P/00/001
Section 29

664229

COMMONWEALTH OF AUSTRALIA

The Patents Act 1990

PATENT REQUEST: CONVENTION PATENT

We, being the person identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification
Full application details follow:-

Applicant:	Rhone-Poulenc Agriculture Ltd.
Address:	Research Station - Fyfield Road, Ongar, Essex CM5 OHW, Great Britain
Nominated Person:	Rhone-Poulenc Agriculture Ltd.
Address:	Research Station - Fyfield Road, Ongar, Essex CM5 OHW, Great Britain
Invention Title:	"HERBICIDAL ISOXAZOLE DERIVATIVES".
Name(s) of actual Inventor(s):	Paul Alfred CAIN and Susan Mary CRAMP
Address for service in Australia:	CALLINAN LAWRIE, 278 High Street, Kew 3101, Victoria, Australia
Attorney Code:	CL

Convention Details

Application Number	Country	Country Code	Date of Application
850,128	USA	US	12 March 1992

DATED this 4th day of February, 1993.

RHONE-POULENC AGRICULTURE LTD.
By their Patent Attorneys:
CALLINAN LAWRIE

Geoffrey A. Ryder

AUSTRALIAN PATENT OFFICE

CALLINAN LAWRIE
Private Bag 7, Kew
Victoria 3101, Australia
Facsimile:
61 (3) 353.0062
61 (3) 853.0728

AUSTRALIA

PATENT

NOTICE OF ENTITLEMENT

We, RHONE-POULENC AGRICULTURE LTD., of Research Station - Fyfield Road, Ongar, Essex CM5 OHW, Great Britain, being the applicant and the person nominated for grant of patent in respect of the Application for an invention entitled HERBICIDES state the following:-

STANDARD CONVENTION FILING

The person nominated for the grant of the patent has entitlement from the actual inventors who are the applicants of the basic application, by virtue of an assignment of the invention from the actual inventors.

The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

Jeffrey A. Ryder — 4 FEB 1993

Jeffrey A. Ryder
Registered Patent Attorney

Date

To: The Commissioner of Patents

0.40293

AU9332819

(12) PATENT ABRIDGMENT (11) Document No. AU-B-32819/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 664229

(54) Title
HERBICIDAL ISOXAZOLE DERIVATIVES

International Patent Classification(s)
(51)[5] **C07D 261/08** **A01N 043/80** **C07D 261/18**

(21) Application No. : **32819/93** (22) Application Date : **04.02.93**

(30) Priority Data

(31) Number **850128** (32) Date **12.03.92** (33) Country **US UNITED STATES OF AMERICA**

(43) Publication Date : **16.09.93**

(44) Publication Date of Accepted Application : **09.11.95**

(71) Applicant(s)
RHONE-POULENC AGRICULTURE LTD.

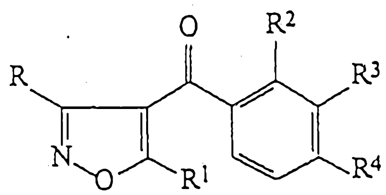
(72) Inventor(s)
PAUL ALFRED CAIN; SUSAN MARY CRAMP

(74) Attorney or Agent
CALLINAN LAWRIE , Private Bag 7, KEW VIC 3101

(56) Prior Art Documents
AU 87977/91 C07D 261/08
EP 418175
AU 20730/92 C07D 261/08

(57) Claim

1. A 4-benzoyl isoxazole derivative of general formula (I)



(I)

wherein:

R represents a hydrogen atom or a group $-CO_2R^5$;

R^1 represents methyl, isopropyl, cyclopropyl or 1-methylcyclopropyl;

R^2 represents $-S(O)_nR^{51}$;

R^3 represents:

a chlorine, bromine or fluorine atom;

.../2

a straight- or branched- chain alkyl or alkoxy group containing up to four carbon atoms optionally substituted by one or more halogen atoms;

a straight- or branched chain alkenyl group containing up to six carbon atoms; or

a group $-CO_2R^{52}$;

R^4 represents:

a chlorine, bromine or fluorine atom;

a straight- or branched- chain alkyl group containing up to four carbon atoms optionally substituted by one or more halogen atoms;

an alkoxy group containing up to four carbon atoms substituted by one or more halogen atoms;

$-S(O)_pR^{53}$ or cyano;

R^5 represents a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

R^{51} and R^{53}, which may be the same or different, each represents a straight- or branched- chain alkyl group containing up to four carbon atoms;

R^{52} represents methyl or ethyl;

n represents zero, one or two; and

p represents zero, one or two.

