

PATENT SPECIFICATION

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(54) RODENTICIDAL COMPOSITIONS

(71) We, BYK GULDEN LOMBERG CHEMISCHE FABRIK GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, of D 7750 Konstanz, Byk-Gulden Strasse 2, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

The invention relates to rodenticidal compositions which comprise two components 1 and 2. Component 1 is an active substance which following oral administration inhibits the clotting of the blood of mammals, more particularly rodents or, respectively, prolongs the clotting time. Component 2 is an active substance, which following oral administration to rodents, produces haemorrhagic lesions in the gut.

The composition, which develops specific effects owing to the cooperation or synergism of the two components comprises, expressed as percentages of the weight of the composition of 1 and 2 as a whole, 5 to 95 of component 1 and 95 to 5 of component 2. Preferably compositions with 20 to 90% by weight of component 1 and 80 to 10% by weight of component 2 are employed. Particularly compositions with 35 to 75% by weight of component 1 and 65 to 25% by weight of component 2 are used.

The compositions can consist exclusively of components 1 and 2. The compositions can, however, also have a total content of components 1 and 2 of only 10^{-3} % by weight. Preferably, however, compositions with a total content of components 1 and 2 of more than 10^{-3} % by weight are employed. It is particularly preferred to employ compositions with a total content of components 1 and 2 of more than 10^{-2} % by weight. The amounts or proportions of the individual components 1 and 2 can be calculated from the data just provided. The ratio of the two components to each other, that is to say the amounts of components 1 and 2 respectively can be selected by those skilled in the art in accordance with accepted criteria, as for example economic aspects, so that if appropriate the cheaper component will be used in excess. Furthermore the compositions can comprise further active substances and adjuvants, which are explained in the following description.

Preferably the compositions are produced in solid form. In this case they then consist either exclusively of the two active substances or comprise the active substances in the above-mentioned concentrations together with further active substances or solid adjuvants.

Solid compositions can exist for example in the form of spheroidal particles, in the form of a powder, of pellets, in the form of a granulate, as a granular material, in the form of particles coated with a film or in the form of a stiff paste.

Preferably solid compositions are so compounded that in them the two active substances are distributed in the desired weight ratio with the most even concentration possible in the overall composition.

Furthermore the compositions can also exist in a liquid form (for example

dissolved in a solvent) or in a suspended form (for example suspended in water, a mineral oil, seed oil or honey).

Component 1 includes all anti-coagulants or anti-clotting materials, which interfere with prothrombin synthesis, or, respectively, block the prothrombin circulating in the blood of mammals.

Examples for the component 1 are more especially derivatives of 1,3-indandione, derivatives of coumarin, 2-azacycloalkylmethyl-substituted benzhydrylketones and -carbinols and salts of the rare earth metals, more particularly of neodymium and cerium.

It is preferred to employ in accordance with the present invention the following 1,3-indandiones: 2-(β -methylbutyryl)-1,3-indandione (whose production is described in the J. Org. Chem. 25, 1860 (1962), 2-phenyl-1,3-indandione (Chem. Ber. 47, 1439 (1914) 2-(*p*-chlorophenyl)-1,3-indandione (Brit. patent No. 748,251), 2-(α,α,α -trifluoro-*p*-tolyl)-1,3-indandione (German Offenlegungsschrift 1,543,287), 2-(*p*-bromophenyl)-1,3-indandione (USP No. 2,847,747), 2-(*p*-methoxyphenyl)-1,3-indandione (USP No. 2,899,358), 2-(diphenylacetyl)-1,3-indandione (USP No. 2,672,483), 2-[1-(*p*-bromophenyl)-1-phenyl]-acetyl-1,3-indandione (French patent No. 1,269,638), 2-[1-(*p*-tolyl)-1-phenyl]-acetyl-1,3-indandione (Russian patent No. 145,417) and 2-phenyl-2-morpholinomethyl-1,3-indandione (German patent No. 1,919,895), 2-hydroxymethyl-2-phenyl-1,3-indandione (Compt. Rend. 257(4), 933-6 (1963), 2-(1-naphthyl)-1,3-indandione (French patent No. 1,085,097), 2-[α -(*p*-ethylphenyl)-benzyl]-1,3-indandione (Zh. Obshch. Khim. 35 (1), 184-5 (1965)) and 2-pivaloyl-1,3-indandione (Ind. Eng. Chem. 34, 494-7 (1941)).

The preferred anti-clotting agents or anticoagulants on a coumarin basis are: 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene (USP No. 2,723,276), 4-hydroxy-2-oxo-3-(3-oxo-1-phenyl-butyl)-2H-chromene (USP No. 2,427,578) and its sodium salt (USP No. 2,765,321), 4-hydroxy-2-oxo-3-[3-oxo-1-(*p*-chlorophenyl)-butyl]-2H-chromene, 4-hydroxy-2-oxo-3-[3-oxo-1-(*p*-nitrophenyl)-butyl]-2H-chromene (USP No. 2,648,682), 2-methoxy-5-oxo-2-methyl-4-phenyl-3,4-dihydro-2H-5H-pyrano-[3,2-c][1]benzopyrane (described in J. Am. Chem. Soc. 66, 902-6 (1944)), 4-hydroxy-2-oxo-3-[4-hydroxy-2-oxo-2H-chromenyl-(3)-methyl]-2H-chromene (Arquiv. inst. biol. (Sao Paulo), 14, 293-303 (1943), 4-hydroxy-2-oxo-3-[1-[4-hydroxy-2-oxo-2H-chromenyl-(3)]-ethyl]-2H-chromene (Czech. patent No. 85918), 4-hydroxy-2-oxo-3-[2-methoxy-1-[4-hydroxy-2-oxo-2H-chromenyl-(3)]-ethyl]-2H-chromene (Rec. trav. chim. 72, 358-364 (1953)), 4-hydroxy-2-oxo-3-[3-methylmercapto-1-[4-hydroxy-2-oxo-2H-chromenyl-(3)]-propyl]-2H-chromene (Proc. Intern. Conf. Thrombosis and Embolism, 1st Basle, 1954, 223-7 (published 1955)), ethyl-bis-[4-hydroxy-2-oxo-2H-chromenyl-(3)]-acetate (USP No. 2,482,510), 3-(1,2,3,4-tetrahydro-1-naphthyl)-4-oxycoumarin (German patent No. 1,014,551), 3-[α -(2-furyl)- β -acetyethyl]-4-oxycoumarin (German patent No. 947,164), 4-hydroxy-coumarin-3-carboxylic acid- β -diethylaminoethylamide (French patent No. 1,369,991), 4-hydroxy-3-(3,5-xylol)-coumarin (Sci. Commun. Research Dept., N.V. Koninkl. Pharm. Fabrieken v/h Brocades-Stheeman & Pharmacia 10, 7-78 (1960-1961)), 3-[1-(*p*-chlorophenyl)-propyl]-4-hydroxycoumarin (Brit. patent No. 734,823), 3-(1-naphthyl)-4-hydroxy-coumarin (USP No. 2,723,276), 3-[1-(*p*-iodophenyl)-3-oxobutyl]-4-hydroxycoumarin (Belg. patent No. 626,118), 4-hydroxy-3-[1-(*p*-nitrophenyl)-3-oxopentyl]-coumarin (USP No. 2,648,682) and 4-hydroxy-3-(3-oxo-1-phenylpentyl)-coumarin (Izv. Vysshikh Uchebn. Zavedenii, Khim. Tekhnol. 5 (1), 107-111 (1962)).

