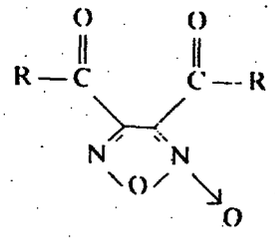
Description

The invention relates to 3,4-bis-substituted 1,2,5-oxadiazole 2-oxides of the formula I



(I)

and their pharmaceutically acceptable acid addition compounds, a process for their preparation and pharmaceutical formulations containing them.

In the formula I, R denotes $-NHR^1$, $-NR^2R^3$, $-NHR^4OR^2$, $-NHR^5COR^6$ or $-N\frown X$, R^1 denotes alkyl having 1 to 6 C atoms or cycloalkyl having 4 to 7 C atoms, R^2 and R^3 denote alkyl having 1 to 4 C atoms, R^4 denotes an alkylene radical of the formula $-C_nH_{2n}-$ wherein n denotes 2, 3 or 4, R^5 denotes an alkylene radical of the formula $-C_mH_{2m}-$ wherein m denotes 1, 2 or 3, R^6 denotes $-OR^2$, $-NHR^1$, $-NH_2$ or $-NR^2R^3$, X denotes $-(CH_2)_p-$,

$-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-\overset{R^2}{\underset{|}{N}}-(CH_2)_2-$ and p is 4, 5 or 6

The alkyl radicals represented by R^1, R^2 and R^3 and also the alkylene radicals represented by R^4 can be straight-chain or branched. Amongst the compounds of the formula I, preferred compounds are those which contain an -NH- grouping in the R radicals. R^4 preferably represents $-(CH_2)_2-$ or $-(CH_2)_3-$ and R^5 preferably represents $-CH_2-$ or $-(CH_2)_2-$. R^2 preferably denotes methyl or ethyl.

The compounds, according to the invention, of the formula I can be prepared from hydroxamoyl chlorides of the formula II by elimination of HCl and subsequent dimerisation:

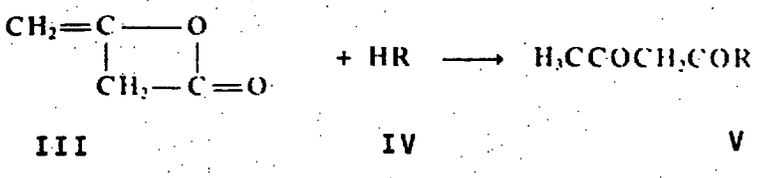
$$2R-CO-\underset{\underset{NOH}{\|}}{C}-Cl \xrightarrow[-2HCl]{\text{base}}$$

(II) (I)

The reaction is carried out in a suitable solvent or dispersing agent, such as, for example, dimethylformamide, dimethyl sulphoxide, N-methylpyrrolidone or a lower alcohol, such as methanol or ethanol, but preferably in water. Mixtures of different solvents or dispersing agents, in particular homogeneous and also heterogeneous mixtures with water, such as, for example, water/methanol or water/diethyl ether, can also be used. In general, the reaction is carried out at 0 to +50°C, preferably at 10 to 25°C.

The reaction frequently takes place of itself after the compound II has been introduced into the solvent or dispersing agent. However, it can be accelerated considerably by adding a base which binds the hydrogen chloride which has been eliminated. The following are examples of bases of this type which can be used: secondary or tertiary organic amines, such as, for example, dimethylamine, trimethylamine, diethylamine, triethylamine or pyridine; alkali metal hydroxides, such as, for example, sodium hydroxide or potassium hydroxide; alkali metal carbonates and alkali metal bicarbonates, such as, for example, potassium carbonate, sodium carbonate and sodium bicarbonate; and alkali metal acetates, such as, for example, sodium acetate. Sodium carbonate and sodium bicarbonate are preferred. The base can also be added in the form of a solution (for example an aqueous solution as in the case of the lower organic amines) or a dispersion to the solution or dispersion of the compound II. Owing to the reaction which sets in, it is appropriate to add the base gradually or in portions and to stir the reaction mixture. The base is preferably added in a molar quantity (2 moles of base for 2 moles of the compound II) or, if appropriate, in an excess of up to 20%. When the reaction is complete, the compound of the formula I which has been formed is separated off and, if desired, is converted into an acid addition compound.

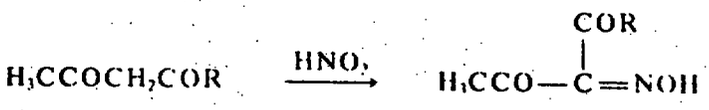
The hydroxamoyl chloride starting compounds of the formula II which are required can be prepared by various processes which are in themselves known, for example by first reacting diketene III with an amine IV to give an acetoacetamide V (compare, for example, U.S. Patent Specification 2,174,239):



III IV V

The reaction between the compounds III and IV is carried out in a suitable solvent, such as, for example, water, or an alcohol, normally at temperatures from 10 to 50°C, preferably at room temperatures.

