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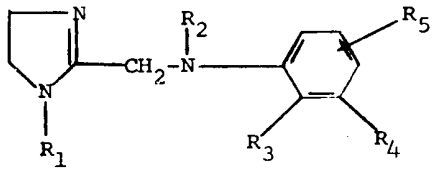
(19)

(54) 2-ANILINOMETHYL-2-IMIDAZOLINE COMPOUNDS AND A METHOD OF COMBATTING ECTOPARASITES USING THEM

(71) We, CIBA-GEIGY AG, a Swiss body corporate, of Basle, Switzerland, 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 2 - anilino - methyl - 2 - imidazoline compounds and a method of combatting ectoparasites using them.

The invention provides a method of controlling mites and ticks which comprises applying thereto a compound of the formula I



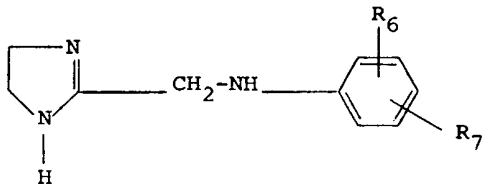
(I)

wherein each of R_1 and R_2 represents hydrogen or alkyl of from 1 to 10 carbon atoms, preferably 1 to 5 carbon atoms; each of R_3 and R_4 represents alkyl of from 1 to 5 carbon atoms or halogen, preferably chlorine; and R_5 represents hydrogen, alkyl of from 1 to 5 carbon atoms or halogen, and acid addition salts thereof.

The alkyl groups within the scope of formula I are straight chain or branched alkyl groups. Thus the C_{1-5} alkyl groups are methyl, ethyl, and all the isomers of the propyl, butyl and pentyl groups. The C_{6-10} alkyl groups are all the isomers of hexyl, heptyl, octyl, nonyl and decyl groups. Halogen is to be understood as meaning fluorine, chlorine, bromine, and iodine, of which chlorine is preferred.

The compounds of the formula I can be converted into their acid additions salts by methods which are known per se. Preferred acid addition salts are the hydrochlorides. In addition to hydrochloric acid suitable acid for the salt formation are for example: hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid, acetic acid, propionic acid, butyric acid, valeric acid, oxalic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, citric acid, benzoic acid, phthalic acid, cinnamic acid and salicylic acid.

British Patent Specification No. 1,174,349 discloses 2 - anilinomethyl - 2 - imidazoline compounds of formula II



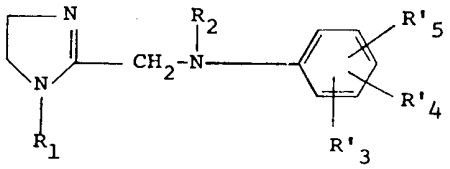
II

in which R_6 denotes a fluorine, chlorine or bromine atom and R_7 denotes a fluorine, chlorine or bromine atom a trifluoromethyl group or a cyano group, or an alkyl or alkoxy group having 1 to 4 carbon atoms and their physiologically compatible acid addition salts. The only uses disclosed for these compounds are as therapeutic agents in human medicine.

Of the 13 compounds of formula II specifically mentioned in British Patent Specification No. 1,174,349, only one has substituents in the 2- and 3- positions of the benzene ring. This compound is 2 - (2′ - methyl - 3′ - chloro)anilinomethyl - 2 - imidazoline hydrochloride. The Specification contains no suggestion that 2,3-substitution of the benzene ring is preferred and most of the exemplified compounds are 2,4-, 2,5- or 2,6- substituted.

The present invention provides as new compounds, all compounds of formula I and their acid addition salts except 2 - (2′ - methyl - 3′ - chloro)anilinomethyl - 2 - imidazoline, and its acid addition salts. The invention also provides an ecto-parasitical composition comprising such a compound together with a solid or liquid carrier and/or compatible additive.

The present invention is based on the observation that the compounds of the formula I possess valuable ectoparasiticidal, especially acaricidal, properties. It has been found that the compounds of the formula I have an outstanding acaricidal action which is in general better than that of other compounds falling within formula III



III

wherein R_1 and R_2 are as defined in formula I and R'_3, R'_4 and R'_5 independently represent hydrogen, alkyl having 1 to 5 carbon atoms, alkoxy having 1 to 5 carbon atoms alkylthio having 1 to 5 carbon atoms, hydroxyl, halogen, nitro, cyano or trifluoromethyl, and their acid addition salts.

