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(54) NEW DEHYDROOLIGOPEPTIDES, THEIR PRODUCTION AND THEIR MEDICINAL USE

(71) We, TROPONWERKE GMBH & CO. KG., a body corporate organised under the laws of Germany of 5000 Cologne 80, Berliner Str. 156, 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 present invention relates to dehydrooligopeptides, to processes for their production and to their use as tumour-resolving and/or histolytic acting agents.

It is known that a tumour-resolving and histolytic action can be achieved with substances of the most diverse nature; however, the general toxicity of such compounds is usually so high that practical treatment regimens which can be easily manipulated therapeutically and which do not harm the patients even further, scarcely exist.

Existing commercial products for use for corresponding indications are cytostatic agents, and cyclophosphamide may be mentioned here as an example.

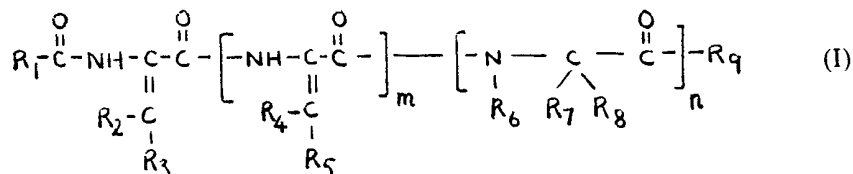
All the agents used hitherto exhibit an extremely high general toxicity. This is frequently so pronounced that it becomes necessary to interrupt therapy, and thus the tumour diseases often end fatally.

The action of cyclophosphamide may be mentioned here as an example of the generally toxic action. Thus, M.H.N. TATTERSALL and J.S. TOBIAS report in The Lancet 1976/II, No. 7,994, page 1,071: "in the case of many anti-cancer agents, twice the dose which kills 10% of the animals (LD₁₀) is fatal for 90% of the animals (LD₉₀). FREI and FREIREICH (Advances in Chemotherapy 2 (1965), 269) were able to demonstrate the significance of using agents such as cyclophosphamide in dosages which approached the toxicity rate (LD₁₀). The decisive characteristic of these experiments was the exponential increase observed in cell destruction with a low (arithmetic) increase in dose. The LD₁₀ dosage of cyclophosphamide destroyed 99.999% of the tumour cells, but one eighth of this dose (which was far less toxic) destroyed only 90% of the tumour cells and was therefore less active clinically by 5 log.

This observation is the reason for the widely held view that chemotherapy of cancer is only effective when it is generally toxic."

The use of dehydrooligopeptides as medicaments has not yet hitherto been disclosed.

The present invention provides compounds which are dehydrooligopeptides of the following general formula or the salts thereof



in which

R_1 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, an optionally substituted heterocyclic radical, optionally substituted aralkyl or optionally substituted aralkenyl or a carbamoyl group,

R_2 is a hydrogen atom or a C_1 to C_8 alkyl group,

5 R_3 is an optionally substituted heterocyclic radical, optionally substituted aryl, optionally substituted aralkenyl, optionally substituted aralkyl, ethyl or cycloalkyl, or

10 R_2 and R_3 , together with the carbon atom to which they are attached, represent a cyclopentylidene, cyclohexylidene, cyclopentenylidene or cyclohexenylidene group,

R_4 is a hydrogen atom, methyl or ethyl,

15 R_5 is an optionally substituted phenyl group, optionally substituted aralkenyl or a heterocyclic radical having from five to seven ring atoms and containing one or two nitrogen or oxygen or sulphur hetero-atoms, optionally substituted by from one to three halogen atoms, hydroxyl, nitro, alkyl or alkoxy,

R_6 is a hydrogen atom or alkyl, or

20 R_6 and R_7 together represent a divalent alkylene chain having three or four carbon atoms, or when R_6 is a hydrogen atom or alkyl, R_7 is a benzyl group substituted by one or two halogen atoms or by hydroxyl, nitro, alkoxy or alkyl, or is hydroxymethyl, methylthioethyl, carbamoyl ethyl or carboxyethyl, and

R_8 is hydrogen, or R_7 and R_8 together represent a divalent alkylene chain having four or five carbon atoms,

25 R_9 is hydroxyl, amino, optionally substituted straight-chain or branched saturated or unsaturated monoalkylamino or dialkylamino, optionally substituted arylamino, optionally substituted aralkylamino, an optionally substituted nitrogen-containing heterocyclic radical with five to seven ring atoms optionally containing a further hetero-atom replacing a ring carbon atom, optionally substituted aralkoxy, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkylthio group or optionally substituted hydrazino and

30 m and n are the same or different and each represents 0 or 1, provided that both m and n are not simultaneously 0, provided that

35 when R_1 is methyl R_2 is hydrogen, R_3 is phenyl, m represents 0, R_6 is hydrogen, R_9 is hydroxyl, R_8 is hydrogen and n is 1, then R_7 does not represent the 4-hydroxybenzyl radical, which compounds possess a suprisingly highly pronounced histolytic and tumour-resolving action.

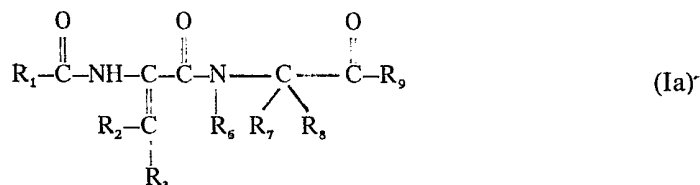
The dehydrooligopeptides according to the invention influence, in an outstanding manner, biological tissues which prevent or interfere with the course of normal biological functions.

40 Substances which are closely related chemically to the dehydrooligopeptides and which have a comparable action have not hitherto been disclosed.

Among the salts of the invention those salts that are pharmaceutically acceptable are particularly important and are preferred.

45 The free acid compounds of the general formula (I) and the salts thereof can be interconverted in any suitable manner; methods for such interconversion are known in the art.

When in the general formula (I), m represents 0 and n represents 1, the following type of structure derived from the general formula (I) results:

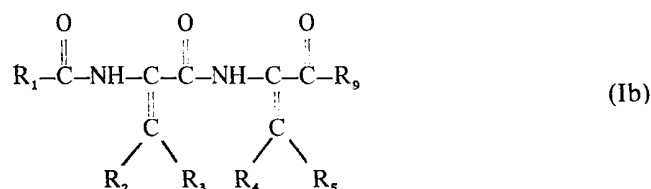


50 wherein, in the formula Ia

the radicals, R_1 , R_2 , R_3 , R_6 , R_7 , R_8 and R_9 have the above mentioned meaning.

55 In preferred compounds of formula (Ia), R_9 is hydroxyl, amino, optionally substituted straight-chain or branched saturated or unsaturated monoalkylamino or dialkylamino, optionally substituted arylamino, optionally substituted aralkylamino, an optionally substituted nitrogen containing heterocyclic radical with five to seven ring atoms optionally containing a further hetero-atom replacing a ring carbon atom, optionally substituted aralkoxy, optionally substituted alkoxy or optionally substituted aryloxy.

When in the general formula (I), m represents 1 and n represents 0, the following type of structure derived from the general formula (I) results:

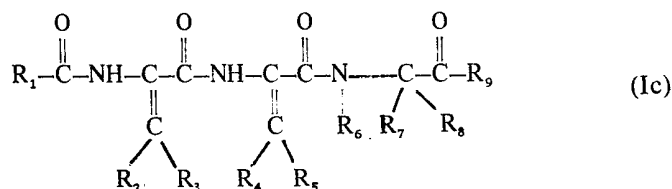


wherein, in the formula (Ib),

the radicals R_1 , R_2 , R_3 , R_4 , R_5 and R_9 have the above mentioned meaning.

In preferred compounds of formula (Ib) R_1 is optionally substituted alkyl, optionally substituted aryl, an optionally substituted heterocyclic radical or optionally substituted aralkyl or optionally substituted aralkenyl, and R_9 is hydroxyl, amino, optionally substituted straight-chain or branched saturated or unsaturated monoalkylamino or dialkylamino, optionally substituted arylamino, optionally substituted aralkylamino, an optionally substituted nitrogen containing heterocyclic radical with five to seven ring atoms optionally containing a further hetero-atom, optionally substituted aralkoxy, optionally substituted alkoxy or optionally substituted aryloxy.

When in the general formula (I) both m and n represent 1, the following type of structure, which can be derived from the general formula (I), results:

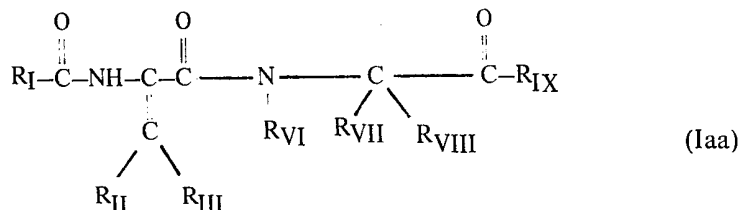


wherein

the radicals R_1 to R_9 have the above mentioned meaning.

Particularly preferred compounds are of the derived structure types (Ia) and (Ib), and in particular of structure type (Ia).

Particularly preferred compounds of structure type (Ia) are the compounds of the following formula:



in which

R_I is alkyl having from one to four carbon atoms, phenyl or styryl,

R_{II} is a hydrogen atom,

R_{III} is thienyl, furyl, or cycloalkyl having five or six carbon atoms,

R_{VI} is a hydrogen atom,

R_{VII} is the 4-hydroxybenzyl radical, 4-nitrobenzyl radical, 4-chlorobenzyl radical, the 2-methylmercaptoethyl radical or the carboxymethyl radical,

R_{VIII} is a hydrogen atom and

R_{IX} is hydroxyl or alkoxy having from one to four carbon atoms.

In the formulae I, Ia, Ib and Ic, the radicals R_1 to R_9 have the preferred meanings listed in the following text:

The optionally substituted alkyl group R_1 in the general formula I denotes a straight-chain or branched optionally substituted alkyl radical preferably having from one to six carbon atoms. Examples which may be mentioned are methyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl and i-pentyl. In each case the alkyl may

be substituted by from one to three halogen atoms, preferably fluorine or chlorine atoms, alkoxy having from one to three carbon atoms, preferably methoxy, or a heterocyclic radical, preferably thienyl.

5 The optionally substituted aryl group R_1 preferably denotes phenyl or naphthyl, optionally substituted by from one to three halogen atoms, preferably chlorine or fluorine atoms, or by alkyl or alkoxy, each having preferably from one to three carbon atoms, hydroxyl, trifluoromethyl or nitro. 5

10 The optionally substituted heterocyclic radical R_1 preferably denotes a five-membered to seven-membered heterocyclic radical, optionally containing one or two nitrogen, oxygen or sulphur atoms. Examples which may be mentioned are pyridyl, thienyl, furyl, pyrrolyl, oxazolyl and imidazolyl, which can each be additionally substituted by one or two halogen atoms or alkyl or alkoxy groups, each preferably having from one to four carbon atoms. 10

15 The optionally substituted aralkyl or optionally substituted aralkenyl group R_1 preferably denotes an optionally substituted aralkyl or optionally substituted aralkenyl group having from eight to twelve carbon atoms, most preferably benzyl or styryl, optionally substituted by from one to three halogen atoms, in particular chlorine or fluorine atoms, alkyl or alkoxy having preferably from one to three carbon atoms, most preferably methyl and methoxy, hydroxyl, C_1 to C_6 acyloxy, or halogenoalkyl most preferably trifluoromethyl. 15

20 An alkyl group R_2 herein preferably denotes an alkyl group having from one to four carbon atoms, most preferably methyl or ethyl. 20

25 The optionally substituted heterocyclic radical R_3 preferably denotes a saturated or unsaturated heterocyclic radical having from five to seven ring members, in which one or two hetero-atoms, for example, nitrogen, oxygen and sulphur atoms, may be present. Examples which may be mentioned are pyrrolyl, thienyl, furyl, oxazolyl, thiazolyl, imidazolyl, piperidinyl, morpholinyl and pyridinyl, thienyl and furyl being particularly preferred. In each case the heterocyclic radical may be substituted by from one to three halogen atoms, preferably chlorine or fluorine atoms, by alkyl or alkoxy having most preferably one or two carbon atoms or by nitro. 25

