, which is used as the starting material without further purification.

EXAMPLE B

4-(2-Methoxyphenyl)-thiazole-2-oxamic acid

A suspension of 2 g of 4-(2-methoxyphenyl)-thiazole-2-ethyl oxamate in 30 ml of 1 N sodium hydroxide is heated while stirring vigorously until a clear solution is formed. By acidifying with 2N hydrochloric acid a precipitate is formed which is filtered off after cooling the mixture and diluting with water. The residue is twice suspended in water (100 ml), filtered off and washed with ethanol. The acid is purified by recrystallization from dimethylformamide/ethanol.

Yield: 1 g (55% of theory) of the *title compound* m.p. 195—197°C.

EXAMPLE 1

4-(2,5-Dimethoxyphenyl)-thiazole-2-ethyl oxamate

To a solution of 3 g of 2-amino-4-(2,5-dimethoxyphenyl)-thiazole in dry pyridine are added dropwise 2 g of oxalic acid ethyl ester chloride in 35 ml of dry pyridine. When addition is finished, the reaction mixture is stirred for $2\frac{1}{2}$ hours and meanwhile the progress of the reaction is followed using thin-layer chromatography.

When the reaction is complete, the mixture is poured onto ice-water and the precipitate formed is washed with water and dried. After recrystallization from ethanol and n-hexane/chloroform, 2.9 g of the *title compound* of m.p. 143—144°C are obtained.

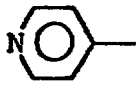
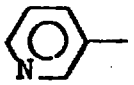
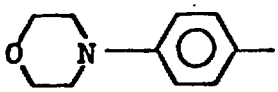
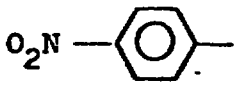
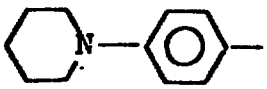
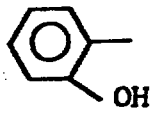
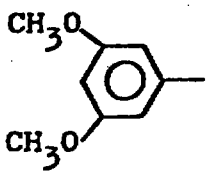
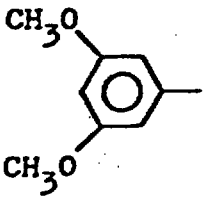
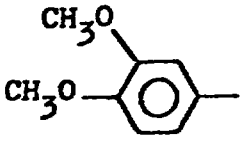
EXAMPLE 2

4-(Pyrid-2-yl)-thiazole-2-ethyl oxamate

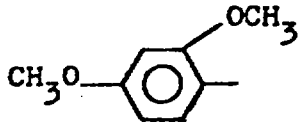
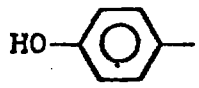
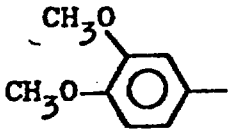
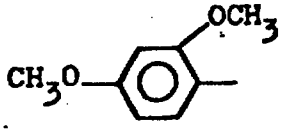
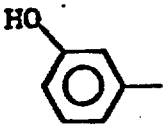
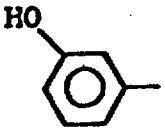
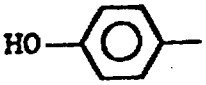
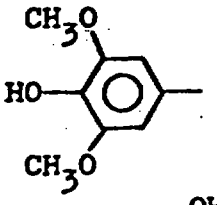
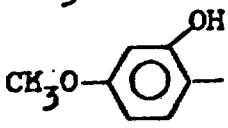
A solution of 1 g of 2-amino-4-(pyrid-2-yl)-thiazole in 25 ml of diethyl oxalate is heated for 20 hours to 125°C. The mixture is cooled, the precipitate is filtered off and subsequently recrystallized from ethanol and then from hexane/chloroform.