14. A method for controlling the growth of weeds at a locus which comprises applying to the locus a herbicidally effective amount of an isoxazole derivative of general formula (I) as defined in any one of claims 1 to 8.

P/00/011
Regulation 3.2

664229

AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

TO BE COMPLETED BY APPLICANT

Name of Applicant: RHONE-POULENC AGRICULTURE LTD.

Actual Inventor(s): Paul Alfred CAIN and Susan Mary CRAMP

Address for Service: CALLINAN LAWRIE, 278 High Street, Kew, 3101, Victoria, Australia

Invention Title: "HERBICIDAL ISOXAZOLE DERIVATIVES".

The following statement is a full description of this invention, including the best method of performing it known to me:-

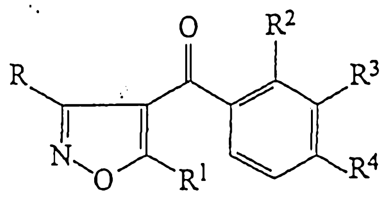
---

AUSTRALIAN PATENT OFFICE

PH92013

"HERBICIDAL ISOXAZOLE DERIVATIVES".

This invention relates to novel 4-benzoylisoxazole derivatives, compositions containing them and their use as herbicides. Herbicidally active 4-benzoylisoxazoles are described in European Patent Publication No. 0418175. The present invention provides 4-benzoylisoxazole derivatives of general formula (I):



(I)

wherein

R represents a hydrogen atom or a group $-CO_2R^5$;

R^1 represents methyl, isopropyl, cyclopropyl or 1-methylcyclopropyl;

R^2 represents $-S(O)_nR^{51}$;

R^3 represents:

a chlorine, bromine or fluorine atom;

a straight- or branched- chain alkyl or alkoxy group containing up to four carbon atoms optionally substituted by one or more halogen atoms;

a straight- or branched chain alkenyl group containing up to six carbon atoms; or

a group $-CO_2R^{52}$;

R^4 represents:

a chlorine, bromine or fluorine atom;

a straight- or branched- chain alkyl group containing up to four carbon atoms optionally substituted by one or more halogen atoms;

an alkoxy group containing up to four carbon atoms substituted by one or more halogen atoms;

$-S(O)_pR^{53}$ or cyano;

R^5 represents a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

R^{51} and R^{53}, which may be the same or different, each represents a straight- or branched- chain alkyl group containing up to four carbon atoms;

R^{52} represents methyl or ethyl;

n represents zero, one or two; and

p represents zero, one or two.

In certain cases the substituents R^1, R^2 R^3, R^4, R^5, R^{51} and R^{53} contribute to optical and/or stereoisomerism. All such forms are embraced by the present invention.

The compounds of the invention show unexpected and remarkably high herbicidal activity in comparison with known compounds against important weed species including foxtail (Setaria viridis and Setaria faberii), barnyard grass (Echinochloa crus-galli), crabgrass (Digitaria sanguinalis) and shattercane (Sorghum bicolor).

Where R represents $-CO_2R^5$, R^5 is preferably methyl or ethyl.

Preferably R^1 represents a cyclopropyl group.

Where R^3 represents an alkenyl group, the alkenyl group preferably contains from two to four carbon atoms, more preferably two or three carbon atoms. Where R^3 represents $-CO_2R^{52}$, R^{52} is preferably methyl. Where R^3 represents a halogen-substituted alkyl group, preferably R^3 is not trifluoromethyl; preferred halogen-substituted alkyl groups include for example difluoromethyl, 2,2,2-trifluoroethyl, fluoromethyl and dichlorofluoromethyl. Preferred compounds include those wherein R^3 represents an optionally halogen-substituted alkoxy group containing one or two carbon atoms, more preferably ethoxy or most preferably methoxy.

Where R^4 represents $-S(O)_pR^{53}$, preferably p is zero and/or R^{53} is ethyl or most preferably methyl.

Compounds in which R^{51} represents ethyl or methyl are also preferred, methyl being particularly preferred.