30 The optionally substituted aryl group R_3 preferably denotes a phenyl or naphthyl group, which may be substituted, for example, by from one to three halogen atoms, preferably chlorine or fluorine atoms, by alkyl or alkoxy having from one to four carbon atoms, by hydroxyl or by nitro. 30

35 The optionally substituted aralkyl or optionally substituted aralkenyl group R_3 preferably denotes a phenylalkyl or phenylalkenyl group having from seven to ten carbon atoms. Examples which may be mentioned are benzyl, phenylethyl and styryl, optionally substituted by from one to three halogen atoms, alkyl or alkoxy having from one to four carbon atoms or by nitro. 35

40 The cycloalkyl radical R_3 denotes a cycloalkyl radical having preferably from four to six carbon atoms, for example, the cyclobutyl, cyclopentyl or, in particular, the cyclohexyl radical, which may be substituted, for example, by one to two alkyl radicals with one to three carbon atoms. 40

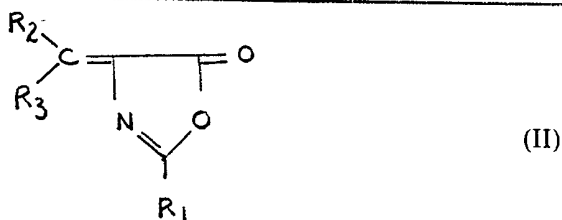
45 The optionally substituted phenyl group R_5 means that the phenyl group may be substituted by from one to three halogen atoms, in particular chlorine or fluorine atoms, by from one to three alkyl or alkoxy groups have preferably from one to three carbon atoms or by nitro or dialkylamino groups, in particular dimethylamino groups. 45

50 The optionally substituted aralkenyl group R_5 denotes an aralkenyl group having preferably from eight to ten carbon atoms, in particular the styryl group, which may be substituted by from one to three halogen atoms, hydroxyl, nitro, or alkyl or alkoxy having preferably from one to three carbon atoms. 50

55 The optionally substituted heterocyclic radical R_5 when substituted by alkyl or alkoxy is preferably substituted by alkyl or alkoxy having from one to three carbon atoms. 55

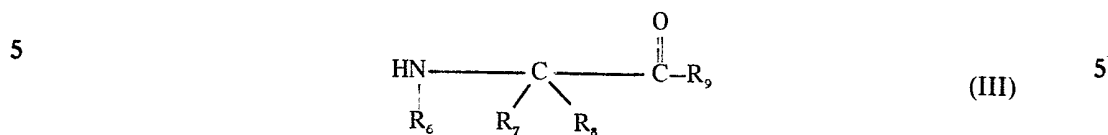
60 The substituted benzyl group R_7 when substituted by halogen atoms is preferably substituted by chlorine or fluorine atoms and when substituted by alkyl or alkoxy is preferably substituted by alkyl or alkoxy having from one to three carbon atoms. 60

65 The optionally substituted alkylamino group R_8 has preferably one to ten, more preferably one to six, carbon atoms. Examples which may be mentioned are the methylamino, dimethylamino, ethylamino, diethylamino, propylamino, isopropyl-amino, butylamino, pentylamino, and hexylamino groups and the 1,1-dimethyl-2-propinylamino group. 65



in which

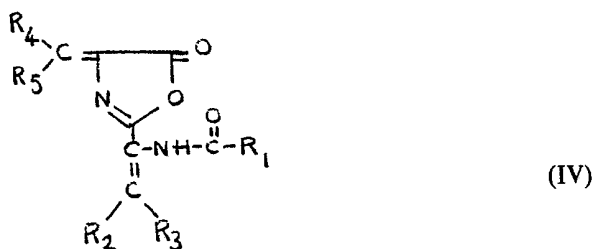
R_1 , R_2 and R_3 have the same meaning as defined hereinbefore in formula I is reacted with a compound of the general formula



in which

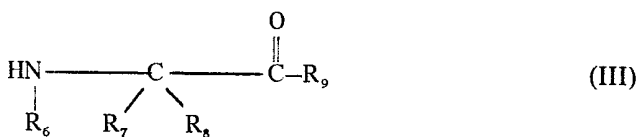
R_6 , R_7 , R_8 and R_9 have the same meaning as defined hereinbefore in formula I so as to yield said compound of formula I, or

(c) (aminolysis) when said compound is a compound of the general formula (I) in which R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ have the same meaning as defined hereinbefore and both m and n represent 1, an oxazolone of the general formula



in which

15 R_1 , R_2 , R_3 , R_4 and R_5 have the same meaning as defined hereinbefore in 15
formula (I)
is reacted with a compound of the general formula



in which

20 R₆, R₇, R₈ and R₉ have the same meaning as defined hereinbefore in formula (I), so as to yield said compound of formula (I), and the resulting compound of formula (I) or salt thereof, is optionally converted into a salt or a corresponding compound of formula (I), respectively.

25 The compounds of the general formula IV may be hydrolysed by stirring it or allowing it to stand in the presence of diluent(s). It is preferred that the above-mentioned preparative reactions should be carried out in the presence of a diluent which is inert under the reaction conditions. 25

Both polar aprotic and protic organic solvents may be used as diluents. Examples of polar aprotic diluents which may be mentioned are ketones, for example, acetone, methyl ethyl ketone and diethyl ketone, and cyclic ethers (tetrahydrofuran and dioxane). Acetone and tetrahydrofuran are particularly preferred.

Examples of polar protic diluents which may be mentioned are water and C₁ to C₈ alcohols, such as methanol, ethanol, propanol or isopropanol.

The reaction may appropriately be carried out in the presence of acid or basic catalysts.

5 Acid catalysts which can be employed are strong mineral acids, such as hydrochloric acid or sulphuric acid, or strong organic acids, such as benzene-sulphonic acid or toluene-sulphonic acid. 5

Inorganic bases, such as sodium hydroxide or potassium hydroxide, and strong organic bases, such as triethylamine, have proved to be preferred basic catalysts. Sodium hydroxide and potassium hydroxide are particularly preferred. 10

The reaction temperatures can be varied within a wide range. Preferably, the reaction is carried out at from 0° to 70°C, more preferably from 10° to 30°C.

If acid catalyst are used, small amounts of the catalyst are sufficient to achieve a satisfactory hydrolysis; if basic catalysts are used, it is preferable to employ 1 mol of base per 1 mol of oxazolone. 15

The reaction time varies with other conditions though in general it is between 15 minutes and 180 minutes, and usually is from 30 to 120 minutes. The reaction solution is usually worked up by acidifying with dilute aqueous mineral acids or relatively strong organic acids and evaporating off the organic diluent, whereupon the reaction product usually precipitates and is then recrystallised from the organic solvents customarily used, for example, dilute alcohols and ethyl acetate. The yields are in general good and are usually over 70%. 20

The preparation of the compounds of the general formula (I) by aminolysis of (II) or (IV) in the presence of (III) is preferably carried out by stirring the reactants together in diluents. 25

Preferred diluents are those organic liquids which are polar aprotic liquids and are miscible with water. Examples which may be mentioned are acetone, methyl ethyl ketone, diethyl ketone, alcohols and cyclic ethers, such as dioxane and tetrahydrofuran. Acetone and tetrahydrofuran have proved to be particularly suitable. 30

The process according to the invention is preferably carried out in the presence of basic catalysts. Sodium hydroxide has proved to be particularly suitable.

If free aminoacid as a reactant is used in the condensation with the oxazolone, 1 mol of aminoacid and 1 mol of sodium hydroxide are preferably employed per 1 mol of oxazolone. The reaction temperatures can be varied within a certain range; preferably, the reaction is carried out at from 0° to 80°C, more preferably at from 10 to 30°C, since at higher temperatures side reactions proceed and the yield is less. 35

The reaction time varies and may be between 30 minutes and several days, though usually it is from one to three hours. The reaction solution may be worked up by filtering and acidifying the filtrate with dilute mineral acids. It is particularly preferable to use 1 mol of mineral acid per 1 mol of sodium hydroxide employed. The reaction products are usually isolated by evaporating off the organic diluent in vacuo, whereupon the reaction product precipitates and is recrystallised from ethereal organic solvents, such as dilute alcohols or acetone. 40

When carrying out the process according to the invention using derivatives of aminoacids, for example aminoacid ester or amides, as reactants with the oxazolones, it is appropriate to carry out the reaction without basic catalysts, since hydrolytic splittings of the ester bonds or amide bonds could take place as side reactions. 45

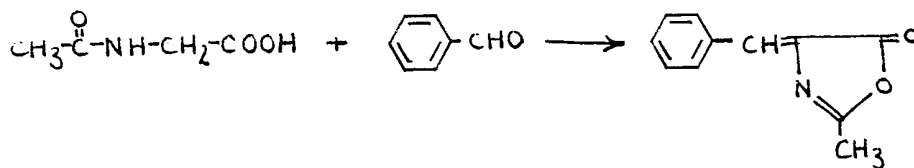
In some cases it has proved appropriate, for reasons of purity and yield, to use, instead of a free aminoacid of the general formula (III) (R₉ = OH), the corresponding ester in the condensation and subsequently to split off the ester grouping hydrolytically in a manner which is in itself known. 50

If the reaction times are extremely long, partial racemisation cannot be excluded, as can be seen from some of the optical rotation values quoted in the examples. 55

The compounds of the invention can exist both in the form of a racemate and in the form of the isolated optical isomers with a definite absolute configuration. In addition, cis/trans isomers can be obtained in the syntheses, for example of N-benzoyldehydro-phenylalanylleucine methyl ester. In some cases, for example in the case of N-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine, only one of the isomers is preferentially formed, as may be demonstrated by ¹³C-NMR spectroscopy. 60

Some of the starting compounds of formulae (II) and (IV), for the preparation of the compounds of the general formula (I) according to the invention, that is to 65

say the corresponding 2,4-disubstituted 5(4H)-oxazolones, are known from the literature. If they are not known, they can be prepared by the methods described in the literature for the preparation of compounds of analogous structure. The reaction of acetylglycine with benzaldehyde may be described here as an example. The reaction takes place according to the equation



The reaction is carried out by mixing the two components in an equimolar ratio in the presence of a condensing agent, usually acetic anhydride, which at the same time serves as the solvent, and a basic component, such as sodium acetate. After standing for several hours, the mixture is worked up by diluting with water and recrystallising the 4-benzylidene-2-methyl-5(4H)-oxazolone, which has precipitated, from ethyl acetate/petroleum ether.

Further examples of starting compounds which can be prepared analogously to the above equation follow.

5(4H)-Oxazolone starting materials of the formula (II) which may be mentioned are: 2-methyl-4-(2-thenylidene)-5(4H)-oxazolone, melting point 130—132°C; 2-methyl-4-(2-naphthylmethylene)-5(4H)-oxazolone, melting point 132—133°C; 4-cyclohexylmethylene-2-phenyl-5(4H)-oxazolone, melting point 114°C; 4-benzylidene-2-trifluoromethyl-5(4H)-oxazolone, melting point 98—100°C; 4-(1-methylpropylidene)-2-phenyl-5(4H)-oxazolone, oil; 2-phenyl-4-(2-thenylidene)-5(4H)-oxazolone, melting point 178°C; 2-(3-pyridyl)-4-(2-thenylidene)-5(4H)-oxazolone, melting point 193°C; 4-(1-methyl-3-phenyl-2-propenylidene)-2-phenyl-5(4H)-oxazolone, melting point 125°C; 4-thenylidene-2-(3-trifluoromethylphenyl)-5(4H)-oxazolone, melting point 156°C; 4-(2-cyclohexenylidene)-2-phenyl-5(4H)-oxazolone, melting point 100°C; 4-(1-methyl-2-phenylethylidene)-2-phenyl-5(4H)-oxazolone, melting point 63°C; 4-(α -methylbenzylidene)-2-phenyl-5(4H)-oxazolone, melting point 105.5°C; 4-cyclohexylidene-2-phenyl-5(4H)-oxazolone, melting point 136°C; 2-benzyl-4-(2-thenylidene)-5(4H)-oxazolone, melting point 97—100°C; 2-cinnamyl-4-benzylidene-5(4H)-oxazolone, melting point 131—135°C; 2-phenyl-4-(α -methyl-2-thenylidene)-5(4H)-oxazolone, melting point 154°C; 2-methyl-4-benzylidene-5(4H)-oxazolone, melting point 148—150°C; 2-methyl-4-(3-nitro-4-acetoxybenzylidene)-5(4H)-oxazolone, melting point 164°C; 2-methyl-4-(4-methylbenzylidene)-5(4H)-oxazolone, crude product; 2-methyl-4-(2-furfurylidene)-5(4H)-oxazolone, crude product (product from the literature); 2-methyl-4-(3-phenyl-2-propenylidene)-5(4H)-oxazolone, crude product; 2-(1-propenyl)-4-(2-thenylidene)-5(4H)-oxazolone, melting point 131—2°C; 2-[2-(3,4,5-trimethoxyphenyl)vinyl]-4-(2-thenylidene)-5(4H)-oxazolone, melting point 163°C; 2-methyl-4-(5-nitrothenylidene)-2-5(4H)-oxazolone, product from the literature; 2-(2-thienyl)-4-(2-thenylidene)-5(4H)-oxazolone, melting point 174°C; 2-phenyl-4-(4-pyridylmethylene)-5(4H)-oxazolone, melting point 237—239°C; 2-(4-nitrophenyl)-4-(2-thenylidene)-5(4H)-oxazolone, melting point 182—183°C; 2-(2-thienylmethyl)-4-(2-thenylidene)-5(4H)-oxazolone, melting point 104°C; and 2-phenyl-4-(1-methylpropylidene)-5(4H)-oxazolone, product from the literature.

