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[54] Title: PARASITICIDES AND INSECTICIDES

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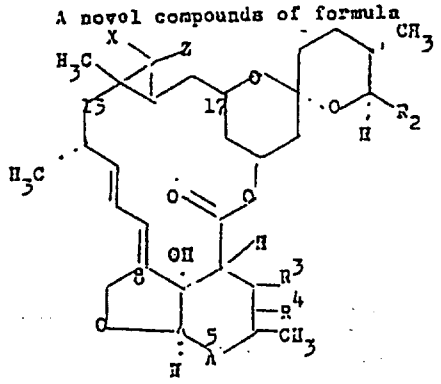
[57] ABSTRACT

A novel compounds of formula



(I)

see attached sheet

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cont. ABSTRACT

in which

A is a $-\underset{\underset{OR_1}{|}}{CH}-$, $-\underset{\underset{O}{\|}}{C}-$ or $-\underset{\underset{N-OR_{11}}{\|}}{C}-$ group

wherein R_1 is hydrogen or an OH-protecting group, and R_{11} is hydrogen, an OH-protecting group, or an alkyl, cycloalkyl or acyl group,

R_2 is methyl, ethyl, isopropyl, sec.-butyl or a $-C(CH_3) = CH - E$ group wherein E is methyl, ethyl or isopropyl,

R_3 and R_4 together represent a bond between the two carbon atoms to which they are bonded, or together represent a $-C(X')(Z')-$ group wherein X' and Z' each represents, independently of the other, hydrogen or halogen and

X and Z each represents, independently of the other hydrogen or halogen,

the preparation of the novel compounds and the use thereof for controlling parasites of productive livestock and for controlling harmful insects.

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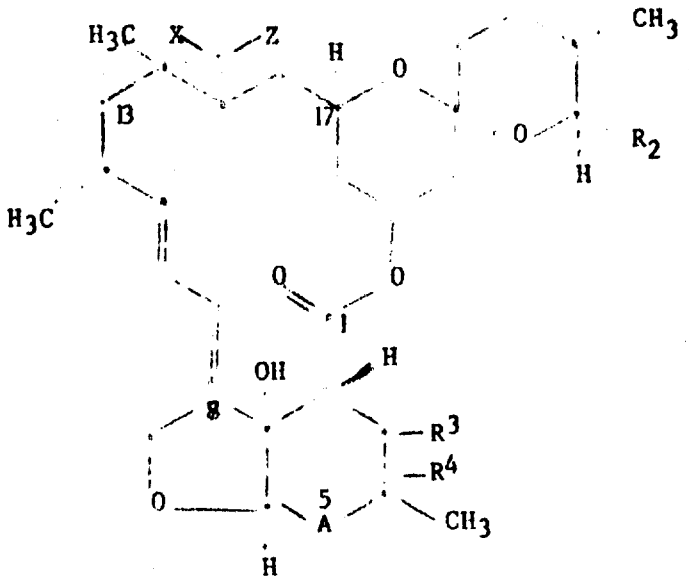
PARASITICIDES AND INSECTICIDES

ABSTRACT

A novel compounds of formula



(I)

in which

A is a $-CH-$ (OR_I), $-C-$ (=O) or $-C-$ (=$N-OR_{II}$) group

wherein R_I is hydrogen or an OH-protecting group, and R_{II} is hydrogen, an OH-protecting group, or an alkyl, cycloalkyl or acyl group,

R_2 is methyl, ethyl, isopropyl, sec.-butyl or a $-C(CH_3) = CH - E$ group wherein E is methyl, ethyl or isopropyl,

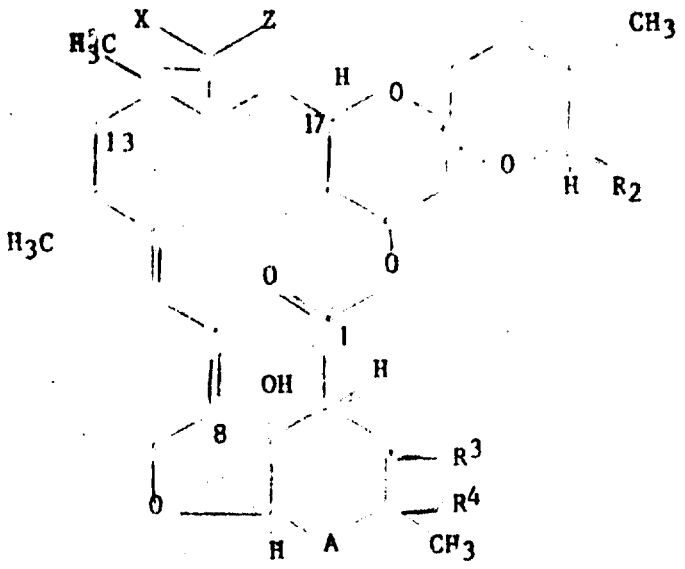
R_3 and R_4 together represent a bond between the two carbon atoms to which they are bonded, or together represent a $-C(X')(Z')-$ group wherein X' and Z' each represents, independently of the other, hydrogen or halogen and

X and Z each represents, independently of the other, hydrogen or halogen,

the preparation of the novel compounds and the use thereof for controlling parasites of productive livestock and for controlling harmful insects.

PARASITICIDES AND INSECTICIDES

The present invention relates to milbemycin derivatives of formula I



(I)

in which

A is a $-\underset{\underset{OR_I}{|}}{CH}-$, $-\underset{\underset{O}{||}}{C}-$ or $-\underset{\underset{N-OR_{II}}{||}}{C}-$ group

wherein R_I is hydrogen or an OH-protecting group, and R_{II} is hydrogen, an OH-protecting group, or an alkyl, cycloalkyl or acyl group,

R_2 is methyl, ethyl, isopropyl, sec.-butyl or a $-C(CH_3) = CH - E$ group wherein E is methyl, ethyl or isopropyl,

R_3 and R_4 together represent a bond between the two carbon atoms to which they are bound, or together represent a $-C(X')(Z')-$ group wherein X' and Z' each represents, independently of the other, hydrogen or halogen, and

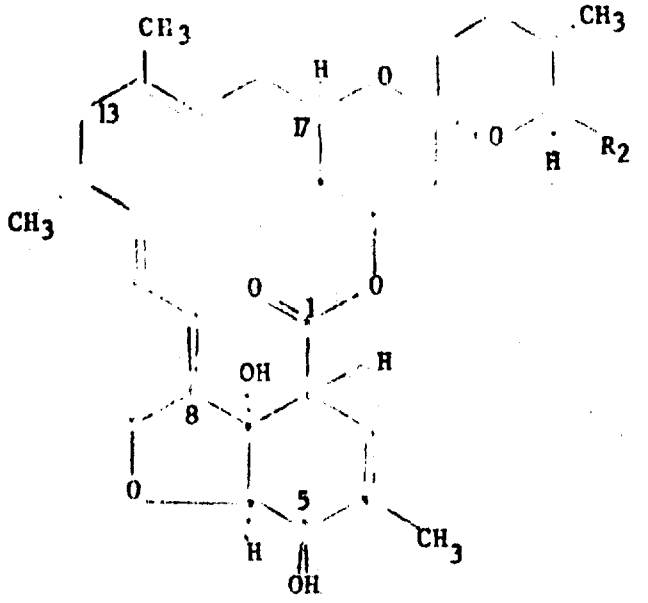
X and Z each represents, independently of the other, hydrogen or halogen.

The invention also relates to the preparation of compounds of formula I and to the use thereof for controlling harmful insects or parasites that infest productive livestock, and to compositions that contain at least one of these compounds as active ingredient.

Throughout this specification, compounds in which R_2 is sec.-butyl are also to be regarded as milbemycin derivatives although, according to conventional classification, they are derived from avermectin derivatives. Avermectin aglycons (having an OH group in the 13a - position) can, however, be converted into milbemycin

homologues in accordance with US-PS 4,173,571.

Naturally occurring milbemycins (R_1=H; R_2=CH_3, C_2H_5 or iso-C_3H_7)correspond to formula M given below (C_{14}-C_{15}-double bond):

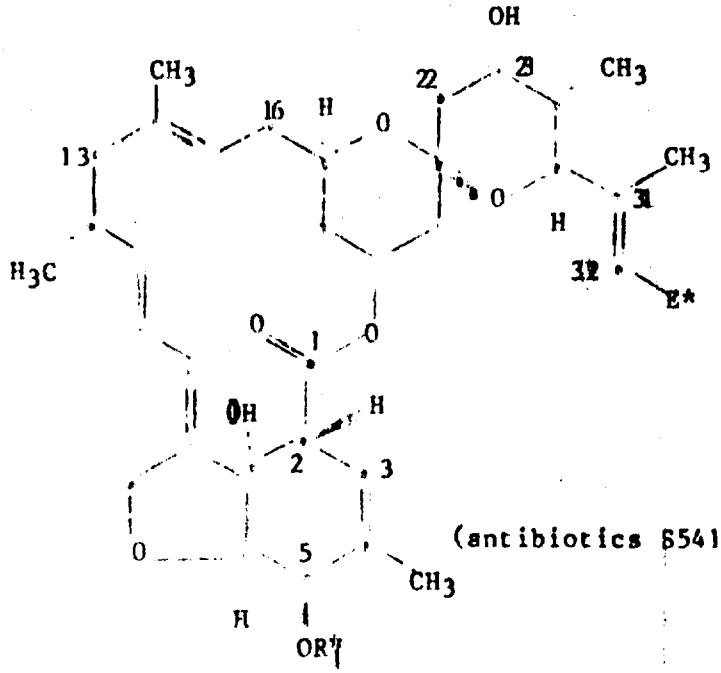


(M)

R_2 = CH_3	milbemycin A_3 (US-PS 3,950,360)
R_2 = C_2H_5	milbemycin A_4 (US-PS 3,950,360)
R_2 = isoC_3H_7	milbemycin D (US-PS 4,346,171)
R_2 = sec.-C_4H_9	13-deoxy-22,23-dihydro-C-076-Bla-aglycon (US-PS 4,173,571, GB 1,573,955 and DE-OS 2717040).

In avermectins, an α - L - oleandrosyl - α - L - oleandrose radical, which is linked via the oxygen atom in α - configuration with the macrolid molecule, is present in the 13-position. Avermectins also differ structurally from milbemycins by a 23-OH group or $\Delta^{22,23}$ -double bond and usually by a substituent R_2 = sec. $-C_4H_9$. By hydrolysing the sugar residue of avermectins it is possible easily to obtain corresponding avermectin aglycons that contain a 13 α - hydroxy group adjacent to a C = C double bond. As tated above, avermectin aglycons can be converted into milbemycin homologues. In the milbemycin derivatives of this Application the 22 - C atom and the 23 - C atom together form the structural moiety $-CH_2-CH_2-$ as also occurs in formula M.

The constitution of natural antibiotics S541 is known from DE - OS 35 32 794 and is as follows:



(antibiotics S541)

Factor A	E*=isoC$_3$7	R$_1$=H
Factor B	E*=CH$_3$	R$_1$=CH$_3$
Factor C	E*=CH$_3$	R$_1$=H
Factor D	E*=C$_2$H$_5$	R$_1$=H
Factor E	E*=[illegible]	R$_1$=CH$_3$
Factor F	E*=isoC$_3$H$_7$	R$_1$=CH$_3$

In order to simplify nomenclature, hereinafter the derivatives of antibiotic S541 are classified, according to factor, as derivatives of S541A, S541B, S541C, S541D, S541E or S541F.