The acetoacetamide V is oximated in a suitable solvent, such as water, glacial acetic acid or an alcohol, by means of nitrous acid produced in situ, the oxime VI being formed:



V VI

This reaction is carried out, for example, at a pH value not less than 4.0 and at temperatures from 10 to 50°C, preferably at room temperature.

The nitrous acid is most simply produced from sodium nitrite and hydrochloric acid.

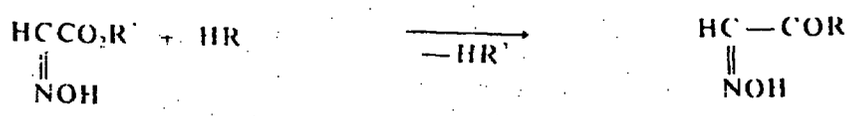
The oxime VI is then chlorinated in a suitable solvent, such as water or an alcohol, for example at temperatures from +10 to 70°C, preferably 30 to 50°C, the hydroxamoyl chloride II being formed.

The hydroxamoyl chloride II can also be prepared from the acetoacetamide V by exchanging the sequence of the oximation and chlorination reactions. In the chlorination reaction, the chlorine compound VII: $CH_3COCHClCOR$ is then first formed from the acetoacetamide V and is then converted into the compound II by reaction with nitrous acid.

The conversion of acetoacetamides V into compounds of the formula II by the possible routes indicated above is described,

for example, in German Auslegeschrift 1,963,061. Starting from diketene III and the amine IV, it is possible to prepare the compounds according to the invention by the stages of synthesis indicated above in a single reaction vessel without isolating the intermediate products. The yields, calculated over all the steps, are generally 20 to 70% of theory.

The hydroxamoyl chlorides II can also be prepared by reacting a glyoxylic acid ester-oxime VII with an amine IV, the oxime compound VIII being formed first.



VII IV VIII

R^7 denotes lower alkyl, in particular methyl or ethyl. The compound VIII is then converted into the compound II by chlorination. The compounds I, according to the invention, which have a basic side chain, form salts with inorganic or organic acids. The following are examples of such acids: hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, oxalic acid, lactic acid, tartaric acid, acetic acid, salicylic acid, benzoic acid, citric acid, ascorbic acid, adipic acid and naphthalene-disulphonic acid. The acid addition compounds are obtained in a known manner by combining the components in a suitable solvent or dispersing agent.

The compounds of the formula I and their pharmacologically acceptable acid addition compounds possess valuable pharmacological properties. Their action on the cardiovascular system is particularly pronounced. In a low dosage they lower the blood pressure, reduce the peripheral resistance and produce a reduction in the heart action via a lowering of the pulmonary arterial pressure at a pulse rate which is only slightly affected.

The compounds of the formula I and their pharmacologically acceptable acid addition salts can, therefore, be administered to humans as drugs on their own, as mixtures with one another or in the form of pharmaceutical formulations which permit enteral or parenteral administration and which contain, as the active constituent, an effective dose of at least one compound of the formula

I or an acid addition salt thereof, together with customary excipients and additives, which are pharmaceutically unobjectionable.

The drugs can be administered orally, for example in the form of pills, tablets, lacquered tablets, dragees, hard and soft gelatine capsules, solutions, syrups, emulsions or suspensions or aerosol mixtures. Administration can, however, also be carried out rectally, for example in the form of suppositories, or parenterally, for example in the form of injection solutions, or percutaneously, for example in the form of ointments or tinctures.

The pharmaceutical formulations are prepared by using pharmaceutically inert inorganic or organic excipients. For example, lactose, maize starch or derivatives thereof, talc, stearic acid or salts thereof and the like are used for the preparation of pills, tablets, dragees and hard gelatine capsules. Excipients for soft gelatine capsules and suppositories are, for example, fats, waxes, semi-solid and liquid polyols, natural or hardened oils and the like. Examples of suitable excipients for the preparation of solutions and syrups are water, sucrose, invert sugar, glucose, polyols and the like. Examples of suitable excipients for the preparation of injection solutions are water, alcohols, glycerol, polyols, vegetable oils and the like.

In addition to the active compounds and excipients, the pharmaceutical formulations can also contain additives, such as, for example, fillers, extenders, disintegrants, binders, lubricants, wetting agents, stabilisers, emulsifying agents, preservatives, sweeteners, colorants, flavouring agents or flavourings, thickeners, diluents, buffer substances and also solvents or solubilisers or agents for achieving a depot effect, and also salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula I or pharmacologically acceptable acid addition salts thereof and also other therapeutically active substances.

