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(21) International Application Number: PCT/AU90/00534 (22) International Filing Date: 8 November 1990 (08.11.90) (30) Priority data: PJ 7280 8 November 1989 (08.11.89) AU (71) Applicant (for all designated States except US): DUNLENA PTY. LTD. [AU/AU]; 168 Walker Street, North Sydney, NSW 2060 (AU). (72) Inventors; and (75) Inventors/Applicants (for US only): HOLAN, George [AU/AU]; 86 Were Street, Brighton, VIC 3186 (AU). O'KEEFE, David, Francis [AU/AU]; 13 Oakern Street, Mount Waverley, VIC 3149 (AU). JARVIS, Karen, Elizabeth [AU/AU]; 118 Brougham Street, Eltham, VIC 3095 (AU).		(74) Agents: CORBETT, Terence, G. et al.; Davies & Collison, 1 Little Collins Street, Melbourne, VIC 3000 (AU). (81) Designated States: AT (European patent), AU, BE (European patent), BR, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US. Published With international search report.
(54) Title: ARTHROPODICIDES (a) $\begin{array}{c} R_1 \\ \\ -A-C- \\ \\ R_6 \end{array}$ (b) $-CH=C(R_1)-$ (c) $\begin{array}{c} O & F \\ & \\ -C- & C- \\ & \\ F & \end{array}$ (57) Abstract Compounds of general formula (I) and their isomeric and racemic forms: characterized in that n is 0 or 1; A is oxygen, sulphur, C=O, CH₂, CF₂, CD₂, CDH, CHOH, CHX wherein X is fluorine, chlorine, bromine or iodine; G is oxygen, sulphur, CH₂ or CX₃X₄ wherein X₃ and X₄ are the same or different and each is fluorine, chlorine or bromine; X₁ and X₂ are the same or different and each is hydrogen or fluorine, chlorine or bromine; and when n is 0, X₁ and X₂ may also be methyl groups; R₁ is hydrogen, deuterium, CN, C≡CH, fluorine, chlorine or bromine and R₆ is hydrogen or deuterium; or R₁ and R₆ may optionally form =O, or (a) in formula (I) may be (b) or (c), R₂ is oxygen, or both H and OH together, or N-OR₈ wherein R₈ is hydrogen or lower alkyl which is optionally substituted with one or more halo groups; R₃ is a halo group, or a lower alkyl, lower alkoxy or lower alkylthio group, in each of which the alkyl group is optionally substituted with one or more halo groups; R₄ is hydrogen or a halo or lower alkyl group; or R₃ and R₄ may optionally form a methylenedioxy bridge which is optionally mono- or di-substituted with fluorine; R₅ is hydrogen, OH, lower alkoxy, SH, or lower thioalkyl, fluorine, chlorine, bromine or iodine; R₇ is H₂, HD, D₂ or oxygen. R₉ is H, lower alkoxy or lower alkylthio.		

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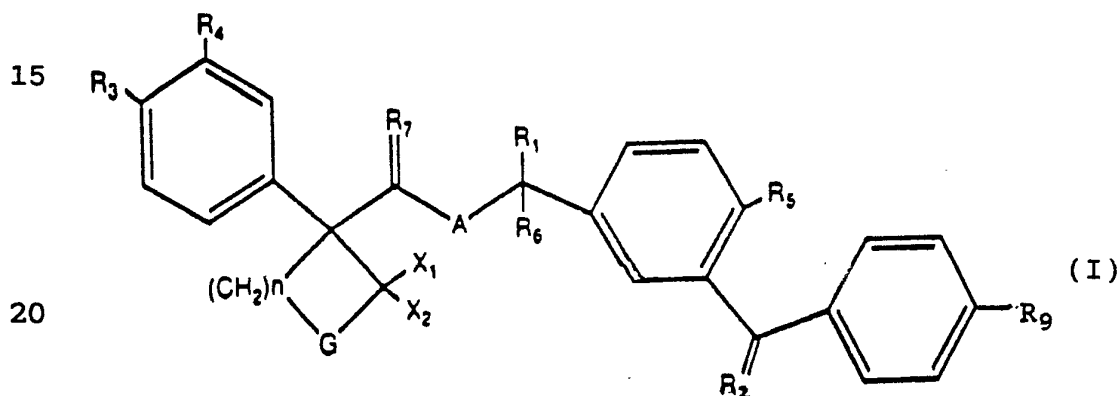
- 1 -

ARTHROPODICIDES

5 This invention relates to new compounds having arthropodidal activity, to methods of preparing these compounds and to the use of the compounds as arthropodicides, especially as insecticides and acaricides.

10

According to the present invention there is provided a compound of the general formula (I):



wherein n is 0 or 1;

A is oxygen, sulphur, C=O, CH₂, CF₂, CD₂, CDH, CHOH,
25 CHX wherein X is fluorine, chlorine, bromine or iodine;

G is oxygen, sulphur, CH₂ or CX₃X₄ wherein X₃ and X₄ are the same or different and each is fluorine, chlorine or bromine;

X₁ and X₂ are the same or different and each is
30 hydrogen or fluorine, chlorine or bromine; and when n is 0, X₁ and X₂ may also be methyl groups;

R₁ is hydrogen, deuterium, CN, C≡CH, fluorine, chlorine or bromine and R₆ is hydrogen or deuterium; or

R₁ and R₆ may optionally form =O, or

35

- 2 -

5
$$-A-\overset{\overset{R_1}{|}}{\underset{\underset{R_6}{|}}{C}}-$$
 in formula (I) may be

10
$$-CH = \overset{\overset{R_1}{|}}{C} -, \text{ or } - \overset{\overset{O}{||}}{\underset{\underset{F}{|}}{C}} - \overset{\overset{F}{|}}{C} -$$

and

15 R_2 is oxygen, or both H and OH together, or N-OR₈
wherein R₈ is hydrogen or lower alkyl which is optionally
substituted with one or more halo groups;

R₃ is a halo group, or a lower alkyl, lower alkoxy or lower alkylthio group, in each of which the alkyl group is optionally substituted with one or more halo groups;

R₄ is hydrogen or a halo or lower alkyl group; or

R₃ and R₄ may optionally form a methylenedioxy bridge which is optionally mono- or di- substituted with fluorine;

25 R₅ is hydrogen, OH, lower alkoxy, SH, lower thioalkyl, fluorine, chlorine, bromine or iodine;

R_7 is H_2 , HD, D_2 or oxygen.

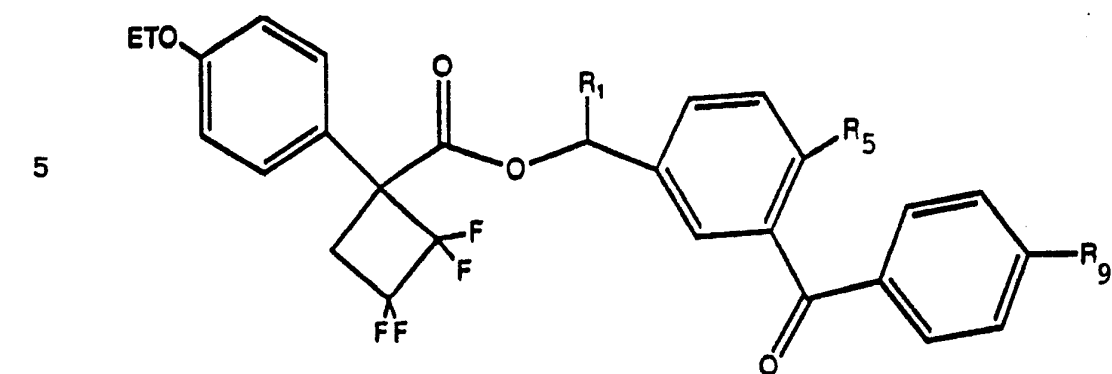
R₉ is H, lower alkoxy or lower alkylthio.

Preferably the lower alkyl groups have from 1 to 6 carbon atoms. Alkyl groups having more than 2 carbon atoms may be straight chain or branched. Halo groups may be fluoro, chloro or bromo.

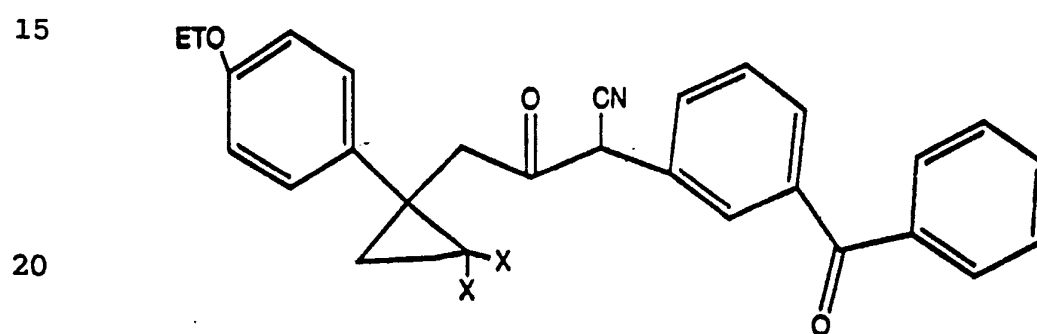
Preferred compounds of the general formula (I) are
35 those which contain the difluorocyclopropane ($n=0$; $G=CH_2$;
 $X_1=X_2=F$) or tetrafluorocyclobutane ($n=1$, $G=CFF$; $X_1=X_2=F$)
moieties.

Particularly preferred compounds are those having
40 the following structures AA, BB and CC:

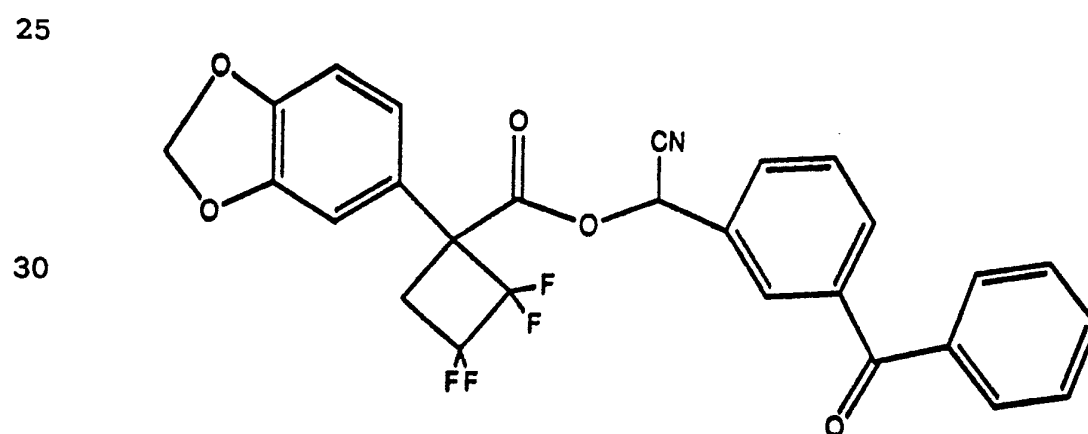
- 3 -



STRUCTURE AA



STRUCTURE BB



35

STRUCTURE CC

- 4 -

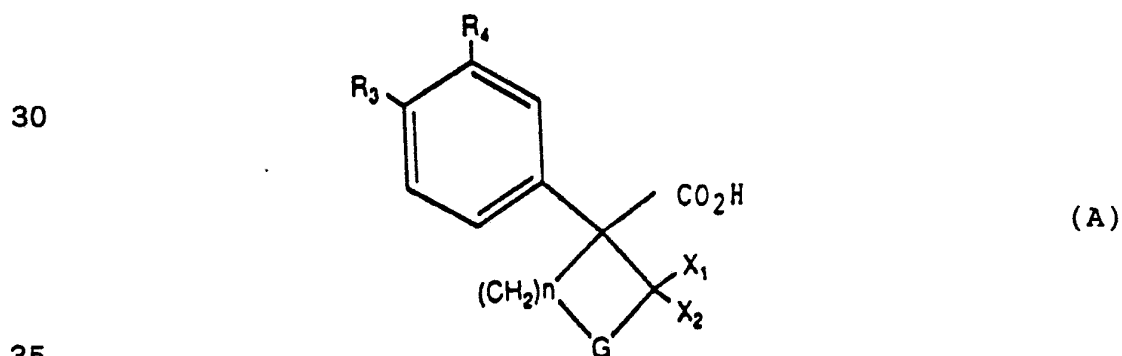
Individual compounds which are presently preferred are those designated in the Examples as follows:

5	Compound No.	Example No.
	VII	6
	VIII(B)	7
	XX	18
10	XXIV	18
	XXV	18
	XXVII	18
	XXVIII	18
15	XXXV	20

The compounds of the invention (formula (I)) are optically active and can be resolved into their optical isomers by conventional methods. The invention thus includes the individual optical isomers of the compounds as well as the racemic forms.

