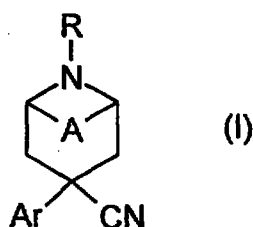


INSECTICIDAL COMPOSITIONS AND METHODS

This invention relates to insecticidal compositions useful for the control of resistant insect pests and to a method of combating resistant insect pests therewith.

The present invention provides an insecticidal composition comprising a first insecticidally active ingredient, to which insect pests have developed a degree of resistance, an insecticidally inert carrier or diluent and, optionally, one or more surface active agents, characterised in that the composition further contains a sufficient amount of a compound of formula (I):



wherein A represents a bidentate group of formula $-\text{CH}_2\text{CH}_2-$ or $\text{CH}=\text{CH}$; Ar is phenyl, pyridinyl, pyridazinyl or pyrazinyl, all being optionally substituted with halogen (especially fluorine, chlorine or bromine), C_{1-4} alkyl (especially methyl), C_{1-4} alkoxy (especially methoxy), C_{2-4} alkenyl, C_{2-4} alkynyl or cyano; R is hydrogen, C_{1-4} alkyl (optionally substituted with cyano, $\text{CO}_2(\text{C}_{1-4}$ alkyl) or phenyl (itself optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkoxy)), C_{2-4} haloalkyl (the α -carbon being unsubstituted), C_{3-4} alkenyl or C_{3-4} alkynyl; provided that when R is alkenyl or alkynyl said group does not have an unsaturated carbon atom bonding directly to the ring nitrogen of formula (I); or an acid addition salt, quaternary ammonium salt or N-oxide derived therefrom; to boost the activity of the composition to overcome the resistance of the insect pests. It is preferred that the ratio of the first insecticidally active ingredient: compound of formula (I) is in the range 1:100 to 100:1 (for example 1:10 to 10:1) weight/weight.

It will be appreciated that the compounds of formula (I) are capable of existing in more than one isomeric form since groups may be positioned in either an exo or endo relationship, and the present invention embraces within its scope both exo and endo forms and mixtures thereof in all proportions and also any further isomeric variants arising from cis and trans substitution patterns or chiral centres.

Halogen includes fluorine, chlorine, bromine and iodine.

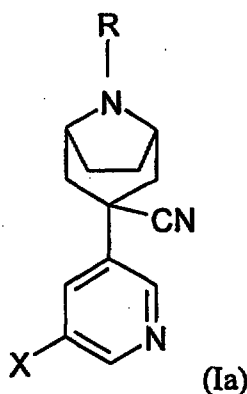
Alkyl moieties can be in the form of straight or branched chains, for example methyl, ethyl, n- or iso-propyl, or n-, sec-, iso- or tert-butyl.

Haloalkyl is especially fluoroalkyl (for example trifluoromethyl, 2,2,2-trifluoroethyl or 2,2-difluoroethyl) or chloroalkyl. For R, haloalkyl is, for example, 2,2,2-trifluoroethyl or
5 2,2-difluoroethyl.

Alkenyl and alkynyl moieties can be in the form of straight or branched chains, and, where appropriate, the alkenyl moieties can be of either (E)- or (Z)-configuration. Examples are vinyl, allyl and propargyl.

Suitable acid addition salts include those with an inorganic acid such as hydrochloric,
10 hydrobromic, sulfuric, nitric and phosphoric acids, or an organic carboxylic acid such as oxalic, tartaric, lactic, butyric, toluic, hexanoic and phthalic acids, or sulphonic acids such as methane, benzene and toluene sulphonic acids. Other examples of organic carboxylic acids include haloacids such as trifluoroacetic acid.

In one particular aspect the present invention provides novel insecticidal
15 compositions comprising an insecticidally active ingredient to which insect pests have developed a degree of resistance in association with an insecticidally inert diluent and, optionally, one or more surface active agents, characterised in that the composition contains an sufficient amount of a compound of formula (Ia):



20 wherein X represents hydrogen or halogen, more particularly chloro or bromo, and R represents lower alkyl or lower haloalkyl of up to 4 carbon atoms, or benzyl or halobenzyl, to boost the activity of the composition to overcome the resistance.

In another aspect the present invention provides a compound of formula (I) wherein Ar is pyridin-3-yl optionally substituted in the 5-position with chlorine or bromine.

In a further aspect the invention provides a method of improving the activity of an insecticide against insect pests which have developed a level of resistance to such insecticides which comprises applying to the pests or the locus of the pests an insecticidal composition comprising the insecticide in association with a compound of formula (I).