As anti-clotting agents it is also possible to make use of the following 2-azacycloalkylmethyl-substituted benzhydryl-ketones and -carbinols: 1-phenyl-3-(2-piperidyl)-1-(*p*-tolyl)-2-propanone; 3,3-diphenyl-1-(2-pyrrolidinyl)-2-pentanone; 1,1-diphenyl-3-[2-(hexahydro-1H-azepinyl)]-2-propanone; 1-(4-fluorophenyl)-1-phenyl-3-(2-piperidyl)-2-propanone; 1-(4-methylthiophenyl)-1-phenyl-3-(5,5-dimethyl-2-pyrrolidinyl)-2-propanone; 1-(*p*-coumenyl)-1-phenyl-3-(4-*tert*-butyl-2-piperidinyl)-2-propanone; 3,3-diphenyl-1-[2-(hexahydro-1H-azepinyl)]-2-butanone; 3-(2,4-dichlorophenyl)-3-phenyl-1-(2-piperidyl)-2-heptanone; 1,1-diphenyl-3-(5-methyl-3-pyrrolidinyl)-2-propanone; 3,3-diphenyl-1-(2-piperidyl)-2-butanone; α -(α -methyl- α -phenylbenzyl)-2-piperidinethanol;

α - (α - ethyl - α - phenylbenzyl) - 2 - pyrrolidinethanol; 2 - (2,5 - dimethyl - α - phenylbenzyl) - 2 - piperidinethanol and α - (diphenylmethyl) - 2 - (hexahydro - 1H - azepin)ethanol and their salts, which are described in the German patent specification 2,417,783, and 4' - (fluorophenyl) - 2 - (2 - pyrrolidinyl) - acetophenone, 4' - phenyl - 2 - (5,5 - dimethyl - 2 - pyrrolidinyl) - acetophenone, 4' - *p* - (trifluoromethyl) - phenyl - 2 - (2 - piperidyl) - acetophenone, 4' - (*p* - butoxy - phenyl) - 2 - (4 - tert. - butyl - 2 - piperidyl) - acetophenone, 2' - phenoxy - 2 - (2 - piperidyl) - acetophenone, 4' - (*p* - fluorophenoxy) - 2 - (5,5 - dimethyl - 2 - pyrrolidinyl) - acetophenone, 4' - (*p* - chlorophenoxy) - 2 - (2 - piperidyl) - acetophenone, 4' - [*m* - (trifluoromethyl) - phenoxy] - 2 - (2 - piperidyl) - acetophenone, 4' - (*p* - butoxyphenoxy) - 2 - (2 - pyrrolidinyl) - acetophenone, 2 - (2 - piperidyl) - 4' - (trans - *p* - tolylvinylene) - acetophenone, 2 - (2 - hexahydro - 1H - azepinyl) - 4' - (trans - styryl) - acetophenone, 4' - (*m* - methoxyphenylvinylene) - 2 - (2 - pyrrolidinyl) - acetophenone, 2 - (2 - piperidyl) - 4' - [*p* - methylthio) - phenyl - vinylene] - acetophenone, 4' - (3 - phenoxypropoxy) - 2 - (2 - piperidyl) - acetophenone, 4' - (4 - phenylbutyl) - 2 - (2 - piperidyl) - acetophenone, 4' - (α , α - dimethylbenzyl) - 2 - (piperidyl) - acetophenone, 4' - phenethyl - 2 - (3,5 - diethyl - 2 - piperidyl) - acetophenone, 4' - phenyl - 2 - (2 - pyrrolidinyl) - acetophenone, α - [2 - (2 - phenyl - ethoxy)phenyl] - 2 - piperidinethanol, α - (*p* - phenoxy phenyl - 2 - pyrrolidinethanol, α - [4 - (4 - bromophenoxy) - phenyl] - 6 - methyl - 2 - piperidinethanol, α - (*p* - phenethyl) - phenyl - 2 - pyrrolidinethanol, α - *p* - biphenyl - 2 - hexahydro - 1H - azepinethanol, α - [3 - (4 - phenoxybutoxy) - phenyl] - 2 - piperidinethanol, and α - (4 - benzyl) - phenyl - 2 - piperidinethanol and their salts, which are described in the German patent specification 2,418,480.

The following salts of rare earth metal can also be used as anti-clotting agents: dineodymiumdihydroxybenzene disulfonate (Acta physiol. Acad. Sci. Hungar. 24, 373), dineodymium - 3 - sulfonate - pyridine - carboxylate - (4) and cerium - (III) - tris - (4 - aminobenzene sulfonate).

As part of the invention it is particularly preferred to use anti-clotting agents which are known as rodenticidally active materials which are readily commercially available.

The second active component 2 of the composition is characterised in that when it is administered alone once orally in a dose of below 50 mg/kg to Sprague-Dawley rats on an empty stomach it causes haemorrhagic gut lesions.

Preferably the component 2 is so selected that after a single oral administration of below 15 mg/kg to Sprague-Dawley rats on an empty stomach it causes haemorrhagic gut lesions.

The components 2, which owing to cooperation with component 1 produce pronounced effects as desired, are compounds which, when administered on an empty stomach once in doses of below 5 mg/kg cause haemorrhagic gut lesions in rats.

In order to determine the gut lesions it is possible to take as a basis the method described by K. P. Bhargava, M. B. Gupta and K. K. Tangri in European J. Pharmacol. 22 (1973), 191-195.

A selection of the compounds coming into question as component 2 can, however, be carried out in a simpler manner by determining the LD₅₀ in mg/kg. In this case the respective dose of a substance is determined which after being administered causes 5% of the animals treated = LD₅₀; determination in accordance with J. T. Litchfield and F. Wilcoxon in J. Pharmacol. exp. 96, 99, 1949) to die owing to massive haemorrhagic gut lesions, that is to say owing to perforation of the gastrointestinal tract. Determination of the cause of death can be done by dissection of the dead animals.

For testing use was made of Sprague-Dawley rats of both sexes. The weight amounted to 150 to 250 g. The rats were fed on commercially available standard food and water ad lib. The rats were kept in groups of 5 and four animals in plastic cages of the type M III. The room temperature amounted to approximately 23°C. For determining the lethal doses as mentioned in the following description the rats were fed on empty stomachs. The animals received the compounds mentioned (for example the component 1 or 2 or the composition) in a volume of liquid amounting to 5 ml per kg of body weight of the rat. The administration of the liquid was carried out once using a feeding tube introduced into the oesophagus. The doses of the active substances, components 1 and 2 or the composition, were varied. The component 2 was administered as a sodium salt in aqueous solution, the number of animals which died within 10 days after administration was counted.

The lethal doses (LD₅₀, LD₅₀ and LD₁₀₀ in mg/kg mentioned were determined

12

by means of simple linear regression while the limits of trust were determined in accordance with the method of Litchfield and Wilcoxon.

In the case of the investigation of the gut lesions and in the case of determination of the lethal doses, more particularly LD₅₀, it is advisable to use a rat strain whose LD₅₀ for 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (= phenylbutazone) amounts to 600 mg/kg body weight of the rat and whose LD₅₀ for 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (= indomethacin) amounts to approximately 7 mg/kg per body weight of the rat.

With these convenient selection criteria for the component 2 (determination of the gut lesions and, respectively the LD₅₀, it was found that more particularly acidic aromatic and heteroaromatic compounds with a molecular weight of approximately 200 to approximately 500, with 1 to 5 rings and 6 to 30 carbon atoms and a pK_A-value of 1.5 to 5.5, and more particularly approximately 2 to 5 (extrapolated* or converted** to apply for an aqueous medium) constitute excellent representatives of the component 2.

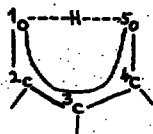
Among these acidic compounds special attention is called to:

- (a) carboxylic acids
- (b) enols
- (c) NH-acidic compounds

(d) salts or derivatives of the compounds (a) to (c), which in the pH-range of the gastric juice of mammals can be converted to release the acidic compound.

The components 2 on a carboxylic acid basis are characterised in that the carboxylic acid radical consists of 1 to 4 carbon atoms and is directly bound to an aromatic or hetero-aromatic ring.

The component 2 on the basis of acidic enol compounds is characterised by the system



containing 5 atoms. Particularly suitable representatives of the component 2 are characterised in that the carbon atoms 2, 3 and 4 form component of further conjugated systems.