Compounds of formula II wherein R_2 is a $-C(CH_3) = CH - E$ group and E is as defined for formula II, which can be used as starting materials in the process of the invention, can be prepared from the natural antibiotics S541 in a manner known per se.

The hydroxy group in the 23-position in the antibiotics S541 can be removed analogously to the method described in US-PS 4,328,335, and the antibiotics S541 can thus be converted into the corresponding 23-deoxy derivatives. Those compounds having a free 5-OH group ($R_1^* = H$) must first be protected selectively by reaction with one of the silylating reagents $Y - Si(R_6)(R_7)(R_8)$ mentioned below or with tert.-butyldimethylsilyloxyacetyl chloride. The reaction of these protected compounds in which R_1^* has been replaced by $Si(R_6)(R_7)(R_8)$ or by $C(= O)CH_2OSi - (CH_3)_2tert.-C_4H_9$ and the 23-C atom has been substituted by OH, with p-methylphenylchlorothionoformate yields derivatives of the antibiotics S541 that are substituted at the 23-position by $p-CH_3-C_6H_4-O-C(= S)-O-$. These

23-O-(4-methylphenoxy)-thiocarbonyl derivatives of antibiotics S541 are then reduced with tributyltin hydride in toluene in the presence of azobisisobutyronitrile at from 80 to 120°C to form the corresponding 23-deoxy derivatives (23-position unsubstituted).

Compounds of formula I wherein R_2 is methyl, ethyl, isopropyl of sec.-butyl are prefered, especially those in which A represents the $-CH(OR_1)-$ and $-C(=N-OR_{11})-$ groups, and R_1 and R_{11} each represents hydrogen.

Throughout this specification, OH-protecting groups for the substituents R_1 and/or R_{11} shall be understood as being the protective functional groups conventionally used in organic chemistry. These are especially acyl and silyl groups. Suitable acyl groups are, for example, $R_5-C(O)-$ radicals wherein R_5 is C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl, or a representative of the group comprising phenyl and benzyl which is unsubstituted or is substituted by at least one substituent selected from the group comprising halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and

is preferably C_1-C_6-alkyl, C_1-C_6-haloalkyl, or phenyl that is unsubstituted or is substituted by halogen, C_1-C_3-alkyl, CF_3 or by nitro. Suitable silyl groups for the radical R_1 are the $-Si(R_6)(R_7)(R_8)$ radical wherein R_6, R_7 and R_8, preferably independently of one another, each represents C_1-C_4-alkyl, benzyl or phenyl and, for example, together with the silicon atom form any one of the groups trimethylsilyl, diphenyl-tert.-butylsilyl, bis (isopropyl) methylsilyl, triphenylsilyl and, especially, tert.-butyldimethylsilyl. The 5-OH group may also be etherified in the form of the benzyl ether or methoxyethoxy methyl ether or, in accordance with published European Patent No. 185,623, may be bonded to a carbohydrate residue, referred to hereinafter as a sugar residue for the sake of simplicity.

In compounds of formula I in which R_1 is a silyl group, especially tert.-butyldimethylsilyl, or is an acyl group, for example an R_5-C(O)- group wherein R_5 has the meanings given above and is especially methyl, R_2, R_3, R_4, X and Z are preferably as defined in

Tables 1 and 2. In compounds of formula I in which R_{11} is a silyl group, especially tert.-butyldimethylsilyl, or is an acyl group, for example an R_5-C(O)- group wherein R_5 has the meanings given above and is especially methyl, R_2, R_3, R_4, X and Z are preferably as defined in Tables 5 add 6.

Compounds of formula I wherein R_1 and/or R_{11} represent(s) a protecting group can be converted into the highly active free 5-hydroxy derivatives (R_1 = H) or 5-hydroxyimino derivatives (R_{11} = H) by simple removal of the protecting group, for example by hydrolysis, and thus have also the character of intermediates. The biological value of these compounds is not, however, reduced by the protecting group or the sugar residue.

Depending on the number of carbon atoms indicated, the term "alkyl" as a substituent or as part of a substituent shall be understood as meaning, for example, the following groups: methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl or decyl, and the isomers thereof, such as, for example, isopropyl,

isobutyl, tert.-butyl or isopentyl. When R_{11} represents al alkyl group, it contains preferably from 1 to 8, especially from 1 to 4, carbon atoms.

Suitable cycloalkyl groups are mono- to tetra-cyclic groups, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, hydrindane, bicyclopheptane, bicyclooctane, norbornane, bornane or adamantyl. These cycloaliphatic groups are preferably unsubstituted or mono- or poly-substituted by methyl. When R_{11} represents a cycloalkyl group, it contains prefebably from 3 to 6 carbon atoms.

The above-mentioned acyl and silyl groups serve as protecting groups not only for the hydroxy groupspppreseht in the substituent A but also for all other hydroxy groups present in the compounds of the invention or in the precursors of those compounds.

Halogen in the meaning of X, X', Z and Z' is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine. Halogen atoms bonded to the same

carbon atom are preferably identical with one another. Preferred dihalomethylene groups -C(X)(Z)- and -C(X')(Z')- are dichloromethylene and dibromomethylene.

The following subgroups of compounds of formula I are preferred on account of their pronounced activity against pests:

Group Ia: compounds of formula I wherein A is any one of the groups $-CH(OR_1)-$, $-C(O)-$ or $-C(=N-OH)-$ wherein R_1 is hydrogen, a silyl group or a monosaccharide group, R_2 is methyl or ethyl, R_3 and R_4 together form a bond between the two carbon atoms to which they are bound, or together form a $-C(X')(Z')-$ group wherein X' and Z' each represents, independently of the other, hydrogen or halogen, and X and Z each represents, independently of the other, hydrogen or halogen;

Group Ib: compounds of formula I wherein A is any one of the groups $-CH(OR_1)-$, $-C(O)-$ or $-C(=N-OH)-$ wherein R_1 is hydrogen, acetyl, tert.-butyldimethylsilyl or 2, 3, 4, 6-

tetraacetylglucopyranosyl, R_2 is methyl or ethyl, R_3 and R_4 together form a bond between the two carbon atoms to which they are bound, or together form a $-C(Cl_2)-$ group, X is hydrogen, chlorine, bromine or fluorine, and Z is hydrogen, chlorine, bromine or fluorine, X preferably being identical with X in compounds in which X is chlorine, bromine or fluorine;

Group Ic: compounds of formula I wherein A is any one of the groups $-CH(OR_1)-$, $-C(O)-$ or $-C(=N-OH)-$ wherein R_1 is hydrogen, tert.-butyldimethylsilyl or 2, 3, 4, 6-tetraacetyl-glucopyranosyl, R_2 is methyl or ethyl, R_3 and R_4 together form a bond between the two carbon atoms to which they are bound, or together form a $-C(Cl_2)-$ group, X is hydrogen, chlorine or bromine, and Z is hydrogen, chlorine or bromine, Z preferably being identical with X in compounds in which X is chlorine or bromine;

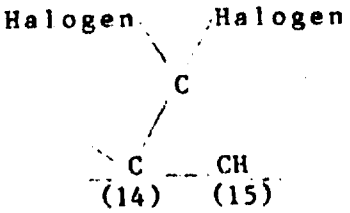
Group Id: compounds of formula I wherein A is a $-CH(OH)-$ or $-C(=N-OH)-$ group, R_2 is methyl or ethyl, R_3 and R_4 togebher form a

bond between the two carbon atoms to which they are bound, X is hydrogen, chlorine, bromine or fluorine, and Z is hydrogen, chlorine, bromine or fluorine;

Group Ie: compounds of formula I wherein A is a -CH(OH)- or -C(= N - OH)- group, R_2 is methyl or ethyl, R_3 and R_4 together from a bond between the two carbon atoms to which they are bound, and X and Z are identical with each other and each represents hydrogen, chlorine, or bromine, or X is hydrogen and Z is chlorine or bromine;

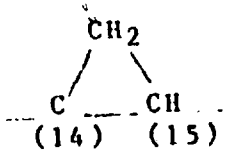
Group I f: compounds of formula I wherein A is a -CH(OH)- group, R_2 is methyl or ethyl, R_3 and R_4 together form a bond between the two carbon atoms to which they are bound, or together form a $-CCl_2-$ group, X is hydrogen, chlorine or bromine, and Z is hydrogen, chlorine or bromine.

Within the scope of this Application, the structural element



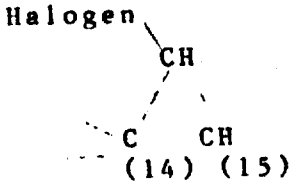
is defined by the term "14, 15-dihalomethylene-14, 15-dihydro";

the structural element



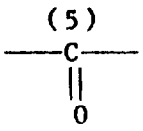
by the term "14, 15-methylene-14, 15-dihydro";

the structural element



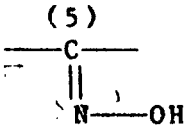
by the term "14, 15-monohalomethylene-14, 15-dihydro";

the structural element



by the term "5-oxo";

and the structural element



by the term "5-hydroxyimino".

The terms used for the optionally halogenated C_3-C_4-methylene group are analogous to those given for C_{14}-C_{15}.

Preferred individual compounds are:

5-O-(tert.-butyldimethylsilyl)-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4,

5-O-(tert.-butyldimethylsilyl)-3, 4-dichloromethylene-14, 15-dichloromethylene-3, 4, 14, 15-tetrahydromilbemycin A_4,

3, 4-dichloromethylene-14, 15-dichloromethylene-3, 4, 14, 15-tetrahydromilbemycin A_4,

5-O-(tert.-butyldimethylsilyl)-14, 15-dibromomethylene-14, 15-dihydromilbemycin A_4,

5-O-(2, 3, 4, 6-tetraacetylglucopyranosyl)-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4,

5-oxo-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4,

5-hydroxyimino-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4,

14, 15-dichloromethylene-14, 15-dihydromilbemycin A_3,

5-O-(tert.-butyldimethylsilyl)-14, 15-monobromomethylene-14, 15-dihydromilbemycin A_4,

5-O-(tert.-butyldimethylsilyl)-14, 15-methylene-14, 15-dihydromilbemycin A_4,

14, 15-methylene-14, 15-dihydromilbemycin A_4, and especially

14, 15-dibromomethylene-14, 15-dihydromilbemycin A_4,

14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4,

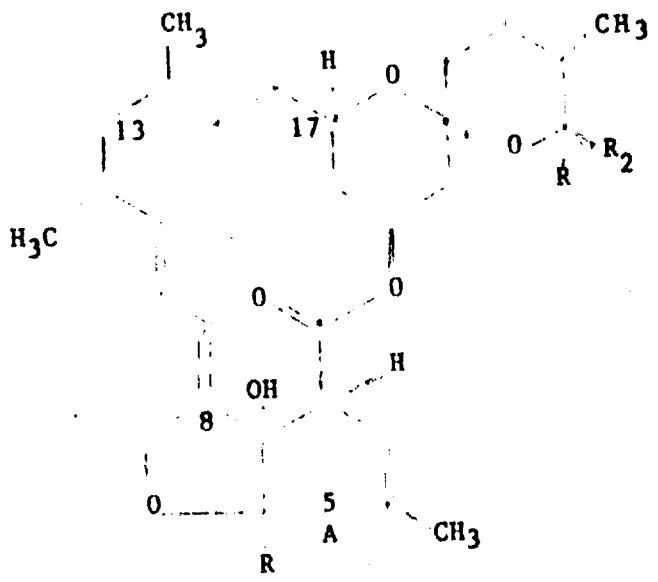
14, 15-monobromomethylene-14, 15-dihydromilbemycin A_4 and

14, 15-monochloromethylene-14, 15-dihydromilbemycin A_4.