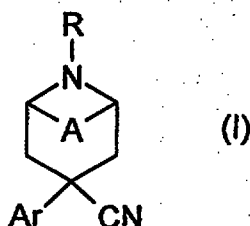
5 Examples of insecticides to which resistance may have developed for which the invention compositions and method will be useful include the following:

- Pyrethroids: Lambdacyhalothrin, cyhalothrin, deltamethrin, fenvalerate, esfenvalerate, cyfluthrin, betacyfluthrin, deltamethrin, etofenprox. A further example is tefluthrin.
- 10 Organophosphates: Chlorpyrifos, profenofos, acephate, dimethoate, parathion-methyl, terbufos, monocrotophos, sulprofos, prothiofos.
- Carbamates: Aldicarb, carbofuran, carbaryl, methomyl, fenobucarb, pirimicarb.
- Benzoyl ureas: Diflubenzuron, chlorfluazuron, teflubenzuron, hexaflumuron, flufenoxuron, lufenuron, flucycloxuron.
- 15 Others: Amitraz, clofentezine, fenpyroximate, hexythiazox, propargite, tebufenpyrad, fenazaquin, pyridaben, spinosad, triazamate, buprofezin, abamectin, fipronil, tebufenozide, diofenolan, imidacloprid. A further example is chlorfenapyr.

Amongst the insect pest which are becoming more difficult to control because of the development of resistance to one or more of the above insecticides are the following:

- Homoptera: Aphids (for example *Myzus persicae*, *Myzus nicotianae*, *Aphis fabae*, *Aphis gossypii*, *Rhopalosiphum padi*, *Aphis nasturtii*, *Macrosiphum euphorbiae*).
- Whitefly (for example *Bemisia tabaci*, *Bemisia argentifolii*, *Trialeurodes vaporariorum*).
- 25 Planthoppers (for example *Nephotettix cincticeps*, *Nilaparvata lugens*).
- Heteroptera (for example *Lygus lineolaris*, *Lygus hesperus*)
- Lepidoptera (for example *Plutella xylostella*, *Heliothis virescens*, *Spodoptera exigua*, *Laspeyresia pomonella*).
- 30 Diptera (for example *Liriomyza trifolii*).
- Coleoptera (for example *Phaedon cochlearae*, *Anthonomus grandis*)

The invention also provides a composition comprising spinosad and a compound of formula (I):



wherein A represents a bidentate group of formula $-\text{CH}_2\text{CH}_2-$; Ar is phenyl, pyridinyl, pyridazinyl or pyrazinyl, all being optionally substituted with halogen (especially fluorine, chlorine or bromine), C_{1-4} alkyl (especially methyl), C_{1-4} alkoxy (especially methoxy), C_{2-4} alkenyl, C_{2-4} alkynyl or cyano; R is hydrogen, C_{1-4} alkyl (optionally substituted with cyano, $\text{CO}_2(\text{C}_{1-4}$ alkyl) or phenyl (itself optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkoxy)), C_{2-4} haloalkyl (the α -carbon being unsubstituted), C_{3-4} alkenyl or C_{3-4} alkynyl; provided that when R is alkenyl or alkynyl said group does not have an unsaturated carbon atom bonding directly to the ring nitrogen of formula (I); or an acid addition salt, quaternary ammonium salt or N -oxide derived therefrom. It is preferred that the ratio of spinosad: compound of formula (I) is in the range 1:100 to 100:1 (for example 1:10 to 10:1) weight/weight. [Spinosad, see, for example, EP-0375316 or abstracts from the 1997 Beltwide Cotton Insect Research and Control Conference pages 1082-1086.]

In another aspect the present invention provides a method of combating and controlling insect, acarine or nematode pests at a locus which comprises treating the pests or the locus of the pests with an effective amount of a composition comprising spinosad and a compound of formula (I), wherein A represents a bidentate group of formula $-\text{CH}_2\text{CH}_2-$; Ar is phenyl, pyridinyl, pyridazinyl or pyrazinyl, all being optionally substituted with halogen (especially fluorine, chlorine or bromine), C_{1-4} alkyl (especially methyl), C_{1-4} alkoxy (especially methoxy), C_{2-4} alkenyl, C_{2-4} alkynyl or cyano; R is hydrogen, C_{1-4} alkyl (optionally substituted with cyano, $\text{CO}_2(\text{C}_{1-4}$ alkyl) or phenyl (itself optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkoxy)), C_{2-4} haloalkyl (the α -carbon being unsubstituted), C_{3-4} alkenyl or C_{3-4} alkynyl; provided that when R is alkenyl or alkynyl said group does not have an unsaturated carbon atom bonding directly to the ring nitrogen of formula (I); or an acid addition salt, quaternary ammonium salt or N -oxide derived therefrom. Insect, acarine or nematode include insect pests such as Lepidoptera, Diptera,

Homoptera and Coleoptera (including *Diabrotica*, that is, corn rootworm), pests associated with agriculture (which term includes the growing of crops for food and fibre products), horticulture and animal husbandry, forestry, the storage of products of vegetable origin, such as fruit, grain and timber, and also those pests associated with the transmission of diseases of man and animals. Examples of insect and acarine pest species include: *Myzus persicae* (aphid), *Aphis gossypii* (aphid), *Aphis fabae* (aphid), *Aedes aegypti* (mosquito), *Anopheles* spp. (mosquitos), *Culex* spp. (mosquitos), *Dysdercus fasciatus* (capsid), *Musca domestica* (housefly), *Pieris brassicae* (white butterfly), *Plutella xylostella* (diamond back moth), *Phaedon cochleariae* (mustard beetle), *Aonidiella* spp. (scale insects), *Trialeurodes* spp. (white flies), *Bemisia tabaci* (white fly), *Blattella germanica* (cockroach), *Periplaneta americana* (cockroach), *Blatta orientalis* (cockroach) *Spodoptera littoralis* (cotton leafworm), *Heliothis virescens* (tobacco budworm) *Chortiocetes terminifera* (locust), *Diabrotica* spp. (rootworms), *Agrotis* spp. (cutworms), *Chilo partellus* (maize stem borer), *Nilaparvata lugens* (planthopper), *Nephotettix cincticeps* (leafhopper), *Panonychus ulmi* (European red mite), *Panonychus citri* (citrus red mite), *Tetranychus urticae* (two-spotted spider mite), *Tetranychus ni*, *Tetranychus cinnabarinus* (carmine spider mite), *Phyllocoptruta oleivora* (citrus rust mite), *Polyphagotarsonemus latus* (broad mite) and *Brevipalpus* spp. (mites).