The components 2 on the basis of NH-acidic compounds are characterised by groups such as the —NHSO₂CHF₂ or the —NHSO₂CF₃ group. The pK_A-values of these compounds lie between approximately 2 and approximately 5.

It has been found that the biological effects of the components 1 and 2 synergistically interact. The type of synergism will be explained in the following description. It has been observed that the degree of synergism in the case of the components 2 on a carboxylic acid basis is the most pronounced type of synergism.

Preferred aromatic and heteroaromatic carboxylic acid and enol compounds in accordance with the invention are compounds which comprise 9 to 25 carbon atoms. The carbon atom skeleton of preferred carboxylic acid radicals bound to aromatic or to heteroaromatic compounds comprises 1, 2 or 3 or more particularly 2 carbon atoms. In accordance with the invention only these carboxylic acids come into question, whose C=O-double bond in the carboxylic acid radical is separated by at least two C—C bonds from the next C=C bond, that is to say whose C=O bonds are not in conjugation with a double bond.

Representatives of the component 2 preferred in accordance with the invention are arylacetic acids, α -aryl- α -methylacetic acids, arylpropionic acids, heteroarylacetic acids, α -heteroaryl- α -methylacetic acids or heteroarylpropionic acids.

The aryl radical bound to the carboxylic acid radical (abbreviated to: Ar in what follows) is preferably an aryl radical (abbreviation: Ar') comprising 6 to 20 carbon atoms. This number is to apply to the carbon atoms not counting substituents on the aryl radical.

The heteroaryl radical (abbreviation: Het) bound to the carboxylic acid radical is preferably a heteroaryl radical (abbreviation: Het') comprising 1 to 20 carbon atoms and preferably 3 to 15 carbon atoms. This number is to apply to the carbon atoms not counting substituents on the heteroaryl radical.

*log pK_A in a dilution series extrapolated to a solution with pure water as a solvent
**J. Am. Chem. Soc. 87, 5275 (1965)

Preferred Het¹ radicals comprise in the ring 1 or 2 nitrogen atoms or 1 oxygen atom or 1 sulfur atom or 1 nitrogen atom and 1 oxygen atom or 1 nitrogen and 1 sulfur atom.

Excellent representatives of the component 2 are arylcarboxylic acids or heteroarylcarboxylic acids which comprise monocyclic radical Ar¹ or Het¹ bound to the carboxylic acid radical. An example for such a radical Ar¹ is the phenyl radical. Examples for such a Het¹ radical are the pyrrolyl, thienyl, furyl, pyrazolyl, thiazolyl, pyridyl and the oxazolyl radicals. In many cases these radicals (Ar¹ or Het¹) carry further substituents, as for example 1 to 3 low molecular weight alkyl radicals and/or low molecular weight alkoxy radicals and/or an alkanoyl radical with up to 12 carbon atoms and/or an aroyl radical with up to 12 carbon atoms and/or a nitro group and/or 1 to 3 halogen atoms, and more particularly 1 to 3 fluorine, chlorine or bromine atoms. The expression "low molecular weight" in conjunction with these substituents includes substituents, whose carbon skeleton comprises 1 to 4 carbon atoms.

Further excellent representatives are compounds with a condensed Ar¹ or Het¹ radical which is characterised in that at least 2 rings of the condensed Ar¹ or Het¹ radical have at least two atoms in common. Examples for condensed Ar¹ radicals are the naphthyl, the indenyl, the anthryl, the acenaphthyl, the fluorenyl, the indanyl and the biphenyl enyl radicals. Examples for condensed Het¹ radicals are the benz[b]-thiophenyl, the thioxanthenyl, the phenoxathiinyl, the indoliziny, the indolyl, the 2H-isoindoliny, the indazolyl, the carbazoyl, the phenothiazinyl and the benzoxazolyl radicals. In many cases these condensed Ar¹ or Het¹ radicals carry further substituents as for example 1 to 3 low molecular weight alkyl radicals and/or low molecular weight alkoxy radicals and/or an alkanoyl radical with up to 12 carbon atoms and/or 1 to 3 halogen atoms, more particularly 1 to 3 fluorine, chlorine or bromine atoms and/or an aroyl radical with up to 12 carbon atoms and/or a nitro group.

In addition to the Ar¹ or Het¹ radical bound to the carboxylic acid radical some representatives comprise further saturated or unsaturated isocyclic or heterocyclic rings. Examples for saturated isocyclic radicals are the cyclohexyl, cyclopentyl, cycloheptyl and the cyclopropyl radicals. Examples for unsaturated isocyclic radicals are the phenyl, cyclohexenyl, cyclopentenyl and the naphthyl radicals. Examples for saturated heterocyclic radicals are the piperidyl and pyrrolidinyl radicals. Examples for unsaturated heterocyclic radicals are the pyrrolinyl, pyrrolyl, thienyl, furyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, benzthiazolyl and benzoxazolyl radicals.

Therefore further excellent representatives of the components 2 are arylcarboxylic acids or heteroarylcarboxylic acids, whose Ar¹ or Het¹ radical bound to the carboxylic acid radical is linked with one or more (up to 4) rings directly by simple bonds to form a ring assembly in accordance with IUPAC Rule A-51. Such a ring assembly comprises 4 to 26 carbon atoms, the carbon atoms of the substituents being counted as well. These ring assemblies are in what follows denoted as R₂. The R₂ radical is termed carbocyclic or heterocyclic aromatic if it comprises an Ar¹ radical, that is to say if the carboxylic acid radical is linked with the aromatic radical. The R₂ radical is termed hetero-aromatic if it has a Het¹ radical, that is to say if the carboxylic acid radical is linked with the hetero-aromatic radical. Examples for unsubstituted aromatic R₂ radicals are the 4-cyclohexylphenyl, the 4-biphenyl, the 3-biphenyl, the 5-cyclohexyl-1-indanyl, the 4-(1-cyclohexeno-1-yl)-phenyl, the 4-(3-pyrroline-1-yl)-phenyl, the 4-(1-piperidyl)-phenyl, the 4-(2-thienyl)-phenyl and the 5-phenyl-1-naphthyl radical.

Examples for hetero-aromatic R₂ radicals are the 1,3,5-triphenyl-4-pyrazolyl, the 1-phenyl-3,5-di(2-thienyl)-4-pyrazolyl, the 2,4,5-triphenyl-3-thienyl, the 1,3,4-triphenyl-5-pyrazolyl, the 2,4-diphenyl-5-thiazolyl, the 2-phenyl-4-(2-thienyl)-5-thiazolyl and the 3-cyclohexyl-1,5-diphenyl-4-pyrazolyl radicals.

In many cases the R₂ radicals carry 1 to 3 substituents, for example 1 to 3 low molecular weight alkyl and/or alkoxy radicals and/or 1 to 3 halogen atoms and more particularly 1 to 3 fluorine, chlorine or bromine atoms and/or an alkanoyl radical with up to 12 carbon atoms and/or an aroyl radical with up to 12 carbon atoms and/or a nitro group.

Examples for substituted R₂ radicals are the 1,3 - diphenyl - 5 - (p - methoxy - phenyl) - 4 - pyrazolyl, the 3,5 - diphenyl - 1 - (p - methoxyphenyl) - 4 - pyrazolyl and the 3 - (p - chlorophenyl) - 1,5 - diphenyl - 4 - pyrazolyl radicals.

