PATENT SPECIFICATION (11) 1 570 140

1 570 140

(21) Application No. 53179/77 (22) Filed 21 Dec. 1977
(31) Convention Application No. 2659154
(32) Filed 28 Dec. 1976
(31) Convention Application No. 2745673
(32) Filed 11 Oct. 1977 in
(33) Federal Republic of Germany (DE)
(44) Complete Specification published 25 June 1980
(51) INT CL³ A61K 31/74 37/02
(52) Index at acceptance
A5B 170 180 190 317 31Y 38Y 394 39X H

(72) Inventors EUGEN ETSCHENBERG
WOLFGANG OPITZ and
SIEGFRIED RADDATZ

(54) TUMOUR-RESOLVING AND HISTOLYTIC MEDICAMENTS COMPRISING DEHYDROOLIGOPEPTIDES

(71) We, TROPONWERKE GmbH & CO. KG., a company 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 use as tumour-resolving and/or histolytic medicaments, of dehydrooligopeptides, some of which are known.

The use of dehydrooligopeptides as medicaments has not previously been disclosed.

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 cystostatic 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.

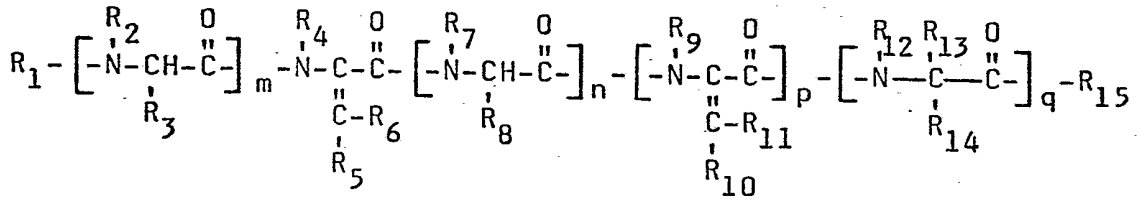
The action of cyclophosphamide may be mentioned here as an example of the generally toxic action. Thus, M. H. N. Tattersall and J. S. Tobias report in The Lancet 1976/II, No. 7994, page 1,071: "In the case of many anti-cancer agents, twice the dose which kills 10% of the animals (LD_{10}) is fatal for 90% of the animals (LD_{90}). Frei and Freireich (Advances in Chemotherapy *2* (1965), 269) were able to demonstrate the significance using agents such as cyclophosphamide in dosages which approached the toxicity rate (LD_{10}. The decisive characteristic of these experiments was the exponential increase observed in cell destruction with a low (arithmetic) increase in dose. The LD_{10} 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 generally widely-held view that "chemotherapy of cancer is only effective when it is not generally toxic."

The present invention thus relates to the use of compounds which are dehydrooligopeptides and their salts, as defined below, some of which are known, as medicaments with a tumour-resolving and histolytic action, which substantially avoid the above mentioned disadvantages of generally toxic actions; they are distinguished by a powerful histolytic action, which depends on the dose used, coupled with good general tolerance. It has been found that the compounds used in the process of the invention possess a very good tumour-resolving and/or histolytic action.

According to the present invention we provide a pharmaceutical composition

containing as an active ingredient a compound which is a dehydrooligopeptide of the following general formula or its salt



(I)

in which

R_1 is a hydrogen atom, optionally substituted alkanoyl, optionally substituted alkenoyl, alkoxycarbonyl, optionally substituted aroyl, optionally substituted aralkanoyl or aralkenoyl, aralkoxycarbonyl, carbamoyl, optionally substituted hetero-aroyl (as hereinafter defined), optionally substituted C_1 to C_6 alkylsulphonyl or optionally substituted arylsulphonyl,

R_2, R_7 and R_{12} are the same or different and each is a hydrogen atom or a C_1 to C_6 alkyl group,

R_3, R_8 and R_{13} are the same or different and each is a hydrogen atom, straight-chain or branched optionally substituted C_1 to C_6 alkyl, optionally substituted aryl optionally substituted aralkyl or aralkenyl, optionally substituted cycloalkyl or cycloalkenyl, indolylmethyl or an optionally substituted heterocyclicmethyl group having from four to seven ring members and one or two hetero-atoms, or one or more of R_2, R_7 and R_{12}, together with, in each case, the adjacent substituent R_3, R_8 or R_{14} respectively, form(s) a divalent alkylene chain having three or four carbon atoms,

R_4 and R_9 each represent a hydrogen atom or a C_1 to C_6 alkyl group, and

R_5 and R_{10} are the same or different and each is a hydrogen atom or optionally substituted C_1 to C_6 alkyl,

R_6 and R_{11} are the same or different and each is optionally substituted alkyl, optionally substituted aryl, an optionally substituted heterocyclic radical having from five to seven ring members and one or two hetero-atoms, optionally substituted aralkyl or optionally substituted aralkenyl, or

R_6 and/or R_{11}, together with R_5 or R_{10}, respectively represent an optionally substituted alkylene or alkenylene chain having from three to seven carbon atoms,

R_{14} is a hydrogen atom or optionally substituted C_1 to C_6 alkyl or, together with R_{13} and the carbon atom between them, represents an alicyclic radical having from four to seven carbon atoms,

R_{15} is hydroxyl, optionally substituted C_1 to C_6 alkoxy or alkenyloxy, optionally substituted C_1 to C_6 alkylthio or alkenylthio, optionally substituted arylthio, optionally substituted hydrazino, amino, optionally substituted C_1 to C_6 alkylamino or dialkylamino or alkenylamino or dialkenylamino or alkinylamino, optionally substituted arylamino, optionally substituted mono- or di-aralkylamino, a nitrogen-containing hetero-cyclic radical having from four to seven ring members optionally containing one or two further hetero-atoms and optionally substituted by C_1 to C_6 alkyl, hydroxyalkyl or phenyl, amino substituted by one or more optionally substituted alicyclic radicals having from three to seven ring members, or aralkyloxyamino, and m, n, p and q are the same or different and each represents a number 0 or 1, with the proviso that m, n, p and q may not all be 1 at the same time, in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent or molecular weight less than 200 except in the presence of a surface-active agent.

It is new and completely surprising that the aforesaid dehydrooligopeptides display such a highly pronounced tumour-resolving and histolytic action.

The active compounds are thus an enrichment of pharmacy.

Our copending application 53180/77 (Specification Serial No. 1,568,137) describes and claims certain other, novel, dehydrooligopeptides and their use in combating tumours and histolysis.

In the general formula (I), the radicals R_1 to R_{15} have the following preferred meanings:

An alkanoyl radical R_1 is preferably straight-chain or branched alkanoyl having from two to six carbon atoms. Examples which may be mentioned are: acetyl, propionyl, butyryl and pentanoyl.

An alkenoyl radical R_1 is preferably straight-chain or branched alkenoyl having from three to six carbon atoms. Examples which may be mentioned are: crotonyl and acrylyl.

Possible substituents of R_1 for the alkanoyl or alkenoyl radical R_1 are preferably: from one to three halogen atoms, preferably fluorine and chlorine atoms, methoxy, ethoxy and hetero-aryl. Examples which may be mentioned are chloro, trichloro, trifluoro and thiophenyl.

The straight-chain or branched (C_1 to C_6 alkoxy)-carbonyl radical R_1 is preferably methoxy, ethoxy, propoxy or butoxycarbonyl, especially tert.-butoxycarbonyl.

The optionally substituted aroyl radical R_1 is preferably benzoyl or naphthoyl.

The optionally substituted aralkanoyl or aralkenoyl radical R_1 preferably has from eight to twelve carbon atoms, in particular from eight to ten carbon atoms. Examples which may be mentioned are phenacetyl, phenpropionyl, phenisopropionyl, cinnamoyl, β-methylcinnamoyl and phenylbutanoyl.

Possible substituents in the aroyl, aralkanoyl or aralkenoyl radical R_1 are: from one to three halogen atoms, alkyl or alkoxy having up to three carbon atoms, especially methoxy, trifluoromethyl, nitro or hydroxyl, optionally acylated with a C_1 to C_6 organic acid radical.

The aralkoxycarbonyl radical R_1 denotes, in particular, aralkoxycarbonyl having from eight to ten carbon atoms, most preferably the benzyloxycarbonyl group.

The "optionally substituted hetero-aroyl" radical R_1 is defined as a heterocyclic radical which has five to seven ring members and can contain from one to three hetero atoms which are the same or different and each of which is a nitrogen, sulphur or oxygen atom and on which there is a carbonyl group. Examples of this radical which may be mentioned are pyridinecarbonyl, thiophenecarbonyl, furanecarbonyl, pyrrolecarbonyl, oxazolecarbonyl, thiazolecarbonyl and pyrazinecarbonyl, optionally substituted by one or more halogen atoms, preferably fluorine and/or chlorine atoms, alkoxy having from one to four carbon atoms or alkyl having from one to four carbon atoms.

The optionally substituted C_1 to C_6 alkylsulphonyl radical R_1 or arylsulphonyl radical R_1 preferably denotes methanesulphonyl or ethanesulphonyl, or benzenesulphonyl or toluenesulphonyl, respectively.

A C_1 to C_6 alkyl group is a radical R_2, R_7 or R_{12} preferably denotes methyl or ethyl.

If R_2, R_7 and R_{12}, together with, in each case, the adjacent substituent R_3, R_8 or R_{14}, respectively, form an alkylene chain with three to four carbon atoms, this means that R_2 forms a pyrrolidine or piperidine ring with the associated nitrogen atom, the adjacent —CH— group of the chain and R_3. Similarly in the case of R_7 and R_8 and, respectively, R_{12} and R_{13}.

A C_1 to C_6 alkyl group as the radicals R_4 and R_9 preferably denotes methyl or ethyl.

An optionally substituted straight-chain or branched alkyl or alkenyl radical R_3, R_8 and R_{13} denotes an aliphatic hydrocarbon radical, preferably having from one to six carbon atoms and optionally a double or triple bond, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl or tert.-butyl, pentyl and hexyl with their possible isomers, and furthermore vinyl, ethinyl, propenyl or crotyl.

Substituents of the alkyl radical R_3, R_8 or R_{13} which may be mentioned are: from one to three halogen atoms, hydroxyl groups, alkoxy groups having preferably from one to four carbon atoms, alkylthio groups having preferably from one to four carbon atoms, sulphhydryl groups, carbamido groups and carbonyl groups.

Examples which may be mentioned of such substituted alkyl groups are carboxymethyl, carboxyethyl, carbamoylmethyl, methylmercaptoethyl, trifluoromethyl, fluoromethyl, chloromethyl and hydroxymethyl.

An optionally substituted aryl group R_3, R_8 and R_{13} in the general formula I is preferably phenyl optionally substituted by one or more halogen atoms, trifluoromethyl groups, hydroxyl groups, alkoxy groups having from one to four

carbon atoms, alkyl groups having from one to four carbon atoms, nitro groups or acyloxy groups having from one to four carbon atoms.

An optionally substituted aralkyl or aralkenyl group R_3, R_8 and R_{13} preferably denotes phenylalkyl or phenylalkenyl having up to four carbon atoms and optionally a double or triple bond in the side chain, in particular a CH_2 group. The aralkyl or aralkenyl radical can be substituted by one or more halogen atoms, nitro, hydroxyl or methoxy or alkyl having from one to four carbon atoms.

An optionally substituted cycloalkyl or cycloalkenyl radical R_3, R_8 or R_{13} represents monocyclic, bicyclic and tricyclic cycloalkyl or cycloalkenyl having preferably from 3 to 10, in particular 3, 5 or 6, carbon atoms. Examples which may be mentioned are optionally substituted cyclopropyl, cyclopropenyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl and adamantyl.

The cycloalkyl or cycloalkenyl radical R_3, R_8 or R_{13} can be substituted by one or more halogen atoms, nitro or hydroxyl groups, or alkoxy or alkyl groups having from one to four carbon atoms in each case.

An optionally substituted heterocyclic-methyl group denotes, in particular, furfuryl, thenyl, pyrrolylmethyl, thiazolylmethyl, oxazolylmethyl, pyridinemethyl, piperidinemethyl, pyrazinemethyl or morpholinemethyl, optionally substituted by from one to three halogen atoms or alkyl or alkoxy groups having from one to three carbon atoms, or by one nitro group.

Optionally substituted alkyl radicals R_5, R_{10} and R_{14} denote alkyl having preferably from one to six, in particular one or two, carbon atoms, optionally substituted by halogen atoms, especially chlorine or fluorine atoms.

An optionally substituted alkyl group R_6 or R_{11} in the general formula I denotes a straight-chain or branched alkyl group having preferably from one to six carbon atoms, in particular from one to three carbon atoms, optionally substituted by from one to three halogen atoms, preferably chlorine or fluorine atoms, or by alkoxy groups having from one to four carbon atoms, in particular methoxy groups.

An optionally substituted aryl radical R_6 or R_{11} denotes, in particular, phenyl or naphthyl, optionally substituted by halogen atoms, preferably fluorine and chlorine atoms, alkyl or alkoxy groups having from one to four carbon atoms, methoxy and methyl groups being preferred, nitro groups, hydroxyl groups, C_1 to C_6 acyloxy groups having from one to four carbon atoms or amino, C_1 to C_6 alkylamino or di- C_1 to C_6 alkylamino groups, preferably dimethyl amino groups.

An optionally substituted heterocyclic radical R_6 or R_{11} denotes a heterocyclic radical having from five to seven ring members and one or two hetero-atoms each of which may be, in particular, nitrogen, sulphur or oxygen. Examples which may be mentioned are thienyl, furyl, pyrrolyl, pyridyl, imidazolyl, pyrazolyl, pyrimidyl, pyrazinyl and morpholinyl, optionally substituted by halogen atoms, alkyl or alkoxy groups having from one to four carbon atoms or hydroxyl, nitro or trifluoromethyl groups.

Optionally substituted aralkyl or aralkenyl groups R_6 and R_{11} denote, in particular, those having from seven to ten carbon atoms; phenylalkyl or phenylalkenyl groups having from one to four carbon atoms in the aliphatic moiety are particularly preferred, for example cinnamenyl and phenethyl, said aralkyl and aralkenyl groups being optionally substituted by one or more halogen atoms, alkyl or alkoxy groups having preferably from one to four carbon atoms, nitro groups and trifluoromethyl groups.

In the general formula I, the radicals R_6 and R_{11}, together with R_5 and R_{10} respectively, and the carbon atom, at the double bond, linking them, can form a cycloalkylidene ring or cycloalkenylidene ring having preferably from three to seven carbon atoms, in particular cyclohexylidene and cyclohexenylidene.

An optionally substituted alkoxy or alkenyloxy radical R_{15} in the general formula I denotes a straight-chain or branched alkoxy or alkenyloxy radical having from one to six carbon atoms, in particular from one to four carbon atoms, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy or tert.-butoxy, said alkoxy and alkenyloxy radicals being optionally substituted by one or more halogen atoms or alkoxy groups having one or two carbon atoms.

An optionally substituted alkylthio or alkenylthio group R_{15} is an alkylthio or alkenylthio group having from one to six carbon atoms, in particular from one to four carbon atoms. Substituents which may be mentioned are from one to three halogen atoms or alkoxy groups or a carboxyl group.

An optionally substituted arylthio group R_{15} is preferably phenylthio,

optionally substituted by one to three halogen atoms or C_1 to C_6 alkyl or alkoxy groups having preferably one or two carbon atoms in each case.

An optionally substituted hydrazine radical R_{15} means that the hydrazine radical can be substituted by C_1 to C_6 alkyl, optionally substituted aryl, preferably by phenyl, optionally substituted in turn by from one to three halogen atoms or C_1 to C_6 alkyl or alkoxy groups, or by a heterocyclic radical, having one or two nitrogen, oxygen and/or sulphur atoms, which in addition can be fused with a phenyl ring.