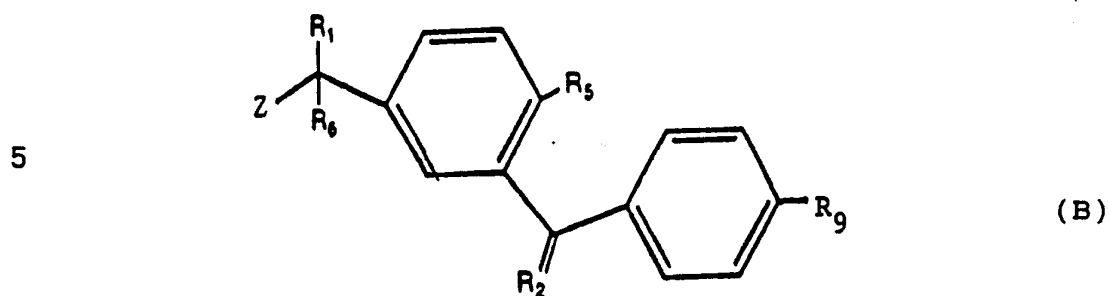
The compounds of formula (I) may be prepared by the conventional methods of synthetic organic chemistry.

For example, the compounds of formula (I) may be prepared by reacting an acid of the formula (A):



wherein R_3 , R_4 , X_1 , X_2 , n and G are as defined above or a reactive derivative of such an acid with a compound of the formula (B):

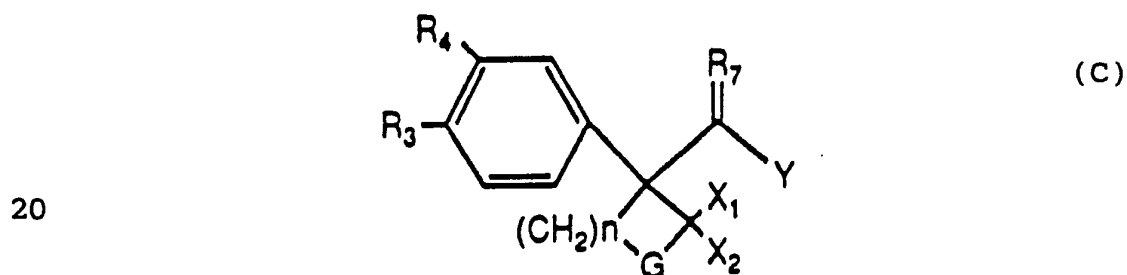
- 5 -



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wherein R_1 , R_2 , R_6 and R_5 are as defined above and Z is a leaving group or a hydroxy group; or
by reacting a compound of the formula (C):

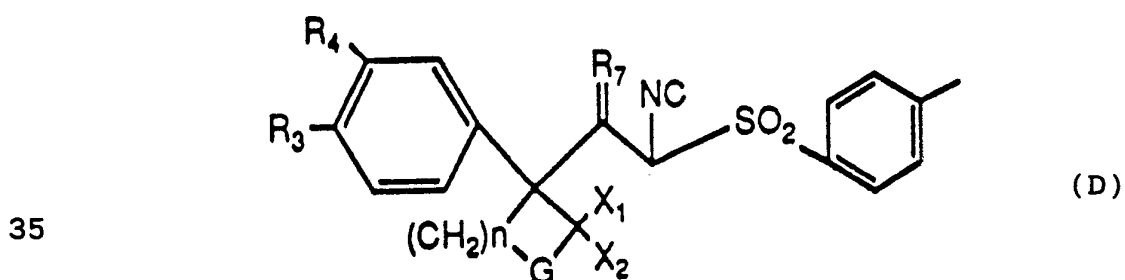
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25

wherein R_3 , R_4 , X_1 , X_2 , n and G are as defined above, R_7 is H_2 , HD or D_2 and Y is a leaving group, with the anion of 4-tosylmethyl isocyanide to produce an intermediate of the formula (D):

30

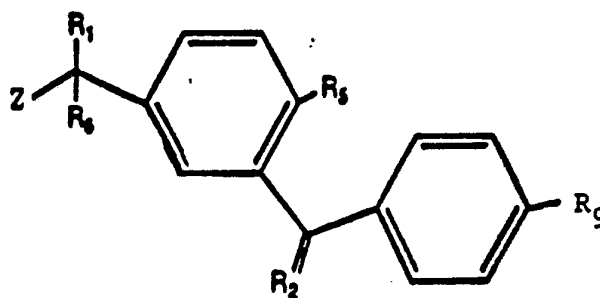


- 6 -

wherein R_3 , R_4 , X_1 , X_2 and G are as defined above
and R_7 is H_2 , HD or D_2 ; and

- 5 reacting the anion of said intermediate with a
compound of the formula (B):

10



(B)

15

wherein R_1 , R_2 , R_5 , R_6 , B and Z are as defined
20 above.

Throughout this specification "leaving group" means
a group which is easily displaced by a nucleophile, for
example, tosylate, mesylate, bromo.

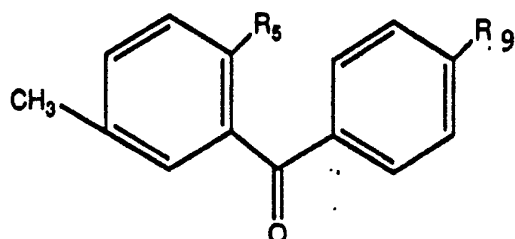
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The compounds of formula (B) where the leaving group Z is
bromo and $R_1=R_6=H$ may be synthesised by the radical
bromination of the corresponding methyl compound, ie $Z=H$,
of formula (E).

30

- 7 -

5



(E)

10

- The compound of formula (E) may be synthesised by
15 Friedel-Crafts acylation, or alkylation followed by
hydrolysis, of the appropriate aromatic compound or by
esterification or alkylation of 2-methyl-5-hydroxy-4'-
substituted benzophenone or the corresponding thiol.
- 20 The compounds of formula (E) are novel and form a part of
this invention.

The active compounds of the invention are well
tolerated by plants, in contrast to many other
25 insecticides have a favourably low level of toxicity to
warm-blooded animals and fish, and can be used for
combating arthropod pests, especially insects or acarids,
which are encountered in agriculture, in veterinary
practice, in forestry, in the protection of stored
30 products and of materials, and in the hygiene field.
They are active against normally sensitive and resistant
species and against all or some stages of development.
The abovementioned pests include Lucilia cuprina (the
Australian sheep blowfly), Blatella germanica (German
35 cockroach), Helicoverpa punctigera (cotton budworm),
Musca domestica housefly, Aedes Australis Australian
mosquito, Periplaneta americana American cockroach,

- 8 -

Pheidole megacephala coastal brown ant, Dermestes maculata hide beetle, Triboleum castaneum flour beetle, Stegobium paniceum, drug store beetle and Sitophilus oryzae rice weevil.

5

The present invention also provides arthropodicidal compositions containing as active ingredient(s) one or more compound(s) of the present invention.

10 The present invention also provides a method of combating arthropods (especially insects or acarids) which comprises applying to the arthropods, or to a habitat thereof, a compound of the present invention alone or in the form of a composition containing as
15 active ingredient a compound of the present invention.

 The present invention also provides a method of freeing or protecting domesticated animals from parasitical insects or acarids which comprises applying
20 to said animals a compound according to the present invention, or a composition containing such a compound as the active ingredient.

 In the compositions of this invention, the active
25 compounds are converted into such customary formulations as solutions, emulsions, wettable powders, suspensions, powders, dusting agents, foams, pastes, soluble powders, granules, aerosols, suspension-emulsion concentrates, seed-treatment powders, natural and synthetic materials
30 impregnated with active compound, very fine capsules in polymeric substances, and coating compositions for use on seed, as well as ULV cold mist and warm mist formulations.

35 These formulations may be produced in known manner, for example by mixing the active compounds with extenders, i.e., liquid or liquefied gaseous or solid

- 9 -

diluents or carriers, optionally with the use of surface-active agents, i.e. emulsifying agents and/or dispersing agents and/or foam-forming agents. Where water is used as an extender, auxiliary solvents, such as for example,
5 organic solvents, can also be used.

Examples of suitable liquid diluents or carriers, especially solvents, are aromatic hydrocarbons, such as xylene, toluene or alkyl naphthalenes, chlorinated
10 aromatic or chlorinated aliphatic hydrocarbons, such as chlorobenzenes, chloroethylenes or methylene chloride; aliphatic or alicyclic hydrocarbons, such as cyclohexane or paraffins, for example mineral oil fractions; alcohols, such as butanol or glycol, as well as their
15 ethers; and esters, ketones, such as acetone, methyl ethyl ketone, methyl isobutyl ketone or cyclohexanone; and strongly polar solvents, such as dimethylformamide and dimethyl sulphoxide, as well as water.

20 By liquefied gaseous diluents or carriers are meant liquids which would be gaseous at normal temperature and under normal pressure, for example aerosol propellants, such as halogenated hydrocarbons as well as butane, propane, nitrogen and carbon dioxide.

25 Examples of solid carriers are ground natural minerals, such as kaolins, clays, talc, chalk, quartz, attapulgite, montmorillonite or diatomaceous earth; and ground synthetic minerals, such a highly-dispersed
30 silicic acid, alumina and silicates. As solid carriers for granules there may be used crushed and fractionated natural rocks such as calcite, marble, pumice, sepiolite and dolomite; as well as synthetic granules or inorganic and organic meals, and granules of organic material such
35 as sawdust, coconut shells, maize cobs and tobacco stalks.

- 10 -

Examples of emulsifying and/or foam-forming agents are non-ionic and anionic emulsifiers, such as polyoxyethylene-fatty acid esters, polyoxy ethylene-fatty alcohol ethers, for example alkylaryl polyglycol ethers, 5 alkyl sulphonates, alkyl sulphates, aryl sulphonates, as well as albumin hydrolysis products. Dispersing agents include, for example, lignin sulphite waste liquors and methylcellulose.

10 Adhesives such as carboxymethylcellulose and natural and synthetic polymers in the form of powders, granules or latices, such as gum arabic, polyvinyl alcohol and polyvinyl acetate, can be used in the formulations.