The following are examples of other therapeutically active substances of this type: β-receptor blockers, such as, for example, propranolol, pindolol or metoprolol; vasodilators, such as, for example carbochromen; sedatives, such as, for example, barbituric acid derivatives, 1,4-benzodiazepines and meprobamate; diuretics, such as, for example, chlorothiazide; heart tonics,

such as, for example, digitalis formulations; agents which lower the blood pressure, such as, for example, hydralazine, dihydralazine, prazosin, clonidine or Rauwolfia alkaloids; agents which lower the fatty acid level in the blood, such as, for example, bezafibrate or fenofibrate; and agents for the prophylaxis of thrombosis, such as, for example, phenprocoumon.

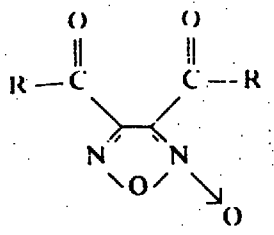
The compounds of the formula I, their pharmacologically acceptable acid addition salts and pharmaceutical formulations, which contain compounds of the formula I or their pharmacologically acceptable acid addition salts as active compounds, can be used on humans in combating or preventing diseases of the cardiovascular system, for example as anti-hypertensive drugs against the various forms of high blood pressure, and in combating or preventing angina pectoris and the like. The dosage can vary within wide limits and should be adapted in each particular case to the individual factors. In general, a daily dose of about 0.2 to 150 mg, preferably 1 to 30 mg, per human individual is appropriate for oral administration. In the case of other administration forms too, owing to the good absorption of the active compounds, the daily dose is within similar ranges of quantity, that is to say in general also 0.2 to 150 mg/person. The daily dose is normally sub-divided into several, for example 2 or 3, part administrations.

The pharmaceutical formulations generally contain 0.1 to 50 mg/dose, preferably 0.5 to 10 mg/dose, of the active compounds of the formula I or pharmacologically acceptable acid addition salts thereof.

The investigations into the anti-anginal and anti-hypertensive action of the compounds of the formula I were carried out on mongrel dogs of both sexes under pentobarbital anaesthesia (30 to 40 mg/kg intravenously) or under urethane-chloralose anaesthesia (3 ml/kg of urethane-chloralose mixture administered intravenously = 20 mg/kg of chloralose and 250 mg/kg of urethane). The artificial respiration of the animals was effected by means of a Bird Mark 7 respirator. The final expiratory content of carbon dioxide (determined by means of the Uras) was between 4.5 and 5% by volume. During the entire experiment, the animals under pentobarbital anaesthesia received a continuous intravenous infusion of pentobarbital, 4 mg/kg/6ml/hour, in order to ensure a constant depth

of anaesthesia; the animals under urethane-chloralose anaesthesia did not receive a continuous infusion. The infusion was administered through the cephalic vein. After the experimental animal had been prepared, there was a waiting period of approx. 1 hour until all the haemodynamic parameters had adjusted themselves (steady state). The actual test was then begun.

The systolic and diastolic blood pressure was determined peripherally in the femoral artery via a Statham pressure recorder. A Millar tip catheter inserted via the carotid artery into the left ventricle provided the signal for the LVEDP (left ventricular end diastolic pressure) and the pulse rate. The average blood pressure in the pulmonary artery was determined by means of a second tip catheter inserted via the jugular vein. The results obtained are shown in the following table:



R	Dose mg/kg	LVEDP Δ mmHg	PAP Δ mmHg	BPa Δ mmHg	PR b/ Δ minute	t/ minute
-NHCH$_2$CHCH$_3$ (CH$_3$)	0.05	-2	-3	-70	-	60
-NH-cyclohexyl	0.05	-3.5	-3	-65	-5	45
-NHCHCH$_3$ (CH$_2$CH$_3$)	0.05	-2	-3	-75	-10	75
-NH-C(CH$_3$)$_2$-CH$_3$	0.05	-2	-2	-60	+5	60
-NHCH$_2$CO$_2$CH$_3$	0.05	-5	-3	-65	+10	45
-NHCH$_2$CH$_3$	0.05	-7	-3	-85	-5	60
piperidino	0.05	-	-1	-25	-20	> 120
-NHC$_4$H$_{9(n)}$	0.05	-5	-2.5	-70	-10	30
-N(CH$_2$CH$_3$)(CH$_2$CH$_3$)	0.1	-2.5	-1	-25	-5	35
-NHCH$_2$CH$_2$OCH$_3$	0.05	-4	-1.5	-65	+30	40
-NH-CH-CH$_3$ (CH$_3$)	0.05	-2.3	-1.5	-45	-1	75
-NHCH$_3$	0.05	-7	-4	-55	-15	60
ISDN	0.05	-2.1	-0.7	-19	±0	30

The abbreviations in the table have the following meanings

LVEDP = left ventricular end diastolic pressure
PAP = average pulmonary arterial pressure
Bpa = average peripheral blood pressure
PR = pulse rate
t/minute= average duration of action
ISDN = isosorbide dinitrate (comparison substance)

The following example serves to illustrate the invention further.