The preparation of compounds of formula I can be effected analogously to those methods described for the addition of carbenes to olefinically unsaturated structures in the literature relating to carbenes, for example in Liebigs Ann. Chem. 744, 42-50 (1971) and in Organic Chemistry, Vol. 1, "Carbene Chemistry", W. Kirmse,

Academic Press, New York, London, 1971, Part II: "Structure and Reactivity of Carbenes and Carbenoids", especially Chapter 8, including the further reading material cited in the above-mentioned literature.

To prepare compounds of formula I, a compound of formula II



(II),

in which A and R_2 are as defined for formula I, is reacted with a carbene of formula IIIa

C(X)(Z) (IIIa),

in which X and Z are as defined for formula I and which is formed in situ and is dissolved in an inert solvent, and, if desired, a resulting compound of formula I in which R_3 and R_4 together form a bond between the carbon atoms to which they are bound is reacted with a carbene of formula IIIb

$$C(X')(Z') \qquad \text{(IIIb)},$$

in which X' and Z' are as defined for formula I and which is formed in situ and is dissolved in an inert solvent. Suitable inert solvents are, for example, 1, 2-dimethoxyethane, bis(2-methoxyethyl) ether, acetonitrile, dichloromethane, chloroform, dichloroethane and alkanes, such as pentane or hexane. Temperature and reaction time are determined to a large extent by the conditions of the chosen carbene preparation. The temperatures are generally within a range of from -70°C to +180°C, preferably from 0°C to 40°C, and the reaction times vary within a range of approximately from 10 minutes to 2 days. Whereas, at low temperature, compounds

of formula I in which R_3 and R_4 together form a bond between the two carbon atoms to which they are bound (monoadduct) will preferably be formed, at higher temperatures the proportion of compounds in which R_3 and R_4 together form a -C(X')(Z')- group (diadduct) will predominate.

The manufacture of carbenes of formulae IIIa and IIIb can be effected in conventional manner, such as, for example

- from a mercury salt, such as, for example, phenyl(trifluoromethyl)-mercury at approximately 80°C;
- from sodium difluorochloroacetate from 100°C to 140°C;
- from trichloroacetic acid ethyl ester and a base, such as, for example, sodium methoxide at approximately from 0°C to 20°C;
- from chloroform or bromoform and a base (for example 30-50% aqueous sodium hydroxide solution, potassium tert.-butoxide or butyllithium) with or without phase-transfer catalysts (such as, for example, tetraalkylammonium chlorides or bromides), at temperatures of approximately from

-40°C to +60°C, chloroform or bromoform simultaneously serving as solvent (yields dihalocarbenes);

- from methylene chloride or methylene bromide and a base (for example 30-50% aqueous sodium hydroxide solution, potassium tert.-butoxide or butyllithium) with or without phase-transfer catalysts (such as, for example, tetraalkylammonium chlorides or bromides), at temperatures of approximately from -40°C to +60°C, it being possible for methylene chloride or methylene bromide to serve simultaneously as solvent (yields monohalocarbenes);

- from chloroform, bromoform, methylene chloride or methylene bromide with solid sodium hydroxide or solid potassium hydroxide with exposure to ultrasonic waves.

In compounds of formula I it is possible by reduction to convert mono- and di-halomethylene groups into unsubstituted methylene groups or to convert dihalomethylene groups into monohalomethylene groups. The reduction can be carried out analogously to known methods, for example using tributyltin hydride or zinc and acid.

Compounds of formula I can be obtained, for example, either by converting a milbemycin of formula M or the 23-deoxy derivatives of S541A, S541C or S541D into a compound of formula II in which A has a meaning other than -CH(OH)- and then reacting with a carbene, or by first reacting a compound of formula M or the 23-deoxy derivative of S541A, S541C or S541D with a carbene and then converting the resulting compound into a compound of formula I in which A has a meaning other than -CH(OH)-.

It is also possible for substituents at the 5-C atom in compounds of formulae I and II to be removed and, if desired, replaced by other substituents provided that these correspond to the definitions according to the invention. The removal and introduction of substituents corresponding to the definitions according to the invention can be carried out by methods that are known per se. In order to introduce acyl, silyl and saccharide groups, it is advantageous to use as starting materials compounds of formulae I and II in which A

represents -CH(OH)- or -C(= N - OH)-, or compounds of formula M or the 23-deoxy derivatives of S541A, S541C or S541D. Compounds of formula I or II in which A represents -C(= N - OR_{11})- can be prepared, for example, by reacting compounds of formula I or II in which A represents -C(O)- with hydroxylamine or salt thereof and, if desired, subsequently introducing the substituent R_{11}, which substituent has the meaning given for formula I with the exeeption of hydrogen, or by carrying out the reaction with a compound of formula NH_2-OR_{11} or in which R_{11} has the meanings given for formula I with the exception of hydrogen, or with a salt thereof. Suitable salts are, for example, those of the above-mentioned amino compounds with sulphuric acid, nitric acid and, especially, hydrochloric acid. The reaction is advantageously carried out in a suitable solvent, for example a lower alkanol, such as methanol, ethanol, propanol; an ethereal compound, such as tetrahydrofuran or dioxan; an aliphatic carboxylic acid, such as acetic acid or propionic acid; water; or in mixtures of

these solvents with each other or with other conventional inert solvents. The reaction temperatures may vary within wide limits. The reaction is advantageously carried out in the range of approximately from +10° to +100°C. If hydroxylamine is employed in the form of one of its salts, for example in the form of the hydrochloride, in order to bind the acid it is advantageous to add one of the bases customarily used for that purpose and, where appropriate, to carry out the reaction in the presence of a water-binding agent, for example a molecular sieve. Suitable bases are organic and inorganic bases, for example tertiary amines such as trialkylamines (trimethylamine, triethylamine, tripropylamine etc.), pyridine and pyridine bases (4-dimethylaminopyridine, 4-pyrrolidylaminopyridine etc.), oxides, hydrides and hydroxides, carbonates and hydrogen carbonates of alkali metals and alkaline earth metals (CaO, BaO, NaOH, KOH, NaH, $Ca(OH)_2$, $KHCO_3$, $NaHCO_3$, $Ca(HCO_3)_2$, K_2CO_3, Na_2CO_3), and alkali metal acetates such as CH_3COONa or CH_3COOK. Also suitable are alkali metal alcoholates such

as C_2H_5ONa, $n\text{-}C_3H_7ONa$ etc.. Thriethylamine is preferred.

Compounds of formulae I and II in which A represents -C(O)- can be obtained, for example, by treating compounds of formula I or II in which A represents -CH(O)- with a reagent suitable for oxidation. Suitable oxidising agents are, for example, activated manganese dioxide, oxalyl chloride/dimethyl sulphoxide/triethylamine or chromium trioxide/pyridine. Another suitable process is the Oppenauer oxidation in which compounds of formulae I and II in which A represents -CH(O)- are reacted with a ketone, preferably cyclohexanone or acetone, in the presence of an aluminium alcoholate, prefesably aluminium isopropoxide or aluminium tert.-butoxide.

The oxidation is advantageously carried out in an inert solvent. Suitable solvents are alkanes, such as, for example, hexane, heptane or octane, aromatic hydrocarbons, such as,,for example, benzene, toluene or xylenes, or, preferably, chlorinated hydrocarbons, especially methylene chloride. The oxidation is advantageously carried out at temperatures of from

-80°C to +60°C, preferably from -60°C to +30°C.

From compounds of formulae I and II in which A represents a -C(O)- group it is possible, by reduction in a manner known per se, to obtain again compounds in which A represents a -CHOH- group. The reduction can be effected, for example, by catalytic hydrogenation with a platinum or Raney nickel catalyst or in accordance with the Meerwein-Ponndorf-Verley reduction with aluminium isopropoxide in isopropanol,

The introduction of a saccharidei into compounds of formula M, into 23-deoxy derivatives of S541A, S541C or S541D or into compounds of formulae I and II in which A represents -CH(OH)- can be effected by reacting these compounds with the corresponding saccharide, advantageously using methods analogous to those generally known in sugar chemistry for linking reactions, such as, for example, the Koenigs-Knorr method, the Ag-triflate process, the so-called orthoester process, the phenylthio systhesis or the 2-pyridylthio method (in accordance with published

European Patent Specification No. 185,623).

For the preparation of compounds of formula II in which R_1 is an acyl group, the 5-OH group of a milbemycin of formula M or of a 23-deoxy derivative of S541A, S541C or S541D is acylated. The introduction of the acyl group is usually carried out using the corresponding acyl halides or acyl anhydrides, the term "acyl halide" meaning acyl chloride or acyl bromide, and is preferably used to introduce the $R_5C(O)$- group defined at the beginning.

For the preparation of compounds of formula II in which R_1 is a silyl group, the 5-OH group of a milbemycin of formula M or of a 23-deoxy derivative of S541A, S541C or S541D is silylated. For the silylation there is advantageously used a silane of formula $Y\text{-}Si(R_6)(R_7)(R_8)$ in which R_6, R_7 and R_8 have the meanings mentioned hereinbefore and Y represents a silyl leaving group. Silyl leaving groups Y include, for example, bromine, chlorine, cyano, azido, acetamide, trifluoroacetoxy and trifluoromethanesulphonyloxy. This list does not constitute any limitation; the

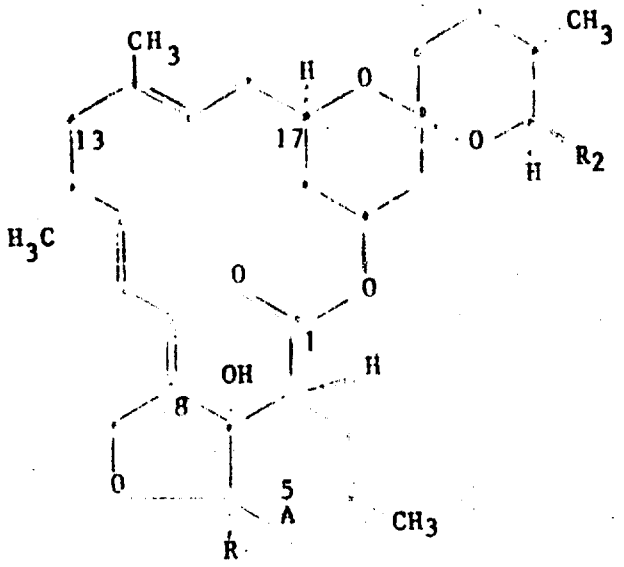
skilled person will know other typical silyl leaving groups.

5-O-acylations and 5-O-silylations are carried out in anhydrous medium, preferably in inert solvents and, especially, in aprotic solvents. The reaction proceeds advantageously within a temperature range of from 0° to $+80^{\circ}C$, preferably from $+10^{\circ}$ to $+40^{\circ}C$. It is preferably to add an organic base. Suitable organic bases are, for example, tertiary amines such as triethylamine, triethylenediamine, triazole and preferably pyridine, imidazole or 1, 8-diazabicyclo [5.4.0] undec-7-ene (DBU).

The removal of these silyl and acyl radicals R_I or R_{II} in the 5-position is effected by selective mild hydrolysis ($\longrightarrow$ R_I or R_{II} = H) for example with dilute acids such as dilute HCl, HF, arylsulphonic acid in alcoholic or aqueous solution, or in accordance with another method familiar to the skilled person. Acyl radicals are preferably removed under basic conditions (for example in alcoholic ammonia solution).