Preferred compounds of formula (I) in the compositions of the present invention are compounds of formula (Ia) wherein X is chloro or bromo and R is 2,2-difluoroethyl or 2,2,2-trifluoroethyl, including, for example 3-(5-chloropyrid-3-yl)-3-cyano-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octane (Compound A) and 3-(5-chloropyrid-3-yl)-3-cyano-8-(2,2-difluoroethyl)-8-azabicyclo[3.2.1]octane (Compound B).

A further preferred compound of formula (I) in the compositions of the present invention is 3-(5-chloropyrid-3-yl)-3-cyano-8-azabicyclo[3.2.1]octane (Compound C).

Compounds of formula (I) may be prepared by adaptation of methods described in the literature (such as J. Med. Chem. (1975) 18(5) 496-501), by use of one or more of the following synthetic techniques described below, or by combining literature methods with those methods described below. Throughout the following description R⁵ is alkyl or phenylalkyl (especially benzyl).

Compounds of formula (I) can be prepared by treating compounds of formula (II) with a compound of formula RL where L is a suitable leaving group such as a halide or triflate, optionally in the presence of a suitable base, such as potassium carbonate.

Compounds of formula (II) (which are compounds of formula (I) wherein R is hydrogen) can be prepared by deprotecting compounds of formula (III) by, for instance, either: (i) treating them with a chloroformate ester (such as vinyl chloroformate) and subjecting the carbamate so formed to acid hydrolysis (with for example, hydrochloric acid); or (ii) treating them with an azodicarboxylate (such as diethyl azodicarboxylate) at a suitably elevated temperature.

A compound of formula (I) can be prepared by reacting a compound of formula (III) with a compound RHal (wherein Hal is a halogen) under suitable conditions (such as in the presence of a base and an alkali metal iodide) in a suitable solvent (such as N,N-dimethylformamide).

Alternatively, compounds of formula (I) can be prepared from compounds of formula (II) by reductive amination with an aldehyde (R^6CHO ; where $R^6CH_2 = R$) in the presence of a suitable reducing agent such as formic acid.

Compounds of formula (III) can be prepared by treating compounds of formula (IV) first with a suitable base, such as lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide, and then reacting the product so formed with a compound ArHal, wherein Hal is a halogen.

Alternatively, compounds of formula (I) can be prepared by treating compounds of formula (VI) with a suitable base, such as lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide, and reacting the product so formed with a compound ArHal, wherein Hal is a halogen.

Compounds of formula (VI) can be prepared by treating compounds of formula (VII) with a suitable base, such as potassium carbonate, in the presence of a compound of formula RHal, wherein Hal is a halogen.

Alternatively, compounds of formula (VI) can be prepared by treating compounds of formula (VIII) with tosylmethyl isocyanide in the presence of a suitable base, such as potassium ethoxide.

Compounds of formula (VIII) can be prepared by a process analogous to the Robinson tropinone synthesis, from, for example, 2-ethoxy-3,4-dihydropyran. (See, for instance, Organic Synthesis (Collective Volume 4), p 816.)

Compounds of formula (I) wherein A is $\text{CH}=\text{CH}$ can be prepared by heating a
5 compound of formula (I) wherein A is CH_2CHZ (wherein Z is a suitable group, such as a thiono-4-tolylthio group) in a suitable solvent (such as xylene) at a suitable temperature (such as reflux).

Compounds of formula (I) wherein A is CH_2CHZ (wherein Z is a suitable group, such as a thiono-4-tolylthio group) can be prepared by treating compounds of formula (I) wherein
10 A is $\text{CH}_2\text{CH}(\text{OH})$ with a suitable chloroformate (such as 4-tolyl chlorothionoformate) in the presence of a suitable base (such as *N,N*-dimethylaminopyridine).

Compounds of formula (I) wherein A is $\text{CH}_2\text{CH}(\text{OH})$ can be prepared by acid hydrolysis of compounds of formula (I) wherein A is $\text{CH}_2\text{CH}(\text{OZ}')$ wherein Z' is a hydrolysable group (such as *tert*-butyldimethylsilyl).

15 A compound of formula (I) wherein A is $\text{CH}_2\text{CH}(\text{OZ}')$ wherein Z' is hydrogen or a hydrolysable group (such as *tert*-butyldimethylsilyl) can be prepared by reacting a corresponding compound of formula (VI) with a suitable base, such as lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide, and reacting the product so formed with a compound ArHal , wherein Hal is a halogen.