The compounds of the formula I as such or as constituents of the compositions of the invention possess valuable ectoparasiticidal properties. They are suitable in particular for controlling mites (Acarina), and preferably parasitic ticks (Ixodidae). This applies to all stages of monoxenous and heteroxenous tick species and to the inhibition of oviposition, that is to say both strains which are normally sensitive and those which are resistant to compounds such as phosphates, carbamates and other already known acaricides.

In addition, these compounds have a pronounced detaching effect, which is of particular importance for the treatment of host animals which are already infested with ticks (e.g. cattle or rabbits). The detaching effect commences directly after application of the active substance, as a consequence of which the ticks are prevented from continuing to feed on the host by sucking blood from it. In the course of the treatment they become detached from the host animal, which is ultimately completely freed from the pests.

Preferred compounds of the present invention are those of the formula I wherein the substituent of the phenyl ring, R_5, represents hydrogen, whilst R_3 and R_4, each independently of the other, are as defined for formula I.

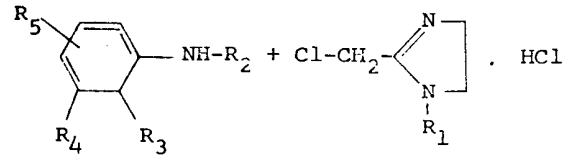
The following compounds are distinguished by particularly excellent acaricidal action:

2 - (2′,3′ - dimethylanilinomethyl) - 2 - imidazoline hydrochloride

2 - (2′,3′ - dichloranilinomethyl) - 2 - imidazoline hydrochloride

The compounds of the formula I can be obtained by methods which are known per se, for example in accordance with the syntheses illustrated by the following formulae:

a)



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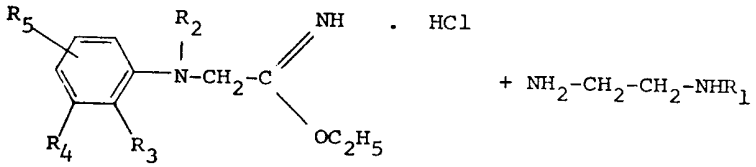

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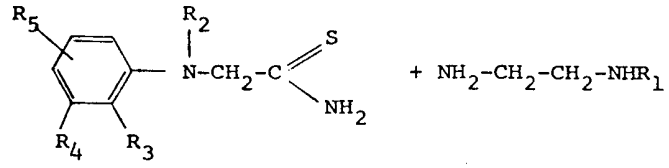
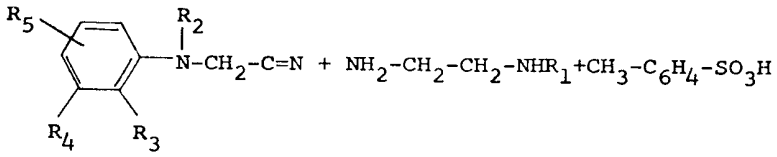


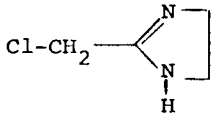
d)

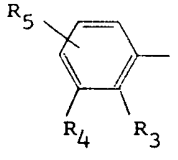


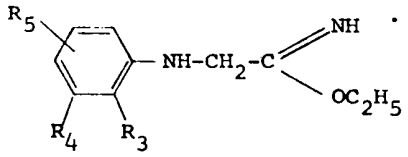
The processes are carried out in the temperature range between 40 and 180°C in the presence of an anhydrous solvent or without a solvent. Examples of suitable solvents are: methanol, ethanol, propanol, butanol, xylene and dichlorobenzene.

The above syntheses are described in the following publications: U.S. Patent 2,252,753; Helv. Chimica Acta *33*, 1386 (1950); U.S. Patent 2,252,721; and British Patent Specification 1,174,349.

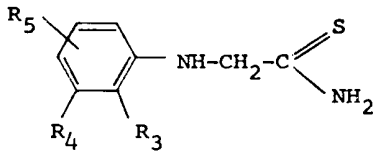
The individual starting materials and their manufacture are known from the following publications:

 · HCl: Helv. Chimica Acta 27, 1762 (1944) Swiss Patent 229.606

 : Helv. Chimica Acta 37, 166 (1954)



: U.S. Patent 2,252,721



: U.S. Patent 2,252,721

The following Examples serve to illustrate some methods of manufacture of the compounds of the formula I:

Example 1.