The process of the invention for the preparation of compounds of formula I wherein A,

R_2, R_3, R_4, X and Z are as defined for formula I comprises reacting a compound of formula II



(II),

in which A and R_2 are as defined for formula I, with a carbene of formula IIIa

$$C(X)(Z) \qquad \text{(IIIa)}$$

in which X and Z are as defined for formula I and which is formed <u>in situ</u> and is dissolved in an inert solvent and, in resulting compounds,

if desired i) reducing a -C(halogen)(halogen)- group that represents -C(X)(Z)- to a -CH(halogen)- or $-CH_2-$ group or ii) reducing a -CH(halogen)- group that represents -C(X)(Z)- to a $-CH_2-$ group or iii) convetting the group that represents A into another of the groups defined under A, or reacting resulting compounds in which R_3 and R_4 together form a bond between the two carbon atoms to which they are bound with a carbene of formula IIIb

$$C(X')(Z') \qquad \text{(IIIb)}$$

in which X' and Z' are as defined for formula I and which is formed <u>in situ</u> and is dissolved in an inert solvent, and, in resulting compounds, if desired iv) reducing a -C(halogen)(halogen)- group that represents -C(X)(Z)- or -C(X')(Z')- to a -CH(halogen)- or $-CH_2-$ group or v) reducing a -CH(halogen)- group that represents -C(X)(Z)- or -C(X')(Z')- to a $-CH_2-$ group or vi) converting the group that represents A into another of the groups defined under A.

The present invention relates also to the described process for the preparation of compounds of formula I.

The compounds of formula I are eminently suitable for controlling pests of animals and plants, especially ectoparasites of animals. These last-mentioned pests comprise, of the order Acarina, especially pests of the families Ixodidae, Ermanyssidae, Sarcoptidae and Psoroptidae; the orders Mallophaga, Siphonaptera and Anoplura (for example the Haemotopinidae family); and the order Diptera, especially pests of the families Muscidae, Calliphoridae, Oestridae, Tabanidae, Hippoboscidae and Gastrophilidae.

The compounds I can also be used to control hygiene pests, especially of the order Diptera comprising the families Sarcophagidae, Anophilidae and Culicidae; of the order Orthoptera, of the order Dictyoptera (for example the Blattidae family) and of the order Hymenoptera (for example the Formicidae family).

The compounds I also have lasting action against mites and insects that are parasites of

plants. When used to control spider mites of the order Acarina, they are effective against eggs, nymphs and adults of Tetranychidae (Tetranychus spp. and Panynychus spp.).

They have high activity against sucking insects of the order Homoptera, especially against pests of the families Aphididae, Delphacidae, Cicadellidae, Psyllidae, Coccidae, Diaspididae and Eriophididae (for example the rust mite on citrus fruits); of the orders Hemiptera, Heteoptera and Thysanoptera; and against plant-eating insects of the orders Lepidoptera, Coleoptera, Diptera and Orthoptera.

They are also suitable as soil insecticides against soil pests.

The compounds of formula I are therefore effective against all developmental stages of sucking and feeding insects in crops such as cereals, cotton, rice, maize, soybeans, potatoes, vegetables, fruits, tobacco, hops, citrus fruit, avocados and others.

The compounds of formula I are also effective against plant nematodes of the species Meloidogyne,

Heterodera, Pratylenchus, Ditylenchus, Radopholus, Rhizoglyphus and others.

The compounds are also effective against helminths in all developmental stages, and among thee the endoparasitic nematodes can be the cause of severe diseases in mammals and fowls, for example sheep, pigs, goats, cattle, horses, donkeys, dogs, cats, guinea pigs, cage birds. Typical nematodes having this indication are: Haemonchus, Trichostrongylus, Ostertagia, Nematodirus, Cooperia, Ascaris, Bunostomum, Oesophagostomum, Chabertia, Trichuris, Strongylus, Trichonema, Dictyocaulus, Capillaria, Heterakis, Toxocara, Ascaridia, Oxyuris, Ancylostoma, Uncinaria, Toxascaris and Parascaris. The particular advantage of the compounds of formula I is their activity against parasites that are resistant to benzimidazole-based active substances.

Certain species of the genera Nematodirus, Cooperia and Oesophagostomum attack the intestinal tract of the host animal, whereas others of the genera Haemonchus and Ostertagia parasiticise the stomach and those of the genus Dictyocaulus the lung tissue. Parasites of the families

Filariidae and Setariidae are found in internal cell tissue and in organs, for example in the heart, blood vessels and lymph vessels and in subcutaneous tissue. In this connection, particular metnion should be made of the dog heartworm, Dirofilaria immitis. The compounds of formula I are highly effective against these parasites.

The compounds of formula I are also suitable for controlling pathogenic parasites in humans, among which parasites there may be mentioned as typical representatives occurring in the alimentary tract those of the genera Ancylostoma, Necator, Ascaris, Strongyloides, Trichinella, Capillaria, Trichuris and Enterobius. The compounds of this invention are also effective against parasites of the genera Wuchereria, Brugia, Onchocerca and Loa of the Filariidae family, which occur in the blood, in tissue and various organs, and, in addition, against Dracunculus and parasites of the genera Strongyloides and Trichinella which infest in particular the gastro-intestinal tract.

The compounds of formula I are used in unmodified form, or preferably together with the adjuvants conventionally employed in the art of formulation, and are therefore formulated in known manner e.g. to emulsifiable concentrates, directly sprayable or dilutable solutions, dilute emulsions, wettable powders, soluble powders, dusts, granulates, and also encapsulations in e.g. polymer substances. As with the nature of the compositions, the methods of application such as spraying, atomising, dusting, scattering or pouring, are chosen in accordance with the intended objectives and the prevailing circumstances.

The compounds of formula I are administered to warm-blooded animals in amounts of from 0.01 to 10 mg/kg of body weight. Over enclosed crop areas they are applied in amounts of from 10 g to 1000 g per hectare. they are also used in pens, paddocks, stalls and other livestock buildings.

The formulations, i.e. the compositions, preparations or mixtures containing the compound (active ingredient) of formula I are prepared

in known manner, e.g. by homogeneously mixing and/or grinding the active ingredients with extenders, such as, e.g. solvents, solid carriers and, where appropriate, surface-active compounds (surfactants).

Suitable solvents are: aromatic hydrocarbons, preferably the fractions containing 8 to 12 carbon atoms, such as, for example, xylene mixtures or substituted naphthalenes, phthalates, such as dibutyl phthalate or dioctyl phthalate, aliphatic hydrocarbons, such as cyclohexane or paraffins, alcohols and glycols and their ethers and esters, such as ethanol, ethylene glycol, ethylene glycol monomethyl or monoethyl ether, ketones, such as cyclohexanone, strongly polar solvents, such as N-methyl-2-pyrrolidone, dimethyl sulphoxide or dimethylformamide, as well as vegetable oils or epoxidised vegetable oils, such as epoxidised coconut oil or soybean oil; or water.

The solid carriers used, for example for dusts and dispersible powders, are normally natural mineral fillers, such as calcite, talcum, kaolin, montmorillonite or attapulgite. In order

to improve the physical properties it is also possible to add highly dispersed silicic acid or highly dispersed absorbent polymers. Suitable granulated adsorptive carriers are porous types, such as, for example, pumice, broken brick, sepiolite or bentonite, and suitable nonsorbent carriers are materials such as calcite or sand. In addition, a great number of pregranulated materials of inorganic or organic nature can be used, such as especially dolomite or pulverised plant residues.

Depending on the nature of the active ingredient to be formulated, suitable surface-active compounds are nonionic, cationic and/or anionic surfactants having good emulsifying, dispersing and wetting properties. The term "surfactants" will also be understood as including mixtures of surfactants.

Both so-called water-soluble soaps and water-soluble synthetic surface-active compounds are suitable anionic surfactants.

Suitable soaps are the alkali metal salts, alkaline earth metal salts or unsubstituted or substituted ammonium salts of higher fatty acids

(C_{10}-C_{22}), such as, for example, the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures which can be obtained, for example, from coconut oil or tallow oil. Other suitable surfactants are also the fatty acid methyltaurin salts.

More frequently, howerver, so-called synthetic surfactants are used, especially fatty sulphonates, fatty sulphates, sulphonated benzimidazole derivatives or alkylarylsulphonates.

THe fatty sulphonates or sulphates are usually in the form of alkali metal salts, alkaline earth metal salts or unsubstituted or substituted ammonium salts and contain a C_8-C_{22}-alkyl radical, alkyl also including the alkyl moiety of acyl radicals, for example the sodium or calcium salt of lignosulphonic acid, of dodecylsulphate or of a mixture of fatty alcohol sulphates obtained from natural fatty acids. These compounds also comprise the salts of the sulphuric acid esters and sulphonic acids of fatty alcohol/ethylene oxide adducts. The sulphonated benzimidazole derivatives preferably contain 2 sulphonic acid groups and

one fatty acid radical containing 8 to 22 carbon atoms. Examples of alkylarylsulphonates are the sodium, calcium or triethanolamine salts of dodecylbenzenesulphonic acid, dibutylnaphthalenesulphonic acid, or of a condensate of naphthalenesulphonic acid and formaldehyde.

Also suitable are corresponding phosphates, such as, for example, salts of the phosphoric acid ester of an adduct of p-nonylphenol with 4 to 14 moles of ethylene oxide; or phospholipids.

Non-ionic surfactants are especially polyglycol ether derivatives of aliphatic or cycloaliphatic alcohols, saturated or unsaturated fatty acids and alkylphenols, said derivatives containing 3 to 30 glyocl ether groups and 8 to 20 carbon atoms in the (aliphatic)hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenols.

Furthee suitable non-ionic surfactants are the water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediaminopolypropylene glycol and alkylpolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethylene

glycol ether groups and 10 to 100 propylene glycol ether groups. These compounds usually contain 1 to 5 ethylene glycol units per propylene glycol unit.

Representative examples of non-ionic surfactants are nonylphenolpolyethoxyethanols, castor oil polyglycol ethers, polypropylene/polyethylene oxide adducts, tributylphenoxy-polyethoxyethanol, polyethlene glycol and octylphenoxypolyethoxyethanol.

Fatty acid esters of polyoxyethylene sorbitan, e.g. polyoxyethylene sorbitan trioleate, are also suitable non-ionic surfactants.

Cationic surfactants are especially quaternary ammonium salts which contain, as N-substituent, at least one C_8-C_{22}-alkyl radical and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl or hydroxy-lower alkyl radicals. The salts are preferably in the form of halides, methyl sulphates or ethyl sulphates, e.g. stearyltrimethylammonium chloride or benzyldi-(2-chloroethyl)ethylammonium bromide.

The surfactants customarily employed in the

art of formulation are described inter alia in the following publication:

"1986 International McCutcheon's Emulsifiers and Detergents", The Manufacturing Confectioner Publishing Co., Glen Rock, New Jersey, USA.

The pesticidal compositions usually contain from 0.01 to 95 %, especially from 0.1 to 80 %, of an active ingredient of formula I, from 5 to 99.99 % of a solid or liquid adjuvant, and from 0 to 25 %, especially from 0.1 to 25 %, of a surfactant.

Whereas commercial products are preferably formulated as concentrates, the end user will normally employ dilute formulations having an active ingredient content of from 1 to 10,000 ppm.