15 It is also possible to use colorants such as inorganic pigments, for example iron oxide, titanium oxide and Prussian Blue, and organic dyestuffs, such as alizarin dyestuffs, azo dyestuffs or metal phthalocyanine dyestuffs.

20

The formulations in general will contain from 0.01 to 99 per cent by weight of active compound, preferably from 0.5 to 95 per cent by weight.

25 The active compounds according to the invention may be used in the form of formulations of the types that are commercially available or in the use forms prepared from these formulations.

30 The active compound content of the use forms prepared from the formulations of the types that are commercially available can vary within wide ranges. Generally, the proportion of the active compound in such use forms can range from 0.0000001% (0.1 ppm) to 99.9% by 35 weight, the preferred range being from 0.1 ppm to 10% by weight.

- 11 -

The compounds may be employed in a customary manner appropriate for the particular use forms.

The active compounds according to the invention are
5 also suitable for combating ectoparasites and
endoparasites in the field of veterinary medicine. The
compounds may be used in a known manner, such as orally
in the form of, for example, tablets, capsules, drenches
and granules; dermally by means of, for example, dipping,
10 spraying, pouring-on, spotting-on and powdering.

The compounds may be employed either as the sole
toxic agent in compositions such as those described
above, or in combination with other insecticides such as
15 pyrethrum, rotenone, or with fungicidal or bactericidal
agents, to provide compositions useful for household and
agricultural dusts and sprays, textile coating and
impregnation.

20 In particular, the compounds of the invention may be
advantageously combined with other substances which have
a synergistic or potentiating action. Generally such
substances are of the class of microsomal oxidase
inhibitors, i.e. they inhibit the detoxification of
25 insecticides in insects produced by the action of
oxidative enzymes. Typical substances of this type are
the pyrethrin synergists of which the following are
examples:-

[2-(2-butoxyethoxy)ethoxy]-4,5-methylenedioxy-2-
30 propyltoluene (Piperonyl butoxide),
3-hexyl-5(3,4-methylenedioxyphenyl)-2-cyclohexanone
(Piperonyl cyclonene),
2-(3,4-methylenedioxy-phenoxy)-3,6,9-trioxaundecane
(Sesoxane or Sesamex),
35 1,2-(methylenedioxy)-4-[2-(octylsulfinyl)propyl]benzene
(Sulfoxide),
dipropyl-5,6,7,8-tetrahydro-7-methylnaphtho-[2,3-d],3-

- 12 -

dioxole-5,6-dicarboxylate (n-Propyl isome),
as well as propynyl ethers and propynyl oximes.

("Sesoxane", "Sesamex" and "Sulphoxide" are Registered
5 Trade Marks).

Piperonyl butoxide is particularly useful as a
potentiator. The amount of piperonyl butoxide used may
vary from 1/1000th to fifty times the weight of the
10 compound (I) the preferred range being from about 1/100th
to five parts by weight. "Sesamex" also is a useful
potentiator in similar amounts.

The preparations and properties of the compounds of
15 the invention are illustrated by the following specific
examples. It should be noted, of course, that these
examples are intended to be illustrative of the methods
and procedures utilized in preparing the compounds and
that they are not intended to be restrictive or to be
20 regarded as embodying the only way in which the compounds
can be formed and recovered.

Example 1

25 1-[4-Ethoxyphenyl]-2,2-difluorocyclopropyliodo-
methane (II)

Triphenylphosphite methiodide (16 g, 35.4 mmole) was
added over 3 minutes to a solution of 1-[4-ethoxyphenyl]-
2,2-difluorocyclopropylmethanol (6.8g, 29.5 mmole) in dry
dimethylformamide (30 ml) maintained at 5-10°C. The
30 mixture was stirred at 10-12°C for 30 minutes and then
added to ice-cold 5% sodium hydroxide solution and
extracted with diethyl ether. The extracts were washed
with water and sodium thiosulphate solution, dried over
anhydrous magnesium sulphate and evaporated, to yield an
35 oil (18.2 g). The oil was chromatographed on silica gel
with 50% benzene/petroleum spirit (40-60°C) to yield
further oil which was crystallised from petroleum spirit

- 13 -

(30-40°C) to give white crystals. 9.7 g, 97%, mp. 54-55°C.

IR(KBr) $\nu_{\max}$ 2915, 1610, 1515, 1473, 1442, 1365,
5 1280, 1251, 1210, 1177, 990, 920, 545 cm^{-1} .

NMR (60 MHz) δ (CDCl_3) 1.31, t, 3H, $J=7$ Hz, CH_3 ;
1.15-1.9, m, 2H, cyclopropyl CH_2 ; 3.4, s, 2H, CH_2I ; 3.88,
q, 2H, $J=7$ Hz, CH_2 CH_3 ; 6.97, q, 4H, aromatic.

10 Example 2

1-(1-[4-Ethoxyphenyl]-2,2-difluorocyclopropyl)-2 -
isocyano-2-(4-toluenesulphonyl)ethane (III)

4-tosylmethylisocyanide (7.5 g, 38.4 mmole) was
added over two minutes to a suspension of sodium hydride
15 (0.235 g, 9.8 mmole) in a mixture of dimethylsulphoxide
(50 ml) and diethyl ether (50 ml), rapidly stirred at 10-
12°C in an argon atmosphere. The mixture was allowed to
stir at 10-12°C for an additional four minutes, then
1-[4-Ethoxyphenyl]-2,2-difluorocyclopropyliodomethane
20 (8.7 g, 25.6 mmole) was added over four minutes at 10-
14°C. The mixture was stirred an additional twelve
minutes then poured into ice-water, neutralised and
extracted with ether. The extracts were washed with ice-
water, dried over anhydrous sodium sulphate and
25 evaporated to yield a dark oil (14.1 g). The dark oil
was dissolved in a small amount of benzene, filtered
through a short column of neutral alumina and washed off
with dichloromethane and evaporated. The residue was
crystallised from benzene/petroleum spirit (40-60°C) to
30 give white crystals. 9.1 g, 87%, mp. 90-91°C.

IR(KBr) $\nu_{\max}$ 2980, 2920, 2140, 1610, 1595, 1519,
1440, 1430, 1335, 1305, 1100, 1248, 1208, 1145, 820, 580,
545 cm^{-1} .

35

NMR (60 MHz) δ (CDCl_3) 1.35, t, 3H, $J=7$ Hz, CH_3 ;
1.2-1.9, m, 2H, cyclopropyl CH_2 ; 1.8-2.9, m, 2H, CH_2CHNC ;

- 14 -

2.4, s, 3H, aromatic CH₃; 3.9, q, 2H, J=7 Hz, CH₂CH₃;
3.85 - 4.23, m, 1H, CHNC; 6.44 - 7.7, m, 8H, aromatic.

Example 3

5 1-[1-(4-Ethoxyphenyl)-2,2-difluorocyclopropyl],3-[3-benzoylphenyl] propan-2-one (IV)

40% w/w sodium hydroxide solution (10 ml) was added dropwise over a ten minute period to a rapidly stirred solution of 1-(1-[4-ethoxyphenyl]-2,2-difluorocyclopropyl) -2-isocyano-2-(4-toluenesulphonyl)ethane (1.0 g, 2.47 mM), 3-benzoylbenzyl bromide (0.883 g, 3.21 mmole) and tetrabutylammoniumbromide (40 mg) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for two hours and then added to ice-water and extracted with dichloromethane. The extracts were washed with water and brine, dried over anhydrous sodium sulphate and evaporated to dryness. The glassy solid was taken up in dichloromethane (8 ml), diethyl ether (2 ml) and concentrated hydrochloric acid (2 ml) and stirred rapidly for one hour. The reaction mixture was added to ice-water and extracted with dichloromethane. The extracts were washed with water and brine, dried over anhydrous sodium sulphate and evaporated to give a brown oil (1.31 g). The crude material was purified by HPLC on silica gel with 10% ethyl acetate/petroleum spirit (40-60°C) to yield a colourless oil. 0.68 g. 64%.

IR (film) $\nu_{\max}$ 2980, 1720, 1660, 1610, 1597, 1578, 1515 cm⁻¹.

30 NMR (60 MHz) δ (CDCl₃) 1.33, t, 3H, J=7 Hz, CH₃; 1.15 - 2.00, m, 2H, cyclopropyl CH₂; 2.52 - 3.23, m, 2H, CH₂; 3.55, s, 2H, benzylic CH₂; 3.91, q, 2H, J= 7 Hz, CH₂CH₃; 6.57 - 7.85, m, 13H, aromatic.

- 15 -

Example 41-[1-(4-Ethoxyphenyl)-2,2-difluorocyclopropyl],3-[3-benzoylphenyl] propan-2,3-dione (V)

A solution of 3-benzoylbenzoic acid (0.84 g, 3.7 mmole) in thionyl chloride (2 ml) in an argon atmosphere was refluxed for forty-five minutes. All traces of thionyl chloride were removed in vacuo at 50°C to yield the acid chloride as an oil.

N-butyl lithium (1.78 ml, 4.44 mmole) (2.5 M in hexane) was added dropwise over five minutes to a stirred solution of 1-(1-[4-ethoxyphenyl]-2,2-difluorocyclopropyl)-2-isocyano-2-(4-toluenesulphonyl) ethane (1.50 g, 3.7 mmole) in anhydrous tetrahydrofuran (15 ml) at -70°C in an argon atmosphere. The reaction mixture was stirred for an additional eight minutes, then a solution of the acid chloride in tetrahydrofuran (10 ml) was added dropwise over seven minutes. The reaction mixture was stirred at -70°C for one hour and then allowed to warm slowly to room temperature and stirred for one hour. Concentrated hydrochloric acid (8 ml) and dichloromethane (10 ml) was then added to the solution and the mixture stirred for one hour. The reaction mixture was added to ice-water and extracted with dichloromethane. The extracts were washed with 5% sodium bicarbonate solution, water and brine, dried over anhydrous sodium sulphate and evaporated to yield a dark yellow oil (1.6 g). The dark yellow oil was chromatographed on silica gel with 10% ethyl acetate/petroleum spirit (40-60°C) to give a brilliant yellow oil. 1.13 g, 68%.

IR (film) $\nu_{\max}$ 2970, 1715, 1675, 1660, 1605, 1590, 1572, 1508 cm^{-1} .

NMR (60 MHz) δ (CDCl_3) 1.33, t, 3H, $J=7$ Hz, CH_3 ; 1.37 - 2.08, m, 2H, cyclopropyl CH_2 ; 3.38, br. s, 2H, CH_2 ; 3.91, q, 2H, $J=7$ Hz, CH_2CH_3 ; 6.55 - 8.23, m, 13H, aromatic.

- 16 -

Example 51-[1-(4-Ethoxyphenyl)-2,2-difluorocyclopropyl]-2,2-difluoro-3-(3-benzoylphenyl)propane (VI)

Diethylaminosulphurtrifluoride (0.555 g, 3.46 mmole)
5 was added to a stirred solution of 1-[1-(4-ethoxyphenyl)-2,2-difluorocyclopropyl]-3-(3-benzoylphenyl)-propan-2-one (0.50 g, 1.15 mmole) in dichloromethane (2ml) contained in a PTFE vessel at 20°C.

The mixture was stirred at room temperature for six weeks
10 and then added to ice-water and extracted with dichloromethane. The extracts were washed with 5% sodium bicarbonate solution, dried over anhydrous sodium sulphate and evaporated to yield a yellow oil (0.51 g). The material was purified by HPLC on silica gel with 10%
15 ethyl acetate/petroleum spirit (40-60°C) to give a colourless oil. 0.34 g. 65%.