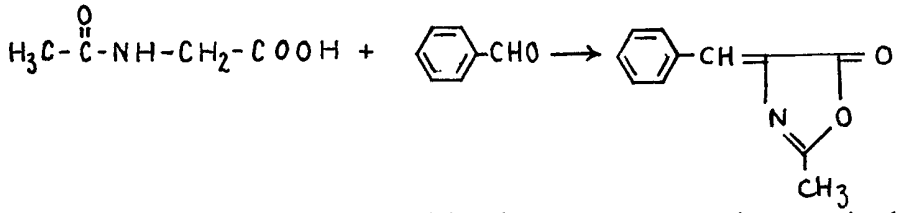
An optionally substituted monoalkylamino or monoalkenylamino or dialkenylamino or dialkylamino group R_{15} denotes, in each case, such a group having a straight-chain and/or branched alkyl or alkenyl moiety(ies) having preferably from one to six carbon atoms, such as, for example, methylamino, ethylamino, pentylamino and 1,1-dimethyl-2-propinylamino. The optional substituent(s) may, for example, be halogen atoms, hydroxyl groups, alkoxy groups having one or two carbon atoms, an amino or C_1 to C_6 monoalkylamino or dialkylamino group, a sulphonic acid radical or a phosphate radical or a heterocyclic radical, in particular a morpholine or imidazole ring.

An optionally substituted arylamino group R_{15} preferably denotes phenylamino, optionally substituted by one to three halogen atoms or alkyl or alkoxy groups with preferably one or two carbon atoms in each case.

An optionally substituted monoaralkylamino or diaralkylamino group R_{15} preferably denotes monophenylalkylamino or diphenylalkylamino, having from one to four carbon atoms in the aliphatic moiety in each case. The optional substituent(s) may be from one to three halogen atoms, or alkyl or alkoxy groups, having from one to four carbon atoms in each case.

An amino group substituted by alicyclic radicals having from three to seven ring members, R_{15}, denotes cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino and cycloheptylamino group, preferably the cyclohexylamino, or the correspondingly di-substituted amino group. This can be substituted by C_1 to C_6 alkyl, alkenyl, alkinyl or aryl groups.

Some of the starting compounds for the preparation of the compounds of the general formula I, that is to 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. The reaction of acetylglycine with benzaldehyde may be described here as an example. The reaction takes place according to the equation



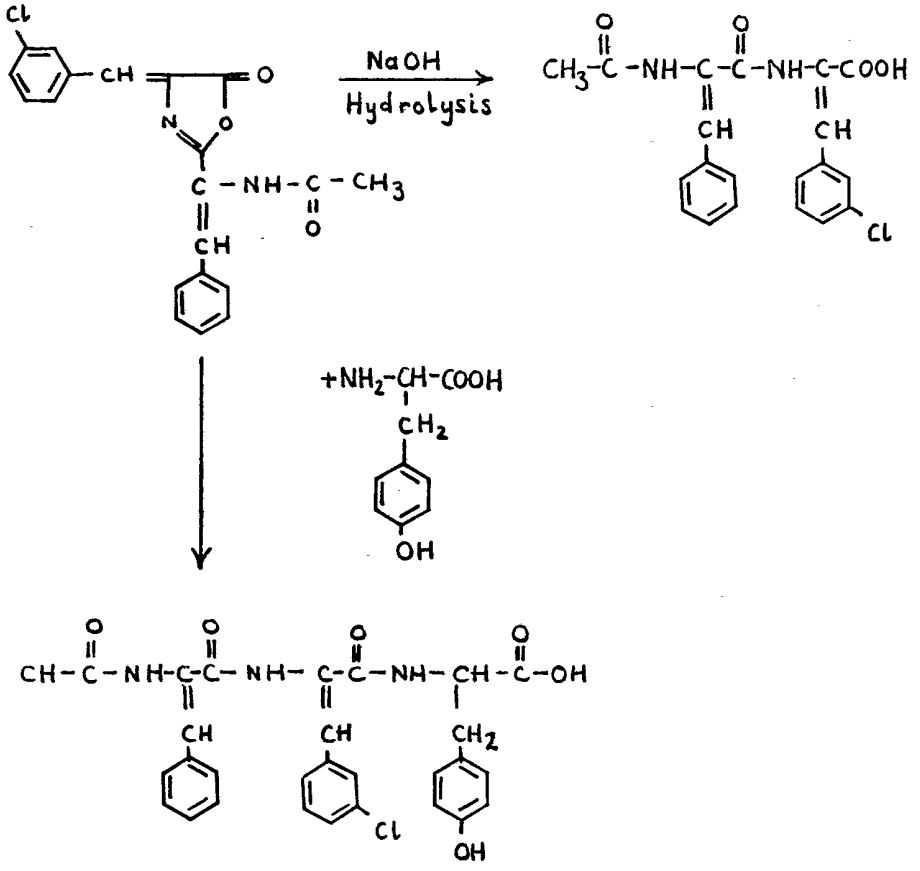
The reaction is carried out by mixing the two components in an equimolar ratio in the presence of a condensing agent, usually acetic anhydride, which conveniently at the same time serves as a solvent, and of a basic component, such as sodium acetate. After standing for several hours, the mixture is worked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

Further examples of starting compounds which may be mentioned are: 2 - methyl - 4 - (2 - thenylidene) - 5(4H) - oxazolone, 2 - methyl - 4 - (2 - naphthylmethyl) - 5(4H) - oxazolone, 4 - (4 - acetoxy - 3 - nitrobenzylidene) - 2 - methyl - 5(4H) - oxazolone, 4 - ethoxymethylene - 2 - phenyl - 5(4H) - oxazolone, 4 - cyclohexylmethylene - 2 - phenyl - 5(4H) - oxazolone, 4 - benzylidene - 2 - trifluoromethyl - 5(4H) - oxazolone, 4 - (1 - methylpropylidene) - 2 - phenyl - 5(4H) - oxazolone, 2 - phenyl - 4 - (2 - thenylidene) - 5(4H) - oxazolone, 2 - (3 - pyridyl) - 4 - (2 - thenylidene) - 5(4H) - oxazolone, 4 - (1 - methyl - 3 - phenyl - 2 - propenylidene) - 2 - phenyl - 5(4H) - oxazolone, 2 - (1 - acetamido - 2 - phenylvinyl) - 4 - (4 - dimethyl - aminobenzylidene) - 5(4H) - oxazolone, 4 - thenylidene - 2 - (3 - trifluoromethylphenyl) - 5(4H) - oxazolone, 4 - (2 - cyclohexenylidene) - 2 - phenyl - 5(4H) - oxazolone, 4 - (3 - phenyl - 2 - propylidene) - 2 - phenyl - 5(4H) - oxazolone, 4 - (α - methylbenzylidene) - 2 - phenyl - 5(4H) - oxazolone,

4 - cyclohexylidene - 2 - phenyl - 5(4H) - oxazolone, 4 - (3 - chlorobenzylidene) - 2 - (1 - acetamido - 2 - phenylethyl) - 5(4H) - oxazolone, 4 - (3 - chlorobenzylidene) - 2 - (L - 1 - tert. - butoxycarbonylamino) - 2 - phenylethyl - 5(4H) - oxazolone, 2 - (1 - acetamido - 2 - phenylvinyl) - 4 - (4 - hydroxybenzylidene) - 5(4H) - oxazolone, 2 - (1 - propenyl) - 4 - (2 - thenylidene) - 5(4H) - oxazolone, 2 - ethoxymethyl - 4 - (2 - thenylidene) - 5(4H) - oxazolone, 2 - phenyl - 4 - benzylidene - 5(4H) - oxazolone, 2 - (2 - phenylvinyl) - 4 - benzylidene - 5(4H) - oxazolone, 2 - [1 - acetamido - 2 - (2 - thienyl)vinyl] - 4 - (2 - thenylidene) - 5(4H) - oxazolone, 2 - [1 - acetamido - 2 - (2 - thienyl)vinyl] - 4 - (5 - methylthenylidene - 2) - 5(4H) - oxazolone, 2 - [1 - acetamido - 2 - (2 - thienyl)vinyl] - 4 - (4 - nitrobenzylidene) - 5(4H) - oxazolone, 2 - [2 - (3,4,5 - trimethoxyphenyl)vinyl] - 4 - (2 - thenylidene) - 5(4H) - oxazolone, 2 - methyl - 4 - (5 - nitrothenylidene - 2) - 5(4H) - oxazolone, 2 - (2 - thienyl) - 4 - (2 - thenylidene) - 5(4H) - oxazolone, 2 - phenyl - 4 - (4 - pyridylmethylene) - 5(4H) - oxazolone, 2 - (4 - nitrophenyl) - 4 - (2 - thenylidene) - 5(4H) - oxazolone, 2 - (3 - thienylmethyl - 4 - (2 - thenylidene) - 5(4H) - oxazolone and 2 - [1 - acetamido - 2 - (2 - thienyl)vinyl] - 4 - (α - methyl - 2 - thenylidene) - 5(4H) - oxazolone.

A number of the active compounds of formula (I) are new; however, they can be prepared by known processes (compare D. G. Doherty et al., J. biol. Chem. *147* (1943), 617). They are obtained, for example, either by alkaline hydrolysis of the corresponding 2,4-disubstituted 5(4H)-oxazolones or by aminolysis of the oxazolones with the alkali metal salts, esters or amides of aminoacids.

The reactions may be illustrated using the syntheses of N-acetyldehydrophenylalanyldehydro-(3-chlorophenyl) alanine and N-acetyldehydrophenylalanyldehydro - (3 - chlorophenyl)alanyl - L - tyrosine as examples:



The reaction is usually carried out by stirring, or leaving the reactant or reactants to stand, in a diluent, such as aqueous acetone, tetrahydrofurane, dimethylformamide or an alcohol, usually at room temperature or slightly elevated

temperature, the reaction time depending on the reactivity of the reactants, for example, the reaction time may be from half an hour to twenty hours.

The mixture is worked up by acidifying with, for example, HCl, and evaporating off the organic solvent, whereupon the end product usually precipitates.

If the reaction times are extremely long, partial racemisation cannot be excluded, as can be seen from the optical rotation values of the products obtained.

In some cases it has proved to be appropriate, for reasons of purity and yield, to use an aminoacid ester instead of the free aminoacid in the aminolysis and to hydrolyse this ester after the condensation.

Examples which may be mentioned of the active compounds are: N - benzoyldehydro - β - (2 - thienyl)alanine methyl ester, N - acetyldehydro - β - (2 - thienyl)alanine ethyl ester, N - acetyldehydrophenylalanine, N - phenylacetyldehydro - β - (thienyl)alanine, N - acetyl - DL - phenylalanyldehydro - (3 - chlorophenyl)alanine, N - tert. - butoxycarbonyl - L - phenylalanyldehydro - (3 - chlorophenyl)alanine, L - phenylalanyldehydro - (3 - chlorophenyl)alanine, N - acetyldehydrophenylalanyl - L - proline, N - acetyldehydrophenylalanyl - D - proline, N - acetyldehydrophenylalanyl - D - tyrosine, N - acetyldehydrophenylalanyl - L - leucine, N - acetyldehydrophenylalanyl - L - methionine, N - acetyldehydrophenylalanyl - L - aspartic acid, N - acetyldehydrophenylalanyl - L - glutamine, N - acetyldehydrophenylalanyl - DL - 3 - fluoroalanine, N - acetyldehydrophenylalanyl - L - serine, N - acetyldehydrophenylalanyl - L - tyrosine, N - acetyldehydrophenylalanylglycine, N - acetyldehydrophenylalanyl - L - (p - nitrophenyl)alanine, N-acetyldehydrophenylalanyl - DL - (p - chlorophenyl)alanine, N - trifluoroacetyldehydrophenylalanyl - 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 - cinnamenylalanyl - L - tyrosine, N - acetyldehydro - 3 - (2 - naphthyl) - alanyl - L - tyrosine, N - benzoyldehydro - 3 - cyclohexylalanyl - L - tyrosine, N - benzoyldehydro - 3 - benzyl - 3 - methylalanyl - L - leucine, N - trifluoroacetyldehydrophenylalanyl - L - tyrosine tert. - butyl ester, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - proline, N - acetyldehydrophenylalanine (1 - carboxy - 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 - tyrosine, N - phenacetyldehydro - 3 - (2 - thienyl)alanyl - L - leucine methyl ester, N - phenacetyldehydro - 3 - (2 - thienyl)alanyl - L - leucine, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - (p - nitrophenyl)alanine, N - nicotinoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - (3 - trifluoromethylbenzoyl)dehydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - proline, N - nicotinoyldehydro - 3 - (2 - thienyl)alanyl - L - (p - nitrophenyl)alanine, N - benzoyl - 3 - methyl - 3 - (2 - thienyl)dehydroalanyl - L - tyrosine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - D - tyrosine, N - cinnamoyldehydrophenylanalylglycine, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - phenylalanine, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - leucine, N - acetyldehydro - 3 - (2 - thienyl) - L - phenylalanine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - leucine, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine methyl ester, N - acetyldehydro - 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 - tyrosine N′ - cyclohexylamide, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine N′,N′ - dimethylamide, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine morpholide, N - acetyldehydrophenylalanyldehydrotyrosine, N - acetyldehydrophenylalanyldehydro - (p - nitrophenyl)alanine, N - acetyldehydrophenylalanyldehydro - (p - fluorophenyl)alanine, N - acetyldehydrophenylalanyldehydro - (4 - dimethylaminophenyl)alanine, N - acetyldehydrophenylalanyldehydro - (3 - chlorophenyl)alanine, N - acetyldehydrophenylalanyldehydro - (3 - chlorophenyl)alanyl - L - tyrosine, N - acetyldehydrophenylalanyl - 3 - phenylserine, N - benzoyldehydrophenylalanylglycine, N - benzoyldehydrophenylalanyl - 3 -

phenylserine, N - acetyldehydroleucylglycine, N - carbobenzoxyglycyldehydrophenylalanine, N - acetyldehydrophenylalanyl - L - alanine, N - acetyldehydrophenylalanyl - L - phenylalanine, N - acetyl - DL - phenylalanyldehydrophenylalanine, N - acetyl - dehydrophenylalanyldehydrophenylalanine, N - benzoyldehydrophenyl - alanyldehydrophenylalanine, N - benzoyldehydrophenylalanyldehydro - tyrosine, N - acetyldehydroleucyldehydrophenylalanine, N - carbobenzoxylglycyldehydrophenylalanyl - L - glutamic acid, N - carbobenzoxyglycyldehydrophenylalanylphenylserine, N - acetyldehydrophenyl - alanyldehydrophenylalanyl - L - alanine, - glycine, - L - leucine, - L - phenylalanine, - L - tyrosine, - L - proline, - 3 - phenylserine, - L - glutamic acid and - L - cystine, N - acetyldehydrophenylalanyl - D - glutamic acid, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosinebenzyl ester, N - benzoyldehydro - 3 - (2 - thienyl) - L - tyrosine N - benzylamide, N - acetyldehydro - 3 - (2 - thienyl)alanine N′ - methylamide, N - acetyldehydro - 3 - (2 - thienyl)alanine morpholide, N - acetyldehydro - 3 - (2 - thienyl)alanine, N - cinnamoyldehydrophenylalanyl - L - tyrosine, N - benzoyldehydroisoleucyl - L - tyrosine, N - cinnamoyldehydrophenyl - alanine N′ - methylamide, N - cinnamoyldehydrophenylalanine 1,1 - dimethyl - 2 - propinylamide, N - cinnamoyldehydrophenylalanine morpholide, N - benzoyl - 3 - methyl - 3 - cinnamenyldehydroalanyl - L - tyrosine, N - benzoyl - 3 - methylphenyldehydroalanyl - L - leucine, N - acetyldehydro - 3 - (2 - thienyl)alanine N′ - methylamide, and N - acetyl - dehydro - 3 - (2 - thienyl)alanine N′ - 1,1 - dimethyl - 2 - propinylamide.