5(4H)-Oxazolone starting materials of the formula IV which may be mentioned are: 2-(1-acetamido-2-phenylvinyl)-4-(4-dimethylaminobenzylidene)-5(4H)-oxazolone, melting point 253—254°C; 2-(1-acetamido-2-phenylvinyl)-4-(4-hydroxybenzylidene)-5(4H)-oxazolone, melting point 187—189°C; 2-(1-acetamido-2-phenylvinyl)-4-(4-fluorobenzylidene)-5(4H)-oxazolone, crude product; 2-(1-acetamido-2-phenylvinyl)-4-(4-nitrobenzylidene)-5(4H)-oxazolone, melting point 235—241°C; 2-(1-acetamido-2-phenylvinyl)-4-(4-chlorobenzylidene)-5(4H)-oxazolone, melting point 216—219°C; 2-[1-acetamido-2-(2-thienyl)vinyl]-4-(2-thenylidene)-5(4H)-oxazolone, melting point 229°C; 2-[1-acetamido-2-phenylvinyl]-4-(5-methyl-2-thenylidene)-5(4H)-oxazolone, melting point 185—187°C; 2-[1-acetamido-2-(2-thienyl)vinyl]-4-(α -methyl-2-thenylidene)-5(4H)-oxazolone, melting point 217°C and 2-(1-acetamido-2-phenylvinyl)-4-(3-chlorobenzylidene)-5(4H)-oxazolone, melting point 207—208°C.

The compounds of the formula III (preferably amino-acids and their amides or esters) used as starting compounds are known from the literature.

5 Examples which may be mentioned are: glycine, alanine, leucine, proline, phenylalanine, tyrosine, serine, threonine, cysteine, methionine, glutamine, aspartic acid, glutamic acid, l-aminocyclopentanecarboxylic acid, tyrosine N-methylamide, fluoroalanine, p-nitrophenylalanine, tyrosine tert.-butyl ester, tyrosine methyl ester, tyrosine amide, tyrosine benzylamide and tyrosine hexyl-
amide and tyrosine ethyl ester.

10 If the aminoacids and their amides or esters used as starting compounds are not known, they can be prepared by processes which are in themselves known for preparing compounds of analogous structure.

15 Examples of the compounds according to the invention which may be mentioned are: N - acetyl - DL - phenylalanyldehydro - (3 - chlorophenyl)alanine, N - acetyldehydrophenylalanyl - D - proline, N - acetyldehydrophenylalanyl - D - tyrosine, N - acetyldehydrophenylalanyl - L - methionine, N - acetyldehydro -
20 phenylalanyl - L - aspartic acid, N - acetyldehydrophenylalanyl - L - glutamine, N - acetyldehydrophenylalanyl - DL - 3 - fluoroalanine, N - acetyldehydrophenyl - alanyl - L - serine, N - acetyldehydrophenylalanyl - L - (p - nitrophenyl)alanine, N - acetyldehydrophenylalanyl - DL - (p - chlorophenyl)alanine, N - trifluoroacetyl -
25 dehydrophenylalanyl - L - tyrosine, N - acetyldehydro(p - methylphenyl)alanyl - L - tyrosine, N - benzoyl - 2 - cyclohexylideneglycyl - L - tyrosine, N - benzoyl - 2 - (2 - cyclohexenylidene)glycyl - L - tyrosine, N - acetyldehydro - 3 - (2 - furyl)alanyl - L - tyrosine, N - acetyldehydro - 3 - cinnamerylalanyl - L - tyrosine, N - acetyl -
30 dehydro - 3 - (2 - naphthyl)alanyl - L - tyrosine, N - benzoyldehydro - 3 - cyclohexyl - alanyl - L - tyrosine, N - trifluoroacetyldehydrophenylalanyl - L - tyrosine tert. - butyl ester, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - proline, N - acetyl -
35 dehydrophenylalanine(1 - carboxyl - 1 - cyclopentyl)amide, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - phenacetyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine tert. - butyl ester, N - phenacetyldehydro - 3 - (2 - thienyl)alanyl - L -
40 tyrosine, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - benzoyl - dehydro - 3 - (2 - thienyl)alanyl - L - (p - nitrophenyl)alanine, N - nicotinoylde - hydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - (3 - trifluoromethylbenzoyl) - de -
45 alanyl - L - (p - nitrophenyl) - alanine, N - benzoyl - 3 - methyl - 3 - (2 - thienyl) - dehydroalanyl - L - tyrosine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - D - tyrosine, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine methyl ester, N - acetyl -
50 dehydro - 3 - (2 - thienyl)alanyl - L - tyrosine methyl ester, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine amide, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine N' - hexylamide, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L -
40 tyrosine N' - cyclohexylamide, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine N',N' - dimethylamide, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine morpholide, N - acetyldehydrophenylalanyldehydro - (p - nitrophenyl) -
55 alanine, N - acetyldehydrophenylalanyldehydro - (p - fluorophenyl) - alanine, N - acetyldehydrophenylalanyldehydro - (4 - dimethylaminophenyl)alanine, N - acetyl - dehydrophenylalanyldehydro(3 - chlorophenyl)alanine, N - acetyldehydrophenyl -
45 alanyldehydro(3 - chlorophenyl)alanyl - L - tyrosine, N - acetyldehydrophenyl - alanyl - D - glutamic acid, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine benzyl ester, N - benzoyldehydro - 3 - (2 - thienyl) - L - tyrosine N' - benzylamide, and N - benzoyl - 3 - methyl - 3 - cinnameryldehydroalanyl - L - tyrosine.
50 Additional examples of compounds according to the invention which may be mentioned are: N - acetyldehydrophenylalanyl - 3 - (5 - methyl - 2 - thienyl) - dehydroalanine, N - acetyldehydrophenylalanyl - 3 - (chlorophenyl)dehydroalanine thiomethyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanyldehydro - 3 - (2 -
55 thienyl)alanine, N - acetyldehydro - 3 - (2 - thienyl)alanyldehydro - 3 - (4 - nitro - phenyl)alanine, N - (3,4,5 - trimethoxycinnamoyl)dehydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - crotonyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - acetyl - dehydro - 3 - (5 - nitro - 2 - thienyl)alanyl - L - tyrosine, N - (2 - thienoyl)dehydro - 3 -
60 (2 - thienyl)alanyl - L - tyrosine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - O - methyl - L - tyrosine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - glutamic acid, N - acetyldehydro - 3 - (2 - thienyl)dehydroalanyl - L - tyrosine tert.-butyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanyl - 3 - (2 - thienyl)dehydro -
65 alanyl - L - tyrosine methyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanyl - N - methyl - L - tyrosine methyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanyl - N - methyl - L - tyrosine, N - acetyldehydro - 3 - (3 - nitro - 4 - hydroxyphenyl)alanyl -

	L - tyrosine tert. - butyl ester, N - acetyldehydro - 3 - (3 - nitro - 4 - hydroxyphenyl) - alanyl - L - tyrosine, N - benzoyldehydro - 3 - (4 - pyridyl)alanyl - L - tyrosine methyl ester, N - benzoyldehydro - 3 - (4 - pyridyl)alanyl - L - tyrosine, N - (4 - nitrophenyl)acetyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - (4 - nitrophenyl)acetyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine methyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanyl - 3 - (2 - thienyl)dehydroalanyl - L - tyrosine tert. - butyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanyl - 3 - (2 - thienyl)dehydroalanyl - L - tyrosine, N - benzoyldehydroisoleucyl - L - tyrosine methyl ester, N - (2-thienyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine, N-(2-thienyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine tert.-butyl ester, N-(2-thienyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine benzyl ester, N-(2-thienyl)acetyldehydro-3-(2-thienyl)alanyl - L - tyrosine methyl ester, the salt of N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine with morpholine, with piperidine, with ethylenediamine, with triethanolamine, with DL - canavanine, with L - arginine and with L - lysine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine 2 - dimethylaminopropylamide, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine amide, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine methylamide, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine hydrazide, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine 6 - aminohexylamide, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine 4 - aminobutylamide, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine hydrazide, N - acetyldehydrophenylalanyl - 3 - (2 - thienyl)dehydroalanine methylamide and N - acetyldehydro - 3 - (2 - thienyl)alanyl - 3 - methyl - 3 - (2 - thienyl)dehydroalanine hexylamide.	
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25	On local administration, the active compounds according to the invention have a tumour-resolving and histolytic action which depends on the dosage used. By local administration there are to be understood herein as being included in particular, the following types of administration: subcutaneous, intracutaneous, intratumoral and peritumoral administration.	25
30	Necroses usually occur in the immediate region of the point of administration, but occasionally also at a distance therefrom (Lymphogenic). If the necrotic region breaks open, it is free from putrid material even for a relatively long period, although in the case of experimental animals feed, faeces, sawdust and other material come into contact with the open wound.	30
35	However, the tumour tissue can also be broken down whilst the external skin remains completely intact.	35
	The activity of the third component of the immunohaemolytic complement system is considerably decreased.	
40	The necrotic tissue is sharply divided from the surrounding healthy tissue; it appears macroscopically and microscopically as if it were "stamped out".	40
	The general behaviour of the experimental animals is not influenced by the size of the necrosis. There is no poisoning of the entire organism.	
	In the acute test for intravenous injection in rats, the LD ₅₀ of the compounds according to the invention is of the order of 300 mg/kg.	
45	A daily injection of 80 mg/kg in rabbits over a period of 27 days was tolerated completely without reaction.	45
	As has been mentioned above, the present invention also includes the use of the active compounds according to the invention for the treatment of those tissues in the field of human and veterinary medicine which prevent and interfere with the course of normal biological functions.	
50	Such tissues are, for example: benign and malignant tumours of a solid and cystic nature, pailomas, adenomas and cystadenomas; adenocarcinomas, including those of the cirrhosis type; basal-cell carcinomas; sarcomas, for example, fibrosarcoma, liposarcoma, myxosarcoma, rhabdomyosarcoma, chondrosarcoma, lymphosarcoma and reticulosarcoma as well as Hodgkin's disease; embryonic tumours, for example, neuroblastoma, nephroblastoma, teratoma, adamantinoma and retroblastoma, haemangioma, chrodoma, odontoma and cranio-pharyngioma; hamartomas, for example, lymphoangioma, exostoses and neurofibromatoses; melanomas, lymphomas; hepatoblastomas; mastocarcinoma; cervical carcinoma; choriocarcinoma and adrenoacanthoma; leiomyoma and androblastoma; arrhenoblastoma; Sertoli cell tumour; granulosa and theca cell tumour; germinoma and seminoma and cancer of the ovary and of the vulva; carcinoma of the bladder, prostate carcinoma and adenocarcinoma; tumours caused by schistosomiasis; astrocytoma and ependymal gliomas; glioblastomas and medulloblastoma; oligodentroglioma and spongioblastoma; meningioma and tumours of Schwann's sheath cells; pinealoma;	50
55		55
60		60
65		65