IR (film) $\nu_{\max}$ 2980, 2930, 1660, 1610, 1595, 1515, 1285, 1245, 1210, 710, 690, 640 cm^{-1} .

NMR (60MHz) $\delta(\text{CDCl}_3)$ 1.36, t, 3H, $J=7\text{Hz}$, CH_3 ; 1.28-
20 1.98, m, 2H, cyclopropyl CH_2 ; 2.33, t, 2H, $J=17\text{Hz}$, CH_2 ; 2.93, t, 2H, $J=17\text{Hz}$, benzylic CH_2 ; 3.99, q, 2H, $J=7\text{Hz}$, CH_2CH_3 ; 6.62-7.95, m, 13H, aromatic.

Example 625 3'-Benzoylbenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (VII)

Triethylamine (0.225 g, 2.23 mmole), followed by 3-benzoylbenzyl bromide (0.612 g, 2.23 mmole) was added to a solution of 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluoro-
30 cyclobutane carboxylic acid (0.5 g, 1.7 mmole) in dry acetone (3 ml) in an argon atmosphere. The reaction mixture was allowed to stir at room temperature for 16 hours, then diluted with petroleum spirit (40-60°C) and filtered through a pad of silica gel. The silica gel was
35 washed with 10% ethyl acetate/petroleum spirit (40-60°C). The filtrate was evaporated to yield a yellow oil (0.85 g). The crude material was purified by HPLC on silica

- 17 -

gel with 10% ethyl acetate/petroleum spirit (40-60°C) to give a colourless oil 0.45 g. 54%.

IR (film) $\nu_{\max}$ 2980, 1736, 1658, 1608, 1580, 1597, 1503, 1250 cm^{-1} .

5

NMR (60 MHz) δ (CDCl_3) 1.35, t, 3H, $J=7$ Hz, CH_3 ; 2.52 - 3.95, m, 2H, cyclobutyl CH_2 ; 3.94, q, 2H, $J=7$ Hz, CH_2CH_3 ; 5.18, s, 2H, CH_2 ; 6.62 - 7.88, m, 13H, aromatic.

10 Example 7

α - Cyano-3'-benzoylbenzyl-1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (VIII)

A solution of 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane carboxylic acid chloride (0.36 g, 1.16 mmole) in benzene (2 ml) was added to a mixture of α -cyano-3-benzoylbenzyl alcohol (0.25 g, 1.06 mmole) and pyridine (0.166 g, 2.1 mmole) in benzene (1 ml), in an argon atmosphere and the reaction mixture stirred at room temperature for 24 hours. The crude mixture was filtered through a pad of silica gel, eluted with dichloromethane, and evaporated to give a yellow oil (0.55 g). This was purified by HPLC on silica gel with 12% ethyl acetate/petroleum spirit (40-60°C) to give the separated diastereoisomeric pairs: Compound A (180 mg) and Compound B (230 mg) 76%.

Compound A: IR (film) $\nu_{\max}$ 2980, 1753, 1658, 1605, 1595, 1512, 1250 cm^{-1} . NMR (60 MHz) δ (CDCl_3) 1.37, t, 3H, $J=7$ Hz, CH_3 ; 2.52 - 4.10, m, 2H, cyclobutyl CH_2 ; 3.98, q, 2H, $J=7$ Hz, CH_2CH_3 ; 6.38, s, 1H, CHCN ; 6.70 - 7.97, m, 13H, aromatic.

Compound B: IR (film) $\nu_{\max}$ 2980, 1752, 1658, 1605, 1595, 1575, 1512, 1250 cm^{-1} . NMR (90 MHz) δ (CDCl_3) 1.34, t, 3H, $J=7\text{Hz}$, CH_3 ; 2.71 - 3.90, m, 2H, cyclobutyl CH_2 ; 3.95, q, 2H, $J=7\text{Hz}$, CH_2CH_3 ; 6.39, s, 1H, CHCN ; 6.67 - 7.97, m, 13H, aromatic.

- 18 -

Example 83-Benzoylbenzyl[1-(4-ethoxyphenyl)-2,2-difluorocyclopropyl-1-methyl] ether (IX)

1-(4-ethoxyphenyl)-2,2-difluorocyclopropyl-1-
5 methanol (0.3 g, 1.32 mmole) in 1,2-dimethoxyethane (1 ml) was added dropwise to a suspension of sodium hydride (48 mg, 2.0 mmole) in anhydrous 1,2-dimethoxyethane (1 ml) in an argon atmosphere. The solution was stirred for forty-five minutes and then 3-benzoylbenzyl bromide (0.54
10 g, 1.97 mmole) in 1,2-dimethoxyethane (1 ml) was added all at once. The reaction mixture was stirred at room temperature for sixteen hours and then filtered through a pad of silica gel with 10% ethyl acetate/petroleum spirit (40-60°C) to yield a yellow oil (0.71 g). The material
15 was purified by HPLC on silica gel with 7.5% ethyl acetate/petroleum spirit (40-60°C) and filtered immediately through a 0.45 micron filter with diethyl ether to give a colourless oil. 0.32 g . 57%.

IR (film) $\nu_{\max}$ 2970, 2860, 1655, 1608, 1595, 1575,
20 1510, 1240 cm^{-1} .

NMR (60 MHz) δ (CDCl_3) 1.35, t, 3H, $J=7$ Hz, CH_3 ;
1.15 - 1.92, m, 2H, cyclopropyl CH_2 ; 3.58 - 3.77, m, 2H, CH_2 ;
3.94, q, 2H, $J=7$ Hz, CH_2CH_3 ; 4.47, s, 2H, benzylic CH_2 ;
6.58 - 7.85, m, 13H, aromatic.

25 Mass Spectrum (c.i.): m/z 423 ($m+1$, 42%), 195(100).

Example 91-[1-(4-Ethoxyphenyl)-2,2-difluorocyclopropyl]-3-[3-benzoylphenyl]-3,3-difluoropropan-2-one (X)

30 Diethylaminosulphurtrifluoride (557 μl , 4.21mmole) was added to a stirred solution of 1-[1-(4-ethoxyphenyl)-2,2-difluorocyclopropyl]-3-[3'-benzoylphenyl]propan-2,3-dione (0.63g, 1.40mmole) in dichloromethane (3 ml) contained in a PTFE vessel at -78°C. The reaction mixture
35 was allowed to warm slowly to room temperature and was then stirred for 20 hours. The reaction mixture was added to ice-water and extracted with dichloromethane. The

- 19 -

extracts were washed with water and brine, dried over anhydrous sodium sulphate and evaporated to give a brown oil. The crude material was purified by recycle HPLC on silica gel with 12% ethyl acetate/petroleum spirit
5 (40-60°C) to yield a colourless oil (Compound X) 0.272g. 66%.

IR (film) $\nu_{\max}$ 2980, 1755, 1665, 1610, 1515, 1300, 1250, 900 cm^{-1} .

NMR (60MHz) $\delta(\text{CDCl}_3)$ 1.35, t, 3H, $J=7\text{Hz}$, CH_3 ;
10 1.27-2.03, m, 2H, cyclopropyl CH_2 ; 3.22, s, 2H, CH_2CO ;
3.94, q, 2H, $J=7\text{Hz}$, CH_2CH_3 ; 6.53-8.00, m, 13H, aromatic.

Example 10

3'-Benzoylbenzyl 1-(4-ethoxyphenyl)-2,2,3,3-
15 tetrafluorocyclobutane-1-carboxylate oxime (XI)

Hydroxylamine hydrochloride (0.70g, 10.1mmole) and 4-dimethylaminopyridine (1.24g, 10.1mmole) were added to a solution of 3'-benzoylbenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (3.27g, 6.73mmole)
20 in anhydrous pyridine (10 ml) in an argon atmosphere. The reaction mixture was stirred at room temperature for 3 days and then at 65°C for 2 hours. The pyridine was removed in vacuo and the residue added to ice-water and extracted with diethyl ether. The extracts were washed
25 with 10% hydrochloric acid, water and brine, dried over anhydrous sodium sulphate and evaporated to yield a colourless oil (Cpd XI) 3.20g. 95%.

IR (film) $\nu_{\max}$ 3700 br, 2980, 1740, 1610, 1590, 1515, 1350, 1250, 695 cm^{-1} .

30 NMR (60MHz) $\delta(\text{CDCl}_3)$ 1.35, t, 3H, $J=7\text{Hz}$, CH_3 ;
2.67 - 3.83, m, 2H, cyclobutyl CH_2 ; 3.95, d, q, 2H, $J=7\text{Hz}$, CH_2CH_3 ;
5.13, d, 2H, $J=5\text{Hz}$, benzylic CH_2 ; 6.67 - 7.97, m, 13H, aromatic; 8.72, br s, 1H, $\text{C}=\text{NOH}$.

- 20 -

Example 113'-Benzoylbenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate O-methyl oxime (XII)

A solution of 3'-benzoylbenzyl 1-(4-ethoxyphenyl)-
2,2,3,3-tetrafluorocyclobutane-1-carboxylate oxime
(0.75g, 1.5mmole) in anhydrous acetonitrile (6 ml) was
added to a suspension of sodium hydride(83% dispersion in
oil)(0.05g, 1.73mmole) in anhydrous acetonitrile (4 ml)
in an argon atmosphere. The reaction mixture was stirred
for 2 hours when, methyl iodide (187 μ l, 3.0mmole) was
added. The reaction mixture was stirred for 20 hours then
the acetonitrile was removed *in vacuo* and the residue
added to ice-water and extracted with diethyl ether. The
extracts were washed with water and brine, dried over
anhydrous sodium sulphate and evaporated to give a brown
oil. The crude material was purified by HPLC on silica
gel with 7% ethyl acetate/petroleum spirit(40-60°C) to
yield a colourless oil(Compound XII) 0.24g. 24%.

IR (film) $\nu_{\max}$ 2930, 2970, 1735, 1605, 1510,
1250, 695 cm^{-1} .

NMR (60MHz) $\delta(\text{CD}_3\text{CN})$ 1.30, t, 3H, $J=7\text{Hz}$, CH_3CH_2 ;
2.83 - 3.80, m, 2H, cyclobutyl CH_2 ; 3.90, s, $\text{C}=\text{NOCH}_3$;
3.93, d,q, 2H, $J=7\text{Hz}$, CH_2CH_3 ; 5.08, d, 2H, $J=3\text{Hz}$,
benzylic CH_2 ; 6.63 - 7.83, m, 13H, aromatic.

Example 123'- α -Hydroxybenzylbenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (XIII)

Diborane:dimethylsulphide (10M in borane)(112 μ l,
1.12mmole) was added to a stirred solution of 3'-
benzoylbenzyl 1-(4-ethoxyphenyl)-2,2,3,3-
tetrafluorobutane-1-carboxylate (1.09g, 2.24mmole) in
anhydrous diethyl ether (20 ml) at 0°C and in an argon
atmosphere. The reaction mixture was allowed to warm
slowly to room temperature and was then heated to reflux
for 5 hours. The reaction mixture was cooled to room
temperature then added to ice-water and extracted with

- 21 -

diethyl ether. The extracts were washed with water, dried over anhydrous sodium sulphate and evaporated to yield a colourless oil. The crude material was purified by HPLC on silica gel with 17% ethyl acetate/petroleum spirit(40-60°C) to give a colourless oil(Compound XIII) 0.7 g. 64%.

IR (film) $\nu_{\max}$ 3420 br, 2970, 1730, 1605, 1575, 1510, 1345, 1250, 700 cm^{-1} .