Additional examples of active compounds which may be mentioned are: N - crotonyldehydro - 3 - (2 - thienyl) - alanine, -alanine methyl ester, -alanine thioethyl ester and alanine thiomethyl ester, N - ethoxyacetyldehydro - 3 - (2 - thienyl)alanine methyl ester, N - acetyldehydrophenylalanyl - 3 - (5 - methylthienyl - 2(dehydroalanine, N - benzoyldehydrophenylalanine methyl ester, N - benzoyldehydrophenylalanine thioethyl ester, N - acetyldehydrophenylalanine thioethyl ester, N - acetyldehydrophenylalanine thiomethyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanine thiomethyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanine 2 - carboxythioethyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanine thioethyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanine 4 - chlorothiophenyl ester, N(3 - trifluoromethylbenzoyl)dehydro - 3 - (2 - thienyl)alanine thioethyl ester, N - acetyldehydrophenylalanine - 3 - (3 - chlorophenyl)dehydroalanine thiomethyl ester, N - cinnamoyldehydrophenylalanine thiomethyl ester, N - (3 - trifluoromethylbenzoyl) - 3 - (2 - thienyl)alanine methyl ester, N - crotonoyldehydro - 3 - (2 - thienyl)alanine, N - acetyldehydro - 3 - (2 - thienyl)alanyldehydro - 3 - (2 - thienyl)alanine, N - benzoyl - dehydro - 3 - (2 - thienyl)alanine, N - (3 - trifluoromethylbenzoyl) - dehydro - 3 - (2 - thienyl)alanine, N - acetyldehydro - 3 - (2 - thienyl)alanyldehydro - 3 - (4 - nitrophenyl)alanine, N - benzoyldehydrophenyl - alanine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - N - methylglycine, N - (3,4,5 - trimethoxycinnamoyl)dehydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - crotonyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - acetyldehydro - 3 - (5 - nitro - 2 - thienyl)alanyl - L - tyrosine, N - (2 - thenoyl)dehydro - 3 - (2 - thienyl)alanyl - L - tyrosine, N - crotonoyl - dehydro - 3 - (2 - thienyl)alanyl - L - leucine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - O - methyl - L - tyrosine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - tryptophan, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - glycine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - 2 - (4 - hydroxy - phenyl) - D - glycine, N - benzoyldehydrophenylalanyl - L - leucylglycine 4 - methoxyphenylamide, N - acetyldehydro - 3 - (2 - thienyl)alanyl - 2 - (1,4 - cyclohexanedien - 1 - yl) - D - glycine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - glutamic acid, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - leucine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - phenyl - alanine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - β - alanine, N - benzoyldehydrophenylalanylglycine, N - acetyldehydro - 3 - (2 - tnienyl) - alanyl - DL - valine, N - (2 - thenoyl)dehydro - 3 - (2 - thienyl)alanyl - 2 - (1,4 - cyclohexanedien - 1 - yl) - D - glycine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - threonine, N - acetyldehydro - 3 - (2 - thienyl)alanyl - L - aspartic acid, N - benzoylde - hydrophenylalanine - L - tryptophan, N - (3 - trifluoromethylbenzoyl)dehydro - 3 - (2 - thienyl)alanyl - L - leucine, N - (3 - trifluoromethylbenzoyl)dehydro - 3 - (2 - thienyl) - alanyl -

L - phenylalanine, N - (3 - trifluoromethylbenzoyl)dehydro - 3 - (2 - thienyl)alanylglycine, 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 benzyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanyl - 3 - (2 - thienyl)dehydroalanyl - 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, N - benzoyldehydrophenylalanyl - L - leucylglycine amide, N - benzoyldehydrophenylalanyl - L - propyl - L - leucylglycine amide, N - acetyldehydro - 3 - (2 - thienyl)alanyl - 2 - methylalanine methyl ester, N - acetyldehydro - 3 - (2 - thienyl)alanyl - 2 - methylalanine, the salt of N - acetyldehydro - 3 - (2 - thienyl)alanine with methylamine, with 1,1 - dimethylpropargylamine and with lithium, 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 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 - aminohexane - amide, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine 4 - aminobutane - amide, N - benzoyldehydro - 3 - (2 - thienyl)alanyl - L - tyrosine hydrazide, N - ethoxyacetyldehydro - 3 - (2 - thienyl)alanine 4 - methylpiperazide, N - ethoxyacetyldehydro - 3 - (2 - thienyl)alanine anilide, N - ethoxyacetyldehydro - 3 - (2 - thienyl)alanine cyclohexylamide, N - ethoxyacetyldehydro - 3 - (2 - thienyl)alanine amide, N - crotonoyldehydro - 3 - (2 - thienyl)alanine 4 - methylpiperazide, N - crotonoyldehydro - 3 - (2 - thienyl)alanine 3 - dimethylaminopropylamide, N - crotonoyldehydro - 3 - (2 - thienyl)alanine 6 - aminohexane - amide, N - crotonoyldehydro - 3 - (2 - thienyl)-alanine 4 - hydroxyanilide, N - acetyldehydrophenylalanyl - 3 - (2 - thienyl)-dehydroalanine methylamide, N - (3 - trifluoromethylbenzoyl)dehydro - 3 - (2 - thienyl)alanine anilide, N - (3 - trifluoromethylbenzoyl)dehydro - 3 - (2 - thienyl)alanine 4 - methylpiperazide, N - (3 - trifluoromethylbenzoyl)dehydro - 3 - (2 - thienyl)alanine 2 - dimethylaminopropylamide, N - (3 - trifluoromethylbenzoyl)dehydro - 3 - (2 - thienyl)alanine amide, N - acetyldehydro - 3 - (2 - thienyl)alanyl - 3 - methyl - 3 - (thienyl)dehydroalanine hexylamide, N - nicotinoyl - 3 - (2 - thienyl)dehydroalanine proparglyamide, N - (2 - thienylacetyl)dehydro - 3 - (2 - thienyl)alanine 3 - dimethylaminopropylamide, N - benzoyldehydro - 3 - (2 - thienyl)alanine 3 - dimethylaminopropylamide, N - benzoyldehydro - 3 - (2 - thienyl)alanine anilide, N - benzoyldehydro - 3 - (2 - thienyl)alanine methylamide, N - benzoyldehydro - 3 - (2 - thienyl)alanine hexylamide, N - benzoyldehydro - 3 - (2 - thienyl)alanine propargylamide, N - benzoylhydro - 3 - (2 - thienyl)alanine hydrazide, N - benzoyldehydrophenylalanine anilide, methylamide,1,1-dimethylproparglyamide, hexylamide, cyclohexylamide, morpholide, 4-methoxyphenylhydrazide, 2-phenylcyclopropylamide, 3,4,5-trimethoxyanilide, 3-dimethylaminopropylamide and propargylamide, N - acetyldehydro - 3 - (2 - thienyl)alanine 2 - (4 - imidazolyl)ethylamide, hexylamide, 2-phenylcyclopropylamide, benzylamide, 3-dimethylaminopropylamide, piperidide, 4-methylpiperazide, 4-phenylpiperazide, 4-(2-hydroxyethyl)piperazide, amide, 2,2-dimethylhydrazide, anilide, 4-methylcyclohexylamide, 3-morpholinopropylamide, 1-phenylethylamide, 3-

carboxypropylamide, hydrazide, 2-sulphonic acid ethylamide, 1-ethinylcyclohexylamide, benzyloxyamide, 2-hydroxyethylamide, esterified with phosphoric acid, and morpholide, N - acetyldehydro - 3 - (2 - thienyl)alanine propargylamide, N - acetyldehydro - 3 - (2 - thienyl)alanine 3,4,5 - trimethoxyanilide and N - acetyldehydro - 3 - (2 - thienyl)alanine - 2 - (benzothiazol - 2 - yl)hydrazide.

The compounds can exist both in the form of a racemate and in the form of isolated optical isomers having a definite absolute configuration. In addition, cis/trans isomers can occur in the synthesis, for example, of N - benzoyldehydrophenylalanyl - L - leucine 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 could be demonstrated by ^{13}C-NMR spectroscopy.

The active compounds have a tumour-resolving and histolytic action, which depends on the dose which is given, preferably by local administration. By local administration there are to be understood herein as being included the following types of administration: subcutaneous, intracutaneous, intratumoral and peritumoral administration.

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.

However, the tumour tissue can also be broken down whilst the external skin remains completely intact.

The activity of the third component of the immunohaemolytic complement system is considerably decreased.

The necrotic tissue is sharply divided from the surrounding healthy tissue; it appears macroscopically and microscopically as if it were "stamped out".

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 in the order of size of 300 mg/kg.

A daily injection of 80 mg/kg in rabbits over a period of 27 days was tolerated completely without reaction.

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 veterinary medicine which prevent and interfere with the course of normal biological functions.

Such tissues are, for example: benign and malignant tumours of solid and cystic nature, papillomas, adenomas and cystadenomas; adenocarcinomas, including those of the cirrhosis type; basal-cell carcinomas; sarcomas, such as, for example, fibrosarcoma, liposarcoma, myxosarcoma, rhabdomyosarcoma, chondrosarcoma, lymphosarcoma and reticulosarcomoa, as well as Hodgkin's disease; embryonic tumours, such as, for example, neuroblastoma, nephroblastoma, teratoma, adamantinoma and retroblastoma, haemangioma, chordoma, odontoma and craniopharyngioma; harmatomas, such as, for example, lymphoangioma, exostoses and neurofibromatoses; melanomas; lymphomas; hepatoblastomas; mastocarcinoma; cervical carcinoma; choriocarcinoma and adrenoacanthoma; leiomyoma and andreoblastoma; 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; haemangioblastoma, osteoblastoma and Ewing's tumour; multiple myeloma; fungoid mucosis; Burkitt's tumour; leucaemias, such as, 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, above all, the metastases of all tumour forms which are accessible via surgical intervention using a local injection.

The active compounds also exhibit therapeutically valuable actions in the case of osteosarcoma; however, in this case the compounds must be injected under a pressure of up to 600 atmospheres gauge using a special device.

In addition, the active compounds 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 clavi and onychomycoses and scar tissue and for the therapy and prophylaxis of emboli and thromboses.

The active compounds can also be used for resolving moles, atheromas and lipomas and for removing deep abscesses which, under certain circumstances, are fistulous.

The active compounds can additionally be used for the regeneration of cavernomas and tuberculomas.

The active compounds 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, above all those which are caused by infections by bacteria, fungi and pathogens of tropical diseases, such as, for example, those of leichmaniasis, framboesia, pinta and the like.

As stated above, the invention also relates to the use in veterinary medicine of the active compounds.

The present invention provides a pharmaceutical composition containing as active ingredient a compound of formula (I) or its salt 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 (preferably less than 350) except in the presence of a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient a compound of formula (I) or its salt in the form of a sterile and/or physiologically isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising a compound of formula (I) or its salt.

"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. 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.

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.

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.

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. chlorofluorohydrocarbons.

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 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.

For parenteral administration, solutions and emulsions should be sterile, and, if appropriate, blood-isotonic. Preferred injection solutions are those having a pH of from 7.0 to 9.5, most preferably from 8 to 9. The active compounds 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.

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

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

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.

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

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

In addition to a compound of formula (I) or its salt, 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 formula (I) or salts thereof.

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.

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.

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.

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).

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 formula (I) or its salt alone or in admixture with a diluent or in the form of a medicament according to the invention.

It is envisaged that these active compounds will be adminstered 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.

In general, it has proved advantageous to administer amounts of from 1 mg to 100 mg preferably from 2 to 40 mg, per kg of body weight per day to achieve 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 limit 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.

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-Benzoyldehydro-β-(2-thienyl)alanine Methyl Ester

2 g of 2 - phenyl - 4 - (2 - thenylidene) - 5(4H) - oxazolone are dissolved in 50 ml of absolute methanol and the solution is kept at room temperature for 16 hours. The reaction solution is then evaporated, the residue is taken up in glacial acetic acid/ethylene chloride, the mixture is filtered and the product is crystallised by concentrating the filtrate. 2 g (88.8% of theory) of N - benzoyldehydro - β - (2 - thienyl)alanine methyl ester of melting point 162°C are obtained.

$C_{15}H_{13}NO_3S$
calculated: C 62.70% H 4.56% N 4.87% S 11.16%
found: C 62.81% H 4.67% N 4.85% S 11.18%

Example 2

N-Acetyldehydro-β-(2-thienyl)alanine Ethyl Ester

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H) - oxazolone and absolute ethanol analogously to Example 1; melting point 109—110°C.

Yield 82%.
$C_{11}H_{13}NO_3S \cdot H_2O$
calculated: C 51.42% H 5.8% N 5.4% S 12.5%
found: C 41.80% H 6.0% N 5.4% S 12.7%

Example 3

N-Acetyldehydrophenylalanine

is obtained by saponifying 2 - methyl - 4 - benzylidene - 5(4H) - oxazolone (preparation in the literature: Beilstein X, page 683); melting point 188—190°C.

Example 4

N-Crotonoyldehydro-3-(2-thienyl)alanine Methyl Ester

is obtained from 2 - (1 - propenyl) - 4 - (2 - thenylidene) - 5(4H) - oxazolone and methanol analogously to Example 1.

Melting point: 174—176°C; yield: 54% of theory.
$C_{12}H_{13}NO_3S$
calculated: C 57.35% H 5.21% N 5.57% S 12.76%
found: C 57.45% H 5.31% N 5.68% S 12.55%

Example 5

N-Crotonoyldehydro-3-(2-thienyl)alanine Thioethyl Ester

is obtained from 2 - (1 - propenyl) - 4 - (2 - thenylidene) - 5(4H) - oxazolone and ethylmercaptan analogously to Example 1

Melting point: 176°C; yield: 80% of theory.
$C_{13}H_{15}NO_2S_2$
calculated: C 55.49% H 5.33% N 4.98% S 22.79%
found: C 55.61% H 5.44% N 4.93% S 22.96%

Example 6

N-Crotonoyldehydro-3-(2-thienyl)alanine Thiomethyl Ester

is obtained from 2 - (1 - propenyl) - 4 - (2 - thenylidene) - 5(4H) - oxazolone and methylmercaptan analogously to Example 1.

Melting point: 178—180°C; yield: 63% of theory.
$C_{12}H_{13}NO_2S_2$
calculated: C 53.91% H 4.90% N 5.24% S 23.99%
found: C 52.52% H 4.91% N 5.25% S 24.21%

Example 7

N-Ethoxyacetyldehydro-3-(2-thienyl)alanine Methyl Ester

is obtained from 2 - ethoxymethyl - 4 - (2 - thenylidene) - 5(4H) - oxazolone and methanol analogously to Example 1.

Melting point: 102°C; yield: 38% of theory.

$C_{12}H_{15}NO_4S$

calculated: C 53.52% H 5.61% N 5.20% S 11.91%
found: C 53.68% H 5.52% N 5.21% S 11.78%

Example 8

N-Benzoyldehydrophenylalanine Methyl Ester

is obtained from 2 - phenyl - 4 - benzylidene - 5(4H) - oxazolene and methanol analogously to Example 1.

Melting point: 141—142°C; yield: 65% of theory.

$C_{17}H_{15}NO_3$

calculated: C 72.6% H 5.3% N 5.0%
found: C 72.7% H 5.3% N 4.9%

Example 9

N-Acetyldehydrophenylalanine Thioethyl Ester

is obtained from 2 - methyl - 4 - benzylidene - 5(4H)oxazolone and ethylmercaptan analogously to Example 1 (in an autoclave for one week at 50°C).

Melting point: 106—107°C; yield: 7% of theory.