Examples for components 2, which in the novel compositions of matter have the strongest synergistic action are

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1,486,137

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- 1 - (*p* - chlorobenzoyl) - 5 - methoxy - 2 - methyl - indole - 3 - acetic acid and its salts
- 3 - chloro - 4 - cyclohexyl - α - methyl - phenylacetic acid, preferably its *d* (+) isomer and its salts
- 5 1,3,5 - triphenyl - 4 - pyrazolylacetic acid and its salts 5
- 1,3,4 - triphenyl - 5 - pyrazolylacetic acid and its salts
- 1 - phenyl - 3,5 - di - (2 - thienyl) - 4 - pyrazolylacetic acid and its salts
- 1 - *p* - chlorophenyl - 3,5 - di - (2 - thienyl) - 4 - pyrazolylacetic acid and its salts
- 10 1,5 - diphenyl - 3 - (*p* - chlorophenyl) - 4 - pyrazolylacetic acid and its salts 10
- 3 - cyclohexyl - 1,5 - diphenyl - 4 - pyrazolylacetic acid and its salts
- 1,3 - diphenyl - 5 - (*p* - methoxyphenyl) - 4 - pyrazolylacetic acid and its salts
- 3,5 - diphenyl - 1 - (*p* - methoxyphenyl) - 4 - pyrazolylacetic acid and its salts
- 6 - chloro - 5 - cyclohexylindan - 1 - carboxylic acid, preferably its (1*S*) - (+) - isomer and its salts
- 15 β - (3 - chloro - 4 - cyclohexylphenyl) - β - methylpropionic acid and its salts 15
- 4 - (2 - chloro - 4' - fluoro - α - methyl - 4 - biphenylacetic acid and its salts
- 2 - chloro - 2',4' - difluoro - α - methyl - 4 - biphenylacetic acid and its salts
- 2,2',4' - trifluoro - α - methyl - 4 - biphenylacetic acid and its salts
- 20 2 - [4 - (1 - oxo - 2 - isoindolyl) - phenyl] - propionic acid and its salts 20
- d* (+) - 2 - (5 - phenyl - 1 - naphthyl) - propionic acid and its salts
- 2 - (2 - fluoroenyl) - propionic acid and its salts
- [1 - (*p* - chlorobenzylidene) - 2 - methyl - 5 - methoxyindene] - 3 - acetic acid and its salts
- 5 - (*p* - chlorobenzoyl) - 1,4, α - trimethylpyrrol - 2 - acetic acid and its salts
- 25 5 - (*p* - fluorobenzoyl) - 1,4 - dimethylpyrrol - 2 - acetic acid and its salts 25
- o* - (2,6 - dichloroanilino)phenylacetic acid and its salts
- 2 - (5*H* - [1] benzopyrano [2,3 - *b*] pyridin - 7 - yl)propionic acid and its salts
- The following acidic enol compounds are particularly significant as component 2:
- 30 N - (2 - thiazolyl) - 4 - hydroxy - 2 - methyl - 2*H* - 1,2 - benzthiazine - 3 - carbox - 30
- amide - 1,1 - dioxide
- N - (4 - methyl - 2 - thiazolyl) - 4 - hydroxy - 2 - methyl - 2*H* - 1,2 - benzthiazine - 3 - carboxamide - 1,1 - dioxide
- 35 N - (4,5 - dimethyl - 2 - thiazolyl) - 4 - hydroxy - 2 - methyl - 2*H* - 1,2 - benzthiazine - 35
- 3 - carboxamide - 1,1 - dioxide
- N - (2 - benzthiazolyl) - 4 - hydroxy - 2 - methyl - 2*H* - 1,2 - benzthiazine - 3 - carboxamide - 1,1 - dioxide
- N - (2 - pyridyl) - 4 - hydroxy - 2 - methyl - 2*H* - 1,2 - benzthiazine - 3 - carbox - 40
- amide - 1,1 - dioxide
- N - (6 - methyl - 2 - pyridyl) - 4 - hydroxy - 2 - methyl - 2*H* - 1,2 - benzthiazine - 3 - 40
- carboxamide - 1,1 - dioxide
- As indicated above, the following named carboxamides can also be formulated in the corresponding keto-form.
- 45 N - (2 - thiazolyl) - 3 - hydroxy - 2 - methyl - 2*H* - 1,2 - benzthiazine - 4 - carbox - 45
- amide - 1,1 - dioxide
- N - (4 - bromophenyl) - 3 - hydroxy - 2 - methyl - 2*H* - 1,2 - benzthiazine - 4 - carboxamide - 1,1 - dioxide
- N - (4 - nitrophenyl) - 3 - hydroxy - 2 - methyl - 2*H* - 1,2 - benzthiazine - 4 - carboxamide - 1,1 - dioxide
- 50 N - (2 - methyl - 4 - nitrophenyl) - 3 - hydroxy - 2 - methyl - 2*H* - 1,2 - benzthiazine - 50
- 4 - carboxamide - 1,1 - dioxide
- 1 - methyl - 2',4' - difluoroxindole - 3 - carboxanilide
- All representatives mentioned of the component 2 can be produced in accordance with the methods described in the literature (see inter alia USP No. 3, 161,654, British Specification No. 1,146,021/2, German Offenlegungsschrift Nr. 2,123,705, British Specification No. 1,273,705, Belg. patent No. 796,465, Greek patent No. 41,535, J. med. chem. 15, 1297—1306 (1972), Angew. Chem. 84, 512—526 (1972), South African patent No. 7201706, Belg. patent no. 704,182., N. med. Chem. 16, 490—493 (1973), German patent application No. 2,143,600, Belg. patent No. 633,314, J. med. Chem. 16, 172—174 (1973), J. med. Chem. 16, 493—96 (1973), J. med. Chem. 14, 973—977 (1971), Compt. Rend. Ser. D, 273, (1971), J. med. Chem. 16, 131—134 (1973), Belgian patent No. 802,258, Dutch Octrooischrift No. 6,604,752.
- 55 55
- 60 60

15

Biological properties.

The compositions of the present invention have outstanding biological properties. Even a single orally administered, small dose of one of the compositions causes haemorrhagic ulcers and perforations on the mucous membrane of the gut, which leads to the death of the respective animal owing to internal bleeding. Accordingly these compositions can be used as materials for combating and control of harmful rodents, that is to say more particularly as rodenticides.

The compositions of the invention not only have a high efficacy against domesticated rats (Sprague-Dawley rats) but also with respect to wild rats (for example *Rattus rattus*, *Rattus norvegicus*, *Rattus alexandrinus*) and they are furthermore effective against *Mus musculus*, *Bandicota bengalensis*, *Geomys spp.*, *Thomomys spp.* and *Citellus spp.* and others.

The new composition of active substances can be used as a rodenticide which can be applied once or several times.

Investigations on domesticated rats and wild rats have shown that the lethal effects of the two components 1 and 2 described act synergistically. The haemorrhagic gut lesions produced by the component 2 lead to the result that the component, which inhibits clotting of the blood, brings about death after one administration of the rodenticide with certainty in the case of rodents, more particularly rats and mice owing to haemorrhage in the gastrointestinal tract.

The novel rodenticides have, in comparison with many rodenticides which are acutely effective, as for example thiourea derivatives, phosphoric acid esters or organic and inorganic heavy metal compounds, the advantage that they are of relatively low toxicity for man and domestic animals and the toxic effects, which appear more slowly, can be limited by doses of vitamin K.

Furthermore the use of the new rodenticides takes into account the good memory and the high intelligence quota of the rat. In the case of rapidly acting poisons the rats are capable of connecting the toxic effect with the type and position of the bait and they warn other rats. Accordingly operations intended to destroy rats with such materials are often completely unsuccessful.

Previously used rodenticides comprising anti-coagulating or clotting agents have admittedly the advantage that after repeated administration of the anti-coagulants the haemorrhage produced only occurs after a few days and cannot be connected by the rats with the effect of the poison and the other rats are not alarmed by the corpses adjacent to the place of feeding, but, however, they have a serious disadvantage. The poison usually only acts lethally if it is consumed a number of times by the rat (cumulative effect). This reduces considerably, as experience has shown, the success of such pest destroying actions despite all the advantages which are offered by materials which prevent clotting of the blood.

The novel rodenticide has, as compared with the use of a known rodenticide comprising as an active substance anti-clotting materials alone, the advantage that even a single consumption of the poison by the rat acts lethally, but the lethal effect only occurs a few days after consumption. Thus the animals cannot recognise any connection between the poison and the effect. The new combination of active substances therefore fulfils all conditions for a reliable rodenticide.