20 A compound of formula (VI) wherein A is $\text{CH}_2\text{CH}(\text{OZ}')$ wherein Z' is hydrogen or a hydrolysable group (such as *tert*-butyldimethylsilyl) can be prepared by treating a corresponding compound of formula (V) with tosylmethyl isocyanide (also known as (4-tolylsulfonyl)methylisocyanide) in the presence of a suitable base, such as potassium *tert*-butoxide.

25 A compound of formula (V) wherein A is $\text{CH}_2\text{CH}(\text{OZ}')$ wherein Z' is a hydrolysable group (such as *tert*-butyldimethylsilyl) can be prepared by reacting a compound of formula (V) wherein A is $\text{CH}_2\text{CH}(\text{OH})$ with a compound $\text{Z}'\text{L}$ wherein L is a leaving group.

Alternatively a compound of formula (I) wherein A is $\text{CH}=\text{CH}$ can be prepared by dehydrating a compound of formula (I) wherein A is $\text{CH}_2\text{CH}(\text{OH})$ with a suitable
30 dehydrating agent, such as diethylaminosulfurtrifluoride.

A compound of formula (I) wherein A is $\text{CH}=\text{CH}$ can be prepared by reacting a compound of formula (I) wherein A is $\text{CH}_2\text{CH}(\text{OZ}')$, wherein Z' is a suitable group (such as SO_2CH_3) with a suitable amine (such as 1,8-diazabicyclo[5.4.0]undec-7-ene).

5 A compound of formula (I) wherein A is $\text{CH}_2\text{CH}(\text{OZ}')$, wherein Z' is a suitable group (such as SO_2CH_3) can be prepared by reacting a compound of formula (I) wherein A is $\text{CH}_2\text{CH}(\text{OH})$ with a suitable acid chloride (such as mesyl chloride).

The amount of composition of the present invention generally applied for the control of insect pests gives a rate of active ingredient from 0.01 to 10 kg per hectare, preferably from 0.1 to 6 kg per hectare.

10 The compositions of the present invention can be applied to the soil, plant or seed, to the locus of the pests, or to the habitat of the pests, in the form of dusting powders, wettable powders, granules (slow or fast release), emulsion or suspension concentrates, liquid solutions, emulsions, seed dressings, fogging/smoke formulations or controlled release compositions, such as microencapsulated granules or suspensions.

15 Dusting powders are formulated by mixing the active ingredient with one or more finely divided solid carriers and/or diluents, for example natural clays, kaolin, pyrophyllite, bentonite, alumina, montmorillonite, kieselguhr, chalk, diatomaceous earths, calcium phosphates, calcium and magnesium carbonates, sulphur, lime, flours, talc and other organic and inorganic solid carriers.

20 Granules are formed either by absorbing the active ingredient in a porous granular material for example pumice, attapulgite clays, Fuller's earth, kieselguhr, diatomaceous earths, ground corn cobs, and the like, or on to hard core materials such as sands, silicates, mineral carbonates, sulphates, phosphates, or the like. Agents which are commonly used to aid in impregnation, binding or coating the solid carriers include aliphatic and aromatic
25 petroleum solvents, alcohols, polyvinyl acetates, polyvinyl alcohols, ethers, ketones, esters, dextrans, sugars and vegetable oils. with the active ingredient. Other additives may also be included, such as emulsifying agents, wetting agents or dispersing agents.

Microencapsulated formulations (microcapsule suspensions CS) or other controlled release formulations may also be used, particularly for slow release over a period of time,
30 and for seed treatment.

Alternatively the compositions of the present invention may be in the form of liquid preparations to be used as dips, irrigation additives or sprays, which are generally aqueous dispersions or emulsions of the active ingredient in the presence of one or more known wetting agents, dispersing agents or emulsifying agents (surface active agents). The compositions which are to be used in the form of aqueous dispersions or emulsions are generally supplied in the form of an emulsifiable concentrate (EC) or a suspension concentrate (SC) containing a high proportion of the active ingredient or ingredients. An EC is a homogeneous liquid composition, usually containing the active ingredient dissolved in a substantially non-volatile organic solvent. An SC is a fine particle size dispersion of solid active ingredient in water. In use, the concentrates are diluted in water and applied by means of a spray to the area to be treated.

Suitable liquid solvents for ECs include methyl ketones, methyl isobutyl ketone, cyclohexanone, xylenes, toluene, chlorobenzene, paraffins, kerosene, white oil, alcohols, (for example, butanol), methylnaphthalene, trimethylbenzene, trichloroethylene, N-methyl-2-pyrrolidone and tetrahydrofurfuryl alcohol (THFA).