NMR (60 MHz) $\delta(\text{CDCl}_3)$ 1.35, t, 3H, $J=7\text{Hz}$, CH_3 ; 2.47, br s, 1H, CHOH ; 2.57 - 3.83, m, 2H, cyclobutyl CH_2 ; 3.97, q, 2H, $J=7\text{Hz}$, CH_2CH_3 ; 5.10, s, 2H, benzylic CH_2 ; 5.68, s, 1H, CHOH ; 6.68 - 7.47, m, 13H, aromatic.

Example 13

15 3'-Benzoyl-4'-methoxybenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (XIV)

(a) 2-Methoxy-5-methylbenzophenone (E1)

2-Hydroxy-5-methylbenzophenone (25g, 117.8mmole) was added in portions over 15 minutes to a stirred suspension of sodium hydride (3.11g, 129.7mmole) in dimethylsulphoxide(130 ml) at 20-25°C. After an additional 15 min stirring, methyl iodide (17.3g, 121.9mmole) was added and the mixture stirred a further 17 hours. The solution was added to ice-water (1500 ml) and extracted with diethyl ether. The extracts were washed with water and sodium bicarbonate solution and dried over anhydrous sodium sulphate. Evaporation yielded a lemon oil which crystallised from methanol in colourless needles 26.0g. 98% mp 40.5-41°C.

IR (KBr) $\nu_{\max}$ 2940, 1665, 1608, 1595, 1495, 1445, 1290, 1252, 1240, 1025, 700 cm^{-1} .

NMR (60MHz) $\delta(\text{CDCl}_3)$: 2.30, s, 3H, CH_3 ; 3.66, s, 3H, OCH_3 ; 6.75-7.85, m, 8H, aromatic.

(b) 2-Methoxy-5-bromomethylbenzophenone (E2)

To a solution of 2-methoxy-5-methylbenzophenone(E1)

- 22 -

- (1g, 4.22 mmole) in anhydrous methyl formate (10 ml), in an argon atmosphere and subjected to illumination by a 150 watt floodlight, was added benzoyl peroxide (10 mg) and N-bromosuccinimide (1g, 5.62mmole). The reaction mixture was stirred under illumination for 2 hours then the solvent was evaporated and the residue added to ice-water and extracted with diethyl ether. The extract was washed with sodium bicarbonate solution and water, then dried over anhydrous sodium sulphate and evaporated to give a yellow oil (1.3 g) which was crystallised from diethyl ether/petroleum spirit (40-60°C) to give colourless needles. (Compound E2) 1.01g. 75% m.p.76-77°C.
- IR (KBr) $\nu_{\max}$ 1664, 1606, 1500, 1270, 1252, 1223, 1025, 985, 703 cm^{-1} .
- NMR (60MHz) $\delta(\text{CDCl}_3)$: 3.73, s, 3H, OCH_3 ; 4.50, s, 2H, CH_2Br ; 6.90-7.93, m, 8H, aromatic.

- (c) 3'-Benzoyl-4'-methoxybenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (XIV)
- Compound E2 was esterified by the method of Example 6 to give 3'-Benzoyl-4'-methoxybenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (Compound XIV)

Example 14

- 3'-Benzoyl-4'-hydroxybenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (XV)

- (a) 2-Acetoxy-5-methylbenzophenone (E3)
- A solution of acetyl chloride (2 ml, 28.1 mmole) in dry tetrahydrofuran (5 ml) was added dropwise to a solution of 2-hydroxy-5-methylbenzophenone (5.0 g, 23.6 mmole) and pyridine (2 ml, 24.7 mmole) in dry tetrahydrofuran (20 ml) at 5°C in an argon atmosphere.
- The reaction mixture was stirred at room temperature for 2 days, then added to ice-water and extracted with diethyl ether. The extracts were washed with 10%

- 23 -

hydrochloric acid, 5% sodium bicarbonate solution and water, dried over anhydrous sodium sulphate, then evaporated to give a yellow solid. The material was recrystallised from diethyl ether and petroleum
5 spirit(40-60°C) to yield pale yellow crystals 4.95g, 83%, mp. 64.1°C.

IR (KBr) $\nu_{\max}$ 3045, 1760, 1655, 1590, 1195, 695 cm^{-1} .

NMR (90 MHz) δ (CDCl_3) 1.89, s, 3H, CH_3CO_2 ;
10 2.37, s, 3H, benzylic CH_2 ; 6.94 - 7.88, m, 8H, aromatic.

(b) 3'-benzoyl-4'-acetoxybenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (XVI)

Compound E3 was brominated by the method of Example
15 13(b) and esterified by the method of Example 6 to give 3'-benzoyl-4'-acetoxybenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (Compound XVI)

(c) 3'-Benzoyl-4'-hydroxybenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (XV)
20

Hydrobromic acid (catalytic amount) was added to a solution of 3'-benzoyl-4'-acetoxybenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate(XVI)(0.20g, 0.37mmole) in methyl formate (5
25 ml), in an argon atmosphere. The reaction mixture was stirred for 2 days then added to ice-water and extracted with diethyl ether. The extracts were washed with 5% sodium bicarbonate solution and water, dried over anhydrous sodium sulphate and evaporated to give a pale
30 yellow oil. The material was purified by recycle HPLC on silica gel with 7.5% ethyl acetate/petroleum spirit(40-60°C) to yield a pale yellow oil (Compound XV) 0.087 g. 47%.

IR (film) $\nu_{\max}$ 3200 br, 2970, 1730, 1625, 1605,
35 1510, 1345, 1245, 1090 cm^{-1} .

NMR (60 MHz) δ (CDCl_3) 1.38, t, 3H, $J=7\text{Hz}$, CH_3 ;
2.63-3.77, m, 2H, cyclobutyl CH_2 ; 4.16, q, 2H, $J=7\text{Hz}$,

- 24 -

CH_2CH_3 ; 5.02, s, 2H, benzylic CH_2 ; 6.70-7.87, m, 12H, aromatic.

Example 15

5 3'-(4-Ethoxybenzoyl)benzyl 1-(4-ethoxyphenyl)-
 2,2,3,3-tetrafluorocyclobutane-1-carboxylate (XVII)

(a) 3-Methyl-4'-ethoxybenzophenone (E4)

A solution of 4-methylbenzoic acid (50g, 367mmole)
10 in thionyl chloride (65 ml) was heated at reflux for 45
minutes. The excess thionyl chloride was removed in
vacuo. The acid chloride was then added dropwise, over a
period of 30 minutes, to a suspension of finely ground
aluminium chloride (55g, 412mmole) in dry chloroform (250
15 ml) at 10°C and in an argon atmosphere. Ethoxybenzene
(48.0 g, 393 mmole) was added to the reaction mixture at
such a rate that the temperature was maintained at 10°C.
The reaction mixture was allowed to warm to room
temperature and then added to ice-water and extracted
20 with dichloromethane. The extracts were washed with
water, dried over anhydrous sodium sulphate and
evaporated. The crude material was distilled at 120°C at
10⁻⁴mbar to give a pale yellow oil(Compound E4) 85g.
97%.

25 IR(film) ν_{max} 2975, 1645, 1600, 1505, 1305, 1280,
1250, 1165, 1040, 750cm⁻¹.

NMR (60 MHz) $\delta(\text{CDCl}_3)$ 1.43, t, 3H, J=7Hz, CH_3CH_2 ;
2.43, s, 3H, benzylic CH_3 ; 4.12, q, 2H, J=7Hz, CH_2 ;
6.80-8.10, m, 8H, aromatic.

30

(b) 3'-(4-Ethoxybenzoyl)benzyl 1-(4-ethoxyphenyl)-
2,2,3,3-tetrafluorocyclobutane-1-carboxylate (XVII)

Compound E4 was brominated by the method of Example
13(b) and esterified by the method of Example 6 to give
35 Compound XVII

- 25 -

Example 163'-Benzoyl-5'-methylthiobenzyl 1-(4-ethoxyphenyl)-
2,2,3,3-tetrafluorocyclobutane-1-carboxylate (XVIII)

5

(a) 2-[N,N-Dimethylthiocarbamyloxy]-5-methylbenzophenone (E5)

Sodium hydride (5.48g, 228.3mmole) was added in portions over 15 minutes at 20°C to a solution of 2-hydroxy-5-methylbenzophenone (41.2 g, 194.1 mmole) in dry dimethylformamide (900 ml). The mixture was stirred for 30 minutes at 20°C then dimethylthiocarbamoyl chloride (38g, 307.4mmole) was added over 1 minute. The stirred mixture was warmed to 30°C for 6 hours then added to ice-water (2000 ml). The precipitate was filtered off, washed with water and dried. The solid was dissolved in a small amount of dichloromethane, filtered and the product precipitated by the addition of diethyl ether, to yield crystals (Compound E5). 41.2 g, 94% m.p. 106.5-107°C.

20

IR (KBr) $\nu_{\max}$ 1655, 1535, 1480, 1390, 1280, 1210, 1118, 695 cm^{-1} .

NMR (60 MHz) $\delta(\text{CDCl}_3)$: 2.36, s, 3H, CH_3 ; 3.00, s, 3H, NCH_3 ; 3.23, s, 3H, NCH_3 , 7.00-8.10, m, 8H, aromatic.

25

(b) 2-[N,N-Dimethylcarbamylothio]-5-methylbenzophenone (E6)

2-[N,N-Dimethylthiocarbamyloxy]-5-methylbenzophenone (35g, 116.9mmole), in an argon atmosphere, was heated with stirring to 235°C for 50 minutes. The mixture was cooled, dissolved in diethyl ether (100 ml) and cooled in ice. The crystalline dark-brown precipitate was filtered off, dried, and subjected to short-path distillation at 200°C/10⁻⁶ mbar to yield a yellow oil. This was crystallised from diethyl ether/dichloromethane to give colourless crystals. 14.9g. 43%, m.p. 89.5-90°C.

35

IR (KBr) $\nu_{\max}$ 1724, 1672, 1655, 1588, 1442, 1355, 1310, 1284, 1245, 1088, 819, 710, 702 cm^{-1} .

- 26 -

NMR(60 MHz) δ (CDCl₃): 2.40, s, 3H, CH₃; 2.83, s, 6H, N(CH₃)₂; 7.30-7.96, m, 8H, aromatic.

(c) 2-Benzoyl-4-methylbenzenethiol (E7)

5 A solution of potassium hydroxide (15g, 267.4mmole) in water (20 ml) was added to a solution of 2-[N,N-dimethylthiocarbamyloxy]-5-methylbenzophenone(E6) (14.9g, 49.7mmole) in methanol (200 ml) in an argon atmosphere. The mixture was heated to reflux for 2 hours then the
10 solvent was removed in vacuo. The residue was dissolved in ice-water (1500 ml) and acidified with hydrochloric acid. The pale yellow precipitate was filtered off, dried, and crystallised from ethanol/petroleum spirit (Compound E7). 11.1g. 98% m.p.71.5-72°C.

15 IR (KBr) $\nu_{\max}$ 1652, 1590, 1555, 1455, 1440, 1315, 1295, 1249, 1210, 1062, 968, 823, 742, 703 cm⁻¹

NMR (60MHz) δ (CDCl₃): 2.30, s, 3H, CH₃; 4.06, s, 1H, SH; 7.03-7.93, m, 8H, aromatic.