(Method a)

2-(2',3'-Dimethylanilinomethyl)-2-imidazoline hydrochloride

31 g of 2 - chloromethyl - 2 - imidazoline hydrochloride and 48.4 g of 2,3-dimethylaniline are refluxed for 5 hours in 65 ml of absolute ethanol. After cooling, the crystallised substance is collected by suction and recrystallized from water, affording 36 g (77% yield) of the final product with a melting point of 242°C.

Example 2.

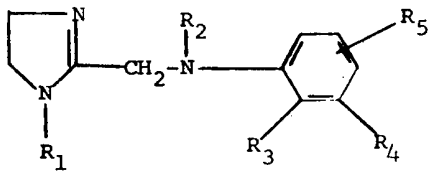
(Method d)

2-(2',3'-Dimethylanilinomethyl)-2-imidazoline

A mixture of 26.4 g of 2,3-dimethylphenylaminoacetonitrile and 39.4 g of ethylenediamine toluenesulfonate is heated to 140°C until the evolution of ammonia ceases. Then 150 ml of 15% aqueous sodium hydroxide are added to the oily reaction product, which is extracted with three 100 ml portions of methylene chloride. The combined methylene chloride extracts are washed with water, dried over sodium sulfate and filtered. The solvent is distilled off and the residual dark oil is distilled in vacuo, affording 13.6 g (39.4% of theory) of 2 - (2' - dimethylphenylaminomethyl) - 2 - imidazoline in the form of an oil with a boiling point of 154—160°C/0.2 torr. On standing, this oil solidifies to crystals with a melting point of 80—82°C.

Example 3.

The following new compounds have been prepared by procedures analogous to those described in the foregoing Examples and to the other indicated methods:



No.	R_1	R_2	R_3	R_4	R_5	salt	melting point in °C
1	H	H	CH_3	CH_3	H	HCl	242
2	H	H	Cl	Cl	H	HCl	260
3	H	H	CH_3	CH_3	6–CH_3	HCl	215
4	CH_3	H	CH_3	CH_3	H	HCl	190–192
5	CH_3	CH_3	CH_3	CH_3	H	HCl	183–184
6	CH_3	H	Cl	Cl	H	HCl	226–227
7	CH_3	CH_3	Cl	Cl	H	HCl	190–191
8	CH_3	H	CH_3	Cl	H	HCl	212–214
9	CH_3	CH_3	CH_3	Cl	H	HCl	
10	H	CH_3	CH_3	CH_3	H	HCl	182–183
11	H	H	CH_3	CH_3	H	–	80–82

The following Examples illustrate the ectoparasitical activity and formulation of the compounds used in this invention. "Sevin" and "Dutrex" are Registered Trade Marks.

Example 4.

Test to determine the effect on ticks: inhibition of oviposition

The test insects used are females of the cattle tick *Boophilus microplus* which have sucked themselves full. There are treated with each concentration 10 ticks of a resistant strain and 10 ticks of a normally sensitive strain. The ticks are immersed for a short time in aqueous emulsions or aqueous solutions of the salts of the compounds to be examined. They are fixed on plates covered with double adhesive tape and kept in an air-conditioned chamber under constant conditions. An evaluation is made after three weeks, and the overall inhibition of the oviposition of fertile eggs is determined.

The inhibitory effect of the substances is expressed in terms of the minimum substance concentration in ppm to produce a 100% effect against normally sensitive adult femal ticks and resistant adult femal ticks, respectively.