Furthermore the danger of poisoning persons or domestic animals by the novel combination of active substances can be substantially avoided by, for example, providing the core of a pellet containing the combination of active substances with a casing which is soluble in the intestinal juice but is not soluble in a gastric juice, and which is for its part provided with a casing comprising an emetic. The outermost layer is not soluble in the saliva, is tasteless but is soluble in the gastric juice. If a domestic animal or a person eats the pellet the outermost layer of the pellet will be dissolved in the gastric juice and the layer comprising the emetic will become effective. The result of this is that domestic animals or man will vomit, while rats or mice are not capable of vomiting.

The subject matter of the application also comprises a novel rodenticide, which comprises the composition of the invention, and application of the composition or of the two components comprised in it for combating and control of undesired rodents, more particularly rats and field mice.

The composition can be manufactured and sold as a concentrate, which on use is diluted with any suitable adjuvants. The lethal effects of the composition however, occur even if a material, suitable for oral consumption, comprises 10^{-3} to 10^{-2} % by weight of component 1 and component 2, that is to say if 1 g of the

(16)

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5 material provided for oral consumption comprises 0.01 to 0.1 mg of the total composition. In the case of concentrations of up to 10^{-2} % by weight, however, many of the compositions only become effective after repeated consumption by the rodent. An acute lethal effect, that is to say leading to mortality of 5 to 100% (= approximately equal to LD_5 to LD_{100}) following a single dose is achieved if 1 g of the material provided for oral administration (for example of the bait) comprises the composition in a concentration which amounts to at least

5

$$\frac{LD_5}{10} \quad \text{to} \quad \frac{LD_{100}}{2} \quad \text{expressed in milligrams.}$$

10 A reliable lethal effect (approximately equal to LD_{100}) after a single dosage is achieved in 1 g of the material provided for oral consumption comprises the composition in a concentration, which amounts to at least

10

$$\frac{LD_{100}}{10} \quad \text{to} \quad \frac{LD_{100}}{2} \quad \text{expressed in milligrams.}$$

15 The factors 2 and 10 in the denominator is to take into account the fact that young rats weigh approximately 100 g and the largest rats reach a weight of approximately 500 g.

15

20 If therefore the composition is already in the form suitable for its application, for example as a bait, the total content of this form of components 1 and 2, in accordance with the particular application, will generally amount to 10^{-3} to 5 and preferably approximately 10^{-2} to 1% by weight. The amounts of this individual components 1 and 2 can be calculated from the data provided above. In the case of particularly effective redenticides it is convenient for both components to be present in approximately equal amounts by weight.

20

25 In the compositions of the invention the components 1 and 2 can be present for example as a more or less homogeneous mixture, as a solution or suspension or emulsion or as separate components.

25

Preferred rodenticidal compositions of matter are specified in the following table I:

Table 1.

Preferred rodenticides

No.	Component 1	No.	Component 2
1.1	4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene	2.1	1,5-diphenyl-3-(<i>p</i> -chlorophenyl)-4-pyrazolyl-acetic acid and salts
1.2	4-hydroxy-2-oxo-3-(3-oxo-1-phenyl-butyl)-2H-chromene		
1.3	2-diphenylacetyl-1,3-indandione		
1.4	2-pivaloyl-1,3-indandione		
1.5	2-(4-chlorophenyl)-1,3-indandione		
1.6	4-hydroxy-2-oxo-3-[3-oxo-1-(4-nitrophenyl)-butyl]-2H-chromene		
1.7	3-(1,2,3,4-tetrahydro-1-naphthyl)-4-hydroxy-coumarin	2.2	1,3,4-triphenyl-5-pyrazole acetic acid and salts
1.1 to 1.7	1.1 to 1.7	2.3	1-phenyl-3,5-di-(2-thienyl)-4-pyrazolyl-acetic acid and salts
1.1 to 1.7	1.1 to 1.7	2.4	1,3,5-triphenyl-4-pyrazolyl-acetic acid and salts
1.1 to 1.7	1.1 to 1.7	2.5	1- <i>p</i> -chlorophenyl-3,5-di-(2-thienyl)-4-pyrazolyl-acetic acid salts
1.1 to 1.7	1.1 to 1.7	2.6	1-(<i>p</i> -chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid and salts

(17)

Table 1.

Preferred rodenticides (continued)

No.	Component 1	No.	Component 2
	1.1 to 1.7	2.7	3-cyclohexyl-1,5-diphenyl-4-pyrazolyl-acetic and salts
	1.1 to 1.7	2.8	1,3-diphenyl-5-(<i>p</i> -methoxyphenyl)-4-pyrazolyl-acetic and salts
	1.1 to 1.7	2.9	3,5-diphenyl-1-(<i>p</i> -methoxyphenyl)-4-pyrazolyl-acetic and salts
	1.1 to 1.7	2.10	N-(2-thiazolyl)-4-hydroxy-2-methyl-2H-1,2-benzthiazine-3-carboxamide-1,1-dioxide and its derivatives
	1.1, 1.2 and 1.7	2.11	6-chloro-5-cyclohexylindane-1-carboxylic acid [(1S)-(+)- isomers and salts]
	1.1, 1.2 and 1.7	2.12	3-chloro-4-cyclohexyl- α -methyl-phenyl acetic acid [d (+)-isomers and salts]
	1.1 to 1.7	2.13	β -(3-chloro-4-cyclohexylphenyl)- β -methyl-propionic acid and salts

As regards application of the rodenticide it is preferred to prepare the two components in such a manner that they are combined together to form a lethal dose, which can be directly laid, mixed with adjuvants or further processed to produce a bait. It is, however, also possible to apply or play the two components on food material for the animal to be poisoned or to apply it to a bait. The application can be carried out in such a manner that the two components are spread in the form of a powder on the food material for the animals or a bait or, as an alternative, the food material for the animals or the bait can be impregnated with solutions, suspensions or emulsions of the two components.

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In accordance with a further embodiment of the invention the two components are administered at different times to the animals in any suitable sequence, for example the component causing gut lesions can firstly be administered and then the animals have administered to them the anti-clotting materials or vice versa. This form of administration, however, involves the disadvantage that it makes it necessary for the animals to consume rodenticide more than once.

The invention also relates to a method for combating harmful rodents, more particularly of rats and field mice, characterised in that the rodents have administered to them a lethal dose of an active substance adapted to cause intestinal lesions and an active substance which hinders or prevents clotting of the blood. The lethal dose (LD₁₀₀ in the case of a single oral administration) of the compositions of the invention lies in many cases between approximately 4 and approximately 25 mg/kg in the case of Sprague-Dawley rats and in the case of wild rats (*Rattus norvegicus* and *Rattus rattus*) lies between approximately 5 and approximately 50 mg/kg.

Particularly effective representatives of the novel composition of matter are characterised by a lethal dose (LD₁₀₀ in the case of single oral administration) between approximately 4 and approximately 10 mg/kg in the case of Sprague-Dawley rats and between approximately 5 and 20 mg/kg in the case of wild rats and are therefore approximately 2 to more than 25 times more effective than commercially available anticoagulants (in the case of Sprague-Dawley rats and wild rats).

Further active substances, which in addition to the components 1 and 2 can also be comprised in the compositions of the invention, are for example additives which inhibit bacterial vitamin K synthesis in the intestine, more particularly sulfonamides as for example 3,4-dimethyl-5-sulfanilamidoisoxazole, N¹-(2-quinoxaliny)-sulfanilamide or 2-sulfanilamido-4-methyl-pyrimidine, antibiotics and antibacterially effective substances, as for example 5-hydroxy-tetracycline, penicillin-G, "Terramycin", chloramphenicol or other materials antagonistic to vitamin K as for example 2-methoxy-1,4-naphthoquinone, 2,3-dichloro-1,4-naphthoquinone or dihydroxy-phenazine-N,N'-dioxide. These active substances can be present in the compositions of the invention in amounts of a weight extending from 10% by weight to approximately the same amounts by weight as the components 1 and 2.