The present invention therefore also relates to pesticidal compositions which contain as active ingredient at least one compound of formula I together with customary carriers and/or dispersing agents.

The compositions may also contain further ingredients such as stabilisers, antifoams, viscosity regulators, binders, tackifiers and also fertilisers or other active ingredients

for obtaining special effects.

Preparation Examples

Example P-1: Preparation of 5-O-(tert.-butyldimethylsilyl)-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4 and 5-O-(tert.-butyldimethylsilyl)-3, 4-dichloromethylene-14, 15-dichloromethylene-3, 4, 14, 15-tetrahydromilbemycin A_4

With continuous stirring at from 0 to 5°C, 15 ml of a 50% aqueous sodium hydroxide solution are added to a solution of 1300 mg of 5-O-(tert.-butyldimethylsilyl)-milbemycin A_4 and 15 mg of tetrabutylammonium chloride in 60 ml of chloroform. After 30 minutes, the reactionmixture is diluted with 200 ml of ethyl acetate and washed until neutral with water/sodium chloride solution. After drying the solution over sodium sulphate and concentrating by evaporation, the residue is purified over silica gel (hexane : ether = 5:1). Freeze-drying of the product yields 1090 mg of 5-O-(tert.-butyldimethyl-

silyl)-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4, m.p. 102-105°C, and 80 mg of 5-O-(tert.-butyldimethylsilyl)-3, 4-dichloromethylene-14, 15-dichloromethylene-3, 4, 14, 15-tetrahydromilbemycin A_4, m.p. approximately 200°C.

By removing the silyl group from 5-O-(tert.-butyldimethylsilyl-3, 4-dichloromethyelene-14, 15-dichloromethylene- 3, 4, 14, 15-tetrahydromilbemycin A_4, 3, 4-dichloromethylene-14 15-dichloromethylene-3, 4, 14, 15-tetrahydromilbemycin A_4, m.p. 153-157°C. is obtained.

Example P-2: Preparation of 14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4

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120 mg of 5-O-(tert.-butyldimethylsilyl)-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4 in 5 ml of a 1% methanolic solution of p-toluenesulphonic acid are stirred at room temperature for one hour and then treated with 5% aqueous sodium hydrogen carbonate solution. After extracting by shaking three times with

20 ml of diethyl ether each time, drying over sodium sulphate, concentrating the organic phase and chromatographing the crude product on 20 g of silica gel (eluant: diethyl ether), 92 mg of 14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4 are obtained; m.p. 127-131°C.

By reacting 14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4 with 2, 3, 4, 6-tetraactyl-glucopyranose, 5-O-(2, 3, 4, 6-tetraacetyl-glucopyranosyl)-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4, m.p. 133-138°C (compound No. 7.1) is obtained.

Example P-3: Preparation of 14, 15-dichloromethylene-14, 15-dihydromilbemycin A_3

With continuous stirring at from 0 to 3°C, 7 ml of a 50% aqueous sodium hydroxide solution are added to a solution of 400 mg (0.75 mmol) of milbemycin A_3 and 5 mg of tetrabutylammonium chloride in 50 ml of chloroform. After 15 minutes, the reaction mixture is diluted with 100 ml of diethyl ether and washed with water/sodium

chloride solution until a neutral reaction is obtained. The solution is dried over sodium sulphate and concentrated by evaporation. The resulting residue is purified over a silica column (hexane : ether = 4:1). Freeze-drying of the resulting product yields 212 mg of 14, 15-dichloromethylene-14, 15-dihydromilbemycin A_3; m.p. 130-135°C.

Example P-4: Preparation of 14, 15-dibromomethylene-14, 15-dihydromilbemycin A_4

0.5 ml of bromoform is added at room temperature to 100 mg of milbemycin A_4 and 100 mg of magnesium chippings in 5 ml of diethyl ether. The reaction mixture, in which an exothermic reaction commences after a few minutes, is maintained at from 30 to 35°C by cooling with an ice bath until, after about one hour, the reaction is oomplete. The reaction mixture is filtered and concentrated. Purification of the crude product by column chromatography (silica gel; diethyl ether/

hexane = 10:1) yields 78 mg of 14, 15-dibromo-methyl-methylene-14, 15-dihydromilbemycin A_4 which decomposes at 141 - 144°C.

By introducing the $-Si(CH_3)_2$-tert.-C_4H_9 group into 14, 15-dibromomethylene-14, 15-dihydromilbemycin A_4, 5-O-(tert.-butyldimethylsilyl)-14, 15-dibromomethylene-14, 15-dihydromilbemycin A_4, m.p. 137-141°C, is obtained.

Example P-5: Preparation of 5-O-(tert.-butyldimethylsilyl)-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4

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1 ml of n-butyllithium is added dropwise at -60°C, under argaon, to 100 mg of 5-O-(tert.-butyldimethyldilyl)-milbemycin A_4 in 4 ml of dry chloroform. The reaction mixture is slowly heated to 20°C, stirred thoroughly for 4 hours and then filtered and concentrated. The resulting crude product is purified by column chromatography (silica gel; diethyl ether/petroleum ether = 1:5). 90 mg of 5-O-(tert.-butyldimethylsilyl)-14, 15-dichloromethyelene-

14, 15-dihydromilbemycin A_4, m.p. 103-105°C, are obtained.

Example P-6: Preparation of 5-O-(tert.-butyldimethylsilyl)-14, 15-monobromomethylene-14, 15-dihydromilbemycin A_4 and 5-O-(tert.-butyldimethylsilyl)-14, 15-methylene-14, 15-dihydromilbemycin A_4

2.0 g of zinc powder are slowly added at 15°C to a solution of 200 mg (0.24 mmol) of 5-O-(tert.-butyldimethylsilyl)-14, 15-dibromomethylene-14, 15-dihydromilbemycin A_4 in 10 ml of glacial acetic acid. AFter 4 hours, the solvent is evaporated off in vacuo and the residue is filtered and purified over a silica gel column (cyclohexane : ethyl acetate = 12:1). Freeze-drying yields 70 mg of 5-O-(tert.-butyldimethylsilyl)-14, 15-monobromomethylene-14, 15-dihydromilbemycin A_4 in the form of an amorphous powder, m.p. 180-185°C, and 100 mg of 5-O-(tert.-butyldimethylsilyl)-14, 15-methylene-14, 15-dihydromilbemycin A_4 in

amorphous form, which melts at approximately 75°C.

Example P-7: Preparation of 14, 15-monobromomethylene-14, 15-dihydromilbemycin A_4

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2 ml of 1% methanolic p-toluenesulphonic acid solution is added at room temperature to 70 mg of 5-O-(tert.-butyldimethylsilyl)-14, 15-monobromomethylene-14, 15-dihydromilbemyicn A_4. Working up in accordance with the foregoing Examples yields 14, 15-monobromomethylene-14, 15-dihydromilbemycin A_4 in the form of an amorphous powder which melts at 85-88°C.

Example P-8: Preparation of 14, 15-methelene-14, 15-dihydromilbemycin A_4

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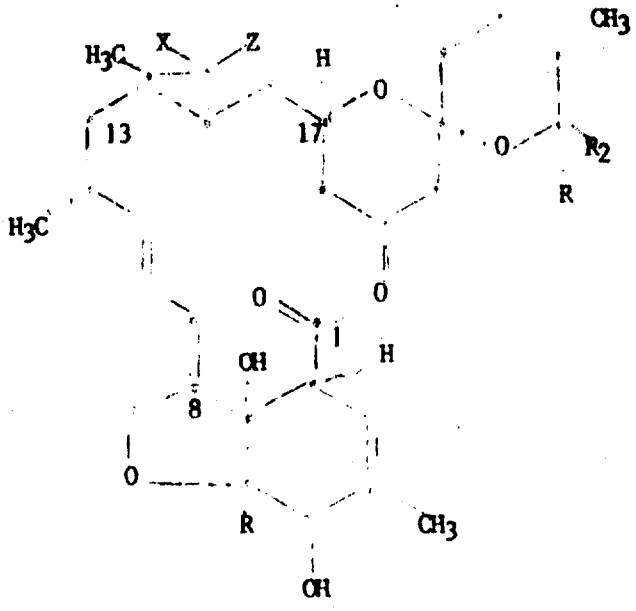
2 ml of 1% methanolic p-toluenesulphonic acid solution is added at room temperature to 100 mg of 5-O-(tert.-butyldimethylsilyl)-14, 15-methylene-14, 15-dihydromilbemycin A_4.

Working up in accordance with the foregoing Examples yields 14, 15-methylene-14, 15-dihydromilbemycin A_4 in the form of an amorphous powder which melts at 80-83°C.

14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4 can be oxidised to 5-oxo-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4 and, by reaction of this 5-oxo compound with hydroxylamine, it is possible to prepare 5-hydroxyimino-14, 15-dihcloro-14, 15-dihydromilbemycin A_4; m.p. 171-173°C.

The following compounds of formula I, listed togebber with compounds of the predeidng Examples, are also prepared analogously to the described procedures. this list does not, however, constitute any limitation.

Table 1



Comp. No.	R_2	X	Z
1.1	CH_3	H	Br
1.2	C_2H_5	H	Br
1.3	C_3H_7-iso	H	Br
1.4	C_4H_9-sec.	H	Br
1.5	CH_3	H	Cl
1.6	C_2H_5	H	Cl
1.7	C_3H_7-iso	H	Cl

Table 1 (continued)

Comp. No.	R_2	X	Z
1.8	C_4H_9-seC.	H	Cl
1.9	CH_3	H	H
1.10	C_2H_5	H	H
1.11	C_3H_7-iso	H	H
1.12	C_4H_9-seC.	H	H
1.13	CH_3	Cl	Cl
1.14	C_2H_5	Cl	Cl
1.15	C_3H_7-iso	Cl	Cl
1.16	C_4H_9-seC.	Cl	Cl
1.17	CH_3	Br	Br
1.18	C_2H_5	Br	Br
1.19	C_3H_7-iso	Br	Br
1.20	C_4H_9-seC.	Br	Br
1.21	CH_3	H	F
1.22	C_2H_5	I	I
1.23	C_3H_7-iso	Cl	Br
1.24	C_4H_9-seC.	H	I
1.25	CH_3	Cl	Br
1.26	C_2H_5	F	F

Table 1 (continued)

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Comp. No.	R_2	X	Z
1.27	C_3H_7-iso	H	F
1.28	C_4H_9-seC.	Cl	I
1.29	CH_3	F	F
1.30	C_2H_5	Cl	Br
1.31	C_3H_7-iso	Br	F
1.32	C_4H_9-seC.	H	F
1.33	CH_3	Br	I
1.34	C_2H_5	H	F
1.35	C_3H_7-iso	F	F
1.36	C_4H_9-seC.	Cl	Br
1.37	CH_3	F	I
1.38	C_2H_5	H	I
1.39	C_3H_7-iso	Cl	I
1.40	C_4H_9-seC.	Br	F
1.41	CH_3	H	I
1.42	C_2H_5	Cl	F
1.43	C_3H_7-iso	Br	I
1.44	C_4H_9-seC.	I	I
1.45	CH_3	Br	F