- haemangioblastoma, osteoblastoma and Ewing's tumour; multiple myeloma; fungoid mucosis; Burkitt's tumour; leucaemias, for example, acute and chronic lymphatic leucaemia, acute and chronic granulocytic leucaemia, acute and chronic monocytic leucaemia and stem-cell leucaemia; basaloma, fibroma and myoma and, especially, the metastases of all tumour forms which are accessible via surgical intervention using a local injection. 5
- The compounds according to the invention also exhibit therapeutically valuable actions in the case of osteosarcoma; however, in this case the compounds must normally be injected under a pressure of up to 600 atmospheres gauge using a special device. 10
- In addition, the compounds according to the invention can be used for fibrotic tissues of every type, in particular for the treatment of keloids, Ulcera crura, burn ulcers, decubital ulcers as well as Claviand onychomycoses and scar tissue and for the therapy and prophylaxis of emboli and thromboses. 15
- The compounds according to the invention can also be used for resolving moles, atheromas and lipomas and for removing deep abscesses which, under certain circumstances, are fistulous. 15
- The compounds according to the invention can additionally be used for the regeneration of cavernomas and tuberculomas. 20
- The compounds according to the invention can also be used for the scar-free regeneration of tissue defects in the case of leprosy and other skin, mucous membrane and epithelium defects of various origins, especially those which are caused by infections by bacteria, fungi and pathogens of tropical diseases, for example, those of leishmaniasis, fromboesia and pinta. 20
- As stated above, the invention also relates to the use in human and veterinary medicine of the compounds of the invention. 25
- The present invention provides a pharmaceutical composition comprising a compound of the invention in admixture with a solid or liquefied gaseous diluent, or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface active agent, especially in admixture with a liquid diluent of molecular weight of 350 or above. 30
- The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention in the form of a sterile and/or isotonic aqueous solution. 35
- The invention also provides a medicament in dosage unit form comprising a compound of the invention. 35
- "Medicament" as used in this specification means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as used in this specification means physically discrete coherent units suitable for medical administration each containing a daily dose or a multiple (up to four times) or sub-multiple (down to a fortieth) of a daily dose of the compound of the invention in association with a carrier and/or enclosed within an envelope. 40
- Whether the medicament contains a daily dose or, for example, a half, a third, or a quarter of a daily dose will depend on whether the medicament is to be administered once or, for example, twice, three times or four times a day respectively. 45
- The pharmaceutical compositions according to the invention may, for example, take the form of ointments, gels, pastes, creams, sprays (including aerosols), lotions, suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granulates or powders. 50
- The pharmaceutical compositions which are ointments, pastes, creams and gels can, for example, contain the usual diluents e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures of these substances. 55
- The pharmaceutical compositions which are powders and sprays can, for example, contain the usual diluents, e.g. lactose, talc, silicic acid, aluminium hydroxide, calcium silicate, and polyamide powder or mixtures of these substances. Aerosol sprays can, for example, contain the usual propellants, e.g. chlorofluoro-hydrocarbons. 60
- The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl 65

carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils for example ground nut oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

5 For parenteral administration, solutions and emulsions should be sterile, and, if appropriate, blood-isotonic. 5

10 Preferred injection solutions are those having a pH of from 7 to 9.5 most preferably from 8 to 9. The compounds of the invention which are free acids may be conveniently dissolved in dilute physiologically acceptable bases and then brought to the required pH by the addition of a dilute physiologically acceptable acid. 10

15 Examples of physiologically acceptable bases which may be mentioned are inorganic hydroxides, carbonates and bicarbonates, in particular those of sodium and potassium. 15

15 Examples of physiologically acceptable acids which may be mentioned are organic acids, such as citric acid, oxalic acid, lactic acid, benzoic acid, salicylic acid and acetic acid, or also inorganic acids, for example, dilute hydrochloric or sulphuric acid. 15

20 The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbite and sorbitane esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures thereof. 20

25 All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives. 25

The pharmaceutical compositions according to the invention preferably contain from 1 to 90%, usually from 5 to 50% of the active ingredient by weight of the total composition.

30 In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention. 30

35 Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent. 35

40 The discrete coherent portions constituting the medicament according to the invention will generally be adapted, by virtue of their shape or packaging, for medical administration and may be, for example, any of the following: ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as ampoules include a protective envelope which renders the portions of the medicament physically discrete and coherent. 40

45 The preferred daily dose for administration of the medicaments of the invention is from 50 mg to 5 g of active ingredient most preferably from 100 mg to 2 g of active ingredient. 45

50 The production of the above mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a solution or suspension) and then forming the composition into the medicament (e.g. ampoules of injection solution or suspension). 50

55 This invention further provides a method of combating (including prevention, relief and cure of) the above mentioned diseases in non-human animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention. 55

60 It is envisaged that these active compounds will be administered parenterally (for example intramuscularly, intracutaneously, subcutaneously, intratumorally or peritumorally), topically, preferably intracutaneously, subcutaneously, intratumorally and peritumorally. Preferred pharmaceutical compositions and medicaments are therefore those adapted for local administration, such as injection solutions and suspensions, ointments, gels, lotions and creams. Administration in the method of the invention is preferably subcutaneous, intracutaneous, intratumoral and peritumoral. 60

65 Preferably, it has proved advantageous to administer amounts of from 1 mg to 100 mg, most preferably from 2 to 40 mg per kg of body weight per day to achieve 65

effective results. Nevertheless, it can at times be necessary to deviate from those dosage rates, and in particular to do so as a function of the nature and body weight of the human or animal subject to be treated, the individual reaction of this subject to the treatment, the type of formulation in which the active ingredient is administered and the mode in which the administration is carried out, and the point in the progress of the disease or interval at which it is to be administered. Thus it may in some case suffice to use less than the above mentioned minimum dosage rate, whilst other cases the upper limited mentioned must be exceeded to achieve the desired results. Where larger amounts are administered it can be advisable to divide these into several individual administrations over the course of the day.

The examples which follow were carried out in accordance with the following general procedures:

0.025 mol of the aminoacid to be subjected to condensation is suspended in 10 ml of acetone, 25 ml of 1 N NaOH are added, whilst stirring, and the solution formed is mixed with a suspension of the appropriately substituted 5(4H)-oxazolone in acetone. The mixture is stirred at room temperature for $\frac{1}{2}$ to 20 hours, depending on the reactivity of the aminoacid. 25 ml of 1 N HCL are then added to the filtered reaction solution and the acetone is distilled off in vacuo. The desired end product crystallises out of the aqueous phase and is recrystallised from aqueous alcohol.

In the examples given below, the optical rotation was measured at $c = 2$ in dimethylformamide.

The melting points were determined in a Tottoli apparatus and are uncorrected.

Example 1.

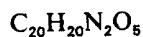
N-Acetyldehydrophenylalanyl-D-proline is obtained from 2-methyl-4-benzylidene-5(4H)-oxazolone and D-proline.
Melting point 151—153°C; $[\alpha]_D^{20} -69.6^\circ$; yield 55% of theory.



calculated: C 61.72%, H 6.15%, N 9.0%;
found: C 61.75%, H 6.30%, N 8.94%.

Example 2.

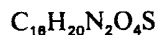
N-Acetyldehydrophenylalanyl-D-tyrosine is obtained from 2-methyl-4-benzylidene-5(4H)-oxazolone and D-tyrosine.
Melting point 210°C; $[\alpha]_D^{20} -43.4^\circ$ ($c = 2$; pyridine); yield 61.3% of theory.



calculated: C 65.21%, H 5.47%, N 7.60%;
found: C 64.56%, H 5.86%, N 7.77%.

Example 3.

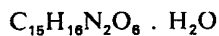
N-Acetyldehydrophenylalanyl-L-methionine is obtained from 2-methyl-4-benzylidene-5(4H)-oxazolone and L-methionine.
Melting point 91—93°C; $[\alpha]_D^{20} -74.4^\circ$; yield 70% of theory.



calculated: C 57.12%, H 5.99%, N 8.33%, S 9.53%;
found: C 57.02%, H 6.03%, N 8.40%, S 9.46%.

Example 4.

N-Acetyldehydrophenylalanyl-L-aspartic acid is obtained from 2-methyl-4-benzylidene-5(4H)-oxazolone and L-aspartic acid.
Melting point 182—184°C; $[\alpha]_D^{20} -46.65^\circ$; yield 63.5% of theory.



calculated: C 53.25%, H 5.36%, N 8.28%;
found: C 53.48%, H 4.92%, N 8.32%.

Example 5.

N-Acetyldehydrophenylalanyl-L-glutamine is obtained from 2-methyl-4-benzylidene-5(4H)-oxazolone and L-glutamine.
Melting point 188°C; $[\alpha]_D^{20} -74.5^\circ$; yield 54% of theory.

$C_{16}H_{19}N_3O_5$
 calculated: C 57.65%, H 5.75%, N 12.61%;
 found: C 58.17%, H 5.79%, N 13.16%.

Example 6.

- 5 *N*-Acetyldehydrophenylalanyl-DL-3-fluoralanine is obtained from 2-methyl-4-benzylidene-5(4H)-oxazolone and DL-3-fluoroalanine. 5
 Melting point 180°C (decomposition); yield 58.7% of theory.

$C_{14}H_{15}FN_2O_4$
 calculated: C 57.14%, H 5.14%, F 6.46%, N 9.52%;
 found: C 57.22%, H 5.22%, F 6.30%, N 9.58%. 10

Example 7.

N-Acetyldehydrophenylalanyl-L-serine is obtained from 2-methyl-4-benzylidene-5(4H)-oxazolone and L-serine.

Melting point 179°C (decomposition); $[\alpha]_D^{20} +1.15^\circ$; yield 48.5% of theory.

$C_{14}H_{16}N_2O_5$
 calculated: C 57.53%, H 5.52%, N 9.58%;
 found: C 57.48%, H 5.47%, N 9.66%. 15

Example 8.

- 20 *N*-Acetyldehydrophenylalanyl-L-(*p*-nitrophenyl)alanine is obtained from 2-methyl-4-benzylidene-5(4H)-oxazolone and L-4-nitrophenylalanine. 20
 Melting point 192—193°C (from ethanol/petroleum ether/isopropyl ether); $[\alpha]_D^{20} -110.7^\circ$; yield 70.3% of theory.

$C_{20}H_{19}N_3O_6$
 calculated: C 60.45%, H 4.82%, N 10.58%;
 found: C 60.40%, H 4.90%, N 10.43%. 25

Example 9.

- 30 *N*-Acetyldehydrophenylalanyl-DL-(*p*-chlorophenyl)alanine is obtained from 2-methyl-4-benzylidene-5(4H)-oxazolone and DL-(4-chlorophenyl)alanine. 30
 Melting point 214—215°C (from diethyl ether/petroleum ether); yield 66.9% of theory.

$C_{20}H_{19}ClN_2O_4$
 calculated: C 62.10%, H 4.95%, Cl 9.17%, N 7.24%;
 found: C 62.39%, H 5.02%, Cl 9.14%, N 7.11%.

Example 10.

- 35 *N*-Trifluoroacetyldehydrophenylalanyl-L-tyrosine is obtained from 2-trifluoro-methyl-4-benzylidene-5(4H)-oxazolone and L-tyrosine. 35
 Melting point 165—175°C; $[\alpha]_D^{20} -57.4^\circ$ (c = 1; dimethylformamide); yield 91% of theory.

$C_{20}H_{17}F_3N_2O_5$
 calculated: C 56.87%, H 4.06%, F 13.50%, N 6.63%;
 found: C 56.92%, H 4.05%, F 13.40%, N 6.61%. 40

Example 11.

- 45 *N*-Acetyldehydro(*p*-methylphenyl)alanyl-L-tyrosine is obtained from 2-methyl-4-(4-methylbenzylidene)-5(4H)-oxazolone and L-tyrosine. 45
 Melting point 220—221°C; $[\alpha]_D^{20} -38.5^\circ$; yield 47.6% of theory.

$C_{21}H_{22}N_2O_5$
 calculated: C 65.95%, H 5.80%, N 7.33%;
 found: C 65.96%, H 5.80%, N 7.16%.

Example 12.

- 50 *N*-Benzoyl-2-cyclohexylideneglycyl-L-tyrosine is obtained from 2-phenyl-4-cyclohexylidene-5(4H)-oxazolone and L-tyrosine. 50
 Melting point 121°C; $[\alpha]_D^{20} -0.5^\circ$; yield 75.8% of theory.