The compositions can, however, comprise as further active substances also compounds with a vitamin D activity as for example ergocalciferol, cholecalciferol or compounds as described in the German Offenlegungsschriften 2,312,256. These active substances can be present in the compositions of the invention in amounts up to the same amounts by weight as the anticoagulating agent.

The auxiliary substances or adjuvants employed for the production of baits and concentrates can be for example natural and artificial animal foodstuffs, human foodstuffs, decoy substances, dyes, inert vehicle substances or film-forming adjuvants. Animal foodstuffs are for example maize, corn, fat, fish, meat, bread, rice, seeds, various sorts of flour, as for example maize, starch, oat or fish meal, chocolate, cacao powder, sugar or butter. Decoy substances are for example sodium glutamate, honey, milk and water and mixtures of these substances. The nature of the dye used is not critical, though blue dyes may be considered to be more advantageous since they have a particular enticing effect as far as rats are concerned. Inert vehicle substances are for example mineral oils, sawdust, talcum, bentonite, pulverised limestone, aluminium oxide or magnesium oxide. Film-forming adjuvants are for example polymers, which form film coatings which are insoluble in saliva or insoluble in the gastric juice. If the compositions are processed to produce pellets, granules, or to granular material, the conventional pelletising and granule-forming adjuvants will be employed.

The components 1 and 2 can be used for the production of compositions in the form of any desired salts. Examples are constituted by salts with ammonia or with any suitable inorganic bases, which can be derived from alkali metals, alkaline earth metals, (earth metals) or heavy metals. As salt forming materials it is, however, also possible to use any suitable organic base as for example aliphatic or aromatic amines.

Example 1.

The example shows how the selection of acidic compounds is undertaken, which are suitable as component 2 for the new compositions of matter.

Using Sprague-Dawley rats the LD₅₀-values of the following substances were determined using the testing methods described above, that is to say:

- | | | |
|----|--|----|
| | (A) 1 - phenyl - 3,5 - di - (2 - thienyl) - 4 - pyrazolyl - acetic acid | |
| | (B) 1,5 - diphenyl - 3 (p - chlorophenyl) - 4 - pyrazolyl - acetic acid | |
| 5 | (C) 1,3,5 - triphenyl - 4 - pyrazolyl - acetic acid | |
| | (D) 1 - p - chlorophenyl - 3,5 - di - (2 - thienyl) - 4 - pyrazolylacetic acid | |
| | (E) 1 - (p - chlorobenzoyl) - 5 - methoxy - 2 - methyl - indolo - 3 - acetic acid | |
| | (F) 3 - cyclohexyl - 1,5 - diphenyl - 4 - pyrazolyl - acetic acid | |
| | (G) 1,3 - diphenyl - 5 - (p - methoxyphenyl) - 4 - pyrazolyl - acetic acid | |
| 10 | (H) 3,5 - diphenyl - 1 - (p - methoxyphenyl) - 4 - pyrazolyl - acetic acid | 10 |
| | (I) salicylic acid | |
| | (K) acetylsalicylic acid | |
| | (L) N - (2 - thiazolyl) - 4 - hydroxy - 2 - methyl - 2H - 1,2 - benzthiazine - 3 - carboxamide - 1,1 - dioxide | |
| 15 | (M) 1 - o - chlorophenyl - 3,5 - di - (2 - thienyl) - 4 - pyrazol acetic acid | 15 |
| | (N) 3 - chloro - 4 - cyclohexyl - α - methyl - phenyl acetic acid | |
| | (O) 1 - phenyl - 3,5 - di - (2 - furyl) - pyrazol - 4 - acetic acid | |
| | (P) 1 - methyl - 2',4' - difluoroxindol - 3 - carboxanilide | |
| 20 | (Q) N - (4 - bromophenyl) - 3 - hydroxy - 2 - methyl - 2H - benzthiazine - 4 - carboxamide - 1,1 - dioxide | 20 |
| | (R) N - (4 - nitrophenyl) - 3 - hydroxy - 2 - methyl - 2H - benzthiazine - 4 - carboxamide - 1,1 - dioxide. | |

Furthermore the animals after death were dissected in order to determine the course of death. In the case of the compounds (A) to (H) and (L) to (R) it was found that a single oral dose in a range extending up to 50 mg/kg body weight of the rat had caused massive haemorrhagic gut lesions before the animals died. The LD₅₀-values lay in the case of this group of compounds below 50 mg/kg of body weight.

In the case of the compounds (A), (B), (C) and (D) the LD₅₀-values were found to be approximately 5 mg/kg body weight, for the compounds (E), (F), (G), (H), (M) and (N) they were found to be approximately 15 mg/kg body weight and for (L), O to (R) an LD₅₀-value of below 50 mg/kg body weight was found. The LD₅₀-values for the compounds (I) and (K) lay far above 100 mg/kg of body weight of the rats. Therefore the compounds (I) and (K) are unsuitable as component 2 for the compositions of the invention, something which was proved by determination of the rodenticidal efficacy of combinations of (I) and (K) with anticoagulants. In this case, in order to be able to detect any synergistic rodenticidal action at all, such large amounts of salicylic or acetylsalicylic acids had been used that the development of a practical rodenticide on the basis of these compositions was understandably out of the question.

In order to investigate the rodenticidal efficacy of the compositions of the invention the LD₁₀₀-values of the combinations of compounds (A) to (H) and (L) to (R) were determined with, respectively, 2 mg/kg per rat of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene in accordance with the methods of investigation specified above. In this respect the compounds (A) to (H) and (L) to (O) and Q as well, were administered as sodium salts in an aqueous solution in a liquid volume of 5 ml/kg of body weight of the rat and 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene suspended in 1% "Tylose" (= carboxymethylcellulose) in a liquid volume of 5 ml/kg body weight of the rat. The compounds (P) and (R) were used as aqueous suspensions in "Tylose."

The number of animals which died within 10 days of the administration of the substance was determined. The following table 2 shows the results of the tests.

(21)

Table 2.

Increase in the rodenticidal efficacy of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene (2 mg/kg) by the addition of component 2 after a single oral dose in the case of Sprague-Dawley rats.

Component 2	Dose mg/kg	number of animals	% of animals which died	LD ₁₀₀ mg/kg (interpolated)
A	0.01	40	13	~2.0
	0.05	20	25	
	0.1	30	27	
	0.5	60	30	
	1.0	60	55	
	1.5	44	95	
	2.0	44	98	
B	0.05	40	8	1.5
	0.1	20	15	
	0.2	40	28	
	0.5	50	40	
	1.0	70	81	
	1.5	40	95	
	2.0	20	100	
C	0.5	30	7	3.0
	1.0	30	27	
	2.0	30	87	
	3.0	20	100	
	5.0	10	100	
D	0.1	10	0	5.0
	0.2	20	10	
	0.5	20	45	
	2.0	20	70	
	5.0	10	100	

Table 2.
Increase in the rodenticidal efficacy of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene (2 mg/kg) by the addition of component 2 after a single oral dose in the case of Sprague-Dawley rats.

Component 2	Dose mg/kg	number of animals	% of animals which died	LD ₅₀ mg/kg (interpolated)
E	1	30	3	7.5
	2	50	22	
	5	40	52	
	7.5	40	100	
F	0.5	10	0	7.5
	1.0	20	15	
	2.0	30	13	
	3.5	10	60	
	5.0	20	95	
	7.5	10	100	
	10.0	30	100	
G	2.0	30	3	~10.0
	5.0	20	25	
	7.5	10	70	
	10.0	30	97	
H	2.0	10	20	~10.0
	5.0	20	40	
	10.0	10	100	
L	2.0	20	35	≤20
	5.0	20	60	
	20.0	20	100	

Table 2.

Increase in the rodenticidal efficacy of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene (2 mg/kg) by the addition of component 2 after a single oral dose in the case of Sprague-Dawley rats.