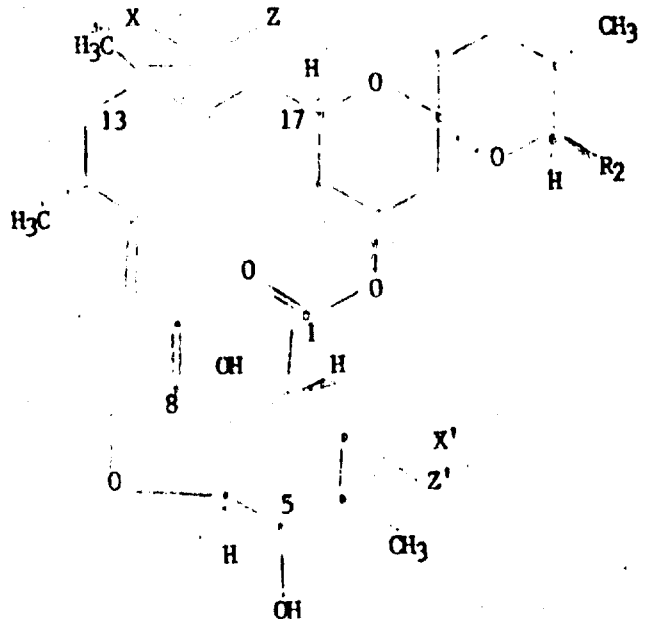
Table 1 (continued)

Comp.	R_2	X	Z
1.46	C_2H_5	Cl	I
1.47	C_3H_7-iso	H	I
1.48	C_4H_9-seC.	F	F
1.49	CH_3	Cl	I
1.50	C_2H_5	Br	F
1.51	C_3H_7-iso	Cl	F
1.52	C_4H_9-seC.	Br	I
1.53	CH_3	I	I
1.54	C_2H_5	Br	F
1.55	C_3H_7-iso	F	I
1.56	C_4H_9-seC.	F	I
1.57	CH_3	Cl	F
1.58	C_2H_5	F	I
1.59	C_3H_7-iso	I	I
1.60	C_4H_9-seC.	Cl	F

and the compounds of Table 1 in which the hydrogen atom of the hydroxy group in the 5-position has been

replaced by a silyl group $-Si(CH_3)_2$-tert.-C_4H_9 (= compounds S-1.1 to S 1.60) and the compounds of Table 1 in which the hydrogen atom of the hydroxy group in the 5-position has been replaced by the acyl group $-COCH_3$ (= compounds A-1.1 to A-1.60).

Table 2:



Comp. No.	R_2	X	Z	X'	Z'
2.1	CH_3	H	Br	H	Br
2.2	C_2H_5	H	Br	H	Br
2.3	C_3H_7-iso	H	Br	H	Cl
2.4	C_4H_9-seC.	H	Br	H	Cl
2.5	CH_3	H	Cl	H	H

Table 2 (continued)

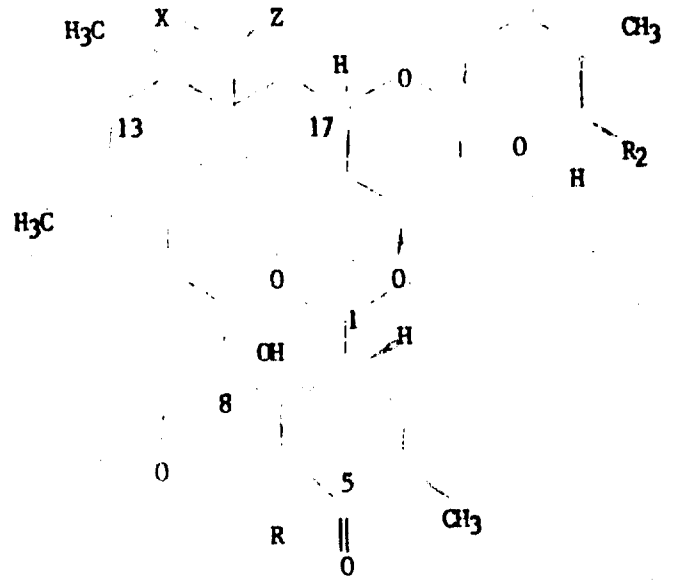
Comp. No.	R_2	X	Z	X'	Z'
2.6	C_2H_5	H	Cl	H	Cl
2.7	C_3H_7-iso	H	Cl	H	H
2.8	C_4H_9-seC.	H	Cl	H	Br
2.9	CH_3	H	H	H	H
2.10	C_2H_5	H	H	Cl	Cl
2.11	C_3H_7-iso	H	H	Br	Br
2.12	C_4H_9-seC.	H	H	H	H
2.13	CH_3	Cl	Cl	Cl	Cl
2.14	C_2H_5	Cl	Cl	Cl	Cl
2.15	C_3H_7-iso	Cl	Cl	Br	Br
2.16	C_4H_9-seC.	Cl	Cl	I	I
2.17	CH_3	Br	Br	H	H
2.18	C_2H_5	Br	Br	Br	Br
2.19	C_3H_7-iso	Br	Br	Br	Br
2.20	C_4H_9-seC.	Br	Br	H	H
2.21	CH_3	H	F	H	F
2.22	C_2H_5	I	I	I	I
2.23	C_3H_7-iso	Cl	Br	Cl	Cl

Table 2 (continued)

Comp. No.	R_2	X	Z	X'	Z'
2.24	CH_3	Cl	Br	Cl	Br
2.25	C_2H_5	F	F	F	F
2.26	CH_3	F	F	Cl	Cl
2.27	C_2H_5	Cl	Br	Cl	Br
2.28	C_4H_9-seC.	H	F	H	H
2.29	C_2H_5	H	F	H	F
2.30	C_3H_7-iso	F	F	F	F
2.31	C_4H_9-seC.	Cl	Br	Cl	Cl
2.32	C_2H_5	H	I	H	Cl
2.33	CH_3	H	I	H	I
2.34	C_2H_5	Cl	F	Cl	F
2.35	CH_3	I	I	Cl	Cl
2.36	CH_3	Cl	F	Cl	Br
2.37	C_2H_5	F	I	H	H

and the compounds of Table 2 in which the hydrogen atom of the hydroxy group in the 5-position has been replaced by the silyl group $-Si(CH_3)_2$-tert.-C_4H_9 (= compounds S-2.1 to S-2.37) and the compounds of Table 2 in which the hydrogen atom of the hydroxy group in the 5-position has been replaced by the acyl group $-COCH_3$ (= compounds A-2.1 to A-2.37).

Table 3:



Comp. No.	R_2	X	Z
3.1	CH_3	H	H
3.2	C_2H_5	H	H
3.3.	C_3H_7-iso	H	H
3.4	C_4H_9-sec.	H	H
3.5	CH_3	Br	Br

Table 3 (continued)

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Comp. No.	R_2	X	Z
3.6	C_2H_5	Br	Br
3.7	C_3H_7-iso	Br	Br
3.8	C_4H_9-seC.	Br	Br
3.9	CH_3	Cl	Cl
3.10	C_2H_5	Cl	Cl
3.11	C_3H_7-iso	Cl	Cl
3.12	C_4H_9-seC	Cl	Cl
3.13	CH_3	H	Br
3.14	C_2H_5	H	Br
3.15	C_3H_7-iso	H	Br
3.16	C_4H_9-seC.	H	Br
3.17	CH_3	H	Cl
3.18	C_2H_5	H	Cl
3.19	C_3H_7-iso	H	Cl
3.20	C_4H_9-seC.	H	Cl
3.21	CH_3	H	F
3.22	C_2H_5	H	F
3.23	C_3H_7-iso	H	F
3.24	C_4H_9-seC.	H	F

Table 4:

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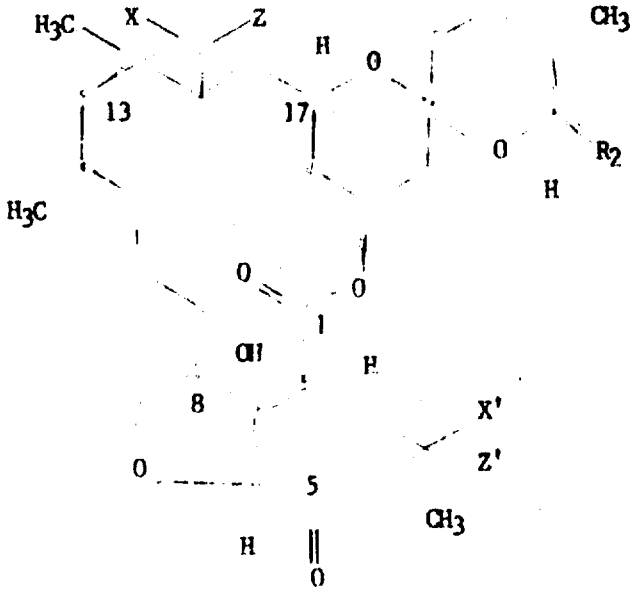

Comp. No.	R_2	X	Z	X'	Z'
4.1	C_3H_7-iso	Cl	Cl	Br	Br
4.2	CH_3	Br	Br	Cl	Cl
4.3	C_2H_5	H	Br	H	Br

Table 4 (continued)

Comp. No.	R_2	X	Z	X'	Z'
4.4.	CH_3	H	H	H	H
4.5	C_4H_9-seC.	Br	Br	H	H
4.6	CH_3	H	Br	H	Cl
4.7	C_3H_7-iso	H	H	H	H
4.8	C_2H_5	Cl	Cl	Cl	Cl
4.9	C_4H_9-seC.	Cl	Cl	H	H
4.10	C_2H_5	H	H	Cl	Cl
4.11	C_2H_5	Br	Br	Br	Br
4.12	CH_3	Cl	Cl	Cl	Cl

Table 5:

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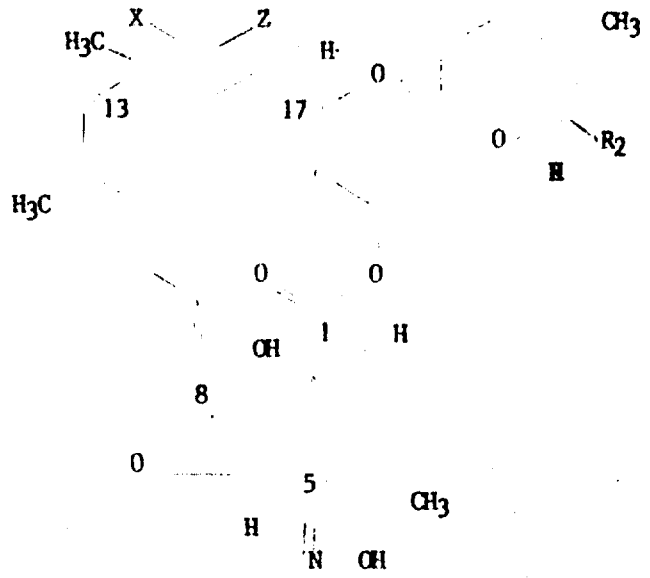


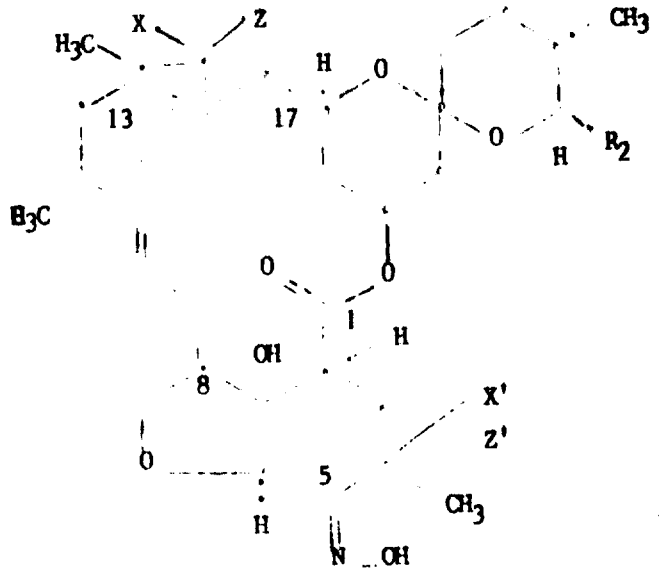
Comp. No.	R_2	X	Z
5.1	CH_3	H	H
5.2	C_2H_5	H	H
5.3	C_3H_7-iso	H	H
5.4	C_4H_9-secC.	H	H
5.5.	CH_3	Br	Br