$C_{13}H_{15}NO_2S$

calculated: C 62.62% H 6.06% N 5.62% S 12.86%
found: C 62.89% H 6.03% N 5.65% S 12.96%

Example 10

N-Acetyldehydrophenylalanine Thiomethyl Ester

is obtained from 2 - methyl - 4 - benzylidene - 5(4H)oxazolone and methylmercaptan, in an autoclave for one week at 50°C, analogously to Example 1.

Melting point: 157—158°C; yield: 51% of theory.

$C_{12}H_{13}NO_2S$

calculated: C 61.25% H 5.57% N 5.95% S 13.63%
found: C 61.31% H 5.62% N 5.91% S 13.51%

Example 11

N-Acetyldehydro-3-(2-thienyl)alanine Thiomethyl Ester

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and methylmercaptan, in an autoclave at 70°C, analogously to Example 1.

Melting point: 144—145°C; yield: 45% of the theory.

$C_{10}H_{11}NO_2S_2$

calculated: C 49.77% H 4.59% N 5.80% S 26.57%
found: C 49.61% H 4.68% N 5.75% S 26.41%

Example 12

N-Acetyldehydro-3(2-thienyl)alanine 3-carboxythioethyl Ester

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and 3-mercaptopropionic acid, in an autoclave, analogously to Example 1.

Melting point: 172—174°C; yield: 66.9% of theory.

$C_{12}H_{13}NO_4S_2$

calculated: C 48.14% H 4.38% N 4.68% S 21.42%
found: C 48.28% H 4.40% N 4.71% S 21.44%

Example 13

N-Acetyldehydro-3-(2-thienyl)alanine Thioethyl Ester

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and ethylmercaptan analogously to Example 1.

Melting point: 110—112°C; yield: 98% of theory.

$C_{11}H_{13}NO_2S_2$
calculated: C 53.18% H 3.60% F 14.9% N 3.50%
found: C 51.84% H 5.12% N 5.57% S 24.97%

Example 14

N-Acetyldehydro-3-(2-thienyl)alanine 4-chlorothiophenyl Ester

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and 4-chlorophenylmercaptan, in the presence of triethylamine, analogously to Example 1.

Melting point: 177—179°C; yield: 48.8% of theory.

$C_{15}H_{12}ClNO_2S_2$
calculated: C 53.33% H 3.58% Cl 10.49% N 4.15% S 18.98%
found: C 53.45% H 3.57% Cl 10.63% N 4.13% S 19.10%

Example 15

N-(3-Trifluoromethylbenzoyl)dehydro-3-(2-thienyl)alanine Thioethyl Ester

is obtained from 2 - (3 - trifluoromethylphenyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and ethylmercaptan, in the presence of NaH, analogously to Example 1.

Melting point: 139—140°C; yield: 50% of theory.

$C_{17}H_{14}F_3NO_2S_2$
calculated: C 52.98% H 3.66% F 14.79% N 3.63% S 16.64%
found: C. 53.18% H 3.60% F 14.9% N 3.50% S 16.63%

Example 16

N-Benzoyldehydrophenylalanine Thioethyl Ester

is obtained from 2 - phenyl - 4 - benzylidene - 5(4H)oxazolone and ethylmercaptan analogously to Example 1.

Melting point: 150°C (decomposition); yield: 47% of theory.

$C_{18}H_{17}NO_2S$
calculated: C 69.43% H 5.50% N 4.50% S 10.30%
found: C 69.27% H 5.55% N 4.54% S 10.32%

Example 17

N-Acetyldehydrophenylalanine-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, analogously to Example 1.

Melting point: 166—167°C; yield: 38.8% of theory.

$C_{21}H_{19}ClN_2O_3S$
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%

Example 18

N-Cinnamoyldehydrophenylalanine Thiomethyl Ester

is obtained from 2 - (2 - phenylvinyl) - 4 - benzylidene - 5(4H)oxazolone and methylmercaptan, in an autoclave for one week, analogously to Example 1.

Melting point: 182—183°C; yield: 28.5% of theory.

$C_{19}H_{17}NO_2S$

calculated C 70.56% H 5.30% N 4.33% S 9.91%
found: C 70.40% H 5.39% N 4.41% S 9.61%

Example 19

N-(3-Trifluoromethylbenzoyl)-3-(2-thienyl)alanine Methyl Ester

is obtained from 2 - (3 - trifluoromethylphenyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and methanol, in the presence of sodium hydride, analogously to Example 1.

Melting point: 117—118°C; yield: 64.8% of theory.

$C_{16}H_{12}F_3NO_3S$

calculated: C 54.08% H 3.40% F 16.04% S 9.03%
found: C 54.01% H 3.47% F 15.90% S 9.05%

Example 20

N-Phenylacetyldehydro-β-(thienyl)alanine

is obtained by saponifying 2 - benzyl - 4 - (2 - thenylidene) - 5(4H) - oxazolone.

Melting point: 193—195°C; yield: 8.2% of theory.

$C_{15}H_{13}NO_3S$

calculated: C 62.70% H 4.56% N 4.88% S 11.16%
found: C 62.68% H 4.55% N 4.96% S 11.26%

Example 21

DL-N-Acetylphenylalanyldehydro-(3-chlorophenyl)alanine

1.8 g (0.005 mol) of 2 - (1 - acetamido - 2 - phenylethyl) - 4 - (3 - chlorobenzylidene) - 5(4H) - oxazolone are suspended in 7 ml of acetone, and 7.5 ml of 2 N NaOH are added.

After stirring for half an hour, the reaction solution is acidified to pH 3 with citric acid and the precipitate which separates out is filtered off and washed until neutral.

Melting point: 195—196°C; yield: 1.6 g (84.2% of theory).

$C_{20}H_{19}ClN_2O_4$

calculated: C 62.10% H 4.95% Cl 9.17% N 7.24%
found: C 62.31% H 4.77% Cl 9.03% N 7.31%

Example 22

L-N-tert.-Butoxycarbonylphenylalanyldehydro-(3-chlorophenyl)alanine

is obtained from 2 - (1 - tert. - butoxycarbonylamido - 2 - phenylethyl) - 4 - (3 - chlorophenyl) - 5(4H) - oxazolone analogously to Example 21, with recrystallisation from aqueous acetone.

Melting point: 173°C (decomposition), $[\alpha]_D^{20}$ +78.6° (c=1; dimethylformamide), yield: 83.3% of theory.

$C_{23}H_{25}ClN_2O_5$

calculated: C 62.90% H 5.66% Cl 7.97% N 6.30%
found: C 62.26% H 5.66% Cl 7.95% N 6.44%

Example 23

L-Phenylalanyldehydro-(3-chlorophenyl)alanine

is obtained from 2.5 g of the above compound by dissolving in 15 ml of anhydrous trifluoroacetic acid, allowing the mixture to stand at room temperature for one hour, evaporating, taking up the residue in water, adjusting the pH of the solution to 8 with NH_3 and evaporating the solution until crystallisation starts.

Melting point: 235—236°C; $[\alpha]_D^{20}$ −31.5° (c=1; dimethylformamide); yield: 1.7 g (89.5% of theory).

$C_{18}H_{17}ClN_2O_3$
calculated: C 62.70% H 4.97% Cl 10.28% N 8.13%
found: C 62.55% H 5.35% Cl 10.15% N 8.19%

Example 24

N-Acetyldehydro-3-(2-thienyl)alanine

is obtained from 4-thenylidene-2-methyl-5(4H)oxazolone analogously to Example 21.

Melting point: 222—223°C; yield: 5.7% of theory.

$C_9H_9NO_3S$
calculated: C 51.17% H 4.30% N 6.63% S 15.18%
found: C 51.21% H 4.37% N 6.65% S 15.32%

Example 25

N-Acetyldehydrophenylalanyl-3-(5-methylthienyl-2)dehydroalanine

is obtained from 4 - (5 - methylthenylidene) - 2 - (1 - acetamido - 2 - phenylvinyl) - 5(4H)oxazolone analogously to Example 21.

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 26

N-Crotonoyldehydro-3-(3-thienyl)alanine

is obtained from 2 - (1 - propenyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone analogously to Example 21.

Melting point: 226°C; yield: 88% of theory.

$C_{11}H_{11}NO_3S$
calculated: C 55.68% H 4.67% N 5.90% S 13.51%
found: C 55.23% H 4.71% N 6.03% S 13.96%

Example 27

N-Acetyldehydro-3-(2-thienyl)alanyldehydro-3-(2-thienyl)alanine

is obtained from 2 - [1 - acetamido - 2 - (2 - thienyl)vinyl] - 4 - (2 - thenylidene) - 5(4H)oxazolone analogously to Example 21.

Melting point: 218°C; yield: 80% of theory.

$C_{16}H_{14}N_2O_4S_2$
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 28

N-Benzoyldehydro-3-(2-thienyl)alanine

is obtained from 2 - phenyl - 5 - (2 - thenylidene) - 5(4H)oxazolone analogously to Example 21.

Melting point: 235°C; yield: 94% of theory.

$C_{14}H_{11}NO_3S$
calculated: C 61.52% H 4.06% N 5.12% S 11.74%
found: C 61.50% H 4.08% N 5.14% S 11.70%

Example 29

N-(3-Trifluoromethylbenzoyl)dehydro-3-(2-thienyl)alanine

is obtained from 4 - thenylidene - 2 - (3 - trifluoromethylphenyl) - 5(4H)oxazolone analogously to Example 21.

Melting point: 200—202°C; yield: 93% of theory.

$C_{15}H_{10}F_3NO_3S$
calculated: C 52.76% H 2.96% F 16.70% N 4.10% S 9.39%
found: C 52.89% H 2.92% F 16.60% N 4.18% S 9.36%

Example 30

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 analogously to Example 21.

Melting point: 196—197°C; yield: 55.7% of theory.

$C_{18}H_{15}N_3O_6S$
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%

Example 31

N-Benzoyldehydrophenylalanine

is obtained from 4 - benzylidene - 2 - phenyl - 5(4H)oxazolone analogously to Example 21.

Melting point: 251°C; yield: 88% of theory.

$C_{16}H_{13}NO_3$
calculated: C 71.90% H 4.90% N 5.24%
found: C 71.98% H 4.80% N 5.25%

The examples which follow were formed according to the following general instructions:

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 ½ to 20 hours, depending on the reactivity of the amino acid. 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.

Example 32

N-Acetyldehydrophenylalanyl-L-proline

is obtained from 2 - methyl - 4 - phenyl - 5(4H) - oxazolone and L-proline.

Melting point: 152—155°C; $[\alpha]_D^{20}$ +69.5°; yield: 59% of theory.

$C_{16}H_{18}N_2O_4 \cdot 1/2\ H_2O$
calculated: C 61.72% H 6.15% N 9.00%
found: C 62.15% H 6.43% N 8.96%

Example 33

N-Acetyldehydrophenylalanyl-D-proline

Melting point: 151—153°C; $[\alpha]_D^{20}$ −69.6°; yield: 55% of theory.

$C_{16}H_{18}N_2O_4$
calculated: C 61.72% H 6.15% N 9.0%
found: C 61.75% H 6.30% N 8.94%

Example 34

N-Acetyldehydrophenylalanyl-D-tyrosine

Melting point: 210°C; $[\alpha]_D^{20}$ −43.4° (c=2; pyridine); yield: 61.3% of theory.

$C_{20}H_{20}N_2O_5$
calculated: C 65.21% H 5.47% N 7.60%
found: C 64.56% H 5.86% N 7.77%

Example 35

N-Acetyldehydrophenylalanyl-L-leucine

Melting point: 206—207°C; $[\alpha]_D^{20}$ −22.5°; yield: 65.7% of theory.

$C_{17}H_{22}N_2O_4$
calculated: C 64.13% H 6.97% N 8.80%
found: C 64.26% H 7.31% N 8.78%

Example 36

N-Acetyldehydrophenylalanyl-L-methionine

Melting point: 91—93°C, $[\alpha]_D^{20}$ −74.4°; yield: 70% of theory.

$C_{16}H_{20}N_2O_4S$
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 37

N-Acetyldehydrophenylalanyl-L-aspartic Acid

Melting point: 182—184°C; $[\alpha]_D^{20}$ −46.65°; yield: 63.5% of theory.

$C_{15}H_{16}N_2O_6 \cdot H_2O$
calculated: C 53.25% H 5.36% N 8.28%
found: C 53.48% H 4.92% N 8.32%

Example 38

N-Acetyldehydrophenylalanyl-L-glutamine

Melting point: 188°C; $[\alpha]_D^{20}$ −74.5°; 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 39

N-Acetyldehydrophenylalanyl-DL-3-fluoroalanine

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%

Example 40

N-Acetyldehydrophenylalanyl-L-serine

Melting point: 179°C (decomposition); $[\alpha]_D^{20}$ +1.15°; 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%

Example 41

N-acetyldehydrophenylalanyl-L-tyrosine

Melting point: 219—220°C; preparation in the literature.

Example 42

N-Acetyldehydrophenylalanylglycine

Melting point: 191—192°C; preparation in the literature.

Example 43

N-Acetyldehydrophenylalanyl-L-(p-nitrophenyl)alanine

Melting point: 192—193°C (from ethanol/petroleum ether/isopropyl ether); $[\alpha]_D^{20}$ −110.7°; 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%

Example 44

N-Acetyldehydroalanyl-DL-(p-chlorophenyl)alanine

Melting point: 214—215°C (from 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 45

N-Acetyldehydro(p-methylphenyl)alanyl-L-tyrosine

Melting point: 220—221°C; $[\alpha]_D^{20}$ −38.5°; 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 46

N-Benzoyl-2-cyclohexylideneglycyl-L-tyrosine

Melting point: 121°C; $[\alpha]_D^{20}$ −0.5°; 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 47

N-Benzoyl-2-(2-cyclohexenylidene)glycyl-L-tyrosine

Melting point: 126°C; $[\alpha]_D^{20}$ −5.7°; yield: 60% of theory.

$C_{24}H_{24}N_2O_5$

calculated: C 68.56% H 5.75% N 6.66%
found: C 68.46% H 5.70% N 6.56%

Example 48

N-Acetyldehydro-3-(2-furyl)alanyl-L-tyrosine

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 49

N-Acetyldehydro-3-cinnamenylalanyl-L-tyrosine

Melting point: 220—221°C; $[\alpha]_D^{20}$ −44.2°; yield: 57.3% of theory.

$C_{22}H_{22}N_2O_5$

calculated: C 66.99% H 5.62% N 7.10%
found: C 66.80% H 5.64% N 7.06%

Example 50

N-Acetyldehydro-3-(2-naphthyl)alanyl-L-tyrosine

Melting point: 221—222°C (precipitated 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 51

N-Benzoyldehydro-3-cyclohexylalanyl-L-tyrosine

Melting point: 126—128°C; $[\alpha]_D^{20}$ +0.8° (c=1; dimethylformamide); yield: 60.3% of theory.

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

Example 52

N-Benzoyldehydro-3-benzyl-3-methylalanyl-L-leucine

Melting point: 98—99°C; $[\alpha]_D^{20}$ −14.1°; yield: 39% of theory.

$C_{24}H_{28}N_2O_4$
calculated: C 70.57% H 6.91% N 6.86%
found: C 70.47% H 6.74% N 6.92%

Example 53

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-proline

Melting point: 125°C (ill-defined); $[\alpha]_D^{20}$ +2.0°; yield: 52% of theory.

$C_{19}H_{18}N_2O_4S$
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%

Example 54

N-Acetyldehydrophenylalanin-(1-carboxy-1-cyclopentyl) Amide

Melting point: 217°C (decomposition); yield: 50.7% of theory.

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

Example 55

N-Acetyldehydro-3-(2-thienyl)analyl-L-tyrosine

Melting point: 227—228°C; $[\alpha]_D^{20}$ −36.75°; yield: 71.06% of theory.

$C_{18}H_{18}N_2O_5S$
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%

Example 56

N-Acetyldehydro-3-(2-thienyl)alanyl-N-methylglycine

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and N-methylglycine.