Wetting agents, dispersing agents and emulsifying agents may be of the cationic, anionic or non-ionic type. Suitable agents of the cationic type include, for example, quaternary ammonium compounds, for example cetyltrimethyl ammonium bromide. Suitable agents of the anionic type include, for example, soaps, salts of aliphatic monoesters of sulphuric acid, for example sodium lauryl sulphate, salts of sulphonated aromatic compounds, for example sodium dodecylbenzenesulphonate, sodium, calcium or ammonium lignosulphonate, or butylnaphthalene sulphonate, and a mixture of the sodium salts of diisopropyl- and triisopropylnaphthalene sulphonates. Suitable agents of the non-ionic type include, for example, the condensation products of ethylene oxide with fatty alcohols such as oleyl alcohol or cetyl alcohol, or with alkyl phenols such as octyl phenol, nonyl phenol and octyl cresol. Other non-ionic agents are the partial esters derived from long chain fatty acids and hexitol anhydrides, the condensation products of the said partial esters with ethylene oxide, and the lecithins.

These concentrates are often required to withstand storage for prolonged periods and after such storage, to be capable of dilution with water to form aqueous preparations which remain homogeneous for a sufficient time to enable them to be applied by conventional spray

equipment. The concentrates may contain 10-85% by weight of the combination of active ingredients. When diluted to form aqueous preparations such preparations may contain varying amounts of the active ingredient depending upon the purpose for which they are to be used.

5 The compositions of the present invention may be in the form of powders (dry seed treatment DS or water dispersible powder WS) or liquids (flowable concentrate FS, liquid seed treatment LS, or microcapsule suspension CS) for use in seed treatments.

 In use the compositions of the present invention are applied to the insect pests, to the locus of the pests, to the habitat of the pests, or to growing plants liable to infestation by the
10 pests, by any of the known means of applying pesticidal compositions, for example, by dusting, spraying, or incorporation of granules.

 The compositions of the present invention may be admixed with one or more additional active ingredients such as insecticides or synergists where appropriate. Suitable additional active ingredients for inclusion in a composition of the present invention may be
15 compounds which will broaden the spectrum of activity of the compositions of the invention or increase their persistence in the location of the pest. They may synergise the activity of the compound of formula (I) or complement the activity for example by increasing the speed of effect or overcoming repellency. The particular additional active ingredient included will depend upon the intended utility of the mixture and the type of complementary action
20 required. Examples of suitable insecticides include the following:

- a) Pyrethroids such as permethrin, esfenvalerate, deltamethrin, cyhalothrin in particular lambda-cyhalothrin, biphenethrin, fenpropathrin, cyfluthrin, tefluthrin, fish safe pyrethroids for example ethofenprox, natural pyrethrin, tetramethrin, s-bioallethrin, fenfluthrin, prallethrin and 5-benzyl-3-furylmethyl-(E)-(1R,3S)-2,2-dimethyl-
25 3-(2-oxothiolan-3-ylidenemethyl) cyclopropane carboxylate;
- b) Organophosphates such as profenofos, sulprofos, methyl parathion, azinphos-methyl, demeton-s-methyl, heptenophos, thiometon, fenamiphos, monocrotophos, profenophos, triazophos, methamidophos, dimethoate, phosphamidon, malathion, chlorpyrifos, phosalone, terbufos, fensulfothion, fonofos, phorate, phoxim, pyrimiphos-methyl,
30 pyrimiphos-ethyl, fenitrothion or diazinon;

- c) Carbamates (including aryl carbamates) such as pirimicarb, cloethocarb, carbofuran, furathiocarb, ethiofencarb, aldicarb, thiofurox, carbosulfan, bendiocarb, fenobucarb, propoxur or oxamyl;
- d) Benzoyl ureas such as triflumuron, or chlorfluazuron;
- 5 e) Organic tin compounds such as cyhexatin, fenbutatin oxide, azocyclotin;
- f) Macrolides such as avermectins or milbemycins, for example such as abamectin, ivermectin, and milbemycin;
- g) Hormones and pheromones;
- h) Organochlorine compounds such as benzene hexachloride, DDT, chlordane or dieldrin;
- 10 i) Amidines, such as chlordimeform or amitraz;
- j) Fumigant agents;
- k) Imidacloprid;
- l) Spinosad.

In addition to the major chemical classes of insecticide listed above, other
15 insecticides having particular targets may be employed in the mixture if appropriate for the intended utility of the mixture. For instance selective insecticides for particular crops, for example stemborer specific insecticides for use in rice such as cartap or buprofezin can be employed. Alternatively insecticides specific for particular insect species/stages for example
20 ovo-larvicides such as chlofentezine, flubenzimine, hexythiazox and tetradifon, motilicidessuch as dicofol or propargite, acaricides such as bromopropylate, chlorobenzilate, or growth regulators such as hydramethylron, cyromazine, methoprene, chlorfluazuron and diflubenzuron may also be included in the compositions.

Examples of suitable synergists for use in the compositions include piperonyl
butoxide, sesamax, safroxan and dodecyl imidazole.

25 The following Examples illustrate the invention.

EXAMPLE 1

The resistance breaking effect of the invention compositions is demonstrated by the following test using resistant (R2) strain of the peach aphid Myzus persicae which is classified as 'strongly resistant' to organophosphorus compounds (OPs), pyrethroids and
30 carbamates due to an increased level of esterase E4. The test compositions were as set out below.