A preferred class of compounds of general formula (I) are those wherein:

R^3 represents a fluorine, chlorine or bromine atom; a methyl or ethyl group; an alkoxy group containing one or two carbon atoms optionally substituted by one or more halogen atoms; an alkenyl group containing from two to four carbon atoms; or $-CO_2R^{52}$;

R^4 represents a fluorine, chlorine or bromine atom; an alkyl group containing one or two carbon atoms substituted by one or more halogen atoms; an alkoxy group containing one or two carbon atoms substituted by one or more halogen atoms; or $-S(O)_pR^{53}$, wherein p represents zero and R^{53} is a methyl or ethyl group; and

R^{51} represents a methyl or ethyl group.

A further preferred class of compounds of general formula (I) are those wherein:

R^3 represents a fluorine, chlorine or bromine atom; a methyl, methoxy or ethoxy group; an alkenyl group containing two or three carbon atoms; or $-CO_2R^{52}$ wherein R^{52} is methyl;

R^4 represents a fluorine, chlorine or bromine atom or a group selected from trifluoromethyl, trifluoromethoxy and $-S(O)_pMe$ wherein p is zero;

R^5 represents a methyl or ethyl group; and

R^{51} represents a methyl or ethyl group.

A further preferred class of compounds of general formula (I) are those wherein:

R^3 is fluorine, chlorine, bromine, methyl or methoxy;

R^4 is fluorine, chlorine, bromine or trifluoromethyl;

R^5 is methyl or ethyl.

A further preferred class of compounds of general formula (I) are those wherein:

R^3 is fluorine, chlorine, bromine or methoxy;

R^4 is fluorine, chlorine, bromine or trifluoromethyl;

R^5 is methyl or ethyl; and

R^{51} is methyl.

A further preferred class of compounds of general formula (I) are those wherein:

R^3 represents a chlorine, bromine or fluorine atom;

R^4 represents fluorine, chlorine, bromine or trifluoromethyl;

R^5 represents methyl or ethyl; and

R^{51} represents methyl.

Compounds of particular interest because of their herbicidal activity include the following:

1. 5-cyclopropyl-4-[3,4-difluoro-2-(methylsulphonyl)benzoyl]-isoxazole;

2. 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphenyl)benzoyl]-isoxazole;

3. 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphinyl)benzoyl]-isoxazole;

4. 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphonyl)-benzoyl]isoxazole;

5. 5-cyclopropyl-4-[4-bromo-3-methoxy-2-(methylsulphenyl)-benzoyl]isoxazole;

6. 5-cyclopropyl-4-[4-bromo-3-methoxy-2-(methylsulphonyl)-benzoyl]isoxazole;

7. 5-cyclopropyl-4-[4-bromo-3-methoxy-2-(methylsulphinyl)-benzoyl]isoxazole;

8. ethyl 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphenyl) benzoyl]isoxazole-3-carboxylate;

9. ethyl 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphinyl) benzoyl]isoxazole-3-carboxylate;

10. 4-[4-chloro-3-methoxy-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

11. ethyl 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphonyl)-benzoyl]isoxazole-3-carboxylate;

12. 4-[4-chloro-3-methoxy-2-(methylsulphinyl)benzoyl]-5-cyclopropylisoxazole;

13. 4-[4-chloro-3-methoxy-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole;

14. 4-[4-chloro-3-methyl-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

15. 4-[4-chloro-3-fluoro-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

16. 4-[4-chloro-3-fluoro-2-(methylsulphinyl)benzoyl]-5-cyclopropylisoxazole;

17. 4-[4-chloro-3-fluoro-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole;

18. 4-[4-chloro-3-methyl-2-(methylsulphinyl)benzoyl]-5-cyclopropylisoxazole;

19. 4-[4-chloro-3-methyl-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole;

20. 5-cyclopropyl-4-[3-methoxycarbonyl-2-(methylsulphenyl)-4-trifluoromethylbenzoyl]isoxazole;

21. 4-[4-chloro-3-methoxycarbonyl-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

22. 4-[4-bromo-3-chloro-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

23. 4-[4-bromo-3-chloro-2-(methylsulphinyl)benzoyl]-5-cyclopropylisoxazole;

24. 4-[4-bromo-3-chloro-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole;

25. 4-[4-chloro-3-methoxycarbonyl-2-(methylsulphinyl)benzoyl]-5-cyclopropylisoxazole;

26. 4-[4-chloro-3-methoxycarbonyl-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole;

27. 4-[3-chloro-2-(methylsulphenyl)-4-trifluoromethylbenzoyl]-5-cyclopropylisoxazole;

28. 4-[3-chloro-2-(methylsulphonyl)-4-trifluoromethylbenzoyl]-5-cyclopropylisoxazole;

29. 4-[4-bromo-3-fluoro-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

30. 4-[4-bromo-3-fluoro-2-(methylsulphinyl)benzoyl]-5-cyclopropylisoxazole;

31. 4-[4-bromo-3-fluoro-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole;

32. 4-[4-chloro-3-isopropenyl-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

33. 5-cyclopropyl-4-[3-methyl-2,4-bis(methylsulphenyl)-benzoyl]isoxazole;

34. 4-[4-chloro-3-isopropenyl-2-(methylsulphinyl)-benzoyl]-5-cyclopropylisoxazole; and

35. 4-[4-chloro-3-isopropenyl-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole.