Example

1,2,5-Oxadiazole-2-oxide-3,4-bis-(carboxylic acid methylamide). 12.5 g of methylamine are dissolved in 400 ml of water. 34g of diketene are added dropwise slowly at room temperature (20°C), a stable pH value of 7 being established. 28 g of sodium nitrite are then dissolved in the resulting solution. 40 g of concentrated hydrochloric acid are then added dropwise at such a rate that the pH value of the solution does not fall below 4. Stirring is then continued for a further 30 minutes and 30 g of chlorine are then passed in at 20-40°C. After the solution has cooled, it is cooled to -10°C and the solid is filtered off. It is suspended in 100 ml of water and a total of 33.6 g of sodium bicarbonate is added cautiously, in portions, at 20°C. The solution now has a pH value of 7.5-8. It is now cooled to 0°C and the solid which has precipitated is filtered off and recrystallised from isopropanol. Colourless crystals, melting point 164-165°C.

The compounds shown in the following table can be prepared in an analogous manner at the reaction temperatures mentioned, in the stated solvents and using the bases mentioned.

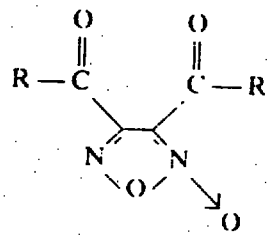
The structure of the compounds synthesised can be confirmed by elementary analysis and by the IR and NMR spectra.

1,2,5-Oxadiazole-2-oxide-3,4-bis-carboxylic acid amide	Melting point in °C	Reaction temperature in °C	Solvent	Base
Bis-dimethylamide	127–129	30	H_2O	$NaHCO_3$
Bis-diethylamide	Oil	35	H_2O	$NaHCO_3$
Bis-morpholide	127–139	30	H_2O	$NaHCO_3$
Bis-butylamide	91–92	25	$H_2O/C_2H_5OC_2H_5$	$NaHCO_3$
Bis-pyrrolidide	106–108	30	$(CH_3)_2SO$	Na_2CO_3
Bis-ethylamide	116–117	0	DMF	$KHCO_3$
Bis-isopropylamide	128–131	20	H_2O	$(i\text{-}C_3H_7)_2NH$
Bis-(2-methoxyethyl)amide	94–95	10	C_2H_5OH	CH_3COONa
Bis-piperidide	115–116	25	H_2O	CH_3COOK
Bis-tert.-butylamide	166–167	50	CH_3OH	$(CH_3)_3N$
Bis-cyclohexylamide	137–139	45	$H_2O/C_2H_5OC_2H_5$	NaOH
Bis-isobutylamide	83,5–87	10	NMP	K_2CO_3
Bis-sek-butylamide	Oil	10	NMP	$NaHCO_3$
Bis-(methoxycarbonyl-methyl)amide	97–99	20	CH_3OH	KOH
Bis-cyclopentylamide	114–146	30	H_2O/C_2H_5OH	$NaHCO_3$
Bis-propylamide	117–118	20	H_2O	$NaHCO_3$
Bis-(4-methyl)piperazide	240 (Decomposition) Dihydrochloride	25	C_2H_5OH	$NaHCO_3$
Bis-(3-methoxypropyl)amide	65–68	10	H_2O	$NaHCO_3$
Bis-(4-methoxybutyl)amide	Oil	20	H_2O	$NaHCO_3$
Bis-hexamethylenimide	103–106	25	$H_2O/C_2H_5OC_2H_5$	$NaHCO_3$
Bis-(2-methoxycarbonyl-ethyl)amide	80–82	10	CH_3OH	$NaHCO_3$
Bis-(2-methoxycarbonyl-propyl)amide	Oil	20	CH_3OH	K_2CO_3
Bis-(diethylaminocarbonyl-methyl)amide	Oil	25	$n\text{-}C_3H_7OH$	K_2CO_3
Bis-(aminocarbonylmethyl)-amide	141–142	20	CH_2OH	$NaHCO_3$
Bis-(di-n-butyl)amide	Oil	30	$H_2O/C_2H_5OC_2H_5$	$NaHCO_3$
Bis-(ethylaminocarbonyl)-methyl)amide	Oil	25	H_2O	$NaHCO_3$
Bis-(2-ethoxyethyl)amide	Oil	20	$H_2O/C_2H_5OC_2H_5$	$NaHCO_3$
Bis-(2-ethoxycarbonylethyl)-amide	Oil	20	C_2H_5OH	K_2CO_3

DMF = Dimethylformamide
NMP = N-Methylpyrrolidone

Patent claims for contracting states: BE, CH, DE, FR, GB, IT, LI, NL, SE.