20 (d) 2-Methylthio-5-methylbenzophenone E8)

2-Benzoyl-4-methylbenzenethiol(E7) (2.0 g, 8.76 mmole) was added over 5 minutes to a stirred suspension of sodium hydride (233mg, 9.68mmole) in dimethylsulphoxide (10 ml) at 20°C under argon. The dark
25 red solution was stirred for 30 minutes, then methyl iodide (1.59g, 11.3mmole) was added over 30 seconds. The mixture turned pale yellow and was stirred for an additional 10 minutes then added to ice-water (250 ml) and extracted with diethyl ether. The extract was washed
30 with water, dried over anhydrous magnesium sulphate, and evaporated to yield a pale yellow oil(Compound E8). 1.73 g. 81%.

IR (Film) $\nu_{\max}$ 2915, 1660, 1590, 1443, 1310, 1288, 1245, 700 cm⁻¹.

35 NMR (60 MHz) δ (CDCl₃) : 2.40, s, 3H, CH₃ ; 3.10, s, 3H, SCH₃; 7.13-7.93, m, 8H, aromatic.

- 27 -

(e) 3'-Benzoyl-5'-methylthiobenzyl 1-(4-ethoxyphenyl)-
2,2,3,3-tetrafluorocyclobutane-1-carboxylate (XVIII)

Compound E8 was brominated by the method of Example
13(b) and esterified by the method of Example 6 to give
5 3'-Benzoyl-5'-methylthiobenzyl 1-(4-ethoxyphenyl)-
2,2,3,3-tetrafluorocyclobutane-1-carboxylate (Compound
XVIII)

Example 17

10 α -cyano-3'-Benzoyl-4'-fluorobenzyl 1-(4-
ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-
carboxylate (XIX)

(a) 2-Fluoro-5-methylbenzophenone (E9)

15 Aluminium chloride (11.62g, 87.15mmole) was added
over 5 minutes to a stirred mixture of 2-fluoro-5-
methylbenzoyl chloride (10.0g, 57.94mmole) and benzene
(20 ml). The mixture was heated to reflux for 2 hours
then cooled, added to ice-water, and extracted with
20 diethyl ether. The extract was washed with dilute
hydrochloric acid, water and sodium bicarbonate solution,
dried over anhydrous sodium sulphate and evaporated to
yield a yellow oil (Compound E9) 11.25g. 90.4%
NMR(60MHz) δ (CDCl₃): 2.34, s, 3H, CH₃; 6.80-8.30, m, 8H,
25 aromatic

(b) 2-Fluoro-5-bromomethylbenzophenone (E10)

A mixture of 2-fluoro-5-methylbenzophenone(E9)
(1.0g, 4.67mmole), N-bromosuccinimide (0.99g, 5.60mmole),
30 benzoyl peroxide (100mg) and carbon tetrachloride (20 ml)
was refluxed for 16 hours. The reaction mixture was
filtered and the solvent evaporated to give an oil. The
oil was chromatographed on silica gel eluting with 5%
ethyl acetate in petroleum spirit(40-60°C) to give a
35 colourless oil (Compound E10). 850 mg. 62%.

NMR (60MHz) δ (CDCl₃): 4.48, s, 2H, CH₂Br, 7.00-8.03,
m, 8H, aromatic.

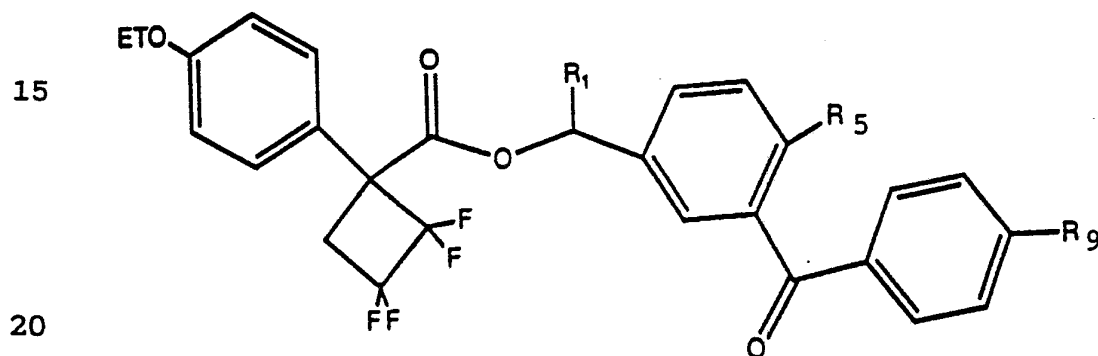
- 28 -

(c) α -cyano-3'-Benzoyl-4'-fluorobenzyl 1-(4-ethoxyphenyl)-2,2,3,3-tetrafluorocyclobutane-1-carboxylate (XIX)

Compound E10 was converted to the aldehyde by a
5 Sommelet reaction, then to the cyanohydrin and esterified by the method of Example 7 to give Compound XIX.

Example 18

Using the methods of the previous examples with the
10 appropriate changes of reagents the further compounds listed below with general structure AA were synthesised.



STRUCTURE AA

25

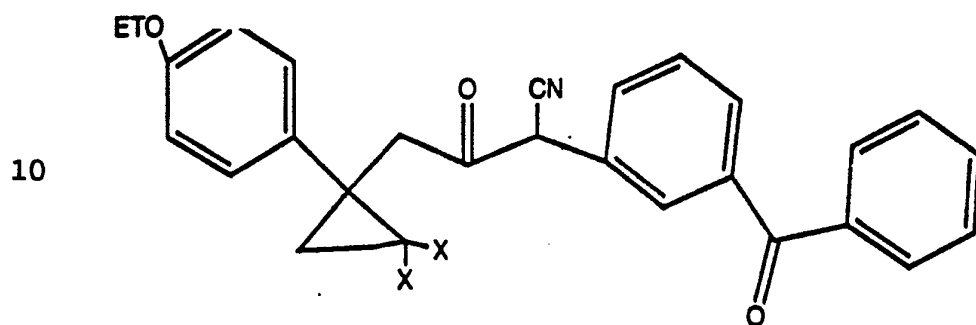
XX	$R_1 = \text{CN};$	$R_5 = R_9 = \text{H}.$	
XXI	$R_1 = \text{CN};$	$R_5 = R_9 = \text{H}.$	(+, -)
XXII	$R_1 = \text{CN};$	$R_5 = R_9 = \text{H}.$	(+, +)
XXIII	$R_1 = \text{CN};$	$R_5 = R_9 = \text{H}.$	(-, +)
30 XXIV	$R_1 = \text{CN};$	$R_5 = R_9 = \text{H}.$	(-, -)
XXV	$R_1 = \text{CN};$	$R_5 = \text{F};$	$R_9 = \text{H}.$ (+, +)(-, -)
XXVI	$R_1 = \text{H};$	$R_5 = \text{F};$	$R_9 = \text{H}.$
XXVII	$R_1 = \text{CCH};$	$R_5 = R_9 = \text{H}.$	
XXVIII	$R_1 = \text{CCH};$	$R_5 = R_9 = \text{H}.$	(+, +)(-, -)
35 XXIX	$R_1 = \text{CCH};$	$R_5 = R_9 = \text{H}.$	(+, -)(-, +)
XXX	$R_1 = \text{H};$	$R_5 = \text{OC}_4\text{H}_9;$	$R_9 = \text{H}.$
XXXI	$R_1 = \text{CN};$	$R_5 = \text{OCH}_3;$	$R_9 = \text{H}.$

- 29 -

Example 19

Using the method of Example 17 with the appropriate changes of reactants the further compounds listed below with general structure BB were synthesised.

5



15

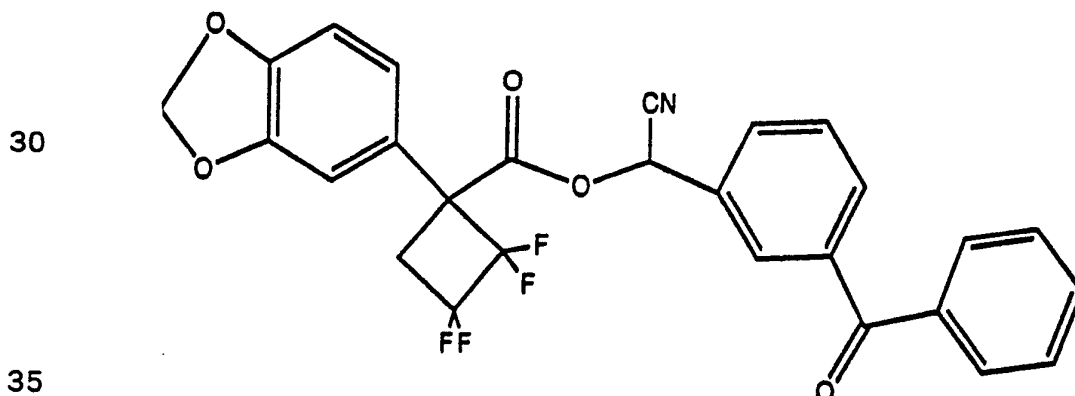
STRUCTURE BB

	Compound No	
	XXXII	X = F
20	XXXIII	X = Cl

Example 20

Using the method of Example 17 with the appropriate changes of reactants the further compounds listed below with general structure CC were synthesised.

25



35

STRUCTURE CC

- 30 -

Compound No

XXXIV (-,+) isomer

XXXV (-,-) isomer

5 Example 21

Insecticidal activity was investigated against blowfly, Lucilia cuprina. The method used was as follows:-

- 10 (a) The compounds were tested for activity against a susceptible strain.

The test compound was applied in acetone solution, 0.5 µl dispensed with a Drummond micropipette to the
15 dorsum of the thorax of 2-3 day old males. Adult flies were fed on water and sugar-only and maintained at 25°C and 60-70% RH. The mortalities were determined after 48 hours. Moribund flies were regarded as dead. The LD₅₀ values, in terms of concentration, were interpolated from
20 the probit/log dose relation using a computer program.

(b) Potentiation

The compound was also treated on the insects described above in conjunction with the potentiator
25 "Sesoxane" by pretreating each insect with 1 µl of a 2% solution of the potentiator in acetone.

The mortalities were counted at 48 hours after treatment and compared with acetone and
30 acetone/potentiator controls.

The LD₅₀ value was determined as described above.

Using the above method the following results were
35 obtained.

- 31 -

TABLE 1 INSECT TOXICITY

5	STRUCTURE	LUCILLIA CUPRINA LD ₅₀ [mg/kg] Compound/Compound+Sesoxane
10	IV	17.1 / 1.7
	V	96.2 / 0.9
	VI	25.43 / 1.29
	VII	5.9 / 0.85
	VIII(A)	25.55 / 1.77
15	VIII(B)	3.07 / 0.13
	IX	12.0 / 0.25
	X	74.57 / 3.45
	XI	13.78 / 0.79
	XII	11.01 / 0.44
20	XIII	20.42 / 10.00
	XIV	9.10 / 1.82
	XV	128.24 / 60.19
	XVII	34.56 / 1.22
	XIX	96.1 / 2.60
25	XX	5.05 / 0.14
	XXI	- / 111.65
	XXII	32.03 / 2.16
	XXIII	11.79 / 0.87
	XXIV	2.63 / 0.09
30	XXV	3.46 / 0.13
	XXVI	26.51 / 0.93
	XXVII	4.26 / 0.43
	XXVIII	1.72 / 0.04
	XXIX	26.29 / 2.16
35	XXX	59.26 / 10.65
	XXXI	- / 12.5
	XXXII	27.62 / 3.81
	XXXIII	35.5 / 3.0
	XXXIV	41.73 / 4.33
40	XXXV	5.51 / 1.97

Example 22

45 Lake collected wild-type mosquito fish (Gambusia affinis) was laboratory adapted in conical flasks each containing 200 ml of filtered lake water (tap water is toxic due to chlorine content). The required concentrations of the compounds in acetone were added to
50 the water and aerated continuously at RT to purge the acetone. The fish were added to each flask (10/concentration), aerators adjusted and left at ambient

- 32 -

temperature for 24 hours. Controls treated similarly with acetone only were used.