$C_{24}H_{26}N_2O_5$
calculated: C 68.23%, H 6.20%, N 6.63%;
found: C 68.16%, H 6.18%, N 6.65%.

Example 13.

- 5 *N-Benzoyl-2-(2-cyclohexenylidene)glycyl-L-tyrosine* is obtained from 2-phenyl-4-(2-cyclohexenylidene)-5(4H)-oxazolone and L-tyrosine. 5
Melting point 126°C; $[\alpha]_D^{20}$ -5.7°; yield 60% of theory.

10 $C_{24}H_{24}N_2O_5$
calculated: C 68.56%, H 5.75%, N 6.66%;
found: C 68.46%, H 5.70%, N 6.56%. 10

Example 14.

- 15 *N-Acetyldehydro-3-(2-furyl)alanyl-D-tyrosine* is obtained from 2-methyl-4-(2-furfurylidene)-5(4H)-oxazolone. 15
Melting point 217°C (ethanol/petroleum ether);
 $[\alpha]_D^{20}$ -29.1°; yield 31% of theory.

$C_{18}H_{18}N_2O_6$
calculated: C 60.33%, H 5.06%, N 7.82%;
found: C 60.37%, H 5.11%, N 7.70%.

Example 15.

- 20 *N-Acetyldehydro-3-cinnamerylalanyl-L-tyrosine* is obtained from 2-methyl-4-(3-phenyl-2-propenylidene)-5(4H)-oxazolone and L-tyrosine. 20
Melting point 220—221°C; $[\alpha]_D^{20}$ -44.2°; yield 57.3% of theory.

25 $C_{22}H_{22}N_2O_5$
calculated: C 66.99%, H 5.62%, N 7.10%;
found: C 66.80%, H 5.64%, N 7.06%. 25

Example 16.

- 30 *N-Acetyldehydro-3-(2-naphthyl)alanyl-L-tyrosine* is obtained from 2-methyl-4-(2-naphthylmethylene)-5(4H)-oxazolone and L-tyrosine. 30
Melting point 221—222°C (precipitate from ethyl acetate/isopropanol with petroleum ether); $[\alpha]_D^{20}$ -11.6° (c = 2; from methanol); yield 55.7% of theory.

$C_{24}H_{22}N_2O_5$
calculated: C 68.89%, H 5.30%, N 6.70%;
found: C 69.04%, H 5.37%, N 6.65%.

Example 17.

- 35 *N-Benzoyldehydro-3-cyclohexylalanyl-L-tyrosine* is obtained from 2-phenyl-4-cyclohexylmethylene-5(4H)-oxazolone and L-tyrosine. 35
Melting point 126—128°C; $[\alpha]_D^{20}$ +0.8° (c = 1; dimethylformamide); yield 60.3% of theory.

40 $C_{25}H_{28}N_2O_5$
calculated: C 68.79%, H 6.46%, N 6.42%;
found: C 68.59%, H 6.32%, N 6.24%. 40

Example 18.

- 45 *N-Acetyldehydrophenylalanyl-3-(5-methyl-2-thienyl)dehydroalanine* is obtained from 4-(5-methylthienylidene)-2-(1-acetamido-2-phenylvinyl)-5(4H)-oxazolone. 45
Melting point: 193—194°C; yield: 40% of theory.

$C_{19}H_{18}N_2O_4S$
calculated: C 61.61%, H 4.90%, N 7.56%, S 8.66%;
found: C 61.54%, H 4.96%, N 7.55%, S 8.70%.

Example 19.

- 50 *N-Acetyldehydro-3-(2-thienyl)alanyldehydro-3-(2-thienyl)alanine* is obtained from 2-[1-acetamido-2-(2-thienylvinyl)]-4-(2-thienylidene)-5(4H)-oxazolone. 50
Melting point: 218°C; yield 80% of theory.

$C_{18}H_{14}N_2O_4S_2$
 calculated: C 53.02%, H 3.89%, N 7.73%, S 17.69%;
 found: C 52.99%, H 3.94%, N 7.96%, S 17.70%.

Example 20.

- 5 *N*-Acetyldehydro-3-(2-thienyl)alanyldehydro-3-(4-nitrophenyl)alanine is obtained from 4-(4-nitrobenzylidene)-2-[1-acetamido-2-(2-thienyl)vinyl]-5(4H)-oxazolone. Melting point: 196—197°C; yield: 55.7% of theory. 5

$C_{18}H_{15}N_3O_6S$
 calculated: C 53.86%, H 3.77%, N 10.47%, S 7.99%;
 found: C 53.80%, H 3.81%, N 10.52%, S 7.85%. 10

Example 21.

- 15 *N*-(3,4,5-Trimethoxycinnamoyl)dehydro-3-(2-thienyl)alanyl-L-tyrosine is obtained from 2-[2-(3,4,5-trimethoxyphenyl)vinyl]-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine. Melting point: 148—150°C; yield: 92.2% of theory. 15

$C_{28}H_{28}N_2O_8S$
 calculated: C 60.86%, H 5.11%, N 5.07%, S 5.80%;
 found: C 60.74%, H 5.15%, N 5.07%, S 5.79%.

Example 22.

- 20 *N*-Crotonyldehydro-3-(2-thienyl)alanyl-L-tyrosine is obtained from 2-(1-propenyl)-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine. Melting point: 157°C; yield: 51% of theory. 20

$C_{20}H_{20}NO_5S$
 calculated: C 59.99%, H 5.03%, N 7.00%, S 8.01%;
 found: C 60.34%, H 4.97%, N 6.63%, S 7.51%. 25

Example 23.

- 30 *N*-Acetyldehydro-3-(5-nitro-2-thienyl)alanyl-L-tyrosine is obtained from 2-methyl-4-(5-nitro-2-thienylidene)-5(4H)-oxazolone and L-tyrosine. Melting point: 148—157°C; yield: 54.6% of theory. 30

$C_{18}H_{17}N_3O_7S$
 calculated: C 51.55%, H 4.09%, N 10.02%, S 7.65%;
 found: C 51.36%, H 4.11%, N 10.01%, S 7.64%.

Example 24.

- 35 *N*-(2-Thienoyl)dehydro-3-(2-thienyl)alanyl-L-tyrosine is obtained from 2-(2-thienyl)-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine. Melting point: 140—150°C; yield: 72% of theory. 35

$C_{21}H_{18}N_2O_5S_2$
 calculated: C 57.00%, H 4.10%, N 6.33%, S 14.49%;
 found: C 57.01%, H 4.28%, N 6.35%, S 14.12%.

Example 25.

- 40 *N*-Acetyldehydro-3-(2-thienyl)alanyl-O-methyl-L-tyrosine is obtained from 2-methyl-4-(2-thienylidene)-5(4H)-oxazolone and O-methyl-L-tyrosine. Melting point: 236°C; yield: 90% of theory. 40

$C_{19}H_{20}N_2O_5S$
 calculated: C 53.75%, H 5.19%, N 7.21%, S 8.25%;
 found: C 53.83%, H 5.36%, N 7.23%, S 8.30%. 45

Example 26.

- 50 *N*-Acetyldehydro-3-(2-thienyl)alanyl-L-glutamic acid is obtained from 2-methyl-4-(2-thienylidene)-5(4H)-oxazolone and L-glutamic acid. Melting point: 205°C (decomposition); yield: 76.5% of theory. 50

$C_{14}H_{16}N_2O_6S$
 calculated: C 49.40%, H 4.74%, N 8.23%, S 9.42%;
 found: C 49.61%, H 4.76%, N 8.16%, S 9.59%.

Example 27.

- 5 *N*-Trifluoroacetyldehydrophenylalanyl-*L*-tyrosine *tert*.-butyl ester is obtained from 2-trifluoromethyl-4-benzylidene-5(4H)-oxazolone and *L*-tyrosine *tert*.-butyl ester. The reaction is carried out in dimethylformamide without NaOH. Melting point 182—183°C; $[\alpha]_D^{20}$ -29.7° (c = 1; dimethylformamide); yield 84% of theory. 5

- 10 $C_{24}H_{25}F_3N_2O_5$
 calculated: C 60.24%, H 5.27%, F 11.91%, N 5.86%;
 found: C 60.30%, H 5.30%, F 11.90%, N 5.93%. 10

Example 28.

- 15 *N*-Benzoyldehydro-3-(2-thienyl)alanyl-*L*-proline is obtained from 2-phenyl-4-(2-thienylidene)-5(4H)-oxazolone and *L*-proline. Melting point 125°C (ill-defined); $[\alpha]_D^{20}$ +2.0°; yield 52% of theory. 15

$C_{19}H_{18}N_2O_4S$
 calculated: C 61.60%, H 4.90%, N 7.56%, S 8.66%;
 found: C 61.59%, H 4.80%, N 7.50%, S 8.79%.

- 20 *N*-Acetyldehydrophenylalanyl-(1-carboxy-1-cyclopentyl)amide is obtained from 2-methyl-4-benzylidene-5(4H)-oxazolone and 1-aminocyclopentanecarboxylic acid. Melting point: 217°C (decomposition); yield 50.7% of theory. 20

- 25 $C_{17}H_{20}N_2O_4$
 calculated: C 64.54%, H 6.37%, N 8.86%;
 found: C 64.85%, H 6.55%, N 8.41%. 25

Example 30.

- 30 *N*-Acetyldehydro-3-(2-thienyl)alanyl-*L*-tyrosine is obtained from 2-methyl-4-(2-thienylidene)-5(4H)-oxazolone and *L*-tyrosine. Melting point 227—228°C; $[\alpha]_D^{20}$ -36.75°; yield 71.06% of theory. 30

$C_{18}H_{18}N_2O_5S$
 calculated: C 57.74%, H 4.85%, N 7.48%, S 8.56%;
 found: C 57.61%, H 4.84%, N 7.49%, S 8.62%.

- 35 *N*-Phenacetyldehydro-3-(2-thienyl)alanyl-*L*-tyrosine *tert*.-butyl ester is obtained from 2-benzyl-4-(2-thienylidene)-5(4H)-oxazolone and *L*-tyrosine *tert*.-butyl ester. Melting point 110—120°C (crude product); yield 51.5% of theory. 35
- 40 This compound was further processed by stirring for $\frac{1}{2}$ hour with trifluoroacetic acid to give *N*-phenacetyldehydro-3-(2-thienyl)alanyl-*L*-tyrosine. Melting point 135—140°C (decomposition); $[\alpha]_D^{20}$ -41°; yield 49% of theory. 40

$C_{24}H_{22}N_2O_5S$
 calculated: C 63.98%, H 4.92%, N 6.22%, S 7.12%;
 found: C 63.79%, H 4.82%, N 6.29%, S 7.07%.

- 45 *N*-Benzoyldehydro-3-(2-thienyl)alanyl-*L*-tyrosine is obtained from 2-phenyl-4-(2-thienylidene)-5(4H)-oxazolone and *L*-tyrosine. Melting point 135°C (ill-defined); yield 41.2% of theory. 45

- 50 $C_{23}H_{20}N_2O_5S$
 calculated: C 63.29%, H 4.62%, N 6.43%, S 7.34%;
 found: C 63.25%, H 4.67%, N 6.37%, S 7.38%. 50

Example 33.

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-(p-nitrophenyl)alanine is obtained from 2-phenyl-4-(2-thienylidene)-5(4H)-oxazolone and 4-nitro-L-phenylalanine. Melting point 125°C (ill-defined); $[\alpha]_D^{20}$ -67.3°; yield 60% of theory.

5	$C_{23}H_{19}N_3O_6S$					5
	calculated:	C 59.35%,	H 4.11%,	N 9.03%,	S 6.89%;	
	found:	C 59.39%,	H 4.36%,	N 9.01%,	S 6.71%.	

Example 34.

10	<i>N-Nicotinoyldehydro-3-(2-thienyl)alanyl-L-tyrosine</i> is obtained from 2-(3-pyridyl)-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine. Melting point 160°C (ill-defined); $[\alpha]_D^{20}$ -8.35°; yield 50% of theory.					10
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	$C_{22}H_{19}N_3O_5S$				
	calculated:	C 60.40%,	H 4.38%,	N 9.60%,	S 7.33%;
	found:	C 60.57%,	H 4.58%,	N 9.75%,	S 7.32%.

Example 35.