Melting point: 207—208°C; yield: 82.4% of theory.

$C_{12}H_{14}NO_4S$
calculated: C 51.05% H 5.00% N 9.92% S 11.36%
found: C 51.19% H 5.09% N 9.97% S 11.19%

Example 57

N-(3,4,5-Trimethoxycinnamoyl)dehydro-3-(2-thienylalanyl-L-tyrosine

is obtained from 2 - [2 - (3,4,5 - trimethoxyphenyl)vinyl] - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-tyrosine.

Melting point: 148—150°C; yield: 92.2% of theory.

$C_{28}H_{28}N_2O_8S$

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 58

N-Crotonoyldehydro-3-(2-thienyl)alanyl-L-tyrosine

is obtained from 2 - (1 - propenyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-tyrosine.

Melting point: 157°C; yield: 51% of theory.

$C_{20}H_{20}NO_5S$

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%

Example 59

N-Acetyldehydro-3-(5-nitrothienyl-2)alanyl-L-tyrosine

is obtained from 2 - methyl - 4 - (5 - nitrothenylidene - 2) - 5(4H)oxazolone and L-tyrosine.

Melting point: 148—157°C; yield: 54.6% of theory.

$C_{18}H_{17}N_3O_7S$

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 60

N-(2-Thenoyl)dehydro-3-(2-thienyl)alanyl-L-tyrosine

is obtained from 2 - (2 - thienyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-tyrosine.

Melting point: 140—150°C; yield: 72% of theory.

$C_{21}H_{18}N_2O_5S_2$

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 61

N-Crotonoyldehydro-3-(2-thienyl)alanyl-L-leucine

is obtained from 2 - (1 - propenyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-leucine.

Melting point: 176°C; yield: 73% of theory.

$C_{17}H_{22}N_2O_4S$

calculated: C 58.27% H 6.33% N 7.99% S 9.15%
found: C 58.18% H 6.26% N 7.97% S 9.23%

Example 62

N-Acetyldehydro-3-(2-thienyl)alanyl-O-methyl-L-tyrosine

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and O-methyl-L-tyrosine.

Melting point: 236°C; yield: 90% of theory.

$C_{19}H_{20}N_2O_5S$

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%

Example 63

N-Acetyldehydro-3-(2-thienyl)alanyl-L-tryptophan

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-tryptophan.

Melting point: 250°C; yield: 43% of theory.

$C_{20}H_{19}N_3O_4S$

calculated:	C 60.44% H 4.82% N 10.57% S 8.07%
found:	C 60.47% H 4.88% N 10.47% S 8.23%

Example 64

N-Acetyldehydro-3-(2-thienyl)alanylglycine

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and glycine.

Melting point: 221—223°C; yield: 76.1% of theory.

$C_{11}H_{12}N_2O_4S$

calculated:	C 49.25% H 4.51% N 10.44% S 11.95%
found:	C 49.14% H 4.57% N 10.45% S 11.92%

Example 65

N-Acetyldehydro-3-(2-thienyl)alanyl-2-(4-hydroxyphenyl)-D-glycine

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and 2 - (4 - hydroxphenyl) - D - glycine.

Melting point: 224—226°C; yield: 66.7% of theory.

$C_{17}H_{16}N_2O_5S$

calculated:	C 56.66% H 4.48% N 7.77% S 8.90%
found:	C 56.62% H 4.58% N 7.63% S 8.75%

Example 66

N-Benzoyldehydrophenylalanyl-L-leucylglycine 4-methoxyphenylamide

is obtained from 2 - phenyl - 4 - benzylidene - 5(4H)oxazolone and L-leucylglycine 4-methoxyphenylamide.

Melting point: 211—230°C; yield: 50% of theory.

$C_{31}H_{34}N_3O_5$

calculated:	C 68.62% H 6.32% N 10.35%
found:	C 68.69% H 6.33% N 10.48%

Example 67

N-Acetyldehydro-3-(2-thienyl)alanyl-2-(1,4-cyclohexanedien-1-yl)-D-glycine

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and 2 - (1,4 - cyclohexanedien - 1 - yl) - D - glycine.

Melting point: 235—240°C; yield: 75.1% of theory.

$C_{17}H_{18}N_2O_4S$

calculated:	C 58.94% H 5.24% N 8.09% S 9.25%
found:	C 58.79% H 5.10% N 7.93% S 9.06%

Example 68

N-Acetyldehydro-3-(2-thienyl)alanyl-L-glutamic Acid

is obtained from 2 - methyl - 4 - (thenylidene) - 5(4H)oxazolone and L-glutamic acid.

Melting point: 205°C (decomposition); yield: 76.5% of theory.

$C_{14}H_{16}N_2O_6S$

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 69

N-Acetyldehydro-3-(2-thienyl)alanyl-L-leucine

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-leucine.

Melting point: 230°C; yield: 89.5% of theory.

$C_{15}H_{20}N_2O_4S$

calculated:	C 55.58% H 6.21% N 8.64% S 9.88%
found:	C 55.72% H 6.27% N 8.59% S 9.87%

Example 70

N-Acetyldehydro-3-(2-thienyl)alanyl-L-phenylalanine

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-phenylalanine.

Melting point: >230°C; yield: 92.6% of theory.

$C_{18}H_{18}N_2O_4S$

calculated:	C 60.34% H 5.07% N 7.82% S 8.93%
found:	C 60.37% H 5.04% N 7.81% S 8.96%

Example 71

N-Acetyldehydro-3-(2-thienyl)alanyl-L-β-alanine

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-β-alanine.

Melting point: 186—189°C; yield: 78.5% of theory.

$C_{12}H_{14}N_2O_4S$

calculated:	C 51.05% H 5.00% N 9.92% S 11.36%
found:	C 50.93% H 5.07% N 9.98% S 11.44%

Example 72

N-Benzoyldehydrophenylalanylglycine

is obtained from 2 - phenyl - 4 - benzylidene - 5(4H)oxazolone and glycine.

Melting point: 233°C (decomposition); yield: 88.7% of theory.

$C_{18}H_{16}N_2O_4$

calculated:	C 66.66% H 4.97% N 8.64%
found:	C 66.87% H 5.12% N 8.54%

Example 73

N-Acetyldehydro-3-(2-thienyl)alanyl-DL-valine

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and DL-valine.

Melting point: 229—230°C (decomposition); yield: 91.5% of theory.

$C_{14}H_{18}N_2O_4S$

calculated:	C 54.18% H 5.84% N 9.03% S 10.33%
found:	C 54.01% H 5.82% N 9.02% S 10.37%

Example 74

N-(2-Thenoyl)dehydro-3-(2-thienyl)alanyl-2-(1,4-cyclohexanedien-1-yl)-D-glycine

is obtained from 2 - (2 - thienyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and 2 - (1,4 - cyclohexanedien - 1 - yl) - D - glycine.

Melting point: 145—155°C; yield: 37.8% of theory.

$C_{20}H_{18}N_2O_4S$	
calculated:	C 57.95% H 4.38% N 6.76% S 15.47%
found:	C 57.82% H 4.39% N 6.57% S 15.12%

Example 75

N-Acetyldehydro-3-(2-thienyl)alanyl-L-threonine

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-threonine.

Melting point: 262—265°C (decomposition); yield: 65% of theory.

$C_{13}H_{16}N_2O_5S$	
calculated:	C 49.99% H 5.16% N 8.97% S 10.27%
found:	C 49.61% H 5.24% N 8.89% S 10.33%

Example 76

N-Acetyldehydro-3-(2-thienyl)alanyl-L-aspartic Acid

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-aspartic acid.

Melting point: 232°C (decomposition); yield: 62.5% of theory.

$C_{13}H_{14}N_2O_6S$	
calculated:	47.85% H 4.32% N 8.58% S 9.83%
found:	47.70% H 4.43% N 8.45% S 9.95%

Example 77

N-Benzoyldehydrophenylalanyl-L-tryptophan

is obtained from 2 - phenyl - 4 - benzylidene - 5(4H)oxazolone and L-tryptophan.

Yield: 38.9% of theory.

$C_{27}H_{23}N_3O_4$	
calculated:	C 71.51% H 5.11% N 9.27%
found:	C 1.745% H 5.25% N 9.12%

Example 78

N-(3-Trifluoromethylbenzoyl)dehydro-3-(2-thienyl)alanyl-L-leucine

is obtained from 2 - (3 - trifluoromethylphenyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-leucine.

Melting point: 100—105°C; yield: 100% of theory.

$C_{21}H_{21}F_3N_2O_4S$	
calculated:	C 55.50% H 4.66% F 12.54% N 6.16%
found:	C 55.57% H 4.74% F 12.5% N 6.10%

Example 79

N-(3-Trifluoromethylbenzoyl)dehydro-3-(2-thienyl)alanyl-L-phenylalanine

is obtained from 2 - (3 - trifluoromethylphenyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-phenylalanine.

Melting point: 103—107°C; yield: 88% of theory.

$C_{24}H_{19}F_3N_2O_4S$	
calculated:	C 59.01% H 3.92% F 11.67% N 5.74%
found:	C 58.86% H 4.01% F 11.3% N 5.72%

Example 80

N-(3-Trifluoromethylbenzoyl)dehydro-3-(2-thienyl)alanylglycine

is obtained from 2 - (3 - trifluoromethylphenyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and glycine.

Melting point: 91—92°C; yield: 81% of theory.

$C_{17}H_{13}F_3N_2O_4S$

calculated:	C 51.26% H 3.29% F 14.31% N 7.03% S 8.04%
found:	C 51.06% H 3.45% F 14.30% N 6.94% S 8.04%

Example 81

N-Trifluoroacetyldehydrophenylalanyl-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.

$C_{24}H_{25}F_3N_2O_5$

calculated:	C 60.24% H 5.27% F 11.91% N 5.86%
found:	C 60.30% H 5.30% F 11.91% N 5.93%

Example 82

N-Acetyldehydro-3-(2-thienyl)alanyl-3-(2-thienyl)dehydroalanyl-L-tyrosine Tert.-butyl Ester

is obtained from 2 - [1 - acetamido - 3 - (2 - thienyl)vinyl] - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-tyrosine tert.-butyl ester analogously to Example 81.

Melting point: 158°C; yield: 94% of theory.

$C_{29}H_{31}N_3O_6S_2$

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%

Example 83

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 - thenylidene) - 5(4H)oxazolone and L-tyrosine benzyl ester analogously to Example 81.

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

$C_{32}H_{29}N_3O_6S_2$

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 84

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 - thenylidene) - 5(4H)oxazolone and L-tyrosine methyl ester analogously to Example 81.

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

$C_{26}H_{25}N_3O_6S_2$

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 85

N-Acetyldehydro-3-(2-thienyl)alanyl-N-methyl-L-tyrosine Methyl Ester

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and N-methyl-L-tyrosine methyl ester analogously to Example 81.

Melting point: 102°C; yield: 38.9% of theory.

$C_{20}H_{22}N_2O_5S \cdot H_2O$
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 86

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 87

N-Acetyldehydro-3-(3-nitro-4-hydrophenyl)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 analogously to Example 81.

Melting point: 148—151°C; yield: 45.5% of theory.

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

Example 88

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 89

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 analogously to Example 81.

Melting point: 155—160°C; yield: 33.7% of theory.

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

Example 90

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.

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

Example 91

N-(4-Nitrophenyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine Methyl Ester

Melting point: 218—222°C; yield: 55.7% of theory.

$C_{25}H_{23}N_3O_7S$

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%

Example 92

N-(4-Nitrophenyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine

is obtained from the above compound by boiling with dilute sodium hydroxide solution.

Melting point: 161—166°C; yield: 41.6% of theory.

$C_{24}H_{21}N_3O_7S$

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%

Example 93

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 - thenylidine) - 5(4H)oxazolone and L-tyrosine tert.-butyl ester analogously to Example 81.

Melting point : 158°C (decomposition); yield: 94% of theory.

$C_{29}H_{31}N_3O_6S_2$

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%

Example 94

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

is obtained from the above compound by adding glacial acetic acid/HCl.

Melting point: 189°C (decomposition); yield: 88% of theory.

$C_{25}H_{23}N_3O_6S_2$

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%

Example 95

N-Benzoyldehydroisoleucyl-L-tyrosine Methyl Ester

is obtained from 2 - phenyl - 4 - (1 - methylpropylidene) - 5(4H)oxazolone and tyrosine methyl ester analogously to Example 81.

Melting point: 163—165°C; yield: 35.5% of theory.

$C_{33}H_{26}N_2O_5$

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

Example 96

N-(2-Thienyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine Tert. Butyl Ester

is obtained from 2 - (2 - thienylmethyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-tyrosine tert.-butyl ester analogously to Example 81.

Melting point: 105°C; yield: 85% of theory.

$C_{26}H_{28}N_2O_5S_2$

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%

Example 97

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.

$C_{22}H_{20}N_2O_5S_2$

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 98

N-(2-Thienyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine Benzyl Ester

is obtained from 2 - (2 - thienylmethyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-tyrosine benzyl ester analogously to Example 81.

Melting point: 95°C; yield: 83% of theory.

$C_{29}H_{26}N_2O_5S_2$

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 99

N-(2-Thienyl)acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine Methyl Ester

is obtained from 2 - (2 - thienylmethyl) - 4 - (2 - thenylidene) - 5(4H)oxazolone and L-tyrosine methyl ester analogously to Example 81.

Melting point: 200°C (decomposition); yield: 80% of theory.

$C_{23}H_{22}N_2O_5S_2$

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%

Example 100

N-Trifluoroacetyldehydrophenylalanyl-L-tyrosine

Melting point: 165—175°C; $[\alpha]_D^{20}$ –57.4° (c=1; dimethylformamide); yield: 91% of theory.

$C_{20}H_{17}F_3N_2O_5$

calculated:	C 56.87% H 4.06% F 13.5% N 6.63%
found:	C 56.92% H 4.05% F 13.4% N 6.61%

Example 101

N-Phenacetyldehydro-3-(2-thienyl)alanyl-L-tyrosine Tert.-butyl Ester

is prepared in dimethylformamide without NaOH.

Melting point: 110—120°C (crude product); yield: 51.5% of theory.

This compound was further processed by stirring for ½ an 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.

$C_{24}H_{22}N_2O_5S$

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%

Example 102

N-Phenacetyldehydro-3-(2-thienyl)alanyl-L-leucine

N - Phenacetyldehydro - 3 - (2 - thienyl)alanyl - L - leucine methyl ester is formed from 4.05 g (0.015 mol) of 2 - benzyl - 4 - (2 - thenylidene) - 5(4H)

oxazolone and 3 g (0.0165 mol) of L-leucine methyl ester hydrochloride in dimethyl formamide in the presence of triethylamine by stirring the mixture for two hours and allowing it to stand for twelve hours, diluting it with water, extracting it with ether, washing the ether extract with dilute citric acid and evaporating the dried ether solution.

Melting point: 160—161°C; yield: 4.75 g (76.3% of theory).

4.66 g (0.011 mol) of the above compound were dissolved in 50 ml of tetrahydrofurane at 0°C, the solution was stirred with 11 ml of N NaOH at room temperature for two hours, the reaction solution was extracted with chloroform and the aqueous phase was acidified and then extracted with chloroform. 3.8 g (63.3% of theory) of N - phenacetyldehydro - 3 - (2 - thienyl) - alanyl - L - leucine of melting point 207—208°C were obtained. $[\alpha]_D^{20}$ −45.2°.

$C_{21}H_{24}N_2O_4S$
calculated: C 62.98% H 6.04% N 6.99% S 8.00%
found: C 62.92% H 6.02% N 7.03% S 7.92%

Example 103

N-Benzoyldehydrophenylalanyl-L-leucylglycine Anilide

is obtained from 2 - phenyl - 4 - benzylidene - 5(4H)oxazolone and L-leucylglycine anilide analogously to Example 102.