1. 3,4-Bis-substituted 1,2,5-oxadiazole 2-oxides of the formula



(I)

and their pharmacologically acceptable acid addition compounds wherein R denotes $-NHR^1$, $-NR^2R^3$, $-NHR^4OR^2$, $-NHR^5COR^6$ or $-N\overset{\frown}{X}$, R^1 denotes alkyl having 1 to 6 C atoms or cycloalkyl having 4 to 7 C atoms, R^2 and R^3 denote alkyl having 1 to 4 C atoms, R^4 denotes an alkylene radical of the formula $-C_nH_{2n}-$ wherein n denotes 2, 3 or 4, R^5 denotes an alkylene radical of the formula $-C_mH_{2m}-$ wherein m denotes 1, 2 or 3, R^6 denotes $-OR^2$, $-NHR^1$, $-NR^2R^3$ or $-NH_2$, X denotes $-(CH_2)_p-$, $-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-\underset{\displaystyle R^2}{N}-(CH_2)_2-$ and p is 4, 5 or 6.

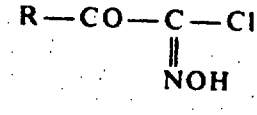
2. 3,4-Bis-substituted 1,2,5-oxadiazole 2-oxides according to Claim 1, characterised in that the radicals R contain an -NH- grouping.

3. 3,4-Bis-substituted 1,2,5-oxadiazole 2-oxides according to Claims 1 and/or 2, characterised in that R^4 denotes $-(CH_2)_2-$ or $-(CH_2)_3-$.

4. 3,4-Bis-substituted 1,2,5-oxadiazole 2-oxides according to Claims 1 and/or 2, characterised in that R^5 denotes $-CH_2-$ or $-(CH_2)_2-$.

5. 1,2,5-Oxadiazole-2-oxide-3,4-bis-(carboxylic acid-isopropyl-amide).

6. Process for the preparation of the 3,4-bis-substituted 1,2,5-oxadiazole 2-oxides according to one or more of Claims 1 to 5, by elimination hydrogen chloride from a hydroxamoyl chloride of the formula II



(II)

and dimerisation and also, if desired, subsequent conversion into the acid addition compound.

7. Process according to Claim 6, characterised in that the reaction is carried out in a solvent or dispersing agent at temperatures from 0 to 50°C, preferably from 10 to 25°C.

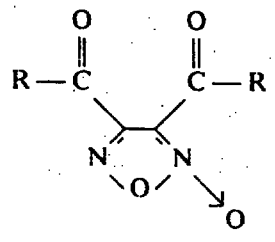
8. Process according to Claims 6 and/or 7, characterised in that a base, preferably in a molar quantity, is added for the reaction.

9. 3,4-Bis-substituted 1,2,5-oxadiazole 2-oxides according to one or more of Claims 1 to 5 or their pharmacologically acceptable acid addition compounds for use as pharmacological active compounds.

10. Pharmaceutical formulation containing an effective dose of a 3,4-bis-substituted 1,2,5-oxadiazole 2-oxide according to one or more of Claims 1 to 5, or of an acid addition compound thereof, together with pharmaceutically permissible excipients and additives and also, if desired, other therapeutically active substances.

Patent claims for contracting state: AT

1. Process for the preparation of 3,4-bis-substituted 1,2,5-oxidiazole 2-oxides of the formula I.

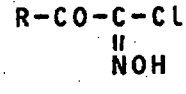


(I)

and their pharmacologically acceptable acid addition compounds wherein

R	denotes $-NHR^1$, $-NR^2R^3$, $-NHR^4OR^2$, $-NHR^5COR^6$ or $-N\ X$,
R^1	denotes alkyl having 1 to 6 C atoms or cycloalkyl having 4 to 7 C atoms,
R^2 and R^3	denotes akyl having 1 to 4 C atoms,
R^4	denotes an alkylene radical of the formula $-C_nH_{2n}-$ wherein n denotes 2, 3 or 4.
R^5	denotes an alkylene radical of the formula $-C_mH_{2m}-$ wherein m denotes 1, 2 or 3.
R^6	denotes $-OR^2$, $-NHR^1$, $-NR^2R^3$ or $-NH_2$,
X	denotes $-(CH_2)_p-$, $-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-\underset{\displaystyle R^2}{N}-(CH_2)_2-$ and
p	is 4, 5 or 6.

characterised in that a hydroxamoyl chloride of the formula II.



(II)

is introduced into a solvent or dispersing agent at temperatures

from 0 to 5°C whereupon a compound of the formula 1 is formed with elimination of HCl and dimerisation, which compound is, if desired, converted in a manner known per se into an acid addition salt.

2. Process according to Claim 1, characterised in that the hydroxamoyl chloride of formula II is introduced into the solvent or dispersing agent at temperatures from 10 to 25°C.

3. Process according to Claims 1 and/or 2, characterised in that a base, preferably in a molar quantity, is added.

4. Process acording to Claim 3, characterised in that the base added is a secondary or tertiary amine, alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate or alkali metal acetate.

5. Process according to Claim 3 and/or 4, characterised in that the base is added gradually or in portions.

6. Process according to one of Claims 1 to 5, characterised in that the solvent used is dimethylformamide, dimethyl sulphoxide, N-methylpyrrolidone, a lower alcohol, diethylether, water or a mixture of these solvents.