15	<i>N-(3-Trifluoromethylbenzoyl)dehydro-3-(2-thienyl)alanyl-L-tyrosine</i> is obtained from 2-(3-trifluoromethylphenyl)-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine. Melting point 125°C (ill-defined); $[\alpha]_D^{20}$ -8.9°; yield 48% of theory.					15
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20	$C_{24}H_{19}F_3N_2O_5S$					20
	calculated:	C 57.14%,	H 3.80%,	F 11.30%,	N 5.55%,	S 6.36%;
	found:	C 56.95%,	H 3.81%,	F 11.40%,	N 5.45%,	S 6.45%.

Example 36.

25	<i>N-Nicotinoyldehydro-3-(2-thienyl)alanyl-L-(p-nitrophenyl)alanine</i> is obtained from 2-(3-pyridyl)-4-(2-thienylidene)-5(4H)-oxazolone and L-4-nitrophenylalanine. Melting point 197°C (decomposition); $[\alpha]_D^{20}$ -98°; yield 75% of theory.					25
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	$C_{22}H_{18}N_4O_6S$				
	calculated:	C 56.64%,	H 3.89%,	N 12.01%,	S 6.87%;
	found:	C 56.55%,	H 3.91%,	N 12.05%,	S 6.89%.

Example 37.

30	<i>N-Benzoyl-3-methyl-3-(2-thienyl)dehydroalanyl-L-tyrosine</i> is obtained from 2-phenyl-4-(α -methyl-2-thienylidene)-5(4H)-oxazolone and L-tyrosine. Melting point 128°C; $[\alpha]_D^{20}$ +15.6°; yield 66.7% of theory.					30
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35	$C_{24}H_{22}N_2O_5S$					35
	calculated:	C 63.98%,	H 4.92%,	N 6.22%,	S 7.12%;	
	found:	C 64.14%,	H 4.93%,	N 6.34%,	S 7.03%.	

Example 38.

40	<i>N-Acetyldehydro-3-(2-thienyl)alanyl-D-tyrosine</i> is obtained from 2-methyl-4-(2-thienylidene)-5(4H)-oxazolone and D-tyrosine. Melting point 221—222°C; $[\alpha]_D^{20}$ +36.8°; yield 51.49% of theory.					40
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	$C_{18}H_{18}N_2O_5S$				
	calculated:	C 57.74%,	H 4.85%,	N 7.48%,	S 8.56%;
	found:	C 57.83%,	H 4.89%,	N 7.44%,	S 8.67%.

Example 39.

45	<i>N-Benzoyldehydroisoleucyl-L-tyrosine</i> is obtained from 2-phenyl-4-(1-methyl-propylidene)-5(4H)-oxazolone and L-tyrosine. Melting point 107°C; $[\alpha]_D^{20}$ -12.1°; yield 31.5% of theory.					45
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50	$C_{22}H_{24}N_2O_5$					50
	calculated:	C 66.65%,	H 6.10%,	N 7.07%;		
	found:	C 66.57%,	H 6.17%,	N 6.90%.		

Example 40.

N-Benzoyl-3-methyl-3-cinnamyldehydroalanyl-L-tyrosine is obtained from 2-phenyl-4-(1-methyl-3-phenyl-2-propenylidene)-5(4H)-oxazolone and L-tyrosine. Melting point 130°C; $[\alpha]_D^{20}$ -5.5°; yield 96% of theory.

5	$C_{28}H_{28}N_2O_5$				5
	calculated:	C 71.47%,	H 5.57%,	N 5.95%;	
	found:	C 71.60%,	H 5.57%,	N 5.87%.	

Example 41.

N-Cinnamyldehydrophenylalanyl-L-tyrosine is obtained from 2-cinnamyl-4-benzylidene-5(4H)-oxazolone and L-tyrosine. Melting point 172—174°C; $[\alpha]_D^{20}$ -24°; yield 30% of theory.

10	$C_{27}H_{24}N_2O_5$				10
	calculated:	C 71.94%,	H 5.3 %,	N 6.14%;	
	found:	C 70.85%,	H 5.39%,	N 6.16%.	

Example 42.

N-Acetyldehydrophenylalanyldehydro(3-chlorophenyl)alanyl-L-tyrosine is obtained from 2-(1-acetamido-2-phenylethylene)-4-(3-chlorobenzylidene)-5(4H)-oxazolone and L-tyrosine. Melting point 191—193°C; $[\alpha]_D^{20}$ -154.3° (c = 1; dimethylformamide); yield 78.5% of theory.

15	$C_{29}H_{26}ClN_3O_6$				15
	calculated:	C 63.56%,	H 4.78%,	Cl 6.47%,	N 7.67%;
	found:	C 63.69%,	H 4.76%,	Cl 6.54%,	N 7.70%.

Example 43.

N-Acetyldehydrophenylalanyldehydro(4-nitrophenyl)alanine
4.5 g (0.0119 mol) of 2-(1-acetamido-2-phenylvinyl)-4-(4-nitrobenzylidene)-5(4H)-oxazolone are suspended in 60 ml of acetone, 31.9 ml of N NaOH are added and the mixture is stirred at room temperature for 100 minutes. After acidifying the reaction solution with 33.5 ml of N HCl, the reaction product precipitates in the analytically pure form. Melting point 181°C; yield 56.4% of theory.

25	$C_{20}H_{17}N_3O_6$				25
	calculated:	C 60.76%,	H 4.33%,	N 10.63%;	
	found:	C 60.86%,	H 4.51%,	N 10.46%.	

Example 44.

N-Acetyldehydrophenylalanyldehydro(4-chlorophenyl)alanine is obtained from 2-(1-acetamido-2-phenylvinyl)-4-(4-chlorobenzylidene)-5(4H)-oxazolone. Melting point 177°C; yield 60.9% of theory.

35	$C_{20}H_{17}ClN_2O_4$				35
	calculated:	C 62.42%,	H 4.45%,	N 7.28%,	Cl 9.21%;
	found:	C 62.49%,	H 4.47%,	N 7.36%,	Cl 9.24%.

Example 45.

N-Acetyldehydrophenylalanyldehydro(p-fluorophenyl)alanine is obtained from 2-(1-acetamido-2-phenylvinyl)-4-(4-fluorobenzylidene)-5(4H)-oxazolone. Melting point 172°C; yield 65.27% of theory.

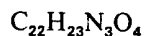
40	$C_{20}H_{17}FN_2O_4 \cdot H_2O$				40
	calculated:	C 62.17%,	H 4.96%,	F 4.92%,	N 7.25%;
	found:	C 62.30%,	H 4.94%,	F 4.70%,	N 7.25%.

45

Example 46.

N-Acetyldehydrophenylalanyldehydro(4-dimethylaminophenyl)alanine is obtained from 2-(1-acetamido-2-phenylvinyl)-4-(4-dimethylaminobenzylidene)-5(4H)-oxazolone.

5 Melting point 153—155°C; yield 36.2% of theory. 5

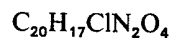


calculated: C 67.16%, H 5.89%, N 10.68%;
found: C 67.03%, H 6.00%, N 10.52%.

Example 47.

10 *N*-Acetyldehydrophenylalanyldehydro(3-chlorophenyl)alanine is obtained from 2-(1-acetamido-2-phenylvinyl)-4-(3-chlorobenzylidene)-5(4H)-oxazolone. 10

Melting point 183°C; yield 88.4% of theory.



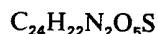
15 calculated: C 62.42%, H 4.45%, Cl 9.21%, N 7.28%;
found: C 62.54%, H 4.45%, Cl 9.23%, N 7.18%. 15

In the examples which follow, the reaction was carried out in tetrahydrofuran without NaOH.

Example 48.

20 *N*-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine methyl ester is obtained from 2-phenyl-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine methyl ester. 20

Melting point 120°C (ill-defined); $[\alpha]_D^{20}$ -4.6°; yield 95% of theory.



calculated: C 63.98%, H 4.92%, N 6.22%, S 7.12%;
found: C 63.78%, H 4.93%, N 6.07%, S 7.02%.

Example 49.

25 *N*-Acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine methyl ester is obtained from 2-methyl-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine methyl ester. 25

Melting point 243—245°C; $[\alpha]_D^{20}$ -78.1° (c = 1; dimethylsulphoxide).

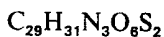


30 yield 65% of theory.
calculated: C 58.75%, H 5.19%, N 7.21%, S 8.26%;
found: C 58.45%, H 5.35%, N 7.17%, S 8.47%. 30

Example 50.

35 *N*-Acetyldehydro-3-(2-thienyl)alanyl-3-(2-thienyl)dehydroalanyl-L-tyrosine tert.-butyl ester is obtained from 2-[1-acetamido-2-(2-thienyl)vinyl]-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine tert.-butyl ester, analogously to Example 81. 35

Melting point: 158°C; yield: 95% of theory.

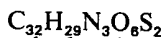


40 calculated: C 59.88%, H 5.37%, N 7.22%, S 11.03%;
found: C 60.01%, H 5.41%, N 7.15%, S 11.08%. 40

Example 51.

45 *N*-Acetyldehydro-3-(2-thienyl)alanyl-3-(2-thienyl)dehydroalanyl-L-tyrosine benzyl ester is obtained from 2-[1-acetamido-2-(2-thienyl)vinyl]-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine benzyl ester, analogously to Example 81. 45

Melting point: 130°C; yield: 83% of theory.



calculated: C 62.42%, H 4.75%, N 6.82%, S 10.42%;
found: C 62.52%, H 4.68%, N 6.83%, S 10.40%.

Example 52.

50 *N*-Acetyldehydro-3-(2-thienyl)alanyl-3-(2-thienyl)dehydroalanyl-L-tyrosine methyl ester is obtained from 2-[1-acetamido-2-(2-thienyl)vinyl]-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine methyl ester, analogously to Example 81. 50

Melting point: 155°C; yield: 96% of theory.

$C_{28}H_{25}N_3O_6S_2$
 calculated: C 57.86%, H 4.67%, N 7.79%, S 11.89%;
 found: C 58.08%, H 4.79%, N 7.75%, S 11.88%.

Example 53.

- 5 *N*-Acetyldehydro-3-(2-thienyl)alanyl-*N*-methyl-*L*-tyrosine methyl ester is obtained from 2-methyl-4-(2-thienylidene)-5(4H)-oxazolone and *N*-methyl-*L*-tyrosine methyl ester.
 Melting point: 102°C; yield: 38.9% of theory.

10 $C_{20}H_{22}N_2O_5S \cdot H_2O$
 calculated: C 58.38%, H 5.63%, N 6.81%, S 7.79%;
 found: C 58.28%, H 5.59%, N 6.89%, S 8.15%.

Example 54.

- 15 *N*-Acetyldehydro-3-(3-thienyl)alanyl-*N*-methyl-*L*-tyrosine is obtained from the above compound by boiling with NaOH.
 Melting point: 150—170°C; yield: 72.6% of theory.

$C_{19}H_{20}N_2O_5S$
 calculated: C 58.75%, H 5.19%, N 7.21%, S 8.25%;
 found: C 58.62%, H 5.36%, N 7.08%, S 8.35%.

Example 55.

- 20 *N*-Acetyldehydro-3-(3-nitro-4-hydroxyphenyl)alanyl-*L*-tyrosine tert.-butyl ester is obtained from 2-methyl-4-(3-nitro-4-acetoxybenzylidene)-5(4H)-oxazolone and *L*-tyrosine tert.-butyl ester.
 Melting point: 148—151°C; yield: 45.5% of theory.

25 $C_{24}H_{27}N_3O_8$
 calculated: C 59.37%, H 5.61%, N 8.66%;
 found: C 59.43%, H 5.71%, N 8.54%.

Example 56.

- 30 *N*-Acetyldehydro-3-(3-nitro-4-hydroxyphenyl)alanyl-*L*-tyrosine is obtained from the above compound by stirring with trifluoroacetic acid.
 Melting point: 145°C; yield: 93% of theory.

$C_{21}H_{22}N_3O_8$
 calculated: C 56.76%, H 4.99%, N 9.24%;
 found: C 56.88%, H 5.09%, N 9.31%.

Example 57.

- 35 *N*-Benzoyldehydro-3-(4-pyridyl)alanyl-*L*-tyrosine methyl ester is obtained from 2-phenyl-4-(4-pyridinylmethylene)-5(4H)-oxazolone and *L*-tyrosine methyl ester.
 Melting point: 155—160°C; yield: 33.7% of theory.