The procedure was as follows:

One day before treatment:

Small plastic pots are filled approx. one third full with 1% agar solution and allowed to set. Discs of Chinese cabbage (variety Tip Top) about 1 inch in diameter were cut and placed top side down on the agar. The leaf disc was infested by placing an infested radish cotyledon (from a main culture) on the surface overnight; the cotyledon dries and the aphids walk on to the disc.

Treatment day:

The dried cotyledons were removed and the pots labelled as required - in this case for 1 rate x 10 replicates. The solutions were sprayed using a Burkhard Potter tower at around 300l/ha. Once air dried, lids with ventilation slits were clipped on top and the test stored for 3 days at 20°C. By this procedure the aphids were dosed by direct contact and residual pick-up as they moved across the leaf surface.

3 days after treatment:

Each pot was assessed for dead and live aphids. The data was analysed and the results set out below in the following Table.

	<u>TEST COMPOSITION</u>	<u>%MORTALITY</u>
1.	pirimicarb (20ppm)	57.68%
2.	pirimicarb (20ppm) + Compound A (1ppm)	98.97%
3.	pirimicarb (20ppm) + Compound B (1ppm)	95.24%
4.	chlorpyrifos (20ppm)	2.28%
5.	chlorpyrifos (20ppm) + Compound A (1ppm)	95.33%
6.	chlorpyrifos (20ppm) + Compound A (1ppm)	96.37%
7.	lambdacyhalothrin (0.5ppm)	5.6%
8.	lambdacyhalothrin (0.5ppm) + Compound A (1ppm)	100%
9.	lambdacyhalothrin (0.5ppm) + Compound B (1ppm)	94.19%

In a similar test against Tetranychus ni the following results were obtained:

<u>TEST COMPOSITION</u>	<u>%MORTALITY</u>
10. lambdacyhalothrin (0.02ppm)	15%
11. Compound A (250ppm)	44%
12. lambdacyhalothrin (0.02ppm) + Compound A (250ppm)	85%

EXAMPLE 2

Cells from the thoracic ganglia of a locust were prepared according to a simplified
 5 version of the methods described by Beadle and Lees {Beadle D.J., Lees G. (1986), In
 Neuropharmacology & Pesticide Action (edited by M.G. Ford et al), pages 423-444,
 Chichester: Ellis Horwood} and Pinnock and Sattelle {Pinnock R.D., Sattelle D.B. (1987), J.
 Neuroscience Methods 20 pages 195-202}. A single animal was used for each experiment.
 The insect was killed and its thoracic ganglia removed under a saline consisting of 214mM
 10 Na⁺; 3.1mM K⁺; 9mM Ca²⁺; 221mM Cl⁻; 10mM TES, adjusted to pH 7.0. All axonal
 processes were trimmed off each of the ganglia and the sheath layer removed using fine
 forceps. The ganglia were then cut into halves or quarters and transferred to a 1mg/ml
 (approx.) collagenase (Sigma Type III) solution in cockroach saline. After 30-50minutes
 (room temperature) the tissue was washed in enzyme free saline and triturated through fire-
 15 polished pasteur-pipettes. The resulting suspension was plated out onto 50mm Falcon Tight-
 Seal petri-dishes containing just enough medium to cover the floor of the dish.

These cells survive overnight in the medium described by Beadle and Hicks {Beadle
 D.J., Hicks D. (1985), Insect Nerve Culture, In Comprehensive Insect Physiology,
 Biochemistry & Pharmacology, Vol. 5, Nervous System: Structure & Motor Function.
 20 (edited by G.A. Kerkut and E.I. Gilbert), pages 181-211, Oxford: Pergamon Press} for the
 differentiation of embryonic cells in culture, an equal parts mixture of Liebowitz's L-15
 medium and Graces Insect T.C. medium (Gibco BRL), supplemented with 50IU/ml
 penicillin/streptomycin and 50µg/ml gentamycin. At 1-2 hours prior to experimentation the
 medium was replaced with the same saline that was used for the dissection. This was
 25 perfused over the cells continuously while results were obtained.

Membrane voltage was recorded using a conventional intracellular (current-clamp)
 technique. Isolated cell bodies were impaled with a borosilicate micro-pipette containing a

silver/silver-chloride electrode in a 3M KCl(aq) electrolyte. Micro-pipettes were prepared using a Sutter P97 horizontal puller to give resistances of around 20M Ω . Cells were stimulated electrically through the intracellular electrode by repetitive pulses of either negative current, to assess membrane resistance, or positive current, to elicit action-potentials (spikes).

Compound C (10 μ M) and Compound A (100 μ M) were applied (separately) to the membrane of the cell from a second micro-pipette placed in close vicinity. This micro-pipette was connected to a pressure-generator (MSC PLi100 Picoinjector) and ejection of the compounds achieved by controlled pulses of nitrogen gas. Spinosad was applied through the perfusing saline.

Compound C (referred to as 'comp. C' in the figures) elicits a depolarisation of the cell coupled to a drop in the membrane resistance as indicated by the shortening of the voltage responses to the negative current steps (Figure 1). The response to Compound A (referred to as 'comp. A' in the figures) in the same cell is shown in Figure 2. There is no depolarisation and even a slight hyperpolarisation.