7. Process according to one or several of Claims 1 to 6, characterised in that the radical R contains an -NH-grouping.

8. Process according to one or more of Claims 1 to 7, characterised in that R^4 denotes $-(CH_2)_2-$ or $-(CH_2)_2^-$.

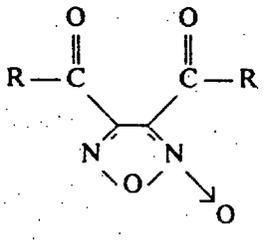
9. Process according to one or more of Claims 1 to 7, characterised in that R^5 denotes $-CH_2-$ or $-(CH_2)_3^-$.

10. Process according to one or more of Claims 1 to 7, characterised in that R^2 denotes methyl or ethyl.

* C L M S *

Patent Claims for Contracting States: BE, CH, DE, F., GB, IT, LI, NL, SE (as printed)

1. 3,4-Bis-substituted 1,2,5-oxadiazole 2-oxides of the formula



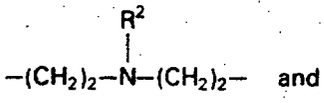
(I)

and their pharmacologically acceptable acid addition compounds wherein

R denotes $-NHR^1$, $-NR^2R^3$, $-NHR^4OR^2$, $-NHR^5COR^6$ or



R^1 denotes alkyl having 1 to 6 C atoms or cycloalkyl having 4 to 7 C atoms,
R^2 and R^3 denote alkyl having 1 to 4 C atoms,
R^4 denotes an alkylene radical of the formula $-C_nH_{2n}-$ wherein n denotes 2, 3 or 4,
R^5 denotes an alkylene radical of the formula $-C_mH_{2m}-$ wherein m denotes 1, 2 or 3,
R^6 denotes $-OR^2$, $-NHR^1$, $-NR^2R^3$ or $-NH_2$,
X denotes $-(CH_2)_p-$, $-(CH_2)_2-O-(CH_2)_2-$ or



and

p is 4, 5 or 6.

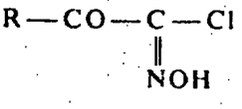
2. 3,4-Bis-substituted 1,2,5-oxadiazole 2-oxides according to Claim 1, characterised in that the radicals r contain an —NH-grouping.

3. 3,4-Bis-substituted 1,2,5-oxadiazole 2-oxides according to Claims 1 and/or 2, characterised in that R^4 denotes $-(CH_2)_2-$ or $-(CH_2)_3-$.

4. 3,4-Bis-substituted 1,2,5-oxadiazole 2-oxides according to Claims 1 and/or 2, characterised in that R^5 denotes $-CH_2-$ or $-(CH_2)_2-$.

5. 1,2,5-Oxadiazole 2-oxide-3,4-bis-(carboxylic acid isopropylamide).

6. Process for the preparation of the 3,4-bis-substituted 1,2,5-oxadiazole 2-oxides of one or several of Claims 1 to 5, by eliminating hydrogen chloride from a hydroxamoyl chloride of the formula II



(II)

and dimerisation and also, if desired, subsequent conversion into the acid addition compound.

7. Process according to Claim 6, characterised in that the reaction is carried out in a solvent or dispersing agent at temperatures from 0 to 50°C, preferably from 10 to 25°C.

8. Process according to Claims 6 and/or 7, characterised in that a base, preferably in a molar quantity, is added for the reaction.

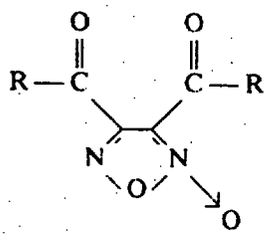
9. 3,4-Bis-substituted 1,2,5-oxadiazole 2-oxides according to one or several of Claims 1 to 5, or their pharmacologically acceptable acid addition compounds for use as pharmacological active compoumds.

10. Pharmaceutical formulation containing an active dose of a 3,4-bis substituted 1,2,5-oxadiazole 2-oxide according to one or several of Claims 1 to 5, or of an acid addition compound thereof, together with pharmaceutically permissible excipients and additives and also, if desired, other therapeutically active substances.

* C L M S *

Patent Claims for the Contracting State: AT (as printed)

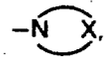
1. Process for the preparation of 3,4-bis-substituted 1,2,5-oxidiazole 2-oxides of the formula