Component 2	Dose mg/kg	number of animals	% of animals which died	LD ₅₀ mg/kg (interpolated)
M	2	10	10	~10-50
	5	20	25	
	10	10	80	
N	1	20	5	~5-10
	2	30	63	
	5	20	95	
	10	10	100	
O	5	30	7	~50
	10	30	17	
	20	20	25	
	50	20	100	

Table 2 shows that the component 2 clearly produces a synergistic action with respect to the effect of the component 1. The LD₅₀ value of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene amounts to 17 mg/kg in the case of Sprague-Dawley rats.

Example 2.

Table 3 shows the mean lethal dose of some anticoagulants or anti-clotting materials alone and in combination with 1-phenyl-3,5-di-(2-thienyl)-4-pyrazolyl-4-acetic acid (component 2) after a single oral administration to Sprague-Dawley rats.

Table 3.

Component 1	LD ₅₀ mg/kg oral* in combination with component 2		
	alone	1 mg/kg	2 mg/kg
4-hydroxy-2-oxo-3-(1-phenylpropyl)- 2H-chromene	3.0	1.7	0.55
4-hydroxy-3-(3-oxo-1-phenylbutyl)- 2H-chromene-2-one	7.0	4	0.4
2-diphenylacetyl-1,3-indandione	3.5	0.5	0.3
2-pivaloyl-1,3-indandione	far above 5	—	far above 1
3-(1,2,3,4-tetrahydro-1-naphthyl)- 4-oxycoumarine	4	—	about 0.5
2-phenyl-indandione-(1,3)	far above 100	—	not less than 50
4-hydroxy-2-oxo-3-[3-oxo-1-(4- nitrophenyl)-butyl]-2H-chromene	above 100	—	1.3

*Injection volume: 5 ml/kg, period of observation: 10 days

Example 3.

Using the methods of investigation of example 1 it was found that in the case of male and female wild rats with full stomachs (*Rattus norvegicus* and *R. rattus*) with a weight of approximately 150 to 350 g the following combinations of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene (component 1) with 1-phenyl-3,5-di-(2-thienyl)-4-pyrazolyl-acetic acid (component 2) lead to death of 100% of the animals investigated after a single oral dose within a period of investigation of 10 days (LD₁₀₀):

	Component 1 mg/kg rat	combined with	Component 2 mg/kg rat	
	45		0	
	4		1.5	
5	3		2	
	2		3	5
	0		7	

10 It can be seen from this component 2 even alone has a high redenticidal efficacy. It, however, will also be seen from this that the effects of the two components of the compositions of the invention have a high mutual synergistic effect. 10

Example 4.

15 0.05 part by weight of 1-phenyl-3,5-di-(2-thienyl)-4-pyrazolyl-acetic acid and 0.05 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are mixed with each other, finely ground and suspended in 4.9 parts by weight of molten mutton suet. This suspension is homogeneously mixed with 95 parts by weight of oat flakes. As a mixing machine use is made of a high speed cutter. This mixture is a highly effective rodenticide ready for use. 15

20 Instead of 4 - hydroxy - 2 - oxo - 3 - (1 - phenylpropyl) - 2H - chromene, 4 - hydroxy - 2 - oxo - 3 - (3 - oxo - 1 - phenyl - butyl) - 2H - chromene, 2 - di - phenylacetyl - indandione - (1,3) or 3 - (1,2,3,4 - tetrahydro - 1 - naphthyl) - 4 - oxycoumarin can be processed with the same quantity ratios to produce an effective rodenticide ready for use. 20

Example 5.

25 0.5 part by weight of 1-phenyl-3,5-di-(2-thienyl)-4-pyrazolyl-acetic acid and 0.5 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are mixed, finely ground and suspended in 4.0 parts by weight of a triglyceride mixture of saturated plant fatty acids with C₈, C₁₀ and C₁₂ (see H.P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, Editio Cantor KG., Aulendorf in Württemberg, 1971, page 382, column 2, 4th title). This suspension is mixed homogeneously with 95 parts by weight of maize meal. The mixture obtained constitutes a concentrate of a rodenticide and is added to animal feeds with a weight ratio between 1 to 5 and 1 to 10. 25

30 Instead of 1-phenyl-3,5-di-(2-thienyl)-4-pyrazolyl-acetic acid, 1,5-diphenyl-3-(p-chlorophenyl)-4-pyrazolyl-acetic acid is used with the same weight ratios and processed with 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene to produce an extremely effective rodenticide concentrate. 30

Example 6.

40 0.05 part by weight of 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid and 0.05 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are suspended in 4.9 parts by weight of liquid paraffin. This suspension is homogeneously mixed with 5 parts by weight of cane sugar and 90 parts by weight of oat flakes. The mixture constitutes an effective rodenticide ready for use. 40

Example 7.

45 0.5 part by weight of 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid and 0.5 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are mixed homogeneously with one part by weight of sodium glutamate and 93 parts of maize meal and thoroughly mixed with a solution of 5 parts by weight of gum arabic in 20 parts by weight of water. 45

50 One part of the moist powder mixture is pressed through a granulating sieve with 1.8 mm mesh clearance width and the moist granulate is dried at 40°C in a hurdle-type drying cupboard or in a fluidised bed. The granulate obtained constitutes a particularly effective rodenticide. 50

The remaining part of the moist powder mixture is processed to form pellets having a diameter of 1.2 to 1.6 mm. They constitute a rodenticide ready for use, which is readily consumed by rats.

Example 8.

0.05 part by weight of 1,5-diphenyl-3-*p*-chlorophenyl-4-pyrazolyl-acetic acid and 0.05 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are mixed with each other, finely ground and suspended in 4.9 parts by weight of molten mutton suet. This suspension is homogeneously mixed with 95 parts by weight of oat flakes. As a mixing apparatus a high speed cutting machine is employed. The mixture represents a highly effective rodenticide ready for use.

Instead of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene, 4-hydroxy-2-oxo-3-(3-oxo-1-phenyl-butyl)-2H-chromene, 2-diphenylacetyl-indandione-(1,3) or 3-(1,2,3,4-tetrahydro-1-naphthyl)-4-oxycoumarine can be processed with the same quantity ratios to form an effective rodenticide ready for use.

Example 9.

0.4 part by weight of 1,5-diphenyl-3-*p*-chlorophenyl-4-pyrazolyl-acetic acid and 0.6 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are mixed, finely ground and suspended in 4.0 parts by weight of a triglyceride mixture of saturated plant fatty acids with C₈, C₁₀ and C₁₂ (see H.P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, Editio Cantor KG., Aulendorf in Württemberg, 1971, page 382, column 2, 4th title). This suspension is homogeneously mixed with 95 parts by weight of maize meal. As a mixing machine use is made of a mixing or kneading machine. The mixture obtained represents a concentrated form of a rodenticide and is added to animal feeds in a weight ratio lying between 1 to 5 and 1 to 10.

Instead of 1,5-diphenyl-3-(*p*-chlorophenyl)-4-pyrazolylacetic acid, 1-*o*-chlorophenyl-3,5-di-(2-thienyl)-4-pyrazolylacetic acid is used in the same amounts by weight and processed with 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene to form an extremely effective rodenticide concentrate.

Example 10.

0.07 part by weight of 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid and 0.03 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are suspended in 4.9 parts by weight of liquid paraffin. This suspension is homogeneously mixed with 5 parts by weight of cane sugar and 90 parts by weight of oak flakes. The mixture constitutes an effective rodenticide ready for use.

Example 11.

0.6 part by weight of 1,5-diphenyl-3-*p*-chlorophenyl-4-pyrazolyl-acetic acid and 0.4 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are homogeneously mixed with one part by weight of sodium glutamate and 93 parts by weight of maize meal and thoroughly moistened with a solution of 5 parts by weight of gum arabic in 20 parts by weight of water.

One part of the moistened powder mixture is forced through a granulating sieve with a clearance mesh width of 1.8 mm and the moist granulate is dried at 40°C in a hurdle-type drying cupboard or using a fluidised bed. The granulate produced constitutes a particularly effective rodenticide.