The effect of spinosad on the response to Compound C is shown in Figures 3 and 4, which show responses to four 50ms pulses of Compound C (Figure 3) compared to a single 50ms pulse in the presence of 1 μ M spinosad (Figure 4). The effects are at least partially reversible, the normal profile of the Compound C response recovered after around 30minutes washing at a flow-rate of 1.3ml/min (Figure 5). Spinosad was active in this experiment at the lowest concentration tested, 100pM.

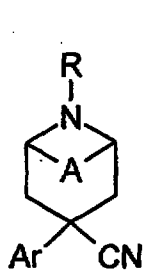
The effect of spinosad on the response to Compound A is shown in Figures 6 to 11. Figures 6 to 8 show the superimposed voltage responses to sixty 90ms pulses of positive current (I_{π}) applied through the electrode at a level just sufficient to elicit a spike (0.4nA), and at a rate of one step event every 1.8secs. A 90ms pulse of Compound A is applied during the tenth step in each case. The square wave at the bottom of each graph indicates the duration of I_{π} which is also the duration of the Compound A pulse during the tenth step-event. The first example (Figure 6) is the control in the absence of spinosad which shows no response to Compound A. Figure 7 was recorded in the presence of 50nM spinosad and shows changes in both the pre I_{π} resting potential and the profile of the spike. Separation of the events in Figure 7 show that prior to application of Compound A (events 1 to 10

inclusive) the spike profile is stable (Figure 7a), but following Compound A application (Figure 7b: events 10-13) there is a depolarisation, resulting in a shortening of the stimulus-to-spike time and eventual abolition of the spike at the peak of the response. As the cell recovers its resting potential, the spike profile is restored (Figure 7c: events 20, 30, 40, 50 and 60). This type of spike inhibition can be mimicked by depolarising the cell slightly with a continuous positive current passed through the electrode, suggesting that the spike abolition is due to the reduction in ΔV at the onset of the step-event, and is little more than a symptom of depolarisation. Figure 8 is of a recording made 10-12 minutes into washing following the application of spinosad. There is clearly some reversal of the effect; there is no abolition of the spike but still some depolarisation and shortening of the stimulus-to-spike time as shown by Figure 8a (events 10 to 13).

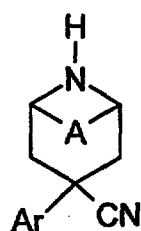
Figures 9 to 11 are plots of the resting potential changes evoked by Compound A in the absence (Figure 9) and presence (Figure 10) of spinosad and after 10 to 12 minutes washing (Figure 11). These graphs were constructed using the incidental voltage at the 19ms point (just before I_{H}) in each of the sixty events shown in Figures 6 to 8 respectively. The scale range of each graph has been kept the same to assist comparison of the Compound A responses. The "response" to Compound A in the absence of spinosad (Figure 9) does not rise above levels of background noise whereas in the presence of spinosad (Figure 10) there is a clear depolarisation of more than 14mV. This steadily reduces as the spinosad is washed away (Figure 11).

Thus, Compound C is a potent depolariser of insect neurones and spinosad reversibly potentiates this action. In the presence of spinosad, significant depolarisation responses can be achieved with Compound A.

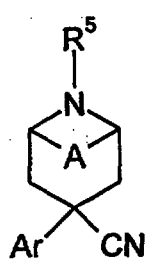
The formula referred to hereinabove are set out as follows



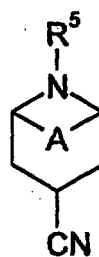
(I)



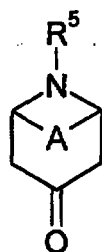
(II)



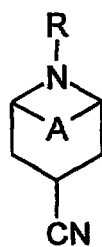
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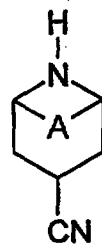
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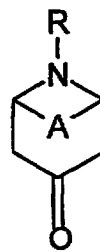
(V)



(VI)



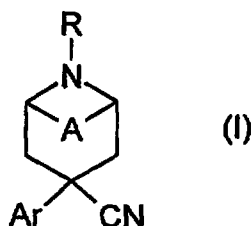
(VII)



(VIII)

CLAIMS

1. An insecticidal composition comprising a first insecticidally active ingredient, to which insect pests have developed a degree of resistance, an insecticidally inert carrier or diluent and, optionally, one or more surface active agents, characterised in that the composition further contains a sufficient amount of a compound of formula (I):



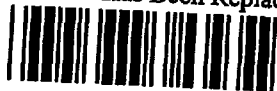
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wherein A represents a bidentate group of formula $-\text{CH}_2\text{CH}_2-$ or $\text{CH}=\text{CH}$; Ar is phenyl, pyridinyl, pyridazinyl or pyrazinyl, all being optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl or cyano; R is hydrogen, C_{1-4} alkyl (optionally substituted with cyano, $\text{CO}_2(\text{C}_{1-4}$ alkyl) or phenyl (itself optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkoxy)), C_{2-4} haloalkyl (the α -carbon being unsubstituted), C_{3-4} alkenyl or C_{3-4} alkynyl; provided that when R is alkenyl or alkynyl said group does not have an unsaturated carbon atom bonding directly to the ring nitrogen of formula (I); or an acid addition salt, quaternary ammonium salt or N-oxide derived therefrom; to boost the activity of the composition to overcome the resistance of the insect pests.