40 $C_{25}H_{23}N_3O_5 \cdot H_2O$
 calculated: C 66.07%, H 5.32%, N 9.25%;
 found: C 66.17%, H 5.59%, N 9.25%.

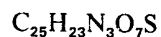
Example 58.

- N*-Benzoyldehydro-3-(4-pyridyl)alanyl-*L*-tyrosine is obtained from the above compound by boiling with dilute sodium hydroxide solution.
 Melting point: 162—166°C; yield: 54.3% of theory.

45 $C_{24}H_{21}N_3O_5$
 calculated: C 66.81%, H 4.91%, N 9.74%;
 found: C 66.63%, H 5.13%, N 9.77%.

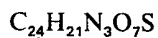
Example 59.

- 50 *N*-(4-Nitrophenyl)acetyldehydro-3-(2-thienyl)alanyl-*L*-tyrosine methyl ester
 Melting point: 218—222°C; yield: 55.7% of theory.



calculated: C 58.93%, H 4.55%, N 8.25%, S 6.29%;
found: C 58.82%, H 4.55%, N 8.13%, S 6.11%.

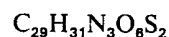
- 5 Example 60.
 N-(4-Nitrophenyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine is obtained from
 the above compound by boiling with dilute sodium hydroxide solution. 5
 Melting point: 161–166°C; yield: 41.6% of theory.



- 10 calculated: C 58.17%, H 4.27%, N 8.48%, S 6.47%;
 found: C 58.26%, H 4.44%, N 8.45%, S 6.63%. 10

Example 61.

- 15 *N*-Acetyldehydro-3-(2-thienyl)alanyl-3-(2-thienyl)dehydroalanyl-L-tyrosine tert.-butyl
 ester is obtained from 2-[1-acetamido-2-(2-thienyl)vinyl]-4-(2-thienylidene)-5(4H)-
 oxazolone and L-tyrosine tert.-butyl ester.
 Melting point: 158°C (decomposition); yield: 94% of theory. 15



calculated: C 59.88%, H 5.37%, N 7.22%, S 11.03%;
found: C 60.01%, H 5.41%, N 7.15%, S 11.08%.

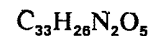
- 20 Example 62.
 N-Acetyldehydro-3-(2-thienyl)alanyl-3-(2-thienyl)dehydroalanyl-L-tyrosine is ob- 20
 tained from the above compound by adding glacial acetic acid/HCl.
 Melting point: 189°C (decomposition); yield: 88% of theory.



- 25 calculated: C 57.13%, H 4.91%, N 7.99%, S 12.20%;
 found: C 56.90%, H 4.63%, N 7.92%, S 12.04%. 25

Example 63.

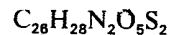
- 30 *N*-Benzoyldehydroisoleucyl-L-tyrosine methyl ester is obtained from 2-phenyl-4-
 (1-methylpropylidene)-5(4H)-oxazolone and tyrosine methyl ester.
 Melting point: 163–165°C; yield: 35.5% of theory. 30



calculated: C 67.30%, H 6.38%, N 6.83%;
found: C 67.23%, H 6.35%, N 6.82%.

Example 64.

- 35 *N*-(2-Thienyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine tert.-butyl ester is ob- 35
 tained from 2-(2-thienylmethyl)-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine
 tert.-butyl ester.
 Melting point: 105°C; yield: 85% of theory.



- 40 calculated: C 60.91%, H 5.50%, N 5.47%, S 12.51%;
 found: C 61.02%, H 5.57%, N 5.60%, S 12.36%. 40

Example 65.

- 45 *N*-(2-Thienyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine is obtained from the
 above compound by adding glacial acetic acid/hydrochloric acid.
 Melting point: 110°C; yield: 95% of theory. 45



calculated: C 57.88%, H 4.41%, N 6.14%, S 14.05%;
found: C 57.64%, H 4.52%, N 6.06%, S 13.90%.

Example 66.

- 50 *N*-(2-Thienyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine benzyl ester is obtained
 from 2-(2-thienylmethyl)-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine benzyl
 ester.
 Melting point: 95°C; yield: 83% of theory. 50

$C_{29}H_{26}N_2O_5S_2$
 calculated: C 63.71%, H 4.79%, N 5.13%, S 11.74%;
 found: C 63.85%, H 4.80%, N 5.06%, S 11.69%.

Example 67.

- 5 *N*-(2-Thienyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine methyl ester is obtained from 2-(2-thienylmethyl)-4-(2-thienylidene)-5(4H)-oxazolone and L-tyrosine methyl ester.
 Melting point: 200°C (decomposition); yield: 80% of theory. 5

10 $C_{23}H_{22}N_2O_5S_2$
 calculated: C 58.70%, H 4.71%, N 5.95%, S 13.63%;
 found: C 58.79%, H 4.76%, N 5.95%, S 13.50%. 10

Example 68.

- 15 *N*-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine benzyl ester is formed from the acid and benzyl alcohol by heating to 80°C for $\frac{1}{4}$ hour in the presence of hydrogen chloride.
 Melting point 95°C (ill-defined); $[\alpha]_D^{20}$ -2.0°; yield 79% of theory 15

$C_{30}H_{26}N_2O_5S$
 calculated: C 68.42%, H 4.98%, N 5.32%, S 6.09%;
 found: C 68.42%, H 4.96%, N 5.30%, S 6.02%.

- 20 The salts below were prepared from the dehydroamino acid by allowing the acid to stand with three times the amount of amine and diluting the mixture with methanol and evaporating it to dryness. 20

Example 69.

- 25 The salt of *N*-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with piperidine
 Melting point: 184—186°C; yield: 58.80% of theory. 25

$C_{29}H_{29}N_3O_5S$
 calculated: C 60.11%, H 6.36%, N 9.14%, S 6.98%;
 found: C 60.29%, H 6.27%, N 9.33%, S 7.17%.

Example 70.

- 30 The salt of *N*-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with ethylenediamine.
 Melting point: 148—158°C; yield: 98.9% of theory. 30

$C_{38}H_{44}N_6O_{10}S_2$
 calculated: C 56.42%, H 5.48%, N 10.39%, S 7.93%;
 found: C 56.38%, H 5.64%, N 10.26%, S 7.81%.

- 35 Example 71.
 The salt of *N*-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with triethanolamine
 Melting point: 125—130°C; yield: 84.1% of theory. 35

40 $C_{24}H_{33}N_3O_8S$
 calculated: C 55.05%, H 6.35%, N 8.03%, S 6.12%;
 found: C 54.77%, H 6.30%, N 7.93%, S 6.00%. 40

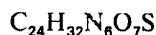
Example 72.

- The salt of *N*-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with DL-canavanine
 Melting point: 165—173°C; yield: 90.9% of theory.

45 $C_{23}H_{30}N_6O_8S$
 calculated: C 50.17%, H 5.49%, N 15.27%, S 5.81%;
 found: C 50.02%, H 5.62%, N 15.35%, S 5.67%. 45

Example 73.

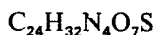
- The salt of *N*-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with L-arginine
 Melting point: 125—140°C; yield: 79.3% of theory.



calculated: C 52.54%, H 5.88%, N 15.32%, S 5.85%;
found: C 52.44%, H 6.00%, N 15.31%, S 5.10%.

Example 74.

- 5 *The salt of N-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with L-lysine* 5
Melting point: 174—182°C; yield: 96.1% of theory.

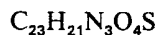


calculated: C 55.37%, H 6.20%, N 10.76%, S 6.16%;
found: C 55.22%, H 6.41%, N 10.87%, S 6.04%.

- 10 The amides below were prepared from N-benzoyldehydro-3-(2-thienyl)- 10
alanyl-L-tyrosine methyl ester (called A in the examples which follow) by allowing
a mixture of the ester with the corresponding amines (1 mol of ester per 8 mols of
amine) to stand in methanol or tetrahydrofuran and working up the mixture by
evaporating and purifying on silica gel (reaction time 3 to 340 hours).

Example 75.

- 15 *N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine amide* is obtained from A and 15
ammonia.
Melting point 210°C; $[\alpha]_D^{20}$ -62.0°; yield 86% of theory.



calculated: C 63.43%, H 4.86%, N 9.65%, S 7.36%;
found: C 63.25%, H 4.96%, N 9.59%, S 7.38%.

- 20 20

Example 76.

- 25 *N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine N'-hexylamide* is obtained from 25
A and n-hexylamine.
Melting point 115°C (ill-defined); $[\alpha]_D^{20}$ -63.4°; yield 80% of theory.



calculated: C 67.03%, H 6.40%, N 8.09%, S 6.17%;
found: C 67.22%, H 6.51%, N 8.19%, S 6.08%.

- 30 *N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine N'-methylamide* is obtained from 30
A and methylamine (aqueous solution).
Melting point 145°C (ill-defined); $[\alpha]_D^{20}$ -61.7°; yield 90.2% of theory.



calculated: C 64.12%, H 5.16%, N 9.35%, S 7.13%;
found: C 64.04%, H 4.99%, N 9.42%, S 7.07%.

- 35 35

Example 78.

- 40 *N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine N'-cyclohexylamide* is obtained 40
from A and cyclohexylamine.
Melting point 110°C (ill-defined); $[\alpha]_D^{20}$ -50.9°; yield 44% of theory.

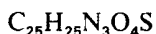


calculated: C 67.29%, H 6.04%, N 8.12%, S 6.19%;
found: C 67.38%, H 6.33%, N 8.09%, S 5.88%.

- 40 40

Example 79.

- 45 *N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine N',N'-dimethylamide* is obtained 45
from A and dimethylamine (aqueous solution).
Melting point 130°C (ill-defined); $[\alpha]_D^{20}$ -2.2°; yield 13% of theory.



calculated: C 64.77%, H 5.44%, N 9.06%, S 6.92%;
found: C 64.64%, H 5.41%, N 9.06%, S 6.77%.

Example 80.

N-benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine morpholide is obtained from A and morpholine.

Melting point 120°C (ill-defined); $[\alpha]_D^{20}$ -0.7; yield 22% of theory.

5	$C_{27}H_{27}N_3O_5S$	5
	calculated: C 64.14%, H 4.38%, N 8.32%, S 6.34%;	
	found: C 63.92%, H 5.53%, N 8.27%, S 6.09%.	

Example 81.

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine *N'*-benzylamide is obtained from A and benzylamine.

Melting point 133°C; $[\alpha]_D^{20}$ -69.83°; yield 68% of theory.

10	$C_{30}H_{27}N_3O_4S$	10
	calculated: C 63.55%, H 5.18%, N 7.99%, S 6.10%;	
	found: C 63.65%, H 5.25%, N 8.13%, S 6.03%.	

Example 82.

N-Acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine-2-dimethylaminopropylamide.

Melting point: 177—179°C (decomposition); yield: 63% of theory.

15	$C_{29}H_{30}N_4O_4S$	15
	calculated: C 60.24%, H 6.59%, N 12.22%, S 6.99%;	
20	found: C 60.39%, H 6.75%, N 12.40%, S 6.89%	20

Example 83.

N-Acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine amide

Melting point: 147°C; yield: 79% of theory.

25	$C_{18}H_{19}N_3O_4S$	25
	calculated: C 57.89%, H 5.13%, N 11.25%, S 8.59%;	
	found: C 57.75%, H 5.20%, N 11.09%, S 8.53%.	

Example 84.

N-Acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine methylamide.

Melting point: 225°C; yield: 50% of theory.

30	$C_{19}H_{21}N_3O_4S$	30
	calculated: C 58.90%, H 5.46%, N 10.85%, S 8.27%;	
	found: C 58.90%, H 5.47%, N 10.85%, S 8.30%.	

Example 85.

N-benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine-6-aminohexylamide.

Melting point: 122°C; yield: 51.4% of theory.

35	$C_{29}H_{34}N_4O_4S$	35
	calculated: C 65.14%, H 5.41%, N 10.48%, S 6.00%;	
	found: C 65.04%, H 6.42%, N 10.45%, S 6.10%.	

Example 86.

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine-4-aminobutylamide

Melting point: 126°C; yield: 70% of theory.