The numbers 1 to 35 are assigned to these compounds for reference and identification hereinafter.

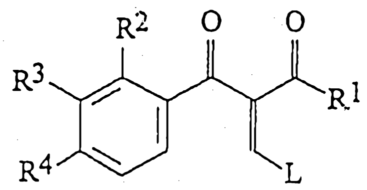
Of the above, compounds 3, 4, 6, 8, 13, 16, 17, 22, 23 and 24 are particularly preferred.

Compounds of general formula (I) may be prepared by the application or adaptation of known methods (i.e. methods heretofore used or described in the literature), for example as hereinafter described.

In the following description where symbols appearing in formulae are not specifically defined, it is to be understood that they are "as hereinbefore defined" in accordance with the first definition of each symbol in the specification.

It is to be understood that in the descriptions of the following processes the sequences may be performed in different orders, and that suitable protecting groups may be required to achieve the compounds sought.

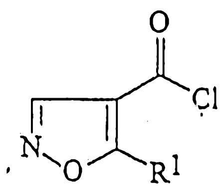
According to a feature of the present invention compounds of general formula (I) in which R represents hydrogen may be prepared by the reaction of a compound of general formula (II):



(II)

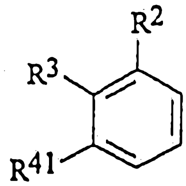
wherein R^1, R^2, R^3 and R^4 are as hereinbefore defined and L is a leaving group, with a salt of hydroxylamine. Hydroxylamine hydrochloride is generally preferred. Generally L is alkoxy, for example ethoxy, or N,N-dialkylamino, for example dimethylamino. The reaction is generally carried out in a solvent such as ethanol or acetonitrile, optionally in the presence of a base or acid acceptor such as triethylamine or sodium acetate.

According to a further feature of the present invention compounds of general formula (I) in which R^2 represents a group $-SR^{51}$, R represents hydrogen and R^4 represents a group R^{41} which is as hereinbefore defined for R^4 provided that p is zero, may be prepared by the reaction of a compound of general formula (III):



(III)

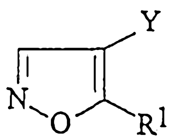
wherein R^1 is as hereinbefore defined, with a compound of general formula (IV):



(IV)

in which R^3 and R^{41} are as hereinbefore defined and R^2 represents $-SR^{51}$. The reaction is generally carried out in the presence of a Lewis acid catalyst such as aluminium chloride at a temperature between room temperature and 100°C.

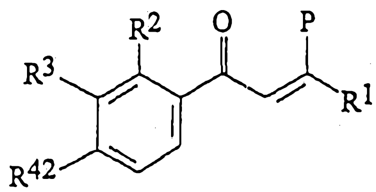
According to a further feature of the present invention compounds of general formula (I) in which R represents hydrogen may be prepared by the reaction of a compound of general formula (V):



(V)

wherein R^1 is as hereinbefore defined and Y represents a carboxy group or a reactive derivative thereof (such as a carboxylic acid chloride or carboxylic ester), or a cyano group, with an appropriate organometallic reagent such as a Grignard reagent or an organolithium reagent. The reaction is generally carried out in an inert solvent such as ether or tetrahydrofuran at a temperature from 0°C to the reflux temperature of the mixture.

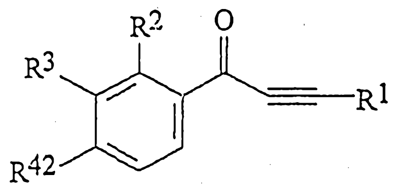
According to a further feature of the invention compounds of formula (I) wherein R represents a group $-CO_2R^5$, n is 0 or 2 and R^4 represents a group R^{42} which is as hereinbefore defined for R^4 provided that p is 0 or 2, may be prepared by the reaction of a compound of general formula (VI):



(VI)

wherein R^1, R^2, R^3 and R^{42} are as hereinbefore defined, n is zero or two and P is a leaving group such as N,N-dialkylamino, with a compound of general formula $R^5O_2CC(X)=NOH$ wherein R^5 is as hereinbefore defined and X is a halogen atom. Generally X is chlorine or bromine. The reaction is generally performed in an inert solvent such as toluene or dichloromethane either in the presence of a base such as triethylamine or a catalyst such as a 4 Angstrom molecular sieve or fluoride ion.