The remaining part of the moistened powder mixture is processed to form pellets with a diameter of 1.2 to 1.6 mm, which represent a ready-to-use rodenticide, which is readily consumed by rats.

The words "TERRAMYCIN" and "TYLOSE" are Registered Trade Marks.
WHAT WE CLAIM IS:—

1. A rodenticidal composition characterised by one component 1 inhibiting the clotting of blood of mammals and one component 2 which after a single oral administration in a dose of below 50 mg/kg to a Sprague-Dawley rat with an empty stomach produces haemorrhagic gut lesions and containing in all an amount of components 1 and 2 of more than 10⁻³% by weight.

2. A composition in accordance with claim 1, characterised in that the total content of components 1 and 2 is made up of 5 to 95% by weight of component 1 and 95 to 5% by weight of component 2.

3. A composition in accordance with either of the preceding claims in a solid form.

4. A composition in accordance with anyone of the preceding claims,



The remaining part of the moist powder mixture is processed to form pellets having a diameter of 1.2 to 1.6 mm. They constitute a rodenticide ready for use, which is readily consumed by rats.

Example 8.

0.05 part by weight of 1,5-diphenyl-3-*p*-chlorophenyl-4-pyrazolyl-acetic acid and 0.05 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are mixed with each other, finely ground and suspended in 4.9 parts by weight of molten mutton suet. This suspension is homogeneously mixed with 95 parts by weight of oat flakes. As a mixing apparatus a high speed cutting machine is employed. The mixture represents a highly effective rodenticide ready for use.

Instead of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene, 4-hydroxy-2-oxo-3-(3-oxo-1-phenyl-butyl)-2H-chromene, 2-diphenylacetyl-indandione-(1,3) or 3-(1,2,3,4-tetrahydro-1-naphthyl)-4-oxycoumarine can be processed with the same quantity ratios to form an effective rodenticide ready for use.

Example 9.

0.4 part by weight of 1,5-diphenyl-3-*p*-chlorophenyl-4-pyrazolyl-acetic acid and 0.6 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are mixed, finely ground and suspended in 4.0 parts by weight of a triglyceride mixture of saturated plant fatty acids with C₈, C₁₀ and C₁₂ (see H.P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, Editio Cantor KG., Aulendorf in Württemberg, 1971, page 382, column 2, 4th title). This suspension is homogeneously mixed with 95 parts by weight of maize meal. As a mixing machine use is made of a mixing or kneading machine. The mixture obtained represents a concentrated form of a rodenticide and is added to animal feeds in a weight ratio lying between 1 to 5 and 1 to 10.

Instead of 1,5-diphenyl-3-(*p*-chlorophenyl)-4-pyrazolylacetic acid, 1-*o*-chlorophenyl-3,5-di-(2-thienyl)-4-pyrazolylacetic acid is used in the same amounts by weight and processed with 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene to form an extremely effective rodenticide concentrate.

Example 10.

0.07 part by weight of 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid and 0.03 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are suspended in 4.9 parts by weight of liquid paraffin. This suspension is homogeneously mixed with 5 parts by weight of cane sugar and 90 parts by weight of oak flakes. The mixture constitutes an effective rodenticide ready for use.

Example 11.

0.6 part by weight of 1,5-diphenyl-3-*p*-chlorophenyl-4-pyrazolyl-acetic acid and 0.4 part by weight of 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene are homogeneously mixed with one part by weight of sodium glutamate and 93 parts by weight of maize meal and thoroughly moistened with a solution of 5 parts by weight of gum arabic in 20 parts by weight of water.

One part of the moistened powder mixture is forced through a granulating sieve with a clearance mesh width of 1.8 mm and the moist granulate is dried at 40°C in a hurdle-type drying cupboard or using a fluidised bed. The granulate produced constitutes a particularly effective rodenticide.

The remaining part of the moistened powder mixture is processed to form pellets with a diameter of 1.2 to 1.6 mm, which represent a ready-to-use rodenticide, which is readily consumed by rats.

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WHAT WE CLAIM IS:—

1. A rodenticidal composition characterised by one component 1 inhibiting the clotting of blood of mammals and one component 2 which after a single oral administration in a dose of below 50 mg/kg to a Sprague-Dawley rat with an empty stomach produces haemorrhagic gut lesions and containing in all an amount of components 1 and 2 of more than 10⁻³% by weight.

2. A composition in accordance with claim 1, characterised in that the total content of components 1 and 2 is made up of 5 to 95% by weight of component 1 and 95 to 5% by weight of component 2.

3. A composition in accordance with either of the preceding claims in a solid form.

4. A composition in accordance with anyone of the preceding claims,



28

characterised by a total content of components 1 and 2 of approximately 5% by weight.

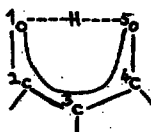
5. A composition in accordance with any one of the preceding claims, characterised in that the component 1 is an anti-coagulant on the basis of 1,3-indandione, coumarine 2-azacycloalkylmethyl-substituted benzhydryl-ketone or -carbinol or a mixture of these anti-coagulants.

6. A composition in accordance with anyone of the preceding claims, characterised in that the component 2 is an acidic aromatic or heteroaromatic compound with a molecular weight of approximately 200 to approximately 500 with 1 to 5 rings and 6 to 30 carbon atoms and a pK_A -value of 1.5 to 5.5 or is a salt or a derivative of the acidic compounds, which in the pH-range of the gastric juice of mammals is split up with the release of the acidic compound or is a mixture of these components causing gut lesions.

7. A composition in accordance with claim 6, characterised by its containing an aromatic or heteroaromatic carboxylic acid, a carboxylic acid salt, a carboxylic acid derivative or a mixture of this component causing gut lesions, whose carboxylic acid radical consists of 1 to 4 carbon atoms, which is directly linked with an aromatic or heteroaromatic ring, in the case of which the C=O-double bond of the carboxylic acid radical is separated by at least two C—C-single bonds from the next C=C-double bond.

8. A composition in accordance with claim 7, characterised by containing an aryl-acetic acid or an α -aryl- α -methylacetic acid or an arylpropionic acid or a heteroarylacetic acid or an α -heteroaryl- α -methylacetic acid or a heteroarylpropionic acid or a salt of these carboxylic acids or of a mixture of these components producing gut lesions.

9. A composition in accordance with claim 6 characterised by the content of an acidic enol compound with the conjugated system



or a salt of the enol compound or of a mixture of these components causing gut lesions.

10. A composition in accordance with anyone of the preceding claims, characterised in that in addition to components 1 and 2 it comprises one or more active substances which inhibit the bacterial vitamin-K synthesis in the intestine and/or one or more active substances with a vitamin-D activity.

11. A method for combating harmful rodents, characterised in that the rodents have administered to them a lethal dose of an active substance adapted to cause intestinal lesions and an active substance which hinders or prevents clotting of the blood in the form of a composition in accordance with anyone of claims 1 to 10.

12. A method for combating harmful rodents, more particularly rats and field mice, characterised in that use is made of a composition in accordance with anyone of claims 1 to 10.

13. The use of the compositions in accordance with claims 1 to 10 as rodenticides.

14. A composition as claimed in claim 1 wherein component 2 after a single oral administration in a dose of below 15 mg/kg to a Sprague-Dawley rat with an empty stomach produces haemorrhagic gut lesions.

15. A composition as claimed in claim 14 wherein component 2 after a single oral administration in a dose of below 5 mg/kg to a Sprague-Dawley rat with an empty stomach produces haemorrhagic gut lesions.

16. A composition as claimed in claim 1 characterised by its containing in all an amount of components 1 and 2 of more than 10⁻²⁰% by weight.

17. A composition as claimed in claim 6 wherein the pK_A -value is between 2—5.

18. A composition as claimed in claim 1 substantially as described with reference to any one of the specific examples hereinbefore set forth.

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