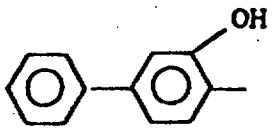
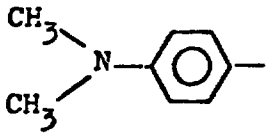
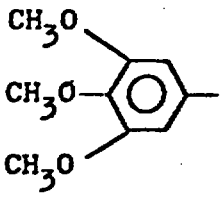
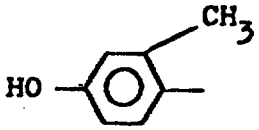
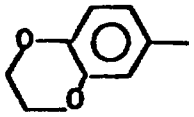
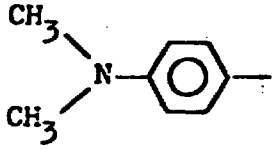
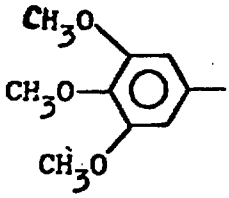
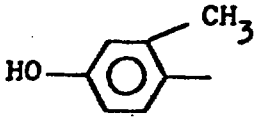
Yield: 0.5 g = 64% of theory of the *title compound* of m.p. 141—144°C.

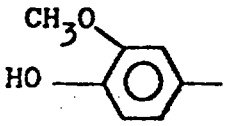
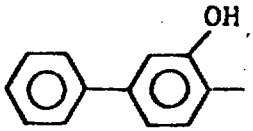
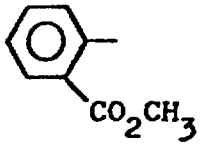
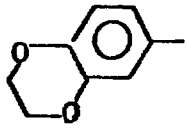
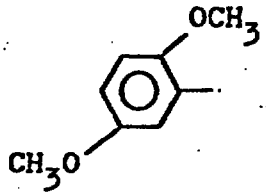
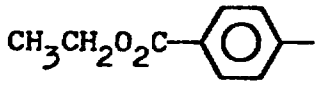
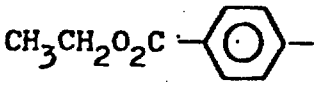
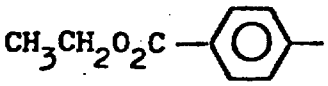
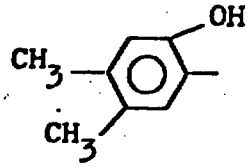
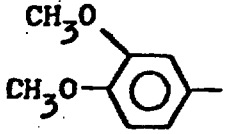
The following compounds were obtained in the same manner:

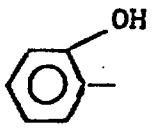
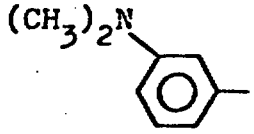
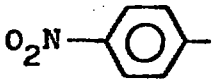
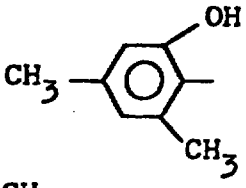
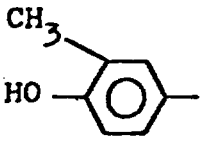
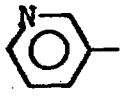
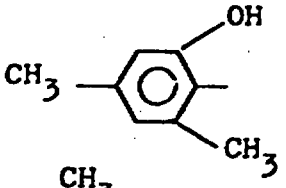
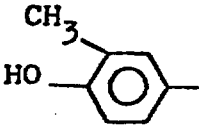
Example No.	R_2 = H A	R_1	m.p. °C
3		C_2H_5	209 - 211
4		C_2H_5	226 - 228
5		C_2H_5	249 - 251
6		C_2H_5	227 - 229
7		C_2H_5	207 - 209
8		C_2H_5	209 - 211
9		C_2H_5	166 - 169
10		H	221 - 223
11		C_2H_5	131 - 133

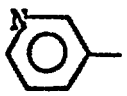
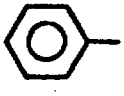
(18)

Example No.	R_2 = H A	R_1	m.p. °C
12		C_2H_5	203 - 207
13		C_2H_5	230 - 233
14		H	> 200(decomp)
15		H	190 - 193
16		C_2H_5	231 - 235
17	 . 1/2 C_2H_5OH	H	211 - 215
18		H	247 - 250
19		C_2H_5	164 - 168
20		C_2H_5	167 - 170

Example No.	R_2 = H A	R_1	m.p. °C
21		C_2H_5	189 - 195
22		C_2H_5	210 - 213
23		C_2H_5	141 - 144
24		C_2H_5	173 - 176
25		C_2H_5	204 - 207
26		H	>220 (decomp.)
27		H	158 - 161 (ethanolamine salt)
28		H	195 - 197 (ethanolamine salt)