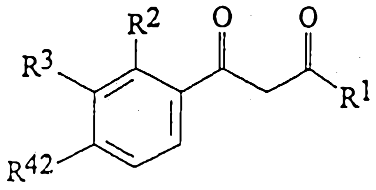
According to a further feature of the present invention compounds of general formula I in which R represents a group $-CO_2R^5$, n is 0 or 2 and R^4 represents a group R^{42} as hereinbefore defined, may be prepared by the reaction of a compound of general formula (VII):



(VII)

wherein R^1, R^2, R^3 and R^{42} are as hereinbefore defined and n is 0 or 2, with a compound of general formula $R^5O_2CC(X)=NOH$, wherein R^5 and X are as hereinbefore defined. The reaction is generally performed in an inert solvent such as toluene or dichloromethane optionally in the presence of a base such as triethylamine or a catalyst such as a 4 Angstrom molecular sieve or fluoride ion. The reaction can be carried out at a temperature between room temperature and the reflux temperature of the mixture.

According to a further feature of the present invention compounds of general formula (I) wherein R represents $-CO_2R^5$, n is 0 or 2 and R^4 represents a group R^{42} as hereinbefore defined, may be prepared by the reaction of a salt of a compound of general formula (VIII):



(VIII)

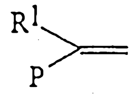
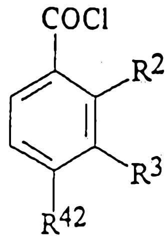
wherein R^1, R^2, R^3 and R^{42} are as hereinbefore defined and n is 0 or 2, with a compound of general formula $R^5O_2CC(X)=NOH$ wherein R^5 and X are as hereinbefore defined. Preferred salts include sodium or magnesium salts. The reaction may be performed in an inert solvent such as dichloromethane or acetonitrile at a temperature between room temperature and the reflux temperature of the mixture.

Intermediates in the preparation of compounds of general formula (I) may be prepared by the application or adaptation of known methods.

Compounds of general formula (II) may be prepared by the reaction of compounds of general formula (VIII) with either a trialkyl orthoformate such as triethyl orthoformate or a dimethylformamide dialkylacetal such as dimethylformamide dimethyl acetal.

The reaction with triethyl orthoformate is generally carried out in the presence of acetic anhydride at the reflux temperature of the mixture and the reaction with dimethylformamidedialkyl acetal is carried out optionally in the presence of an inert solvent at a temperature from room temperature to the reflux temperature of the mixture.

Compounds of general formula (VI) may be prepared by the reaction of a compound of general formula (IX) wherein R^1 and P are as hereinbefore defined with a benzoyl chloride of general formula (X) wherein R^2, R^3 and R^{42} are as hereinbefore defined:

(IX) (X).

The reaction is generally carried out in the presence of an organic base such as triethylamine in an inert solvent such as toluene or dichloromethane at a temperature between -20^{o}C and room temperature.

Compounds of general formula (VII) may be prepared by the metallation of the appropriate acetylene of general formula (XI):

$$R^1\text{—}C{\equiv}CH \qquad \text{(XI)}$$

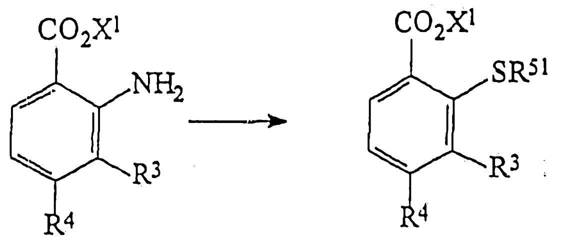
wherein R^1 is as hereinbefore defined, followed by reaction of the metal salt thus obtained with a benzoyl chloride of general formula (X). The metallation is generally performed using n-butyl lithium in an inert solvent such as ether or tetrahydrofuran at a temperature from -78^{o}C to 0^{o}C. The subsequent reaction with the benzoyl chloride is carried out in the same solvent at a temperature between -78^{o}C and room temperature.