Melting point: 179—180°C; yield: 35.3% of theory.

$C_{30}H_{32}N_4O_4$
calculated: C 70.29% H 6.29% N 10.93%
found: C 69.44% H 6.41% N 10.82%

Example 104

N-Benzoyldehydrophenylalanyl-L-prolyl-L-leucylglycine Anilide

is obtained from 2 - phenyl - 4 - benzylidene - 5(4H)oxazolone and L-prolyl-L-leucylglycine amide.

Melting point: 192°C; yield: 98% of theory.

$C_{35}H_{39}N_5O_5$
calculated: C 68.95% H 6.45% N 11.49%
found: C 69.03% H 6.42% N 11.45%

Example 105

N-Acetyldehydro-3-(2-thienyl)alanyl-2-methylalanine Methyl Ester

is obtained from 2 - methyl - 4 - (2 - thenylidene) - 5(4H)oxazolone and 2-methylalanine methyl ester analogously to Example 102.

Melting point: 181—182°C; yield: 69% of theory.

$C_{14}H_{18}N_2O_4S$
calculated: C 54.18% H 5.85% N 9.03% S 10.33%
found: C 54.32% H 5.83% N 9.12% S 10.51%

Example 106

N-Acetyldehydro-3-(2-thienyl)alanyl-2-methylalanine

is obtained from the above compound by boiling with dilute sodium hydroxide solution.

Melting point: 241°C (decomposition); yield: 94% of theory.

$C_{13}H_{16}N_2O_4S$
calculated: C 52.69% H 5.44% N 9.45% S 10.82%
found: C 52.64% H 5.37% N 9.47% S 10.76%

Example 107

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

Melting point: 135°C (ill-defined); yield: 41.2% of theory.

$C_{23}H_{20}N_2O_5S$
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%

Example 108

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-(p-nitrophenyl)-alanine

Melting point: 125°C (ill-defined); $[\alpha]_D^{20}$ –67.3°; yield: 60% of theory.

$C_{23}H_{19}N_3O_6S$
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 109

N-Nicotinoyldehydro-3-(2-thienyl)alanyl-L-tyrosine

Melting point: 160°C (ill-defined); $[\alpha]_D^{20}$ –8.35°; yield: 50% of theory.

$C_{22}H_{19}N_3O_5S$
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 110

N-(3-Trifluoromethylbenzoyl)dehydro-3-(2-thienyl)-alanyl-L-tyrosine

Melting point: 125°C (ill-defined); $[\alpha]_D^{20}$ –8.9°; yield: 48% of theory.

$C_{24}H_{19}F_3N_2O_5S$
calculated: C 57.14% H 3.80% F 11.30% N 5.55% S 6.36%
found: C 56.95% H 3.81% F 11.4 N 5.45% S 6.45%

Example 111

N-Nicotinoyldehydro-3-(2-thienyl)alanyl-L-(p-nitrophenyl)alanine

Melting point: 197°C (decomposition); $[\alpha]_D^{20}$ –98°; yield: 75% of theory.

$C_{22}H_{18}N_4O_6S$
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 112

N-Benzoyl-3-methyl-3-(2-thienyl)dehydroalanyl-L-tyrosine

Melting point: 128°C; $[\alpha]_D^{20}$ +15.6°; yield: 66.7% of theory.

$C_{24}H_{22}N_2O_5S$
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 113

N-Acetyldehydro-3-(2-thienyl)alanyl-D-tyrosine

Melting point: 221—222°C; $[\alpha]_D^{20}$ +36.8°; yield: 51.49% of theory.

$C_{18}H_{18}N_2O_5S$
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 114

N-Cinnamoyldehydrophenylalanylglycine

Melting point: 159—160°C; yield: 75% of theory.

$C_{20}H_{18}N_2O_4 \cdot H_2O$
calculated: C 65.20% H 5.47% N 7.61%
found: C 65.27% H 5.32% N 7.76%

Example 115

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-phenylalanine

Melting point: 100°C; $[\alpha]_D^{20}$ −4.8° (c=1; dimethylsulphoxide); yield: 80% of theory.

$C_{23}H_{20}N_2O_4S$

calculated:	C 65.70% H 4.79% N 6.66% S 7.63%
found:	C 65.64% H 5.01% N 6.50% S 7.41%

Example 116

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-leucine

Melting point: 110—120°C; $[\alpha]_D^{20}$ +24.8° (c=1; dimethylsulphoxide); yield: 90% of theory.

$C_{20}H_{22}N_2O_4S$

calculated:	C 62.16% H 5.74% N 7.25% S 8.29%
found:	C 62.19% H 5.84% N 7.20% S 8.23%

Example 117

N-Acetyldehydro-3-(2-thienyl)-L-phenylalanine

Melting point: >230°C; $[\alpha]_D^{20}$ −68.8° (c=1; dimethylsulphoxide); yield: 90% of theory.

$C_{18}H_{18}N_2O_4S$

calculated:	C 60.32% H 5.07% N 7.82% S 8.93%
found:	C 60.37% H 5.04% N 7.81% S 8.96%

Example 118

N-Benzoyl-3-methylphenyldehydroalanyl-L-leucine

Melting point: 102—104°C; $[\alpha]_D^{20}$ −8.1°; yield: 75% of theory.

$C_{23}H_{26}N_2O_4$

calculated:	C 70.03% H 6.64% N 7.10%
found:	C 69.29% H 6.48% N 7.02%

Example 119

N-Cinnamoyldehydrophenylalanyl-L-tyrosine

Melting point: 172—174°C; $[\alpha]_D^{20}$ −24°; yield: 30% of theory.

$C_{27}H_{24}N_2O_5$

calculated:	C 71.04% H 5.3% N 6.14%
found:	C 70.85% H 5.39% N 6.16%

Example 120

N-Acetyldehydro-3-(2-thienyl)alanine

Melting point 230°C (decomposition). Preparation in the literature.

Example 121

N-Acetyldehydro-3-(2-thienyl)alanyl-L-leucine

Melting point: >230°C; $[\alpha]_D^{20}$ −11.0° (c=1; dimethylsulphoxide); yield: 90% of theory.

$C_{15}H_{20}N_2O_4S$

calculated:	C 55.54% H 6.21% N 8.64% S 9.88%
found:	C 55.72% H 6.27% N 8.59% S 9.87%

Example 122

N-Benzoyldehydroisoleucyl-L-tyrosine

Melting point: 107°C; $[\alpha]_D^{20}$ −12.1°; yield: 31.5% of theory.

$C_{22}H_{24}N_2O_5$

calculated:	C 66.65% H 6.10% N 7.07%
found:	C 66.57% H 6.17% N 6.90%

Example 123

N-Benzoyl-3-methyl-3-cinnamenyldehydroalanyl-L-tyrosine

Melting point: 130°C; $[\alpha]_D^{20}$ −5.5°; yield: 96% of theory.

$C_{28}H_{26}N_2O_5$
calculated: C 71.47% H 5.57% N 5.95%
found: C 71.60% H 5.57% N 5.87%

Example 124

N-Acetyldehydrophenylalanyldehydro(3-chlorophenyl)alanyl-L-tyrosine

is obtained by aminolysis of 4 - (3 - chlorobenzylidene) - 2 - (1 - acetamido - 2 - phenylethylene) - 5(4H) - oxazolone with L-tyrosine.

Melting point: 191—193°C; $[\alpha]_D^{20}$ −154.3° (c=1; dimethylformamide); yield: 78.5% of theory.

$C_{29}H_{26}ClN_3O_6$
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 125

N-Acetyldehydrophenylalanyldehydrotyrosine

6.09 g (0.0175 mol) of 2 - (1 - acetamido - 2 - phenylethylene) - 4 - (4 - hydroxybenzylidene) - 5(4H) - oxazolone are mixed with 46.9 ml of N NaOH and 40 ml of acetone and the mixture is stirred at room temperature for three hours. After distilling off the acetone, acidifying the aqueous reaction solution with 47.6 ml of N HCl and recrystallising the precipitate, which has separated out and been filtered off, from ethanol/petroleum ether, 3.75 g (58.6% of theory) of N-acetyldehydrophenylalanyldehydrotyrosine of melting point 202—206°C are obtained. Preparation in the literature.

The following compounds were prepared analogously from the corresponding oxazolones:

Example 126

N-Acetyldehydrophenylalanyldehydro-(p-nitrophenyl)alanine

Melting point: 181°C; yield: 56.4% of theory.

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

Example 127

N-Acetyldehydrophenylalanyldehydro(4-chlorophenyl)alanine

Melting point: 177°C; yield: 60.9% of theory.

$C_{20}H_{17}ClN_2O_4$
calculated: C 62.42% H 4.45% N 7.28% Cl 9.21%
found: C 62.49% H 4.47% N 7.37% Cl 9.24%

Example 128

N-Acetyldehydrophenylalanyldehydro(p-fluorophenyl)alanine

Melting point: 172°C; yield: 65.27% of theory.

$C_{20}H_{17}FN_2O_4 \cdot H_2O$
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%

Example 129

N-Acetyldehydrophenylalanyldehydro(4-dimethylaminophenyl)alanine

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

$C_{22}H_{23}N_3O_4$
calculated: C 67.16% H 5.89% N 10.68%
found: C 67.03% H 6.00% N 10.52%

Example 130

N-Acetyldehydrophenylalanyldehydro(3-chlorophenyl)alanine

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

$C_{20}H_{17}ClN_2O_4$

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%

In the following examples, the reaction was carried out in tetrahydrofurane without NaOH.

Example 131

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine Methyl Ester

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

$C_{24}H_{22}N_2O_5S$

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 132

N-Acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine Methyl Ester

Melting point: 243—245°C; $[\alpha]_D^{20}$ −78.1° (c=1; dimethylsulphoxide); yield: 65% of theory.

$C_{19}H_{20}N_2O_5S$

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%

Example 133

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine Benzyl Ester

is obtained from the acid and benzyl alcohol by heating to 80°C for ½ an hour in the presence of hydrogen chloride.

Melting point: 95°C (ill-defined); $[\alpha]_D^{20}$ −2.0°; yield: 79% of theory.

$C_{30}H_{26}N_2O_5S$

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%

Example 134

The Salt of N-acetyldehydro-3-(2-thienyl)alanine with Morpholine

To 1.5 g of the dehydroamino acid, three times the amount of morpholine is added and the mixture is diluted with methanol and evaporated to dryness.

Melting point: 173°C (decomposition); yield: 89% of theory.

$C_{13}H_{18}N_2O_4S$

calculated: C 52.4% H 6.0% N 9.4% S 10.7%
found: C 52.8% H 6.2% N 9.4% S 11.1%

The following compounds are prepared analogously to Example 134:

Example 135

The salt of N-acetyldehydro-3-(2-thienyl)alanine with Methylamine

Melting point: 178°C; yield: 99% of theory.

$C_{10}H_{14}N_2O_3S$

calculated: C 49.57% H 5.82% N 11.56% S 13.24%
found: C 49.74% H 5.92% N 11.60% S 13.23%

Example 136

The Salt of N-acetyldehydro-3-(2-thieny)alanine with 1,1-dimethylpropargylamine

Melting point: 221°C (decomposition); yield: 99% of theory.

$C_{14}H_{18}N_2O_3S$
calculated: C 57.12% H 6.16% N 9.52% S 10.89%
found: C 57.24% H 6.21% N 9.68% S 11.06%

Example 137

The Lithium Salt of N-acetyldehydro-3-(2-thienyl)alanine

Melting point: >300°C; yield: 66.80% of theory.

$C_9H_8LiNO_3S$
calculated: C 49.77% H 3.71% N 6.45% S 14.76% Li 3.21%
found: C 49.79% H 3.92% N 6.30% S 14.45% Li 3.55%

Example 138

The salt of N-acetyldehydro-3(2-thienyl)alanyl-L-tyrosine with Morpholine

Melting point: 136—150°C; yield: 69.40% of theory.

$C_{22}H_{27}N_3O_6S$
calculated: C 57.25% H 5.90% N 9.11% S 6.95%
found: C 56.54% H 6.14% N 8.85% S 6.42%

Example 139

The Salt of N-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with Piperidine

Melting point: 184—186°C; yield: 58.80% of theory.

$C_{23}H_{29}N_3O_5S$
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 140

The Salt of N-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with Ethylenediamine

Melting point: 148—158°C; yield: 98.9% of theory.

$C_{38}H_{44}N_6O_{10}S_2$
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%

Example 141

The Salt of N-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with Triethanolamine

Melting point: 125—130°C; yield: 84.1% of theory.

$C_{24}H_{33}N_3O_8S$
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%

Example 142

The Salt of N-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with DL-canavanine

Melting point: 165—173°C; yield: 90.9% of theory.

$C_{23}H_{30}N_6O_8S$
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%

Example 143

The Salt of N-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with L-arginine

Melting point: 125—140°C; yield: 79.3% of theory.

$C_{24}H_{32}N_6O_7S$

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 144

The Salt of N-acetyldehydro-3-(2-thienyl)alanyl-L-tyrosine with L-lysine

Melting point: 174—182°C; yield: 96.1% of theory.

$C_{24}H_{32}N_4O_7S$

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%

The amides which follow were prepared from the corresponding methyl esters by allowing a mixture of the esters and the corresponding amines (1 mol of ester per 8 moles of amine) in methanol or tetrahydrofurane to stand and working up the mixture by evaporation and purification on silica gel (reaction time 3—340 hours).

Example 145

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine Amide

Melting point: 210°C; $[\alpha]_D^{20}$ –62.0°; yield: 86% of theory.

$C_{23}H_{21}N_3O_4S$

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%

Example 146

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine N'-hexylamide

Melting point: 115°C (ill-defined); $[\alpha]_D^{20}$ –63.4°; yield: 80% of theory.

$C_{29}H_{33}N_3O_4S$

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%

Example 147

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine N'-methylamide

Melting point: 145°C (ill-defined); $[\alpha]_D^{20}$–61.7°; yield: 90.2% of theory.

$C_{24}H_{23}N_3O_4S$

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%

Example 148

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-Tyrosine N'-cyclohexylamide

Melting point: 110°C (ill-defined); $[\alpha]_D^{20}$ –50.9°; yield: 44% of theory.

$C_{29}H_{31}N_3O_4S$

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%

Example 149

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine N',N'-dimethylamide

Melting point: 130°C (ill-defined); $[\alpha]_D^{20}$ –2.2°; yield: 13% of theory.

$C_{25}H_{25}N_3O_4S$

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 150

N-Benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine Morpholide

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

$C_{27}H_{27}N_3O_5S$
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 151

N-Benzoyldehydro-3-(2-thienyl)-L-tyrosine N'-benzylamide

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

$C_{30}H_{27}N_3O_4S$
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 152

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

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

$C_{23}H_{30}N_4O_4S$
calculated: C 60.24% H 6.59% N 12.22% S 6.99%
found: C 60.39% H 6.75% N 12.40% S 6.89%

Example 153

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

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

$C_{18}H_{19}N_3O_4S$
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 154

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

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

$C_{19}H_{21}N_3O_4S$
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 155

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

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

$C_{29}H_{34}N_4O_4S$
calculated: C 65.14% H 6.41% N 10.48% S 6.00%
found: C 65.04% H 6.42% N 10.45% S 6.10%

Example 156

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

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

$C_{27}H_{30}N_4O_4S$
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 157

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

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

$C_{18}H_{20}N_4O_4S$
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 158

N-benzoyldehydro-3-(2-thienyl)alanyl-L-tyrosine Hydrazide

Melting point: 135°C; yield: 82.2% of theory.

$C_{23}H_{22}N_4O_4S$

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%

If instead of sodium hydroxide a corresponding amine is used, the following compounds are formed from the corresponding 5(4H)oxazolones:

Example 159

N-Acetyldehydro-3-(2-thienyl)alanine N'-methylamide

Melting point: 183°C; yield: 89% of theory.