Example No.	R_2 = H A	R_1	m.p. °C
29		H	177 - 180 (ethanolamine salt)
30		H	> 225 (decomp.)
31		C_2H_5	139 - 140
32		H	179 - 181 (ethanolamine salt)
33		H	160 - 162 (ethanolamine salt)
34		C_2H_5	184 - 185
35		CH_3	209 - 211
36		n-Butyl	175 - 177
37		C_2H_5	185 - 187
38		CH_3	170 - 174

Example No.	R_2 = H A	R_1	m.p. °C
39		H	186 - 190 (ethanolamine salt)
40		H	147 - 150 (ethanolamine salt)
41		H	230 - 233 (ethanolamine salt)
42		C_2H_5	167 - 170
43		C_2H_5	212 - 215
44		H	215 - 219 (ethanolamine salt)
45		H	207 - 208 (ethanolamine salt)
46		H	203 - 206 (ethanolamine salt)
47		H	167 - 176 (ethanolamine salt)

Example No.	A	R_2	R_1	m.p. C°
48		-COOH	H	204 - 207 (ethanolamine salt)
49		$-CH_3$	H	188 - 190 (ethanolamine salt)

EXAMPLE I: Tablets
Composition

Active ingredient according to invention	0.100 g
stearic acid	0.010 g
glucose	1.890 g
	2.000 g

The components are processed to form tablets of the composition indicated above in the conventional way.

EXAMPLE II: Tablets
Composition:

Active ingredient according to invention	0.200 g
stearic acid	0.020 g
glucose	1.780 g
	2.000 g

The components are processed to form tablets of the composition indicated above in the conventional way.

EXAMPLE III: Ointment:
Composition:

	g/100 g of ointment
Active ingredient according to invention	2.000
foaming hydrochloric acid	0.011
sodium pyrosulfite	0.050
mixture of equal parts of cetyl alcohol and stearyl alcohol	20.000
white Vaseline (Vaseline is a registered Trade Mark)	5.000
synthetic Bergamot oil	0.075
distilled water	*ad* 100.000

The components are processed to form an ointment in the conventional way.

EXAMPLE IV: Inhalation Aerosol:
Composition:

Active ingredient according to invention	1.00 parts
soya lecithin	0.20 parts
mixture of propellant gases (Freon 11, 12 and 14 — Freon is a registered Trade Mark)	*ad* 100.00 parts

The preparation is preferably filled into aerosol containers with metering valve. The single dose is adjusted in such a way that it provides 5 to 20 mg of active substance. For higher dosage units within the indicated range preparations with a higher content of active substance are used.

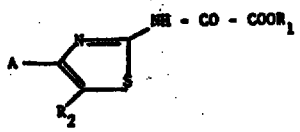
EXAMPLE V: Ampoules (Injection Solutions)
Composition:

Active ingredient according to invention	50.0 parts by weight
sodium pyrosulfite	1.0 part by weight
disodium salt of ethylenediamine tetraacetic acid	0.5 part by weight
sodium chloride	8.5 parts by weight
double distilled water	*ad* 1000.0 parts by weight

The active ingredient and the excipients are dissolved in a sufficient quantity of water and brought to the desired concentration with the required quantity of water. The solution is filtered and filled into 1 ml ampoules under aseptic conditions. Finally, the ampoules are sterilized and sealed. Each ampoule contains 50 mg of active ingredient.

CLAIMS

1. Compounds of general formula



(I)

EXAMPLE I: Tablets

Composition

Active ingredient according to invention	0.100 g
stearic acid	0.010 g
glucose	1.890 g
	2.000 g

The components are processed to form tablets of the composition indicated above in the conventional way.

EXAMPLE II: Tablets

Composition:

Active ingredient according to invention	0.200 g
stearic acid	0.020 g
glucose	1.780 g
	2.000 g

The components are processed to form tablets of the composition indicated above in the conventional way.

EXAMPLE III: Ointment:

Composition:

	g/100 g of ointment
Active ingredient according to invention	2.000
foaming hydrochloric acid	0.011
sodium pyrosulfite	0.050
mixture of equal parts of cetyl alcohol and stearyl alcohol	20.000
white Vaseline (Vaseline is a registered Trade Mark)	5.000
synthetic Bergamot oil	0.075
distilled water	*ad* 100.000

The components are processed to form an ointment in the conventional way.