Those skilled in the art will appreciate that some compounds of general formula (I) may be prepared by the interconversion of other compounds of general formula (I) and such interconversions constitute yet more features of the present invention. Examples of such interconversions are hereafter described.

According to a further feature of the present invention compounds in which n is one or two and/or p is one or two may be prepared by the oxidation of the sulphur atom of compounds in which n is zero or one and/or p is zero or one . The oxidation of the sulphur atom is generally carried out using for example 3-chloroperoxybenzoic acid in an inert solvent such as dichloromethane at a temperature from -40°C to room temperature, or hydrogen peroxide in acetic acid in the presence of acetic anhydride or concentrated sulphuric acid.

Benzoic acids required as intermediates in the preparation of compounds of general formula I may be prepared according to a number of processes for example as hereinafter described.

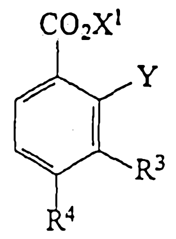
Benzoic acids or esters of general formula XII may be prepared by diazotization of compounds of general formula XIII followed by treatment with a dialkyl disulphide, $R^{51}S\text{-}SR^{51}$:



XIII XII

wherein R^3, R^4 and R^{51} are as hereinbefore defined and X^1 represents hydrogen, methyl or ethyl. Diazotization may be performed using an alkyl nitrite such as t-butyl nitrite in the presence of a dialkyl disulphide in an inert solvent such as chloroform at a temperature from room temperature to the reflux temperature of the mixture. Alternatively diazotization may be carried out using sodium nitrite followed by treatment with a dialkyl disulphide in the presence of a catalyst such as copper.

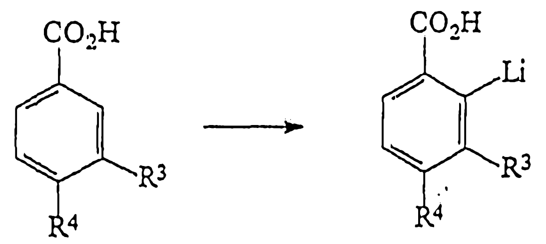
Alternatively benzoic acids or esters of general formula XII may be prepared from compounds of general formula XIV:



XIV

wherein R^3, R^4 and X^1 are as hereinbefore described and Y is a halogen atom (e.g. chlorine, fluorine or bromine) or a nitro group, with an alkyl mercaptan of formula R^{51}-SH wherein R^{51} is as hereinbefore defined, in the presence of a base. Typical bases used in the above reaction include lithium hydroxide and potassium carbonate and the reaction may be carried out in a solvent such as dimethyl formamide or acetone at a temperature from room temperature to the reflux temperature of the mixture.

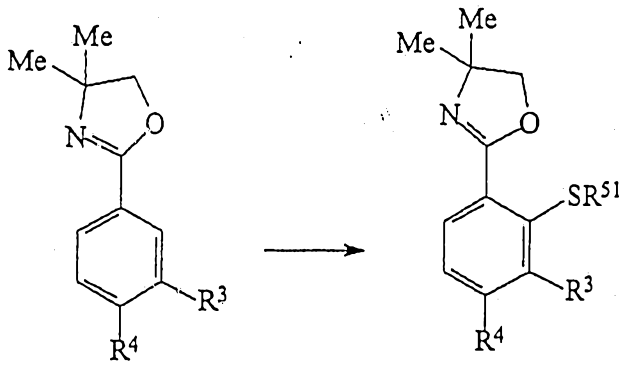
Alternatively benzoic acids of general formula XII in which R^3 represents a halogen atom may be prepared by lithiation of compounds of general formula XV to give the lithiated intermediate XVa:



XV XVa

wherein R^4 is as hereinbefore defined and R^3 represents a halogen atom, which is treated with a dialkyl disulphide, $R^{51}S\text{-}SR^{51}$, wherein R^{51} is as hereinbefore defined. The lithiation is typically carried out using alkyl lithium compounds such as n-butyl lithium or lithium diisopropylamide in an inert solvent such as tetrahydrofuran at a temperature from -70°C to -40°C. The reaction is preferably performed under an inert atmosphere. This reaction, giving the lithiated intermediate (XVa) is novel and as such constitutes a further feature of the present invention.