Results

Compound	Minimum concentration in ppm for 100% inhibitory effect	
	♂ ♀ sensitive	♂ ♀ resistant
1) 2-(2',3'-dimethylanilino-methyl)-2-imidazoline hydrochloride	50	50
2) 2-(2',3'-dichloroanilino-methyl)-2-imidazoline hydrochloride	50	50
3) 2-(2'-methyl-3'-chloro-anilinomethyl)-2-imi-dazoline hydrochloride	100	100

Comparison

2-(3,4-dichlorophenylimino)-N-n-butyl-pyrrolidine ("Bimarit")	1000	1000
2-(3,4-dichlorophenylimino)-3-methyl-thiazoline (Swiss Patent Specification No. 439,858)	>1000	>1000
2-(3,4-dichlorophenylimino)-3-methyl-thiazoline-HCl (Swiss Patent Specification No. 439,858)	>1000	>1000
2-(4-chlorophenylimino)-3-methyl-thiazoline-HCl (Swiss Patent Specification No. 439,858)	>1000	>1000
1-naphthyl-N-methylcarbamate ("Sevin"; U.S. Pat. Spec. No. 2,903,478	1000	>1000
empir. $C_{10}H_{10}Cl_8$ ("Toxaphen"; U.S. Pat. Spec. No. 2,565,471)	1000	1000

Example 5.

Test to determine the effect on ticks: destroying action at various stages of development

As test objects are used larvae (in each case about 50), nymphs (in each case about 25) and imagines (in each case about 10) of the tick species Amblyomma hebraeum and Rhipicephalus bursa. The test insects are immersed for a short time in aqueous emulsions or solutions of the salts of the substances to be examined at a specific concentration. The emulsions or solutions in small test tubes are absorbed with cotton wool and the wetted test insects are then left in the contaminated test tubes. An evaluation with respect to larvae is made after 3 days, and with respect to nymphs and imagines after 14 days. There is determined the minimum substance concentration which effects a 100% destruction (LC_{100}), expressed in ppm of active substance relative to the total amount of emulsion or solution.

Results

Compound	LC_{100}			
	A. hebraeum		R.bursa	
	Nymphs	Larvae	Imagines	Larvae
1) 2-(2',3'-dimethyl-anilinomethyl)-2-imidazoline hydrochloride	1	1	50	1
2) 2-(2',3'-dichloro-anilinomethyl)-2-imidazoline hydrochloride	1	1	100	1

Comparison

2-(3,4-dichloro-phenylimino)-N-n-butylpyrrolidine ("Bimarit")	100	100	100	10
1-naphthyl-N-methylcarbamate ("Sevin": U.S. Patent 2,903,478)	10	5	100	10

The compounds of the formula I and acid addition salts thereof for ectoparasitic application are used on their own or together with suitable carriers and/or additives. Suitable carriers and additives can be solid or liquid and they can be any of the substances common in formulation practice such as natural or regenerated substances, solvents, dispersing agents, wetting agents, adhesives, thickeners and binders.

For application, the compounds of the formula I and acid addition salts thereof can be processed into the form of dusts, emulsifiable concentrates, granulates, dispersions, sprays or solutions, the formulation of these preparations being effected in a manner commonly known in the art. The compositions according to the invention can be produced in a manner known per se by the intimate mixing and/or grinding of the active substance with suitable carriers, optionally with the addition of dispersing agents or solvents which are inert to the active substance. The active substance can be obtained and used in the following forms:

solid preparations: dusts, scattering agents, granules (coated granules, impregnated granules and homogeneous granules);

liquid preparations:
(a) water-dispersible concentrates of active substance: wettable powders, pastes or emulsions;
(b) solutions: "pour-on"

The content of active substance in the described compositions is between 1 and 80%.

Example 6.

Emulsifiable concentrate

20 parts by weight of active substance are dissolved in 70 parts by weight of xylene, and to the solution are added 10 parts by weight of an emulsifying agent consisting of a mixture of an arylphenyl polyglycol ether and the calcium salt of

dodecylbenzenesulphonic acid. A milk emulsion is formed by adding water to the emulsion concentrate in the desired proportion.

Example 7.

Emulsifiable concentrate

5 to a maximum of 30 parts by weight of active substance are dissolved at room temperature, with stirring, in 30 parts by weight of dibutylphthalate, 10 parts by weight of Solvent 200 (low-viscous, highly aromatic petroleum distillate) and 15 to 35 parts by weight of Dutrex 238 FC (viscous, highly aromatic petroleum distillate; and to this solution are added 10 parts by weight of an emulsifier mixture consisting of castor oil polyglycol ether and the calcium salt of dodecylbenzene sulphonic acid. The emulsion concentrate thus obtained gives milky emulsions in water.

Example 8.