$C_{10}H_{12}N_2O_2S$

calculated: C 53.55% H 5.39% N 12.49% S 14.30%
found: C 53.66% H 5.52% N 12.52% S 14.23%

Example 160

N-Acetyldehydro-3-(2-thienyl)alanine N'-1,1-dimethyl-2-propinylamide

Melting point: 197—200°C; yield: 36.2% of theory.

$C_{14}H_{16}N_2O_2S$

calculated: C 60.85% H 5.84% N 10.14% S 11.60%
found: C 60.64% H 6.06% N 10.08% S 11.38%

Example 161

N-Acetyldehydro-3-(2-thienyl)alanine Morpholide

Melting point: 159°C; yield: 82.7% of theory.

$C_{13}H_{16}N_2O_3S$

calculated: C 55.69% H 5.75% N 9.99% S 11.44%
found: C 55.80% H 5.73% N10.09% S 11.22%

Example 162

N-Cinnamoyldehydroalanine N'-methylamide

Melting point: 114—118°C; yield: 70% of theory.

$C_{19}H_{18}N_2O_2$

calculated: C 74.5% H 5.9% N 9.1%
found: C 74.4% H 6.0% N 9.0%

Example 163

N-Cinnamoyldehydroalanine 1,1-dimethyl-2-propinylamide

Melting point: 200—203°C; yield: 40% of theory.

$C_{23}H_{22}N_2O_2$

calculated: C 77.1% H 6.2% N 7.8%
found: C 77.1% H 6.2% N 8.0%

Example 164

N-Cinnamoyldehydroalanine Morpholide

Melting point: 179—182°C; yield: 50% of theory.

$C_{22}H_{22}N_2O_3$

calculated: C 72.9% H 6.1% N 7.7%
found: C 72.8% H 6.2% N 7.5%

Example 165

N-Ethoxyacetyldehydro-3-(2-thienyl)alanine 4-methylpiperazide

Melting point: 95—97°C; yield: 71.4% of theory.

$C_{16}H_{23}N_3O_3S$
calculated: C 56.95% H 6.87% N 12.45% S 9.50%
found: C 56.79% H 6.94% N 12.44% S 9.56%

Example 166

N-Ethoxyacetyldehydro-3-(2-thienyl)alanine Anilide

Melting point: 158—159°C; yield: 97.9% of theory.

$C_{17}H_{18}N_2O_3S$
calculated: C 61.80% H 5.49% N 8.48% S 9.70%
found: C 61.90% H 5.48% N 8.48% S 9.65%

Example 167

N-Ethoxyacetyldehydro-3-(2-thienyl)alanine Cyclohexylamide

Melting point: 142—144°C; yield: 72% of theory.

$C_{17}H_{24}N_2O_3S$
calculated: C 60.69% H 7.19% N 8.32% S 9.53%
found: C 60.27% H 7.25% N 8.32% S 9.42%

Example 168

N-Ethoxyacetyldehydro-3-(2-thienyl)alanine Amide

Melting point: 145—147°C; yield: 50.6% of theory.

$C_{11}H_{14}N_2O_3S$
calculated: C 51.95% H 5.55% N 11.01% S 12.62%
found: C 51.92% H 5.50% N 10.86% S 12.66%

Example 169

N-Crotonoyldehydro-3-(2-thienyl)alanine 4-methylpiperazide

Melting point: 172—173°C; yield: 90% of theory.

$C_{16}H_{21}N_3O_2S$
calculated: C 60.16% H 6.63% N 13.16% S 10.04%
found: C 60.18% H 7.04% N 13.16% S 9.92%

Example 170

N-Crotonoyldehydro-3-(2-thienyl)alanine 3-dimethylaminopropylamide

Melting point: 137—138°C; yield: 83% of theory.

$C_{16}H_{23}N_3O_2S$
calculated: C 59.78% H 7.21% N 13.07% S 9.98%
found: C 59.44% H 7.16% N 13.02% S 9.93%

Example 171

N-Crotonoyldehydro-3-(2-thienyl)alanine 6-aminohexylamide

Melting point: 113—114°C; yield: 70% of theory.

$C_{17}H_{25}N_3O_2S$
calculated: C 60.86% H 7.51% N 12.53% S 9.56%
found: C 60.73% H 7.58% N 12.56% S 9.37%

Example 172

N-acetyldehydrophenylalanyl-3-(2-thienyl)dehydroalanine Methylamide

Melting point: 226°C; yield: 89% of theory.

$C_{19}H_{19}N_3O_3S$
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%

Example 173

N-(3-Trifluoromethylbenzoyl)dehydro-3-(2-thienyl)alanine Anilide

Melting point: 240—243°C; yield: 56% of theory.

$C_{21}H_{15}F_3N_2O_2S$

calculated: C 60.57% H 3.63% F 13.69% N 6.73% S 7.70%
found: C 60.55% H 3.73% F 13.5% N 6.75% S 7.71%

Example 174

N-(3-Trifluoromethylbenzoyl)dehydro-3-(2-thienyl)alanine 4-methylpiperazide

Melting point: 187—188°C; yield: 63.8% of theory.

$C_{20}H_{20}F_3N_3O_2S$

calculated: C 56.73% H 4.76% N 9.92% F 13.46% S 7.57%
found: C 56.57% H 4.63% N 9.98% F 13.4% S 7.56%

Example 175

N-(3-Trifluoromethylbenzoyl)dehydro-3-(2-thienyl)alanine 3-dimethylaminopropylamide

Melting point: 152—154°C

$C_{20}H_{22}F_3N_3O_2S$

calculated: C 56.46% H 5.21% N 9.88% F 13.4%
found: C 56.55% H 5.32% N 10.0% F 13.6%

Example 176

N-(3-Trifluoromethylbenzoyl)dehydro-3-(2-thienyl)alanine Amide

Melting point: 205—207°C

$C_{15}H_{11}F_3N_2O_2S$

calculated: C 52.94% H 3.26% N 8.23% F 16.75% S 9.42%
found: C 53.05% H 3.25% N 8.26% F 16.9% S 9.46%

Example 177

N-Acetyldehydro-3-(2-thienyl)alanyl-3-methyl-3-(2-thienyl)dehydroalanine Hexylamide

Melting point: 110°C; yield: 90% of theory.

$C_{23}H_{29}N_3O_3S_2$

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%

Example 178

N-Nicotinoyl-3-(2-thienyl)dehydroalanine Propargylamide

Melting point: 140—143°C; yield: 98% of theory.

$C_{16}H_{13}N_3O_2S \cdot H_2O$

calculated: C 58.34% H 4.59% N 12.76% S 9.74%
found: C 58.21% H 4.58% N 13.15% S 10.01%

Example 179

N-(2-Thienylacetyl)dehydro-3-(2-thienyl)alanine 3-dimethylaminopropylamide

Melting point: 143°C; yield: 74% of theory.

$C_{18}H_{23}N_3O_2S_2$

calculated: C 57.26% H 6.14% N 11.13% S 16.99%
found: C 57.41% H 6.09% N 11.08% S 17.05%

Example 180

N-Benzoyldehydro-3-(2-thienyl)alanine 3-dimethylaminopropylamide

Melting point: 174—176°C; yield: 91% of theory.

$C_{19}H_{23}N_3O_2S$
calculated: C 63.84% H 6.49% N 11.76% S 8.96%
found: C 63.92% H 6.47% N 11.91% S 9.06%

Example 181

N-Benzoyldehydro-3-(2-thienyl)alanine Anilide

Melting point: 231°C; yield: 84% of theory.

$C_{20}H_{16}N_2O_2S$
calculated: C 68.94% H 4.63% N 8.04% S 9.20%
found: C 69.20% H 4.48% N 8.03% S 9.16%

Example 182

N-Benzoyldehydro-3-(2-thienyl)alanine Methylamide

Melting point: 231°C (decomposition); yield: 92% of theory.

$C_{15}H_{14}N_2O_2S$
calculated: C 62.91% H 4.93% N 9.78% S 11.20%
found: C 62.94% H 5.10% N 9.58% S 11.30%

Example 183

N-Benzoyldehydro-3-(3-thienyl)alanine Hexylamide

Melting point: 121°C; yield: 95% of theory.

$C_{20}H_{24}N_2O_2S$
calculated: C 67.38% H 6.79% N 7.86% S 8.99%
found: C 67.31% H 6.85% N 7.95% S 8.89%

Example 184

N-Benzoyldehydro-3-(2-thienyl)alanine Propargylamide

Melting point: 185—186°C; yield: 75% of theory.

$C_{17}H_{14}N_2O_2S$
calculated: C 65.79% H 4.55% N 9.03% S 10.33%
found: C 65.93% H 4.65% N 8.88% S 10.39%

Example 185

N-Benzoyldehydrophenylalanine Hydrazide

Melting point: 151—153°C; yield: 28% of theory.

$C_{16}H_{15}N_3O_2$
calculated: C 68.31% H 5.37% N 14.94%
found: C 68.14% H 5.53% N 14.89%

Example 186

N-Benzoyldehydrophenylalanine Anilide

Melting point: 213—233°C; yield: 80% of theory.

$C_{22}H_{18}N_2O_2$
calculated: C 77.17% H 5.3% N 8.18%
found: C 77.63% H 5.7% N 8.09%

Example 187

N-Benzoyldehydrophenylalanine Methylamide

Melting point: 172—174°C; yield: 71% of theory.

$C_{17}H_{16}N_2O_2$
calculated: C 70.6% H 5.9% N 9.7%
found: C 70.4% H 5.9% N 9.8%

Example 188

N-Benzoyldehydrophenylalanine 1,1-dimethylpropargylamide

Melting point: 169—174°C; yield: 85% of theory.

$C_{21}H_{20}N_2O_2$

calculated:	C 75.88%	H 6.06% N 8.43%
found:	C 75.74%	H 6.07% N 8.36%

Example 189

N-Benzoyldehydrophenylalanine Hexylamide

Melting point: 139—140°C; yield: 63% of theory.

$C_{22}H_{26}N_2O_2$

calculated:	C 75.4%	H 7.48% N 7.99%
found:	C 75.43%	H 7.45% N 8.09%

Example 190

N-Benzoyldehydrophenylalanine Cyclohexylamide

Melting point: 197—199°C; yield: 85% of theory.

$C_{22}H_{24}N_2O_2$

calculated:	C 75.83%	H 6.94% N 8.04%
found:	C 75.81%	H 7.02% N 8.08%

Example 191

N-Benzoyldehydrophenylalanine Morpholide

Melting point: 158—160°C; yield: 63% of theory.

$C_{20}H_{20}N_2O_3$

calculated:	C 71.41%	H 5.99% N 8.33%
found:	C 71.3%	H 6.03% N 8.2%

Example 192

N-Benzoyldehydrophenylalanine 4-methoxyphenyl Hydrazide

Melting point: 207—209°C; yield: 38% of theory.

$C_{23}H_{21}N_3O_3$

calculated:	C 71.3%	H 5.46% N 10.85%
found:	C 71.4%	H 5.44% N 10.96%

Example 193

N-Benzoyldehydrophenylalanine 2-phenylcyclopropylamide

Melting point: 140—143°C; yield: 89% of theory.

$C_{25}H_{22}N_2O_2$

calculated:	C 78.51%	H 5.80% N 7.33%
found:	C 78.52%	H 5.83% N 7.22%

Example 194

N-Benzoyldehydrophenylalanine 3,4,5-trimethoxy Anilide

Melting point: 209—212°C; yield: 72% of theory.

$C_{25}H_{24}N_2O_5$

calculated:	C 69.43%	H 5.59% N 6.48%
found:	C 69.3%	H 5.55% N 6.37%

Example 195

N-Benzoyldehydrophenylalanine 3-dimethylaminopropylamide

Melting point: 124—126°C; yield: 68% of theory.

$C_{21}H_{25}N_3O_2$

calculated:	C 71.77%	H 7.14% N 11.96%
found:	C 71.67%	H 7.17% N 12.13%

Example 196

N-Benzoyldehydrophenylalanine Propargylamide

Melting point: 190—191°C; yield: 81% of theory.

$C_{19}H_{16}N_2O_2$		
calculated	C 74.98%	H 5.30% N 9.21%
found:	C 74.93%	H 5.37% N 9.20%

Example 197

N-Acetyldehydro-3-(2-thienyl)alanine-2-(4-imidazolyl) Ethylamide

Melting point: 105°C; yield: 76.2% of theory.

$C_{14}H_{16}N_4O_2S$		
calculated:	C 55.24%	H 5.30% N 18.41% S 10.53%
found:	C 55.26%	H 5.47% N 18.41% S 10.30%

Example 198

N-Acetyldehydro-3-(2-thienyl)alanine Hexylamide

Melting point: 152—153°C; yield: 91.8% of theory.

$C_{15}H_{22}N_2O_2S$		
calculated:	C 61.19%	H 7.53% N 9.52% S 10.89%
found:	C 61.24%	H 7.57% N 9.48% S 10.98%

Example 199

N-Acetyldehydro-3-(2-thienyl)alanine 2-phenylcyclopropylamide

Melting point: 204°C; yield: 82.8% of theory.

$C_{18}H_{18}N_2O_2S$		
calculated:	C 66.23%	H 5.56% N 8.58%
found:	C 66.30%	H 5.61% N 8.67%

Example 200

N-Acetyldehydro-3-(2-thienyl)alanine Benzylamide

Melting point: 193—195°C; yield: 93.3% of theory.

$C_{16}H_{16}N_2O_3S$		
calculated:	C 63.98%	H 5.37% N 9.33% S 10.67%
found:	C 63.93%	H 5.31% N 9.23% S 10.40%

Example 201

N-Acetyldehydro-3-(2-thienyl)alanine 3-dimethylaminopropylamide

Melting point: 137—139°C; yield: 78% of theory.

$C_{14}H_{21}N_3O_2S$		
calculated:	C 56.92%	H 7.17% N 14.23% S 10.85%
found:	C 56.79%	H 7.09% N 14.16% S 10.71%

Example 202

N-Acetyldehydro-3-(2-thienyl)alanine Piperidide

Melting point: 160—161°C; yield: 61.1% of theory.

$C_{14}H_{18}N_2O_2S$		
calculated:	C 60.40%	H 6.51% N 10.06% S 11.52%
found:	C 60.6%	H 6.48% N 10.1% S 11.44%

Example 203

N-Acetyldehydro-3-(2-thienyl)alanine 4-methylpiperazide

Melting point: 183—184°C; yield: 68.3% of theory.

$C_{14}H_{19}N_3O_2S$		
calculated:	C 57.31%	H 6.53% N 14.32% S 10.93%
found:	C 57.40%	H 6.46% N 14.49% S 10.96%

Example 204

N-Acetyldehydro-3-(2-thienyl)alanine 4-phenylpiperazide

Melting point: 197°C; yield: 64.8% of theory.

$C_{19}H_{21}N_3O_2S$

calculated: C 64.20% H 5.95% N 11.82% S 9.02%

found: C 64.09% H 5.94% N 11.84% S 9.06%

Example 205

N-Crotonyldehydro-3-(2-thienyl)alanine 4-hydroxyanilide

Melting point: 245°C; yield: 53% of theory.

$C_{17}H_{10}N_2O_3S$

calculated: C 62.18% H 4.92% N 8.53% S 9.76%

found: C 61.97% H 5.23% N 8.57% S 9.65%

Example 206

N-Acetyldehydro-3-(2-thienyl)alanine 4-(2-hydroxyethyl)-Piperazide

Melting point: 227—230°C; yield: 80.5% of theory.

$C_{15}H_{21}N_3O_3S$

calculated: C 55.71% H 6.59% N 12.99% S 9.91%

found: C 55.68% H 6.54% N 12.97% S 9.64%

Example 207

N-Acetyldehydro-3-(2-thienyl)alanine Amide

Melting point: 189°C; yield: 76.2% of theory.