The benzoic acids of general formula (XII) may also be prepared from benzoic acids of general formula (XV) by first protecting the benzoic acid function as a 4,4-dimethyloxazoline to give a compound of general formula (XVI):



XVI XVII

wherein R^3 and R^4 are as hereinbefore defined, which is then lithiated using for example n-butyllithium or lithium diisopropyl amide followed by treatment with a dialkyl disulphide of formula $R^{51}S\text{-}SR^{51}$, wherein R^{51} is as hereinbefore defined. Compounds of formula XVI are described in the literature, for example by A Metikian et al, Eur. J. Med. Chem. 25 (1990) 267-270. The oxazoline of general formula XVII is then converted to the benzoic acid as described for example by A.I. Meyers J.Org.Chem. 40 (1975) 3158-3159.

Intermediates of general formula (III), (IV), (V), (VIII), (IX), (X), (XI), (XIII), (XIV) and (XV) are known or may be prepared by the application or adaptation of known methods.

The following examples illustrate the preparation of compounds of general formula (I) and the following reference examples illustrate the preparation of intermediates of the invention. In the present specification b.p. means boiling point; m.p. means melting point. Where the letters NMR appear the characteristics of the proton nuclear magnetic resonance spectrum follow.

Example 1

Sodium acetate (0.31g) was added with stirring to a mixture of 3-cyclopropyl-1-[3,4-difluoro-2-(methylsulphonyl)phenyl]-2-ethoxymethylene-propane-1,3-dione (1.1g) and hydroxylamine hydrochloride (0.26g) in ethanol. The mixture was stirred for 2.5 hours. The mixture was evaporated to dryness and the residue was suspended in ethyl acetate, washed with water, dried (anhydrous $MgSO_4$) and filtered. The filtrate was evaporated to dryness. The residue was triturated with n-hexane and filtered to give 5-cyclopropyl-4-[3,4-difluoro-2-(methylsulphonyl)benzoyl]isoxazole (compound 1) (0.59g) as an orange solid, m.p.115-118°C.

By proceeding in a similar manner the following compounds of general formula (I) were prepared from the appropriately substituted starting materials.

Cpd No	R	R^1	R^2	R^3	R^4	m.p/NMR
2	H	Cp	SMe	Cl	Cl	83.5-84.5°C
5	H	Cp	SMe	OMe	Br	a
6	H	Cp	SO_2Me	OMe	Br	146.4-146.8°C
10	H	Cp	SMe	OMe	Cl	b
14	H	Cp	SMe	Me	Cl	85-87°C
15	H	Cp	SMe	F	Cl	73-74°C
20	H	Cp	SMe	CO_2Me	CF_3	c
21	H	Cp	SMe	CO_2Me	Cl	d
22	H	Cp	SMe	Cl	Br	93-94°C
27	H	Cp	SMe	Cl	CF_3	89-90°C

Cpd No	R	R1	R2	R3	R4	m.p/NMR
29	H	Cp	SMe	F	Br	e
32	H	Cp	SMe	$C(CH_3)=CH_2$	Cl	140-141.5°C
33	H	Cp	SMe	Me	SMe	103-105°C

Note: Cp = Cyclopropyl

a = ^{1}H NMR ($CDCl_3$): 1.2(m,2H), 1.3(m,2H), 2.4(s,3H), 2.6(m,1H), 4.0(s.3H), 7.0(d,1H), 7.6(d,1H), 8.15(s,1H).

b = ^{1}H NMR ($CDCl_3$): 1.2(m,2H) 1.4(m,2H), 2.4(s,3H), 2.6(m,1H), 4.0(s,3H), 7.05(d,1H), 7.45(d,1H), 8.15(s,1H).

c = ^{1}H NMR ($CDCl_3$): 1.25(m,2H), 1.35(m,2H), 2.4(s,3H), 2.55(m,1H), 4.0(s,3H), 7.5(d,1H), 7.8(d,1H), 8.15(s,1H).

d = ^{1}H NMR ($CDCl_3$): 1.2(m,2H), 1.35(m,2H), 2.4(s,3H), 2.5(m,1H), 4.0(s,3H), 7.35(d,1H), 7.55(d,1H), 8.15(s,1H).

e = ^{1}H NMR ($CDCl_3$): 1.25 (m, 2H), 1.35(m,2H), 2.45(s,3H), 2.65(m,1H), 7.05(d,1H), 7.6(t,1H), 8.15(s,1H).