In each run, the commercial insecticides, fish-toxic
5 Fenvalerate (technical) and fish non-toxic Cycloprothrin were used as standards.

Limiting doses of 10 ppm, 1 ppm, 0.1 ppm, were applied and the last dose to give 100% kill was noted for
10 the three concentrations with the exceptions where an LD₅₀ was determined for the compounds.

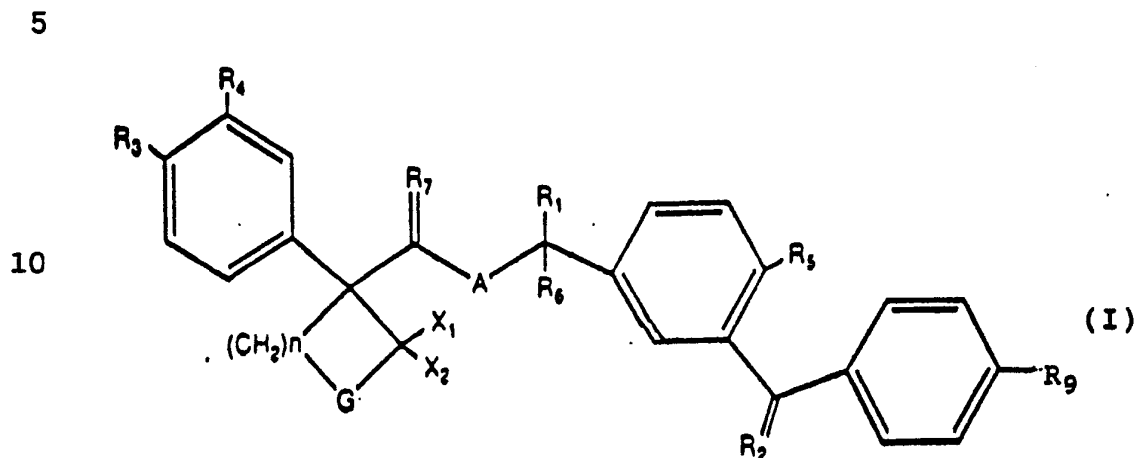
TABLE 2

15	COMPOUND	FISH TOXICITY (GAMBUSIA AFFINIS) PERCENTAGE KILL @ PPM.		
		0.1	1.0	10
20	PERMETHRIN	80	100	100
	DELTAMETHRIN	100	100	100
25	FENVALERATE	10	80	100
	IV	-	-	-
	V	-	-	-
	VI	-	-	-
30	VII	0	0	0
	VIII (A)	0	0	0
	VIII (B)	0	0	0
	XV	0	0	10
	XXII	0	0	10
35	XXIV	0	0	0
	XIX	0	0	10
	XXVI	0	10	60
	XXIV	0	0	0
40	XXXIII	0	0	0

- 33 -

CLAIMS

1. Compounds of the general formula (I) and their isomeric and racemic forms:



characterized in that n is 0 or 1;

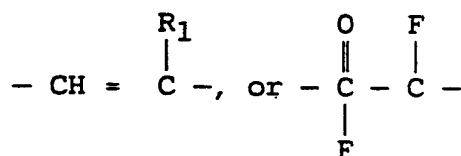
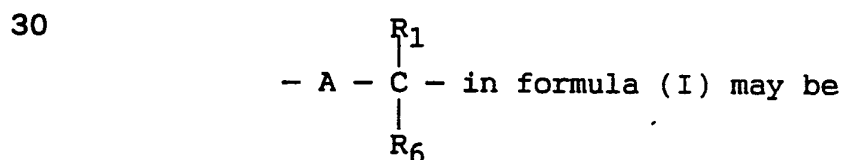
A is oxygen, sulphur, C=O, CH₂, CF₂, CD₂, CDH, CHOH, CHX wherein X is fluorine, chlorine, bromine or iodine;

20 G is oxygen, sulphur, CH₂ or CX₃X₄ wherein X₃ and X₄ are the same or different and each is fluorine, chlorine or bromine;

X₁ and X₂ are the same or different and each is hydrogen or fluorine, chlorine or bromine; and when n is 25 0, X₁ and X₂ may also be methyl groups;

R₁ is hydrogen, deuterium, CN, C≡CH, fluorine, chlorine or bromine and R₆ is hydrogen or deuterium; or

R₁ and R₆ may optionally form =O, or



and

- 34 -

R_2 is oxygen, or both H and OH together, or $N-OR_8$ wherein R_8 is hydrogen or lower alkyl which is optionally substituted with one or more halo groups;

R_3 is a halo group, or a lower alkyl, lower alkoxy or lower alkylthio group, in each of which the alkyl group is optionally substituted with one or more halo groups;

R_4 is hydrogen or a halo or lower alkyl group; or

R_3 and R_4 may optionally form a methylenedioxy bridge which is optionally mono- or di- substituted with fluorine;

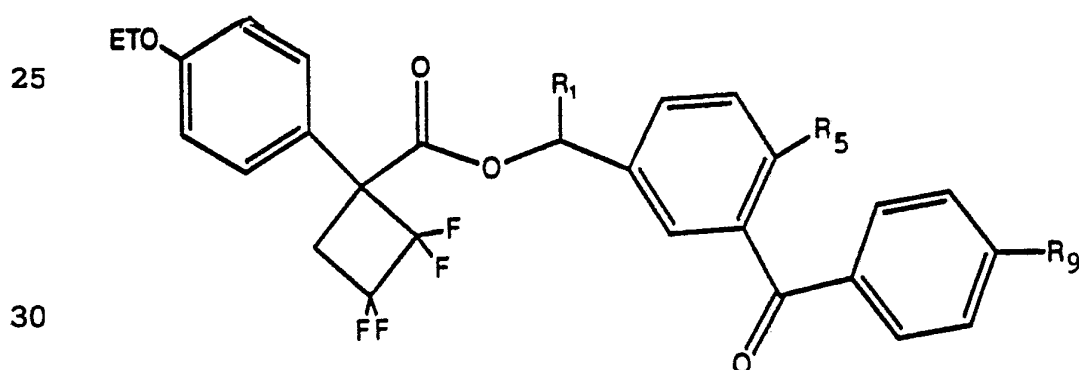
R_5 is hydrogen, OH, lower alkoxy, SH, or lower thioalkyl, fluorine, chlorine, bromine or iodine;

R_7 is H_2 , HD, D_2 or oxygen.

R_9 is H, lower alkoxy or lower alkylthio.

2. Compounds as claimed in Claim 1, characterized in that either $n=0$, $G=CH_2$ and $X_1=X_2=F$; or $n=1$, $G=CFF$ and $X_1=X_2=F$.

3. Compounds as claimed in Claim 1, having the structure AA.

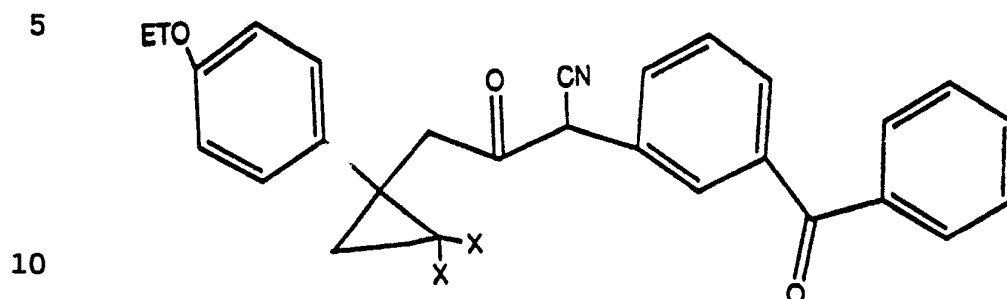


STRUCTURE AA

4. Compounds as claimed in Claim 1, having the structure BB.

- 35 -

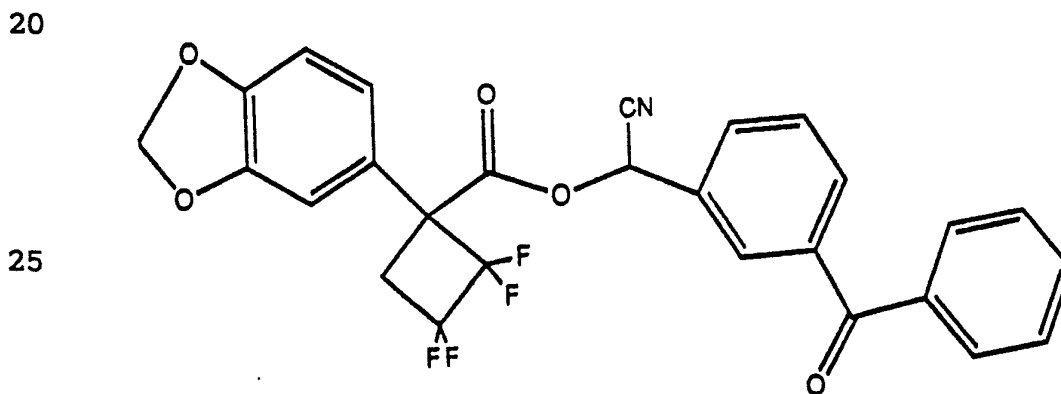
4. Compounds as claimed in Claim 1, having the structure BB.



15

STRUCTURE BB

5. Compounds as claimed in Claim 1, having the structure CC.



30

STRUCTURE CC

6. Compounds as claimed in any one of Claims 1 to 5, characterised in that lower alkyl groups, when present, contain from 1 to 6 carbon atoms.

35

7. An arthropodocidal composition, characterized in that it comprises as an active ingredient a compound of

- 36 -

the formula (I) in admixture with a diluent or carrier.

8. A composition as claimed in Claim 7, characterized in that it includes at least one other active ingredient
5 which is an arthropodical, fungicidal or bactericidal compound.

9. A composition as claimed in Claim 7 or Claim 8, characterized in that it includes at least one substance
10 which has a synergistic or intensifying effect on pyrethroids.

10. A composition as claimed in Claim 5, wherein the substance is selected from
15 [2-(2-butoxyethoxy)ethoxy]-4,5-methylenedioxy-2-propyltoluene,

3-hexyl-5(3,4-methylenedioxyphenyl)-2-cyclohexanone,
20 2-(3,4-methylenedioxy-phenoxy)-3,6,9-trioxaundecane,

1,2-(methylenedioxy)-4-[2-(octylsulfinyl)propyl]benzene,

dipropyl-5,6,7,8-tetrahydro-7-methylnaphtho-[2,3-d]-3-
25 dioxole-5,6-dicarboxylate,

propynyl ethers and propynyl oximes.

11. A composition as claimed in Claim 10, characterized
30 in that the substance is present in the composition in an amount of from 1/1000th to fifty times the weight of the compound of formula (I).

12. A composition as claimed in Claim 10, characterized
35 in that the amount is from 1/100th to five times the weight of the compound of formula (I).