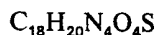
40	$C_{27}H_{30}N_4O_4S$	40
	calculated: C 64.00%, H 5.96%, N 11.06%, S 6.32%;	
	found: C 64.28%, H 5.98%, N 10.84%, S 6.19%.	

Example 87.

N-Acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine hydrazide.

Melting point: 240°C (decomposition); yield: 35.3% of theory.

45		45
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calculated: C 55.66%, H 5.19%, N 14.42%, S 8.25%;
found: C 55.58%, H 5.28%, N 14.56%, S 8.34%.

Example 88.

- 5 *N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine hydrazide.* 5
Melting point: 135°C; yield: 82.2% of theory.



calculated: C 61.32%, H 4.92%, N 12.44%, S 7.11%;
found: C 61.12%, H 5.02%, N 12.38%, S 7.26%.

- 10 If instead of sodium hydroxide an appropriate amine is used, the compounds 10
which follow are formed from the corresponding 5(4H)-oxazolones:

Example 89.

N-Acetyldehydrophenylalanyl-3-(2-thienyl)dehydroalanine N'-methylamide.
Melting point: 226°C; yield: 89% of theory.



calculated: C 61.77%, H 5.18%, N 11.37%, S 8.68%;
found: C 61.65%, H 5.25%, N 11.6%, S 8.63%.

- 15 15

Example 90.

- 20 *N-Acetyldehydro-3-(2-thienyl)alanyl-3-methyl-3-(2-thienyl)dehydro-* 20
alanine N'-n-hexylamide.
Melting point: 110°C; yield: 90% of theory.

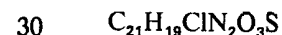


calculated: C 60.10%, H 6.36%, N 9.14%, S 13.96%;
found: C 60.20%, H 6.56%, N 9.26%, S 13.91%.

- 25 25

Example 91.

N-Acetyldehydrophenylalanyl-3-(3-chlorophenyl)dehydroalanine thiomethyl ester
is obtained from 4-(3-chlorobenzylidene)-2-(1-acetamido-2-phenylvinyl)-5(4H)-
oxazolone and methylmercaptan, in a pressure flask for one week.
Melting point: 166—167°C; yield: 39% of theory.

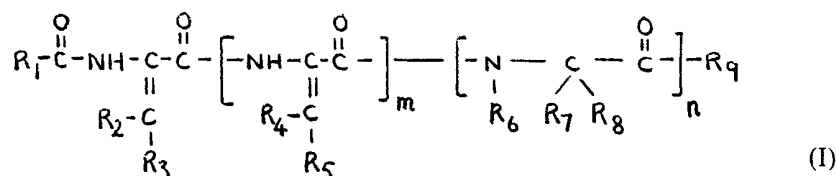


calculated: C 60.79%, H 4.61%, Cl 8.54%, N 6.75%, S 7.73%;
found: C 60.74%, H 4.48%, Cl 8.58%, N 6.82%, S 7.80%.

- 30 30

WHAT WE CLAIM IS:—

- 35 1. Compounds which are dehydrooligopeptides of the following general 35
formula or the salts thereof:



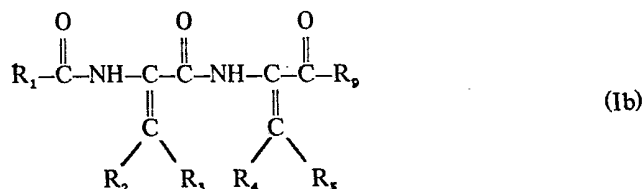
in which

- 40 R_1 is optionally substituted alkyl, optionally substituted alkenyl, optionally 40
substituted aryl, an optionally heterocyclic radical, optionally substituted aralkyl or
optionally substituted aralkenyl or a carbamoyl group.

R_2 is a hydrogen atom or a C_1 to C_8 alkyl group,

- 45 R_3 is an optionally substituted heterocyclic radical, optionally substituted aryl, 40
optionally substituted aralkenyl, optionally substituted aralkyl, ethyl or cycloalkyl,
or R_2 and R_3 , together with the carbon atom to which they are attached, represent
a cyclopentylidene, cyclohexylidene, cyclopentenylidene or cyclohexenylidene
group.

R_{III} is thienyl, furyl, or cycloalkyl having five or six carbon atoms,
 R_{VI} is a hydrogen atom,
 R_{VII} is the 4-hydroxybenzyl radical, 4-nitrobenzyl radical, 4-chlorobenzyl
 radical, the 2-methylmercaptoethyl radical or the carboxymethyl radical,
 R_{VIII} is a hydrogen atom, and
 R_{IX} is hydroxyl or alkoxy having from one to four carbon atoms.
 4. Compounds according to claim 1 which are dehydrooligopeptides of the
 following general formula



in which

R_1 is optionally substituted alkyl, optionally substituted aryl, an optionally
 substituted heterocyclic radical, optionally substituted aralkyl or optionally
 substituted aralkenyl, R_2 , R_3 , R_4 and R_5 have the same meaning as in claim 1, and

R_9 is hydroxyl or amino, optionally substituted straight-chain or branched
 saturated or unsaturated monoalkylamino or dialkylamino, optionally substituted
 arylamino, optionally substituted aralkylamino, an optionally substituted nitrogen-
 containing heterocyclic radical with five to seven ring atoms optionally containing
 a further hetero-atom replacing a ring carbon atom, optionally substituted
 aralkoxy, optionally substituted alkoxy or optionally substituted aryloxy.

5. Compounds according to claim 1 in which R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , m
 and n have the same meaning as in claim 1, and

R_9 is hydroxyl, amino, optionally substituted alkylamino, optionally substituted
 arylamino, optionally substituted aralkylamino, an optionally substituted nitrogen-
 containing heterocyclic radical with five to seven ring atoms optionally containing
 a further hetero-atom replacing a ring carbon atom, optionally substituted
 aralkoxy, optionally substituted alkoxy or optionally substituted aryloxy.

6. Compounds according to claim 1 as described hereinbefore with particular
 reference to any one of Examples 1 to 17, 27 to 49, 68 and 75 to 81.

7. Compounds according to claim 1 as described hereinbefore with particular
 reference to any one of Examples 18 to 26, 50 to 67, 69 to 74 and 82 to 91.

8. Compounds according to claim 1 which are hereinbefore specifically
 mentioned other than those according to Examples 1 to 91.

9. Compounds according to claim 8 other than those hereinbefore listed from
 N-acetyldehydrophenylalanyl-3-(5-methyl-2-thienyl)-dehydroalanine to N-acetyl-
 dehydro-3-(2-thienyl)alanyl-3-methyl-3-(2-thienyl)dehydroalanine hexylamide
 inclusive.

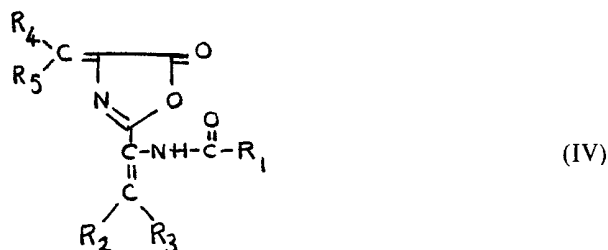
10. Compounds according to any one of claims 1 to 5 in the form of a racemic
 mixture.

11. Compounds according to any one of claims 1 to 5 in the form of an
 optically pure isomer.

12. Compounds according to any one of the preceding claims when in the form
 of a pharmaceutically acceptable salt.

13. A process for the production of a compound according to any of claims 1
 to 12 in which

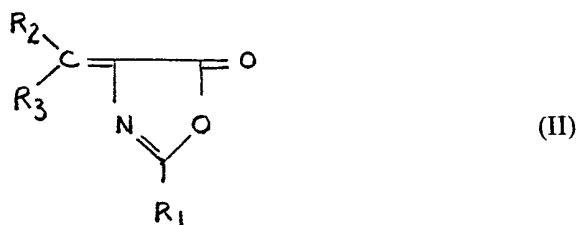
(a) when said compound is a compound of the formula (I) in which the radicals
 R_1 , R_2 , R_3 , R_4 and R_5 have the same meaning as in claim 1, R_9 is hydroxyl, n
 represents 0 and m represents 1, an oxazolone of the general formula



in which

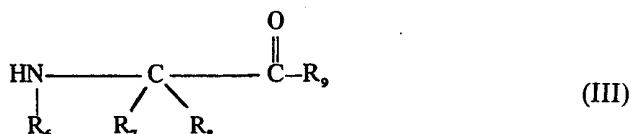
R_1 , R_2 , R_3 , R_4 and R_5 have the same meaning as in claim 1, is hydrolysed so as to yield said compound of the formula (I),

- 5 (b) when said compound is a compound of the general formula (I) in which R_1 , R_2 , R_3 , R_6 , R_7 , R_8 and R_9 meaning as in claim 1, n represents 1 and m represents 0, an oxazolone of the general formula 5



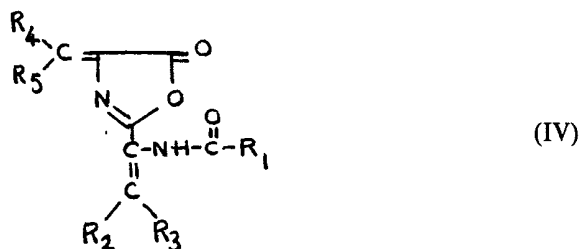
in which

- 10 R_1 , R_2 and R_3 have the same meaning as in claim 1 is reacted with a compound of the general formula 10



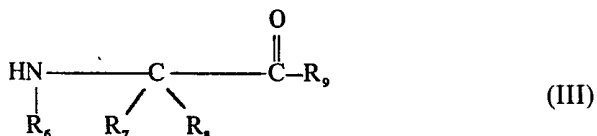
in which

- 15 R_6 , R_7 , R_8 and R_9 have the same meaning as in claim 1 so as to yield said compound of formula (I), or 15
(c) when said compound is a compound of the general formula (I) in which R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 have the same meaning as in claim 1 and both m and n represent 1, an oxazolone of the general formula



20 in which

R_1 , R_2 , R_3 , R_4 and R_5 have the same meaning as in claim 1 is reacted with a compound of the general formula 20



in which

- 25 R_6 , R_7 , R_8 and R_9 have the same meaning as in claim 1 so as to yield said compound of formula (I), 25
and the resulting compound of formula (I) or salt thereof, is optionally converted into a salt or a corresponding compound of formula (I), respectively.

- 30 14. A process according to claim 13 wherein said compound is a compound according to any one of claims 5, 6 and 9. 30

15. A process according to claim 13 or claim 14 in which the process is carried out at from 0 to 70°C.

16. A process according to any one of claims 13 to 15 in which the reaction is carried out in the presence of a diluent which is inert under the reaction conditions.
17. A process according to any one of claims 13 to 16 in which an acid or basic catalyst is employed.
- 5 18. A process for the production of a compound according to claim 13 substantially as hereinbefore described in any of Examples 18 to 26, 50 to 67, 69 to 74 and 82 to 91. 5
- 10 19. A process for the production of a compound according to claim 14 substantially as hereinbefore described in any one of Examples 1 to 17, 27 to 49, 68 and 75 to 81. 10
20. Compounds according to claim 1 whenever prepared by a process according to any one of claims 12 to 19.
- 15 21. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 12 and 20 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface-active agent. 15
22. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 12 and 20 in the form of a sterile and/or isotonic aqueous solution. 20
23. A composition according to claim 21 or claim 22 wherein said compound is a compound according to any one of claims 5, 6 and 9.
24. A composition according to any one of claims 20 to 22 containing from 1 to 90% by weight of the said active ingredient.
- 25 25. A medicament in dosage unit form comprising a compound according to any one of claims 1 to 12 and 20. 25
26. A medicament according to claim 25 wherein said compound is a compound according to any one of claims 5, 6 and 9.
- 30 27. A method of combating tumours and histolysis in non-human animals which comprises administering to the animals an active compound according to any one of claims 1 to 12 and 20 either alone or in admixture with a diluent or in the form of a medicament according to either of claims 25 or 26. 30
28. A method according to claim 27 wherein said compound is a compound according to any one of claims 5, 6 and 9 and the medicament is a medicament according to claim 26. 35
29. A method according to claim 27 or claim 28 in which the active compound is administered in an amount of 1 to 100 mg per kg body weight per day.
- 40 30. A method according to any one of claims 27 to 29 in which the active compound is administered subcutaneously, intracutaneously, intratumorally or peritumorally. 40

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