Wettable powder

5 to 30 parts by weight of the active substance are thoroughly mixed, in a mixing apparatus, with 5 parts by weight of an absorbent carrier silica K 320 or Wessalon S) and 55 to 80 parts by weight of a carrer (bolus alba or Kaolin B 24) and a dispersing agent mixture consisting of 5 parts by weight of an Na-lauryl-sulphonate and 5 parts by weight of an alkyl-aryl polyglycol ether. This mixture is ground in a dowelled disc mill or in an air-jet mill to 5 8 15 μm. The wettable powder obtained in this manner gives a good suspension in water.

Example 9.

Dust

5 parts by weight of finely ground active substance are thoroughly mixed with 2 parts by weight of a precipitated silica and 93 parts by weight of talcum.

Example 10.

Pour-on solution

active substance	30.0 g
sodium dioctylsulphosuccinate	3.0 g
benzyl alcohol	48.0 g
peanut oil	19.8 g
	100.8 g

The active substance is dissolved in the benzyl alcohol with stirring and if necessary also with slight heating. To the solution are added the sodium dioctyl-sulphosuccinate and the peanut oil, and dissolved with heating and vigorous mixing.

Example 11

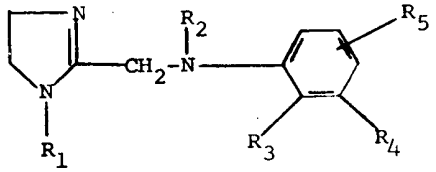
Pour-on solution

active substance	30.00 g
sodium dioctylsulphosuccinate	3.00 g
benzyl alcohol	35.46 g
ethylene glycol monomethyl ether	35.46 g
	103.92 g = 100 ml

The active substance is dissolved in the major part of the mixture of the two solvents with vigorous stirring. The sodium dioctylsulphosuccinate is subsequently dissolved, if necessary with heating, and the amount is made up with the remainder of the solvent mixture.

WHAT WE CLAIM IS:—

1. A method for controlling mites and ticks which comprises applying thereto a compound of the formula:



wherein each of R_1 and R_2 represents hydrogen or alkyl of from 1 to 10 carbon atoms,
each of R_3 and R_4 represents alkyl of from 1 to 5 carbon atoms or halogen, and
R_5 represents hydrogen, alkyl of from 1 to 5 carbon atoms or halogen, or an acid addition salt thereof.

2. The method according to claim 1 in which each of R_3 and R_4 represents alkyl of from 1 to 5 carbon atoms or chlorine.

3. The method according to claim 2 in which the compound is 2 - 2',3' - dimethylanilinomethyl) - 2 - imidazoline hydrochloride.

4. The method according to claim 2 in which the compound is 2 - (2',3' - dichloroanilinomethyl) - 2 - imidazoline hydrochloride.

5. A method for controlling mites and ticks which comprise applying thereto a compound of formula (I) defined in claim 1 wherein each of R_1 and R_2 represents hydrogen or alkyl of 1 to 5 carbon atoms or an acid addition salt thereof.

6. A method for controlling mites and ticks which comprises applying thereto a compound of formula (I) defined in claim 1 mentioned in Example 3.

7. Compounds of formula (I) as defined in claim 1 and their acid addition salts except 2 - (2' - methyl - 3' - chloro)anilinomethyl - 2 - imidazoline and its acid addition salts.

8. Compounds according to claim 7 wherein each of R_1 and R_2 represents hydrogen or alkyl of 1 to 5 carbon atoms.

9. 2 - (2',3' - Dimethylanilinomethyl) - 2 - imidazoline hydrochloride.

10. 2 - (2',3' - Dichloroanilinomethyl) - 2 - imidazoline hydrochloride.

11. Each of the compounds numbered 3 to 11 mentioned in Example 3.

12. A process for producing a compound claimed in claim 7 by method a, b, c or d, hereinbefore set forth.

13. A compound according to claim 7 when produced by a process claimed in claim 12.

14. An ectoparasiticidal composition comprising a solid or liquid carrier and/or additive and at least one compound claimed in claim 7 or 13.

15. An ectoparasiticidal composition comprising a solid or liquid carrier and/or additive and at least one compound claimed in claim 8, 9, 10 or 11.

16. A composition according to claim 14 in the form or a dust, emulsifiable concentrate, granulate, dispersion, spray or solution.

17. A composition according to claim 15 in the form of a dust, emulsifiable concentrate, granulate, dispersion, spray or solution.

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