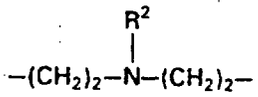
(I)

and their pharmacologically acceptable acid addition compounds wherein

R denotes $-NHR^1$, $-NR^2R^3$, $-NHR^4OR^2$, $-NHR^5COR^6$ or



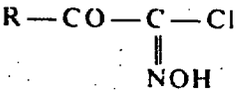
R^1 denotes alkyl having 1 to 6 C atoms or cycloalkyl having 4 to 7 C atoms,
R^2 and R^3 denote alkyl having 1 to 4 C atoms,
R^4 denotes an alkylene radical of the formula $-C_nH_{2n}-$ wherein n denotes 2, 3 or 4,
R^5 denotes an alkylene radical of the formula $-C_mH_{2m}-$ wherein m denotes 1, 2 or 3,
R^6 denotes $-OR^2$, $-NHR^1$, $-NR^2R^3$ or $-NH_2$,
X denotes $-(CH_2)_p-$, $-(CH_2)_2-O-(CH_2)_2-$ or



and

p is 4, 5 or 6,

characterised in that a hydroxamoyl chloride of the formula II



(II)

is introduced into a solvent or dispersing agent at temperatures from 0 to 50°C whereupon a compound of the formula I is formed with elimination of HCl and dimerisation, which compound is, if desired, converted in a manner known per se into an acid addition salt.

2. Process according to Claim 1, characterised in that the hydroxamoyl chloride of formula II is introduced into the solvent or dispersing agent at temperatures from 10 to 25°C.

3. Process according to Claims 1 and/or 2, characterised in that a base, preferably in a molar quantity, is added.

4. Process according to Claim 3, characterised in that the base added is secondary or tertiary amine, alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate or alkali metal acetate.

5. Process according to Claims 3 and/or 4, characterised in that the base is added gradually or in portions.

6. Process according to one of Claims 1 to 5, characterised in that the solvent used is dimethylformamide, dimethylsulphoxide, N-methylpyrrolidone, a lower alcohol, diethylether, water or a mixture of these solvents.

7. Process according to one or several of Claims 1 to 6, characterised in that the radical R contains an —NH-grouping.

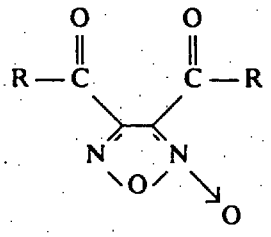
8. Process according to one or serveral of Claims 1 to 7, characterised in that R^4 denotes $-(CH_2)_2-$ or $-(CH_2)_3-$.

9. Process according to one or several of Claims 1 to 7, characterised in that R^5 denotes $-CH_2-$ or $-(CH_2)_2-$.

10. Process according to one or several of Claims 1 to 7, characterised in that R^2 denotes methyl or ethyl.

Revendications pour les Etats contractants: BE, CH, DE, FR, GB, IT, LI, NL, SE (as printed)

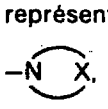
1. Oxadiazole-1,2,5 oxydes-2 disubstitués en 3,4 qui répondent à la formule:



(I)

dans laquelle:

R représente $-NHR^1$, $-NR^2R^3$, $-NHR^4OR^2$, $-NHR^5COR^6$ ou



R^1 représente un alkyle contenant de 1 à 6 atomes de carbone ou un cycloalkyle contenant de 4 à 7 atomes de carbone,

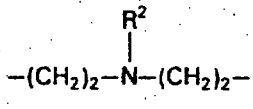
R^2 et R^3 représentent chacun un alkyle contenant de 1 à 4 atomes de carbone,

R^4 représente un radical alkylène $-C_nH_{2n}-$ dans lequel n désigne un nombre égal à 2, à 3 ou à 4,

R^5 représente un radical alkylène $-C_mH_{2m}-$ dans lequel m désigne un nombre égal 1, à 2 ou à 3,

R^6 représente $-OR^2$, $-NHR^1$, $-NR^2R^3$ ou $-NH_2$,

X représente $-(CH_2)_p-$, $-(CH_2)_2-O-(CH_2)_2-$ ou



et

p représente un nombre égal à 4, à 5 ou à 6, ainsi

que leurs composés d'addition d'acides acceptables du point de vue pharmacologique.

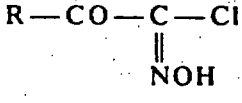
2. Oxadiazole-1,2,5 oxydes-2 disubstitués en 3,4 selon la revendication 1, caractérisés en ce que les radicaux R contiennent un radical $-NH-$.

3. Oxadiazole-1,2,5 oxydes-2 disubstitués en 3,4 selon l'une des revendications 1 et/ou 2, caractérisés en ce que R^4 représente un radical $-(CH_2)_2-$ ou $-(CH_2)_3-$.

4. Oxadiazole-1,2,5 oxydes-2 disubstitués en 3,4 selon l'une des revendications 1 et/ou 2, caractérisés en ce que R^5 représente un radical $-CH_2-$ ou $-(CH_2)_2-$.

5. Bis-(isopropylaminocarbonyl)-3,4 oxidiazole-1,2,5 oxyde-2.

6. Procédé de préparation des oxadiazole-1,2,5 oxydes-2 disubstitués en 3,4 selon l'une quelconque des revendications 1 à 5, par déshydrochloration à partir d'un chlorure d'hydroxamoyle de formule (II):



(II)

et dimérisation, puis transformation éventuelle en composé d'addition d'acide.