Table 5 (continued):

Comp. No.	R_2	X	Z
5.6	C_2H_5	Br	Br
5.7	C_3H_7-iso	Br	Br
5.8	C_4H_9-seC.	Br	Br
5.9	CH_3	Cl	Cl
5.10	C_2H_5	Cl	Cl
5.11	C_3H_7-iso	Cl	Cl
5.12	C_4H_9-seC	Cl	Cl
5.13	CH_3	H	Br
5.14	C_2H_5	H	Br
5.15	C_3H_7-iso	H	Br
5.16	C_4H_9-seC.	H	Br
5.17	CH_3	H	Cl
5.18	C_2H_5	H	Cl
5.19	C_3-H_7-iso	H	Cl
5.20	C_4H_9-seC	H	Cl
5.21	CH_3	H	F
5.22	C_2H_5	H	F
5.23	C_3H_7-iso	H	F
5.24	C_4H_9-seC.	H	F

and the compounds of Table 5 in which the hydrogen atom of the oxime group in the 5-position has been replaced by the silyl group $-Si(CH_3)_2$-tert.-C_4H_9 (= compounds S-5.1 to S-5.24) and the compounds of Table 5 in which the hydrogen atom of the oxime group in the 5-position has been replaced by the acyl group $-COCH_3$ (= compounds A-5.1 to A-5.24).

Table 6:



Comp. No.	R_2	X	Z	X'	Z'
6.1	CH_3	Cl	Cl	Cl	Cl
6.2	C_2H_5	Br	Br	Br	Br
6.3	C_2H_5	H	H	H	H
6.4	C_4H_9-seC.	Cl	Cl	H	H
6.5	C_2H_5	Cl	Cl	Cl	Cl

Table 6 (continued):

Comp. No.	R_2	X	Z	X'	Z'
6.6.	C_3H_7-iso	H	H	Br	Br
6.7	CH_3	H	Br	H	Br
6.8	C_4H_9-seC.	Br	Br	Cl	Cl
6.9	CH_3	H	H	H	Cl
6.10	C_2H_5	H	Br	H	Br
6.11	CH_3	Br	Br	H	H
6.12	C_3H_7-iso	Cl	Cl	Br	Br
6.13	C_2H_5	Cl	Br	Br	Cl
6.14	C_4H_9-seC.	Br	Cl	Br	Cl

and the compounds of Table 6 in which the hydrogen atom of the oxime group in the 5-position has been replaced by the silyl group $-Si(CH_3)_2$-tert.-C_4H_9 (= compounds S-6.1 to S-6.14) and the compounds of Table 6 in which the hydrogen atom of the oxime group in the 5-position has been replaced by the acyl group $-COCH_3$ (= compounds A-6.1 to A-6.14).

Formulation Examples for the active ingredients of formula I

(% = per cent by weight)

Wettable powders	a)	b)	c)
an active ingredient from Tables 1 to 6	25%	50%	75%
sodium lignosulphonate	5%	5%	-
sodium laurylsulphate	3%	-	5%
sodium diisobutylnaphthalenesulphonate	-	6%	10%
octylphenol polyethylene glycol ether (7-8 moles of ethylene oxide)	-	2%	-
highly dispersed silicic acid	5%	10%	10%
kaolin	62%	27%	-

The active ingredient is thoroughly mixed with the adjuvants and the mixture is thoroughly ground in a suitable mill. Wettable powders are obtained which can be diluted with water to give suspensions of any desired concentration.

Emulsifiable concentrate

an active ingredient from Tables 1 to 6	10%
octylphenol polyethylene glycol ether (4-5 moles of ethylene oxide)	3%
calcium dodecylbenzene-sulphonate	3%
castor oil polyglycol ether (36 moles of ethylene oxide)	4%
cyclohexanone	30%
xylene mixture	50%

Emulsions of any desired concentration can be prepared from this concentrate by dilution with water.

Dusts	a)	b)
an active ingredient from Tables 1 to 6	5%	8%
talcum	95%	-
kaolin	-	92%

Ready-for-use dusts are obtained by mixing the active ingredient with the carrier and grinding the mixture in a suitable mill.

Extruder granulate	
an active ingredient from Tables 1 to 6	10%
Sodium lignosulphonate	2%
Carboxymethylcellulose	1%
kaolin	87%

The active engredient is mixed and ground with the adjuvants, and the mixture is moistened with water. This mixture is extruded and then dried in a stream of air.

Tablets or boli

I	an active ingredient from Tables 1 to 6	33.00%
	methylcellulose	0.80%
	highly dispersed silicic acid	0.80%
	maizemaisestarch	8.40%

The methylcellulose is stirred in water and allowed to swell; silicic acid is stirred in to give a homogeneous suspension. The active ingredient and the maize starch are mixed and the aqueous suspension is incorporated into this mixture, which is kneaded to a paste. This mass is granulated through a sieve (mesh width 12 M) and the granulate is then dried.

II	crystalline lactose	22.50%
	maize starch	17.00%
	microcrystalline cellulose	16.50%
	magnesium stearate	1.00%

All 4 adjuvants are thoroughly mixed.

Phases I and II are mixed and compressed to form tablets or boli.

Injectable composition

A. Oily vehicle (slow release)

an active ingredient from the Tables	0.1-1.0g
groundnut oil	ad 100 ml

an active ingredient from the Tables	0.1-1.0 g
sesame oil	ad 100 ml

Preparation: The active ingredient is dissolved in some of the oil while stirring,and, if necessary, while heating gently; after cooling, the solution is made up to prescribed volume and sterile-filtered through a suitable membrane filter having a pore diameter of 0.22 um.

B. Water-miscible solvent(medium rate of release)

an active ingredient from the Tables	0.1-1.0 g
4-hydroxymethyl-1,3-dioxolane (glycerol formal)	40.0 g
1,2-propanediol	ad 100 ml

an active ingredient from the Tables	0.1-1.0 g
glycerin dimethyl ketal	40.0 g
1,2-propanediol	ad 100 ml

Preparation: the active ingredient is dissolved in some of the solvent while stirring, and the solution is made up to the prescribed volume and sterile-filtered through a suitable membrane filter having a pore diameter of 0.22 um.

C. Aqueous solubilisate (rapid release)

an active ingredient from the Tables	0.1-1.0 g
polyethoxylated castor oil (40 ethylene oxide units)*	10 g
1,2-propanediol	20 g
benzyl alcohol	1 g
aqua ad inject.	ad 100 ml

*Available commercially under the name CREMOPHOR® EL (BASF AG);

an active ingredient from the Tables	0.1-1.0 g
polyethoxylated sorbitan monooleate (20 ethylene oxide units)**	8 g
4-hydroxymethyl-1,3-dioxolane (glycerol formal)	20 g
benzyl alcohol	1 g
aqua ad inject.	ad 100 ml

**Available commercially under the name TWEEN(R) 80 (ICI);

Preparation: the active ingredient is dissolved in the solvents and the surfactant and the solution is made up to prescribed volume with water. Sterile-filtration is carried out through a suitable membrane filter having a pore diameter of 0.22 µm.

The aqueous systems can preferably also be used for oral and/or intraruminal administration.

When compounds of formula I or corresponding compositions are used for controlling endoparasitic nematodes, cestodes and trematodes in domestic animals and productive livestock, such as cattle, sheep, goats, cats and dogs, the compounds or compositions can be administered to the animal either as a single dose or repeatedly, the individual doses preferably being from 0.1 to 10 mg per kg of body weight depending on the type of animal. By protracted administration it is possible in some cases to achieve a better action of lower overall doses can suffice. The active ingredient, or the composition containing it, can also be added to the feed or the drink. The concentration of active ingredient in the prepared feed is preferably from 0.005 to 0.1 % by weight. The compositions can be administered to the animals perorally in the form of solutions, emulsions, suspension, powders, tablets, boli or capsules. Provided that the physical and toxicological properties of solutions or emulsions permit, the compounds

of formula I, or the compositions containing them, can also be administered to the animal, for example, by subcutaneous injection or itraruminally, or can be applied to the body of the animal by means of the pour-on method. It is also possible to administer the active ingredient to the animal by means of licks (salt) or molasses blocks.

Biological Examples

B-1: Action against L_1 larvae of Lucilia sericata

1 ml of an aqueous suspension of the active substance to be tested is mixed in such a manner with 3 ml of a special larval culture medium at about 50°C that a homogeneous composition containing, as desired, 250 ppm or 125 ppm of active ingredient is obtained. About 30 Lucilia larvae (L_1) are put into each test tube containing active ingredient. The mortality rate is ascertained after 4 days. Compounds from the Preparation Examples, such as for example, compounds Nos. 1.14, 1.18, 5.5 and

7.1 (compound from Example p-2), achieve 100 % effectiveness at 100 ppm.

These results are also obtained in the same test against L_1 larvae of Lucilia cuprina.

B-2: Acaricidal action agains Boophilus microplus (Biarra strain)

Adhesive tape is so applied horizontally across a PVC plate that 10 female Boophilus microplus ticks (Biarra strain) fully replete with blood can be affixed thereto on their backs, side by side, in a row. Each tick is injected from an injection needle with 1 ul of a liquid which is a 1:1 mixture of polyethyleneglycol and acetone, in which mixture a specific amount of active ingredient of, as desired, 1, 0.1 or 0.01 ul per tick is dissolved. Control ticks are injected with a corresponding mixture that does not contain the active ingredient. After this treatment, the ticks are kept in an insectarium under normal conditions at about 28°C and 80 % relative humidity until oviposition

has taken place and the larvae have emerged from the eggs of the control ticks.

The activity of a tested substance is determined by the IR_{90}, i.e. that dose of active ingredient is determined at which 9 out of 10 female ticks (90%), even after 30 days, lay eggs from which larvae are unable to emerge. Compounds from the Preparation Examples achieve an IR_{90} of 1 ug.

B-3: Trial with sheep infected with nematoides (Haemonchus contortus and Trichostrongylus colubriformis)

The active ingredient is formulated as a suspension and administered using a stomach probe or by intraruminal injection to sheep that have been artificially infected with Haemonchus contortus and Trichostrongylus colubriformis. 1 to 3 animals are used for each dose. Each sheep is treated only once with a single dose of, as desired, 0.5 mg or 0.1 mg/kg of body weight. Evaluation is made by comparing the number of worm eggs

excreted in the faeces of the sheep before and after treatment.

Sheep infected simultaneously and in the same manner but untreated are used as controls. In comparison with untreated but infected control groups, nematode infestation was reduced by from 50 to 100% (= reduction of worm eggs in the faeces) in sheep that had been treated with 0.1 mg/kg of one of the compounds from the Preparation Exmaples, such as, for example, No. 1.14, 1.18, 2.14 or 5.5.

B-4: Larvicidal action against Aedes aegypti

A 0.1% solution of the active ingredient in acetone is pipetted onto the surface of 150 ml of water in containers in amounts sufficient to give concentrations of, as desired, 10 ppm, 3.3 ppm and 1.6 ppm. After the acetone has evaporated, about 30 to 40 three-day-old Aedes larvae are put into each container. Mortality counts are made after 1, 2 and 5 days.