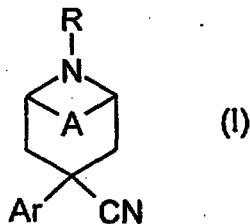
2. A composition as claimed in claim 1 wherein the first insecticidally active ingredient is selected from the group consisting of: Lambdacyhalothrin, cyhalothrin, deltamethrin, fenvalerate, esfenvalerate, cyfluthrin, betacyfluthrin, deltamethrin, etofenprox, tefluthrin, chlorpyrifos, profenofos, acephate, dimethoate, parathion-methyl, terbufos, monocrotophos, sulprofos, prothiofos, aldicarb, carbofuran, carbaryl, methomyl, fenobucarb, pirimicarb, diflubenzuron, chlorfluazuron, teflubenzuron, hexaflumuron, flufenoxuron, lufenuron, flucycloxuron, amitraz, clofentezine, fenpyroximate, hexythiazox, propargite, tebufenpyrad, fenazaquin,





pyridaben, spinosad, triazamate, buprofezin, abamectin, fipronil, tebufenozide, diofenolan, imidacloprid and chlorfenapyr.

3. A method of improving the activity of an insecticide against insect pests which have developed a level of resistance to such insecticides which comprises applying to the pests or the locus of the pests an insecticidal composition comprising the insecticide in association with a compound of formula (I), wherein A represents a bidentate group of formula $-\text{CH}_2\text{CH}_2-$ or $\text{CH}=\text{CH}$; Ar is phenyl, pyridinyl, pyridazinyl or pyrazinyl, all being optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl or cyano; R is hydrogen, C_{1-4} alkyl (optionally substituted with cyano, $\text{CO}_2(\text{C}_{1-4}$ alkyl) or phenyl (itself optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkoxy)), C_{2-4} haloalkyl (the α -carbon being unsubstituted), C_{3-4} alkenyl or C_{3-4} alkynyl; provided that when R is alkenyl or alkynyl said group does not have an unsaturated carbon atom bonding directly to the ring nitrogen of formula (I); or an acid addition salt, quaternary ammonium salt or N-oxide derived therefrom.
4. A method of combating or controlling insect, acarine or nematode pests at a locus which comprises treating the pests or the locus of the pests with an effective amount of a composition according to claim 1.
5. A composition comprising spinosad and a compound of formula (I):



wherein A represents a bidentate group of formula $-\text{CH}_2\text{CH}_2-$; Ar is phenyl, pyridinyl, pyridazinyl or pyrazinyl, all being optionally substituted with halogen (especially fluorine, chlorine or bromine), C_{1-4} alkyl (especially methyl), C_{1-4} alkoxy (especially methoxy), C_{2-4} alkenyl, C_{2-4} alkynyl or cyano; R is hydrogen, C_{1-4} alkyl (optionally substituted with cyano, $\text{CO}_2(\text{C}_{1-4}$ alkyl) or phenyl (itself optionally substituted with

halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl or C₁₋₄ haloalkoxy)), C₂₋₄ haloalkyl (the α -carbon being unsubstituted), C₃₋₄ alkenyl or C₃₋₄ alkynyl; provided that when R is alkenyl or alkynyl said group does not have an unsaturated carbon atom bonding directly to the ring nitrogen of formula (I); or an acid addition salt, quaternary ammonium salt or N-oxide derived therefrom.

6. A method of combating and controlling insect, acarine or nematode pests at a locus which comprises treating the pests or the locus of the pests with an effective amount of a composition comprising spinosad and a compound of formula (I), wherein A represents a bidentate group of formula -CH₂CH₂-; Ar is phenyl, pyridinyl, pyridazinyl or pyrazinyl, all being optionally substituted with halogen (especially fluorine, chlorine or bromine), C₁₋₄ alkyl (especially methyl), C₁₋₄ alkoxy (especially methoxy), C₂₋₄ alkenyl, C₂₋₄ alkynyl or cyano; R is hydrogen, C₁₋₄ alkyl (optionally substituted with cyano, CO₂(C₁₋₄ alkyl) or phenyl (itself optionally substituted with halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl or C₁₋₄ haloalkoxy)), C₂₋₄ haloalkyl (the α -carbon being unsubstituted), C₃₋₄ alkenyl or C₃₋₄ alkynyl; provided that when R is alkenyl or alkynyl said group does not have an unsaturated carbon atom bonding directly to the ring nitrogen of formula (I); or an acid addition salt, quaternary ammonium salt or N-oxide derived therefrom.

7. A method according to claim 4 or 6 wherein the pests are insect pests of growing plants.

8. A composition or method as claimed in any one of the preceding claims wherein the compound of formula (I) is:

3-(5-chloropyrid-3-yl)-3-cyano-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octane;
3-(5-chloropyrid-3-yl)-3-cyano-8-(2,2-difluoroethyl)-8-azabicyclo[3.2.1]octane; or,
3-(5-chloropyrid-3-yl)-3-cyano-8-azabicyclo[3.2.1]octane.