7. Procédé selon la revendication 6, caractérisé en ce qu'on effectue la réaction dans un solvant ou milieu de dispersion à des températures de 0 à 50°C, de préférence de 10 à 25°C.

8. Procédé selon l'une des revendications 6 et/ou 7, caractérisé en ce qu'on ajoute, lors de la réaction, une base, de préférence en la quantité molaire.

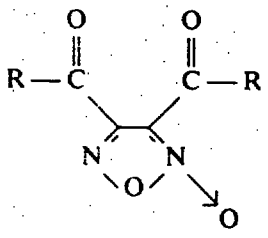
9. Oxadiazole-1,2,5 oxydes-2 disubstitués en 3,4 selon l'une quelconque des revendications 1 à 5, ou leurs composés d'addition d'acides acceptables du point de vue pharmacologique, pour l'application comme substances actives pharmacologiques.

10. Compositions pharmaceutiques contenant une dose efficace d'un oxadiazole-1,2,5 oxyde-2 disubstitué en 3,4 selon l'une quelconque des revendications 1 à 5, ou d'un composé d'addition d'acide d'un tel oxadiazole, ainsi que des excipients et additifs acceptables du point de vue pharmaceutique et, éventuellement, d'autres substances douées d'activités thérapeutiques.



Revendications pour l'Etat contractant: AT (as printed)

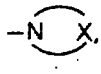
1. Procédé de préparation d'oxadiazole-1,2,5 oxydes-2 disubstitués en 3,4 qui répondent à la formule (I):



(I)

dans laquelle:

R représente $-NHR^1$, $-NR^2R^3$, $-NHR^4OR^2$, $-NHR^5COR^6$ ou



R^1 représente un alkyle contenant de 1 à 6 atomes de carbone ou un cycloalkyle contenant de 4 à 7 atomes de carbone,

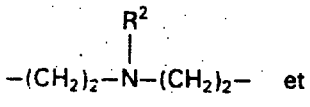
R^2 et R^3 représentent chacun un alkyle contenant de 1 à 4 atomes de carbone,

R^4 représente un radical alkylène $-C_nH_{2n}-$ dans lequel n désigne un nombre égal à 2, à 3 ou à 4,

R^5 représente un radical alkylène $-C_mH_{2m}-$ dans lequel m désigne un nombre égal 1, à 2 ou à 3,

R^6 représente $-OR^2$, $-NHR^1$, $-NR^2R^3$ ou $-NH_2$,

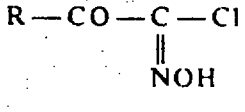
X représente $-(CH_2)_p-$, $-(CH_2)_2-O-(CH_2)_2-$ ou



et

p représente un nombre égal à 4, à 5 ou à 6,

et de leurs composés d'addition d'acides acceptables du point de vue pharmacologique, procédé caractérisé en ce qu'on introduit un chlorure d'hydroxamoyle der formule (II):



(II)

dans un solvant ou milieu de dispersion, à des températures de 0 à 50°C, opération qui a pour effet de donner naissance, avec enlèvement d'HCl et dimérisation, à un composé de formule (I), que l'on transforme éventuellement, de manière connue, en un sel d'addition d'acide.

2. Procédé selon la revendication 1, caractérisé en ce que l'introduction du chlorure d'hydroxamoyle de formule (II) dans le solvant ou milieu de dispersion est effectuée à des températures de 10 à 25°C.

3. Procédé selon l'une des revendications 1 et/ou 2, caractérisé en ce qu'on ajoute une base, de préférence en la quantité molaire.

4. Procédé selon la revendication 3, caractérisé en ce qu'on ajoute, comme base, une amine secondaire ou tertiaire, un hydroxyde de métal alcalin, un carbonate de métal alcalin, un hydrogénocarbonate de métal alcalin ou un acétate de métal alcalin.

5. Procédé selon l'une des revendications 3 et 4, caractérisé en ce la base est ajoutée peu à peu ou par portions.

6. Procédé selon l'une quelconque des revendications 1 à 5, caractérisé en ce qu'on utilise, comme solvant, le diméthylformamide, le diméthylsulfoxyde, la N-méthylpyrrolidone, un alcool inférieur, le diéthyléther, l'eau ou un mélange de ces solvants.

7. Procédé selon l'une quelconque des revendications 1 à 6, caractérisé en ce que le radical R contient un radical —NH—.

8. Procédé selon l'une quelconque des revendications 1 à 7, caractérisé en ce que R^4 représente un radical $-(CH_2)_2-$ ou $-(CH_2)_3-$.

9. Procédé selon l'une quelconque des revendications 1 à 7, caractérisé en ce que R^5 représente un radical $-CH_2-$ ou $-(CH_2)_2-$.

10. Procédé selon l'une quelconque des revendications 1 à 7, caractérisé en ce que R^2 représente un radical méthyle ou éthyle.

* C L M S *