In this test, compounds from Tables 1 to 6 at a concentration of 10 ppm achieve complete

kill of all larvae after only 1 day.

B-5: Miticidal action against Sermanyssus gallinae

2 to 3 ml of a test solution (100, 10, 1 and 0.1 ppm of active substance) are put into a glass container which is open at the top and about 200 mites in different stages of development are put into this container. The glass container is sealed with a wad of cotton wool and is uniformly shaken for 10 minutes until the mites are ocmpletely wet. The container is then inverted until excess test solution has been absorbed by the cotton wool. The container is then stood upright again and the treated mites are kept under observation for 3 days under laboratory conditions to evaluate the effectiveness of the test substances. Mortality is the criterion for effectiveness.

Compounds from the Preparation Examples, such as, for example, Nos. 1.14, 1.18 and 5.5, exhibit 100% effectiveness at 100 ppm.

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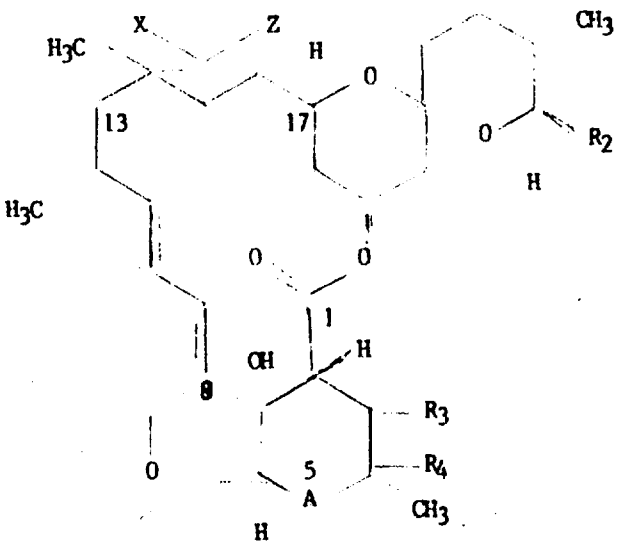
Patent Claims

1. Compounds of formula I



(I)

in which

A is a $-\overset{|}{\underset{OR_1}{CH}}-$, $-\overset{\|}{\underset{O}{C}}-$ or $-\overset{\|}{\underset{N-OR_{11}}{C}}-$ group

wherein R_1 is hydrogen or an OH-protecting group,

and R_{11} is hydrogen or an OH-protecting group,

R_2 is methyl, ethyl, isopropyl or sec-butyl,

R_3 and R_4 together represent a bond between the two carbon atoms to which they are bound, or together represent a -C(X')(Z')- group wherein X' and Z' each represents, independently of the other, hydrogen or halogen, and

X and Z each represents, independently of the other, hydrogen or halogen.

2. Compounds of formula I according to claim 1, wherein A is any one of the groups $-CH(OR_1)-$, -C(O)- or -C(=N-OH)- wherein R_1 is hydrogen, a silyl group or a mono-saccharide group, R_2 is methyl or ethyl, R_3 and R_4 together form a bond between the two carbon atoms to which they are bound, or together form a -C(X')(Z')- group wherein X' and Z' each represents, independently of the other, hydrogen or halogen, and X and Z each represents, independently of the other, hydrogen or halogen.

3. Compounds of formula I according to claim 1, wherein A is any one of the groups $-CH(OR)_1-$, -C(O)- or -C(=N-OH)- wherein R_1 is hydrogen, acetyl, tert.-butyldimethylsilyl or 2, 3, 4, 6-tetraacetylglucopyranosyl,

R_2 is methyl or ethyl, R_3 and R_4 together form a bond between the two carbon atoms to which they are bound, or together form a $-C(Cl_2)-$ group, X is hydrogen, chlorine, bromine or fluorine, and Z is hydrogen, chlorine, bromine or fluorine.

4. Compounds of formula I according to claim 1, wherein A is any one of the groups $-CH(OR_1)-$, $-C(O)-$ or $-C(=N-OH)-$ wherein R_1 is hydrogen, tert.-butyl-dimethylsilyl or 2, 3, 4, 6-tetraacetylglucopyranosyl, R_2 is methyl or ethyl, R_3 and R_4 together form a bond between the two carbon atoms to which they are bound, or together form a $-C(Cl_2)-$ group, X is hydrogen, chlorine or bromine and Z is hydrogen, chlorine or bromine.

5. Compounds of formula I according to claim 1, wherein A is a $-CH(OH)-$ or $-C(=N-OH)-$ group, R_2 is methyl or ethyl, R_3 and R_4 together form a bond between the two carbon atoms to which they are bound, X is hydrogen, chlorine, bromine or fluorine, and Z is hydrogen, chlorine, bromine or fluorine.

6. Compounds of formula I according to claim 1, wherein A is a -CH(OH)- or -C(=N-OH)- group, R_2 is methyl or ethyl, R_3 and R_4 together form a bond between the two carbon atoms to which they are bound, and X and Z are identical with each other and reach represents hydrogen, chlorine or bromine, or X is hydrogen and Z is chlorine or bromine.

7. Compounds of formula I according to claim 1, wherein A is a -CH(OH)- group, R_2 is methyl or ethyl, R_3 and R_4 together form a bond between the two carbon atoms to which they are bound, or together form a $-CCl_2-$ group, X is hydrogen, chlorine or bromine, and Z is hydrogen, chlorine or bromine.

8. 5-O-(Tert.-butyldimethylsilyl)-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4.

9. 5-O-(Tert.-butyldimethylsilyl)-3, 4-dichloromethylene-14, 15-dichloromethylene-3, 4, 14, 15-tetrahydromilbemycin A_4.

10. 3, 4-Dichloromethylene-14, 15-dichloromethylene-3, 4, 14, 15-tetrahydromilbemycin A_4.

11. 5-O-(Tert.-butyldimethylsilyl)-14, 15-dibromomethylene-14, 15-dihydromilbemycin A_4.

12. 5-O-(2, 3, 4, 6-Tetraacetylglucopyranosyl)-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4.

13. 5-Oxo-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4.

14. 5-Hydroxyimino-14, 15-dichloromethylene-14, 15-dihydromilbemycin A_4.

15. 14, 15-Dichloromethylene-14, 15-dihydromilbemycin A_4.

16. 5-O-(Tert.-butyldimethylsilyl)-14, 15-monobromomethylene-14, 15-dihydromilbemycin A_4.

17. 14, 15-Monobromomethylene-14, 15-dihydromilbemycin A_4.

18. 14, 15-Monochloromethylene-14, 15-dihydromilbemycin A_4.

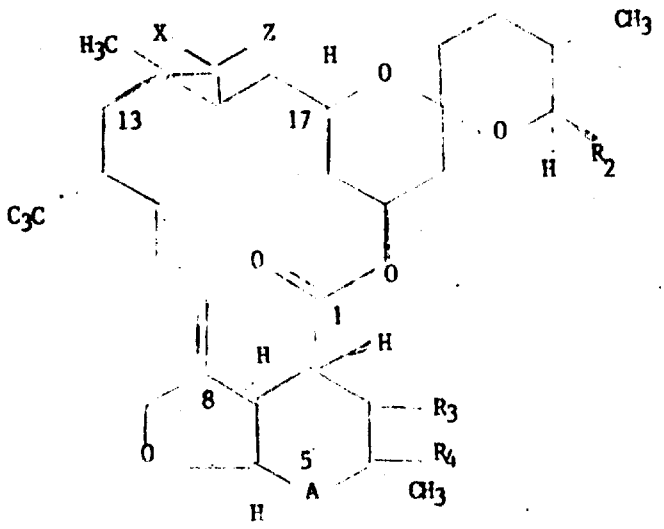
19. 5-O-(tert.-butyldimethylsilyl)-14, 15-methylene-14, 15-dihydromilbemycin A_4.

20. 14, 15-Methylene-14, 15-dihydromilbemycin A_4.

21. 14, 15-Dibromomethyelene-14, 15-dihydromilbemycin A_4.

22. 14, 15-Dichloromethylene-14, 15-dihydromilbemycin A_4.

23. A process for the preparation of compounds of formula I



(I)

BAD ORIGINAL

in which

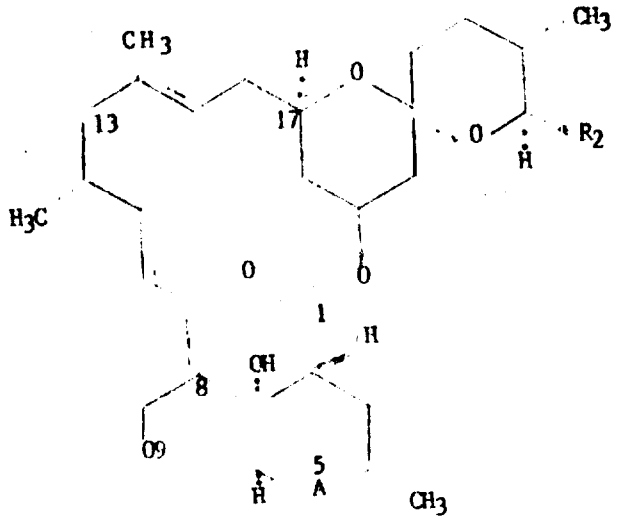
A is a $-CH(OR_1)-$, $-C(=O)-$ or $-C(=N-OR_{11})-$ group

wherein R_1 is hydrogen or an OH-protecting group, and R_{11} is hydrogen or an OH-protecting group,

R_2 is methyl, ethyl, isopropyl or sec.-butyl,

R_3 and R_4 together represent a bond between the two carbon atoms to which they are bound, or together represent a $-C(X')(Z')-$ group wherein X' and Z' each represents, independently of the other hydrogen or halogen, and

X and Z each represents, independently of the other hydrogen, wherein a compound of formula II



(II),

in which A and R_2 are as defined for formula I, is reacted with a carbene of formula IIIa

C(X)(Z) (IIIa),

in which X and Z are ad defined for formula I and which is formed in situ and is dissolved in an inert solvent, and, in resulting compounds, if desired i) a -C(halogen)(halogen)- group that represents -C(X)(Z)- is reduced to a -CH(halogen)- or $-CH_2-$ group or ii) a -CH(halogen)- group that represents -C(X)(Z)- is reduced to a $-CH_2-$ group or iii) the group that represents A is convetted into another of the groups defined under A, or resulting compounds in which R_3 and R_4 together form a bond between the two carbon atoms to which they are bound are reacted witha carbene of formula IIIb

C(X')(Z') (IIIb)

in which X' and Z' are as defined for formula I and which is formed in situ and is dissolved in an inert solvent, and, in resulting compounds, if

desired iv)a -C(halogen)(halogen)- group that represents -C(X)(Z)- or -C(X')(Z')- is reduced to a -CH(halogen)- or $-CH_2-$ group or v) a -CH(halogen)- group that represents -C(X)(Z)- or -C(X')(Z')- is reduced to a $-CH_2-$ group or vi) the group that represents A is converted into another of the groups defined under A, the reaction being carried out in the range of from -70° to $+80^{\circ}$ C, the reaction time varying within a range of from 10 minutes to 2 days.

24. A composition for controlling ecto- and endo-parasites in productive livestock or for controlling harmful insects, containing as active ingredient, at least one compound of formula I according to claim 1, together with carriers, distributing agents of a mixture of carriers and distributing agents.