- 37 -

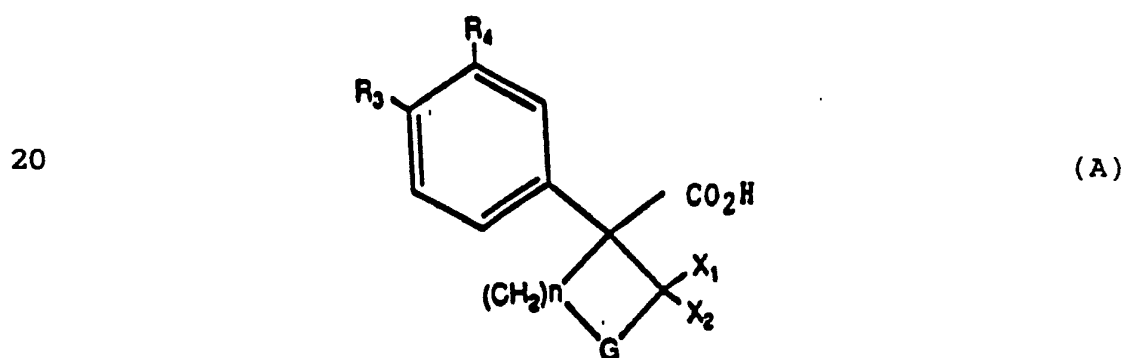
13. A method of combating arthropods, characterized in that a compound of the formula (I) alone or in the form of a composition as claimed in any one of Claims 7 to 12, is applied to the arthropods, or to a habitat thereof.

5

14. A method of freeing or protecting domesticated animals from parasitical insects or acarids, characterized in that a compound of the formula (I) alone or in the form of a composition as claimed in any one of
10 Claims 7 to 12 is applied to said animals.

15. A method for producing a compound of formula (I), as stated and defined in Claim 1, characterized in that an acid of the formula (A):

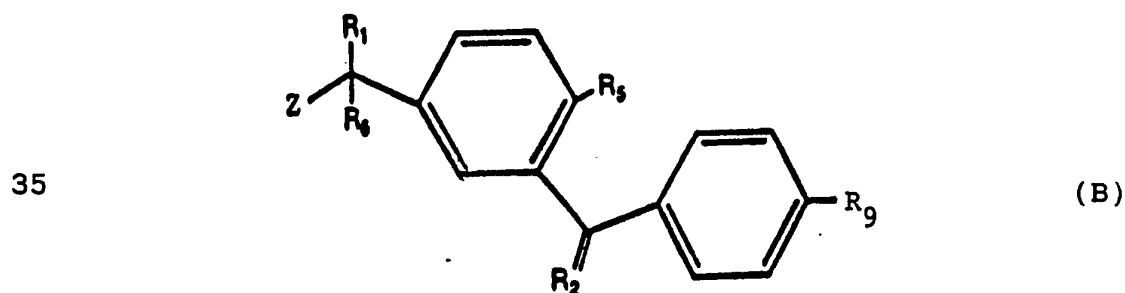
15



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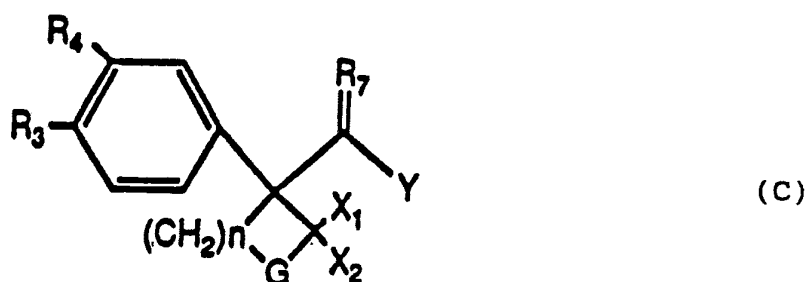
wherein R_3 , R_4 , X_1 , X_2 , n and G are as defined in Claim 1, or a reactive derivative of such an acid, is reacted with a compound of the formula (B):

30



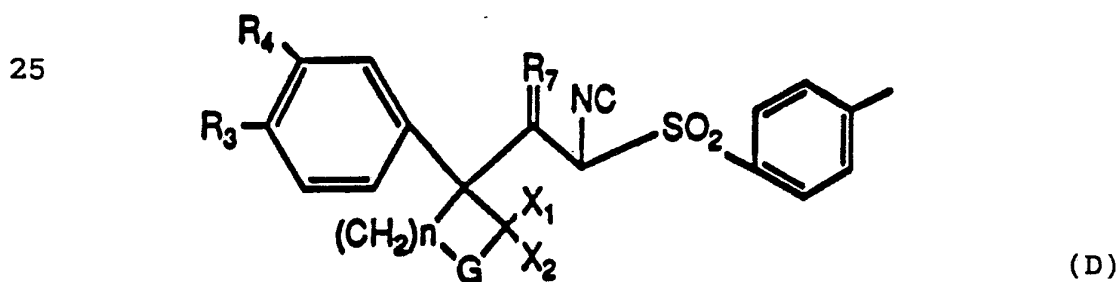
- 38 -

wherein R_1 , R_2 , R_6 and R_5 are as defined in Claim 1
 and Z is a leaving group or a hydroxy group; or
 5 a compound of the formula (C):



15

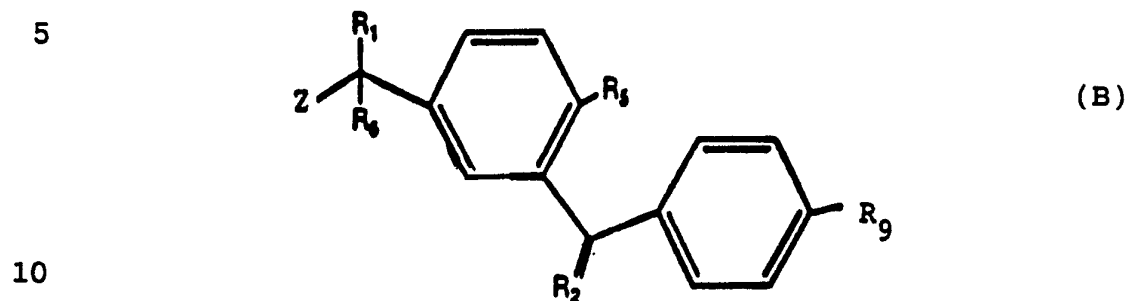
wherein R_3 , R_4 , X_1 , X_2 , n and G are as defined in
 Claim 1 above, R_7 is H_2 , HD or D_2 and Y is a leaving
 20 group, is reacted with the anion of 4-tosylmethyl
 isocyanide to produce an intermediate of the formula (D):



wherein R_3 , R_4 , X_1 , S_2 and G are as defined above
 35 and R_7 is H_2 , HD or D_2 ; and

- 39 -

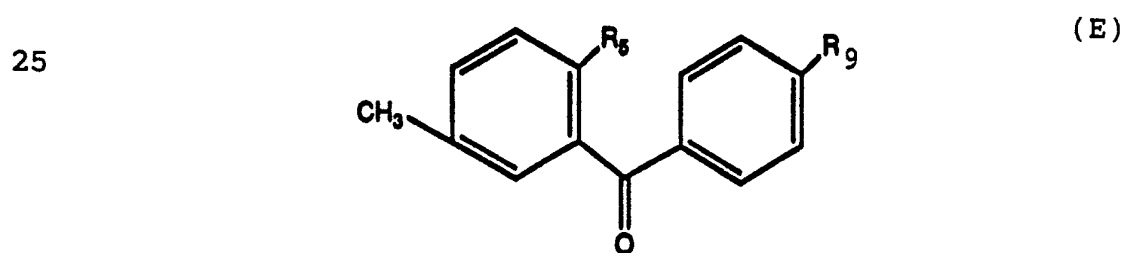
the anion of said intermediate is reacted with a compound of the formula (B):



wherein R_1 , R_2 , R_5 , R_6 and Z are as defined above.

15

16. A method as claimed in Claim 15, characterized in that a compound of formula (B), wherein the leaving group Z is bromo and R_1 - R_6 =H, is synthesised by the radical bromination of the corresponding methyl compound, ie Z =H, of formula (E):
- 20



30

35

wherein R_5 and R_9 are as stated in Claim 1.

- 40 -

17. A method as claimed in Claim 16, characterized in
that the compound of formula (E) is synthesised by
Friedel-Crafts acylation, or alkylation followed by
hydrolysis, of the appropriate aromatic compound or
5 by esterification or alkylation of 2-methyl-5-
hydroxy-4'-substituted benzophenone or the
corresponding thiol.
18. Compounds of the formula (E) as stated and defined
10 in Claim 16.

INTERNATIONAL SEARCH REPORT

International Application No. **PCT/AU 90/00534**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl. ⁵ : C07C 255/40, 251/48, 323/22, 49/80, 49/84, 69/757; C07D 317/60; A01N 43/30, 37/38, 37/34, 35/04		
II. FIELDS SEARCHED		
Minimum Documentation Searched 7		
Classification System	Classification Symbols	
IPC	C07C 255/40, 251/48, 323/22, 49/80, 49/84, 69/757, 121/76, 131/00, 149/36, 149/40, 69/76, 49/82; C07D 317/60	
Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched 8		
AU : IPC as above Chemical Abstracts: molecular formula, C27H22F4O4, C28H21F4NO4 JOPAL: IPC as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT 9		
Category*	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages 12	Relevant to Claim No 13
X	Dictionary of Organic Compounds, Fifth Edition (1982), Chapman & Hall. See Compounds: C01502, vol 1, page 1138; D05723, vol 2, page 2086; H02334, vol 3, page 3117; M01030, vol 4, page 3757	(18)
X	Patents Abstracts of Japan, C-421, page 166, JP,A, 61-282335 (HONSYU KAGAKU KOGYO K.K.) 12 December 1986 (12.12.86)	(18)
X	US,A, 4042613 (DIA NIPPON CO., LTD, SHIN-ETSU CHEMICAL CO., LTD) 16 August 1977 (16.08.77) See Claim 1	(18)
X	US,A, 4141995 (LILLY IND CO., LTD) 27 February 1979 (27.02.79) See Claim 1	(18)
X	US,A, 4305839 (CARSTAB CORPORATION) 15 December 1981 (15.12.81) See Claim 1	(18)
		(contd)
* Special categories of cited documents: 10 "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Z" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
15 February 1991 (15.02.91)	25 February 1991	
International Searching Authority	Signature of Authorized Officer	
Australian Patent Office	 JACQUELINE ROESSGEN	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	GB,A, 2021559 (SYNTHELABO) 5 December 1979 (05.12.79) See Claim 9	(18)
X	GB,A, 1410542 (BADISCHE ANILIN & SODA-FABRIK AKTIENGESELLSCHAFT) 15 October 1975 (15.10.75) See Example 3	(18)
X	EP,A2, 209831 (FRATELLI LAMBERTI) 28 January 1987 (28.01.87) See Claim 1	(18)
X	EP,A1, 273528 (SHELL AGRAR) 6 July 1988 (06.07.88) See Claim 1	(18)
X	EP,A2, 279475 (WARD BLENKINSOP) 24 August 1988 (24.08.88) See Claim 9	(18)
X	DE,A, 1568718 (GENERAL MILLS) 26 March 1970 (26.03.70) See Claim 1	(18)

V. [] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.[] Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:

2.[] Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.[] Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4 (a):

VI. [] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this international application as follows:

1.[] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2.[] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3.[] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[] The additional search fees were accompanied by applicant's protest.

[] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 90/00534

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Members			
US	4042613				
US	4141995	AU 502015 GB 1549171	DE 2546738	FR 2307524	
US	4305839	AU 513379 GB 2033388	DE 2929511	FR 2439763	
GB	2021559	AU 520618 GB 2021559	DE 2907379	FR 2418222	
EP	209831	DE 3671233	EP 209831	US 4755541	
EP	273528	DE 3643403			
DE	1568718	US 3925472			
EP	279475	AU 596888	EP 279475	GB 8703606	

END OF ANNEX