$C_9H_{10}N_2O_2S$

calculated: C 51.41% H 4.79% N 13.32% S 15.25%

found: C 51.34% H 4.88% N 13.33% S 15.42%

Example 208

N-Acetyldehydro-3-(2-thienyl)alanine 2,2-dimethylhydrazide

Melting point: 174—175°C; yield: 59.3% of theory.

$C_{11}H_{15}N_3O_2S$

calculated: C 52.15% H 5.97% N 16.59% S 12.66%

found: C 52.09% H 6.00% N 16.69% S 12.50%

Example 209

N-Acetyldehydro-3-(2-thienyl)alanine Anilide

Melting point: 95—97°C; yield: 73.4% of theory.

$C_{15}H_{14}N_2O_2S$

calculated: C 62.92% H 4.93% N 9.78% S 11.20%

found: C 62.85% H 4.99% N 9.83% S 11.32%

Example 210

N-Acetyldehydro-3-(2-thienyl)alanine 4-methycyclohexylamide

Melting point: 195—197°C; yield: 57.4% of theory.

$C_{16}H_{22}N_2O_2S$

calculated: C 62.71% H 7.24% N 9.14% S 10.47%

found: C 62.73% H 7.37% N 8.99% S 10.53%

Example 211

N-Acetyldehydro-3-(2-thienyl)alanine 3-morpholinopropylamide

Melting point: 135—137°C; yield: 48.9% of theory.

$C_{16}H_{23}N_3O_3S$

calculated: C 56.95% H 6.87% N 12.45% S 9.51%

found: C 56.92% H 6.87% N 12.30% S 9.59%

Example 212

N-Acetyldehydro-3-(2-thienyl)alanine 1-phenylethylamide

Melting point: 171—173°C; yield: 50.9% of theory.

$C_{17}H_{18}N_2O_2S$
calculated: C 64.94% H 5.77% N 8.91% S 10.20%
found: C 65.14% H 5.91% N 8.89% S 10.30%

Example 213

N-Acetyldehydro-3-(2-thienyl)alanine 3-carboxypropylamide

Melting point: 195—197°C; yield: 65.9% of theory.

$C_{13}H_{16}N_2O_4S$
calculated: C 52.69% H 5.44% N 9.45% S 10.82%
found: C 52.87% H 5.55% N 9.54% S 10.98%

Example 214

N-Acetyldehydro-3-(2-thienyl)alanine Hydrazide

Melting point: 170°C; yield: 75.5% of theory.

$C_9H_{11}N_3O_2S \cdot H_2O$
calculated: C 44.43% H 5.39% N 17.27% S 13.18%
found: C 44.21% H 5.37% N 17.30% S 13.26%

Example 215

N-Acetyldehydro-3-(2-thienyl)alanine 2-sulphonic Acid Ethylamide

Melting point: 192—194°C; yield: 68.7% of theory.

$C_{11}H_{14}N_2O_5S_2$
calculated: C 41.50% H 4.42% N 8.80% S 20.14%
found: C 41.36% H 4.60% N 8.73% S 19.99%

Example 216

N-Acetyldehydro-3-(2-thienyl)alanine 1-ethinycyclohexylamide

Melting point: 223—224°C; yield: 82.5% of theory.

$C_{17}H_{20}N_2O_2S$
calculated: C 64.54% H 6.37% N 8.86% S 10.12%
found: C 64.37% H 6.26% N 8.70% S 10.24%

Example 217

N-Acetyldehydro-3-(2-thienyl)alanine Benzyloxyamide

Melting point: 142—144°C; yield: 47.5% of theory.

$C_{16}H_{16}N_2O_3S$
calculated: C 60.74% H 5.10% N 8.86% S 10.13%
found: C 60.60% H 5.15% N 8.99% S 10.04%

Example 218

N-Acetyldehydro-3-(2-thienyl)alanine 2-hydroxyethylamide Phosphate

Melting point: 180—182°C; yield: 35.9% of theory.

$C_{11}H_{15}N_2O_6PS \cdot H_2O$
calculated: C 37.50% H 4.86% N 7.95% P 8.79% S 9.11%
found: C 36.96% H 4.78% N 7.99% P 8.69% S 8.91%

Example 219

N-Acetyldehydro-3-(2-thienyl)alanine Morpholide

Melting point: 159°C; yield: 82.7% of theory.

$C_{13}H_{16}N_2O_3S$
calculated: C 55.69% H 5.75% N 9.99% S 11.22%
found: C 55.80% H 5.73% N 10.09% S 11.22%

Example 220

N-Acetyldehydro-3-(2-thienyl)alanine Propargylamide

Melting point: 202—204°C; yield: 72% of theory.

$C_{12}H_{12}N_2O_2S$

calculated: C 58.05% H 4.87% N 11.28% S 12.91%
found: C 57.96% H 4.9% N 11.33% S 12.96%

Example 221

N-Acetyldehydro-3-(2-thienyl)alanine 3,4,5-trimethoxyanilide

Melting point: 203—205°C; yield: 51.3% of theory

$C_{18}H_{20}N_2O_5S$

calculated: C 57.43% H 5.36% N 7.44% S 8.52%
found: C 57.50% H 5.32% N 7.39% S 8.63%

Example 222

N-Acetyldehydro-3-(2-thienyl)alanine 2-(benzothiazol-2-yl)hydrazide

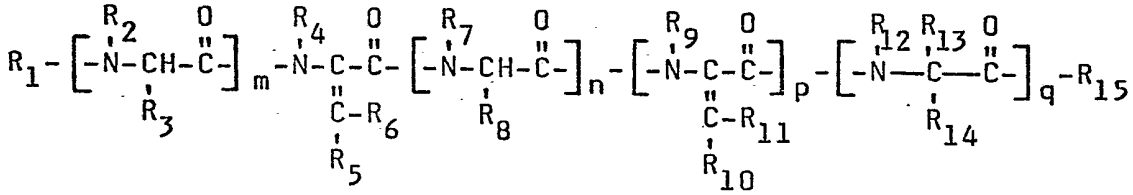
Melting point: 183—185°C; yield: 22% of theory.

$C_{16}H_{14}N_4O_2S_2$

calculated: C 53.61% H 3.94% N 15.63% S 17.89%
found: C 53.41% H 4.06% N 15.45% S 17.89%

WHAT WE CLAIM IS:—

1. A pharmaceutical composition containing as an active ingredient a compound which is a dehydrooligopeptide of the following general formula or its salt



(I)

in which

R_1 is a hydrogen atom, optionally substituted alkanoyl, optionally substitituted alkenoyl, alkoxycarbonyl, optionally substituted aroyl, optionally substituted aralkanoyl or aralkenoyl, aralkoxycarbonyl, carbamoyl, optionally substituted hetero-aroyl (as herein defined), optionally substituted C_1 to C_6 alkylsulphonyl or optionally substituted arylsulphonyl,

R_2, R_7 and R_{12} are the same or different and each is a hydrogen atom or a C_1 to C_6 alkyl group,

R_3, R_8 and R_{13} are the same or different and each is a hydrogen atom, straight-chain or branched optionally substituted C_1 to C_6 alkyl, optionally substituted aryl, optionally substituted aralkyl or aralkenyl, optionally substituted cycloalkyl or cycloalkenyl, indolylmethyl or an optionally substituted heterocyclicmethyl group having from four to seven ring members and one or two hetero-atoms, or one or more of R_2, R_7 and R_{12}, together with, in each case, the adjacent substituent R_3, R_8 or R_{14} respectively, form(s) a divalent alkylene chain having three or four carbon atoms,

R_4 and R_9 each represent a hydrogen atom or a C_1 to C_6 alkyl group, and

R_5 and R_{10} are the same or different and each is a hydrogen atom or optionally substituted C_1 to C_6 alkyl,

R_6 and R_{11} are the same or different and each is optionally substituted alkyl, optionally substituted aryl, an optionally substituted heterocyclic radical having from five to seven ring members and one or two hetero-atoms, optionally substituted aralkyl or optionally substituted aralkenyl, or

R_6 and/or R_{11}, together with R_5 or R_{10}, respectively represent an optionally substituted alkylene or alkenylene chain having from three to seven carbon atoms,

R_{14} is a hydrogen atom or optionally substituted lower C_1 to C_6 alkyl or, together with R_{13} and the carbon atom between them, represents an alicyclic radical having from four to seven carbon atoms,

R_{15} is hydroxyl optionally substituted C_1 to C_6 alkoxy or alkenyloxy, optionally substituted C_1 to C_6 alkylthio or alkenylthio, optionally substituted arylthio, optionally substituted hydrazino, amino, optionally substituted C_1 to C_6 alkylamino or dialkylamino or alkenylamino or dialkenylamino or alkinylamino, optionally substituted arylamino, optionally substituted mono- or di-aralkylamino, a nitrogen-containing optionally substituted heterocyclic radical having from four to seven ring members, optionally containing one or two further hetero-atoms and optionally substituted by C_1 to C_6 alkyl, C_1 to C_6 hydroxyalkyl or phenyl, amino substituted by one or more optionally substituted alicyclic radicals having from three to seven ring members, or aralkyloxyamino, and

m, n, p and q are the same or different and each represents a number 0 or 1, with the proviso that m, n, p and q may not all be 1 at the same time, 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.

2. A composition according to claim 1 in which in formula (I): R_1 is straight-chain or branched, alkanoyl having from 2 to 6 carbon atoms or alkenoyl having from 3 to 6 carbon atoms, optionally substituted by from 1 to 3 halogen atoms, methoxy, ethoxy or hetero-aryl; straight-chain or branched alkoxycarbonyl having from 1 to 4 carbon atoms in the alkoxy moiety; benzoyl, naphthoyl, or aralkinoyl or aralkenoyl having from 8 to 12 carbon atoms, optionally substituted by from 1 to 3 halogen atoms, alkyl or alkoxy having from 1 to 3 carbon atoms, trifluoromethyl, nitro or hydroxyl optionally acylated with a C_1 to C_6 organic acid radical; aralkoxycarbonyl having from 8 to 10 carbon atoms; heteroaryl having from 5 to 7 ring members and containing from 1 to 3 hetero-atoms which are the same or different and each of which is nitrogen, sulphur or oxygen and on which there is a carbonyl group, optionally substituted by one or more halogen atoms, or alkyl or alkoxy having from 1 to 4 carbon atoms; methane- or ethane-sulphonyl; benzene- or toluene-sulphonyl; each of

R_2, R_7 and R_{12} is a hydrogen atom or methyl or ethyl; each of

R_3, R_8 and R_{13} is straight-chain or branched alkyl or alkenyl having from 1 to 6 carbon atoms and optionally a double or triple bond, optionally substituted by from 1 to 3 halogen atoms, hydroxyl alkoxy having from 1 to 4 carbon atoms, sulphhydryl, carbamido, or carboxyl; phenyl optionally substituted by one or more halogen atoms, trifluoromethyl, nitro, hydroxyl, or alkyl, alkoxy or acyloxy having from 1 to 4 carbon atoms; phenyl-alkyl or phenylalkenyl having from 1 to 4 carbon atoms and optionally a double or triple bond in the side chain, optionally substituted by one or more halogen atoms, nitro, hydroxyl methoxy or alkyl having from 1 to 4 carbon atoms; monocyclic, bicyclic or tricyclic, cycloalkyl or cycloalkenyl, having from 3 to 10 carbon atoms, optionally substituted by one or more halogen atoms, nitro, hydroxyl or alkyl or alkoxy, having from 1 to 4 carbon atoms; furfuryl, thenyl, pyrrolymethyl, thiazolylmethyl, oxazolylmethyl, pyridinemethyl, piperidinemethyl, pyrazinemethyl or morpholinemethyl, optionally substituted by from one to three halogen atoms, or alkyl or alkoxy having from 1 to 3 carbon atoms, or by one nitro group; or each of

R_4 and R_9 is a hydrogen atom or methyl or ethyl; each of

R_5, R_{10} and R_{14} is a hydrogen atom or alkyl having from 1 to 6 carbon atoms and optionally substituted by from 1 to 3 halogen atoms or alkoxy having from 1 to 4 carbon atoms; each of

R_6 and R_{11} is phenyl or naphthyl, optionally substituted by halogen atoms, alkyl or alkoxy having from 1 to 4 carbon atoms, nitro, hydroxyl, acyloxy having from 1 to 4 carbon atoms, amino, C_1 to C_6 alkylamino, or di(C_1 to C_6 alkyl)-amino; a heterocyclic radical having from 5 to 7 ring members and 1 to 2 hetero-atoms each of which may be nitrogen, sulphur or oxygen, and optionally substituted by halogen atoms, alkyl or alkoxy having from 1 to 4 carbon atoms, nitro or trifluoromethyl; or

R_6 and/or R_{11} together with R_5 and/or R_{10}, respectively, and the carbon atom, at the double bond, linking them, form(s) a cycloalkylidene or cycloalkenylidene ring, having from 3 to 7 carbon atoms; and

R_{15} is straight-chain or branched alkoxy or alkenyloxy having from 1 to 6 carbon atoms, optionally substituted by one or more halogen atoms or alkoxy having 1 or 2 carbon atoms; alkyl-thio or alkenylthio having from 1 to 6 carbon atoms, optionally substituted by from 1 to 3 halogen atoms or alkoxy or carboxyl; phenylthio optionally substituted by from 1 to 3 halogen atoms or alkyl or alkoxy having 1 or 2 carbon atoms; hydrazinyl optionally substituted by C_1 to C_6 alkyl, aryl optionally substituted by phenyl optionally substituted by from 1 to 3 halogen atoms, C_1 to C_6 alkyl or alkoxy, or a heterocyclic radical having 1 or 2 nitrogen, oxygen and/or sulphur atoms, and optionally fused with a phenyl ring; straight-chain or branched, mono- or di-(alkyl- or alkenyl-) amino having from 1 to 6 carbon atoms in each alkyl or alkenyl moiety and optionally substituted by halogen atoms, hydroxyl, alkoxy having 1 or 2 carbon atoms, amino, lower mono- or di-alkylamino, a sulphonic acid radical or a phosphate or heterocyclic radical; mono- or di-phenylalkylamino, having from 1 to 4 carbon atoms in each aliphatic moiety and optionally substituted by from 1 to 3 halogen atoms, or alkyl or alkoxy having from 1 to 4 carbon atoms; a heterocyclic group containing a nitrogen atom, having from 4 to 7 ring members, optionally containing 1 or 2 further hetero-atoms and optionally substituted by C_1 to C_6 alkyl, C_1 to C_6 hydroxyalkyl or phenyl; mono- or di-(cyclo- propyl-, -butyl-, -pentyl-, -hexyl- or -heptyl-) amino, optionally substituted by C_1 to C_6 alkyl, alkenyl or alkinyl, or by aryl.

3. A composition according to claim 1 in which the active ingredient is a compound substantially as described hereinbefore with particular reference to any one of Examples 1 to 222.

4. A composition according to claim 1 in which the active ingredient is any compound as defined in claim 1 which is hereinbefore specifically mentioned other than those mentioned in claim 3.

5. A pharmaceutical composition containing as an active ingredient a compound as defined in any of claims 1 to 4 in the form of a sterile or isotonic aqueous solution.

6. A composition according to any of claims 1 to 4 containing from 1 to 90% of the said active ingredient, by weight.

7. A medicament in dosage unit form comprising a compound as defined in any of claims 1 to 4.

8. A medicament in the form of ampoules containing a compound as defined in any of claims 1 to 4.

9. A method for the lysis of non-human animal tissues and/or tumours which comprises administering to the animals a compound as defined in any of claims 1 to 4 either alone or in admixture with a diluent or in the form of a medicament according to claim 7 or 8.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43 Bloomsbury Square,
London, WC1A 2RA.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1980
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.