EXAMPLE IV: Inhalation Aerosol:

Composition:

Active ingredient according to invention	1.00 parts
soya lecithin	0.20 parts
mixture of propellant gases (Freon 11, 12 and 14 — Freon is a registered Trade Mark)	*ad* 100.00 parts

The preparation is preferably filled into aerosol containers with metering valve. The single dose is adjusted in such a way that it provides 5 to 20 mg of active substance. For higher dosage units within the indicated range preparations with a higher content of active substance are used.

EXAMPLE V: Ampoules (Injection Solutions)

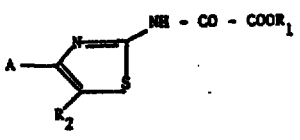
Composition:

Active ingredient according to invention	50.0 parts by weight
sodium pyrosulfite	1.0 part by weight
disodium salt of ethylenediamine tetraacetic acid	0.5 part by weight
sodium chloride	8.5 parts by weight
double distilled water	*ad* 1000.0 parts by weight

The active ingredient and the excipients are dissolved in a sufficient quantity of water and brought to the desired concentration with the required quantity of water. The solution is filtered and filled into 1 ml ampoules under aseptic conditions. Finally, the ampoules are sterilized and sealed. Each ampoule contains 50 mg of active ingredient.

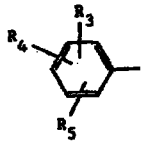
CLAIMS

1. Compounds of general formula



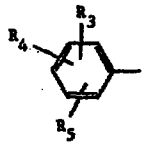
(I)

[wherein R_1 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms;
R_2 represents a hydrogen atom or a methyl or —COOH group; and
A represents a pyridyl or benzodioxanyl group, or a group of the formula



(in which R_3, R_4 and R_5, which may be the same or different, each represents a hydrogen or halogen atom or a hydroxy, alkoxy, alkyl, alkoxycarbonyl, dialkylamino, carboxamido, nitro or cyano group, or one of R_3, R_4 and R_5 represents a morpholino, piperidino, hydroxypiperidino or phenyl group and the remaining two symbols from R_3, R_4 and R_5 are as defined above), subject to the proviso that where R_2 represents a hydrogen atom then A represents other than an unsubstituted phenyl group or a phenyl group substituted only by one halogen atom or one alkyl or alkoxy group] and salts thereof.

2. Compounds of general formula I as claimed in claim 1 in which R_1 represents a hydrogen atom or an ethyl group;
R_2 represents a hydrogen atom, and A represents a pyridyl or benzodioxanyl group, or a group of the formula



(wherein R_3 represents a hydrogen atom or a hydroxy group, R_4 represents a hydrogen atom or a methyl or methoxy group and R_5 represents a methyl, methoxy or dimethylamino group), and salts thereof.

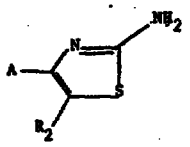
3. 4-(3,4-Dimethoxyphenyl)-thiazole-2-oxamic acid and salts thereof.

4. 4-(4-Dimethylaminophenyl)-thiazole-2-oxamic acid and salts thereof.

5. 4-(Benzodioxan-6-yl)-thiazole-2-oxamic acid and salts thereof.

6. Compounds as claimed in claim 1 as herein specifically disclosed with the exception of the compounds claimed in any one of claims 3 to 5.

7. A process for the preparation of compounds as defined in claim 1 which comprises reacting a substituted 2-aminothiazole of formula



(II)

(wherein R_2 and A are as defined in claim 1) with an oxalic acid ester halide or a dialkyl oxalate and, if desired, subsequently saponifying the ester produced.

8. A process for the preparation of salts of the compounds of general formula I as defined in claim 1 which comprises converting a compound of formula I produced by a process as claimed in claim 7 into a salt thereof.

9. A process for the preparation of compounds as defined in claim 1 substantially as herein described in any one of Examples 1 to 49.

10. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 7 to 9.

11. Pharmaceutical compositions comprising as active ingredient at least one compound of formula I as defined in claim 1 or a physiologically acceptable salt thereof in association with a pharmaceutical carrier or excipient.

12. Compositions as claimed in claim 11 in the form of dosage units for parenteral, inhalation or oral administration, wherein each dosage unit for parenteral or inhalation administration contains from 5 to 50 mg of said active ingredient, or wherein each dosage unit for oral administration contains from 50 to 500 mg of said active ingredient.

13. Compositions as claimed in claim 11 substantially as herein described in any one of Examples I to V.

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