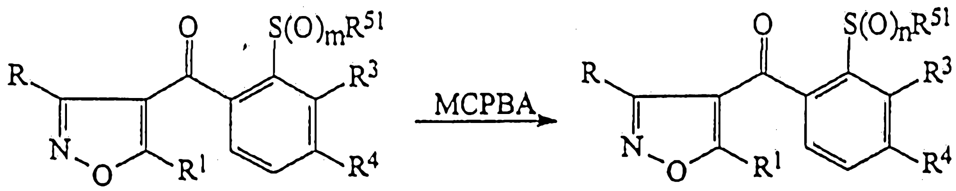
Example 2

A mixture of magnesium (0.17g) and methanol containing approximately 0.1 ml of carbon tetrachloride was heated at reflux for 0.5 hours, cooled and 3-cyclopropyl-1-[3,4-dichloro-2-(methylsulphenyl)phenyl]propane-1,3-dione (2.0g) was added. The mixture was stirred and heated at reflux for 2 hours. It was cooled and evaporated to dryness. The residue was dissolved in dichloromethane and a solution of ethyl chloro-oximidoacetate (1.37g) in dichloromethane was added. The mixture was stirred at room temperature overnight. Hydrochloric acid (2M) was added and the layers were separated. The organic layer was washed with water, dried (anhydrous Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by dry column flash chromatography eluted with a mixture of ethyl acetate and n-hexane (1:9) to give ethyl 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphenyl) benzoyl]isoxazole-3-carboxylate (compound 8) (2.19g) as an orange oil NMR: ($CDCl_3$) 1.15-1.3(m,5H), 1.4(m,2H), 2.4(s,3H), 2.45(m,1H), 4.1(q,2H), 7.2(d,1H), 7.5(d,1H).

Example 3

3-Chloroperoxybenzoic acid (2.0g) was added to a solution of 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphenyl)benzoyl]isoxazole (1.86g) in dichloromethane while maintaining the temperature around -15°C. The mixture was stirred at -15°C for 1 hour and at room temperature for 1 hour. It was recooled to -15°C and filtered. The filtrate was evaporated to dryness and the residue was purified by dry column flash chromatography eluted with a mixture of ethyl acetate and n-hexane. The product was recrystallized from a mixture of ethyl acetate and n-hexane to give 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphinyl)benzoyl]isoxazole (compound 3) (0.3g) as a white solid, m.p. 110-112°C.

By proceeding in a similar manner the following compounds were prepared from the appropriately substituted starting materials:



Cpd No	R	R^1	R^{51}	R^3	R^4	m	n	m.p (^oC) /NMR
4	H	Cp	Me	Cl	Cl	1	2	149-150
7	H	Cp	Me	OMe	Br	0	1	a
9	CO_2Et	Cp	Me	Cl	Cl	0	1	129-130
11	CO_2Et	Cp	Me	Cl	Cl	1	2	106-107.5
12	H	Cp	Me	OMe	Cl	0	1	95-96
13	H	Cp	Me	OMe	Cl	0	2	63-67
16	H	Cp	Me	F	Cl	0	1	136-137
17	H	Cp	Me	F	Cl	0	2	151-152
18	H	Cp	Me	Me	Cl	0	1	115.4-118
19	H	Cp	Me	Me	Cl	0	2	132-134.6
23	H	Cp	Me	Cl	Br	0	1	133-134
24	H	Cp	Me	Cl	Br	0	2	147-148
25	H	Cp	Me	CO_2Me	Cl	0	1	163-164
26	H	Cp	Me	CO_2Me	Cl	0	2	123.4-132
28	H	Cp	Me	Cl	CF_3	0	2	136-137
30	H	Cp	Me	F	Br	0	1	125-126
34	H	Cp	Me	$C(CH_3)=CH_2$	Cr	0	1	215-217
35	H	Cp	Me	$C(CH_3)=CH_2$	Cr	0	2	130-132

Note: Cp = Cyclopropyl

a = ^1H NMR ($CDCl_3$): 1.1-1.4(m,4H), 2.6(m,1H), 3.0(s,3H), 3.95(s,3H), 7.0(d,1H), 7.7(d,1H), 8.1(s,1H).

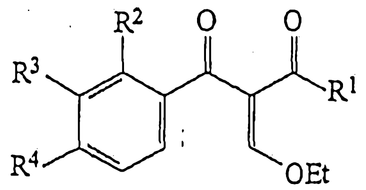
Example 4

Hydrogen peroxide (30%; 1.3 ml) was added dropwise to a solution of 4-[4-bromo-3-fluoro-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole (1.2 g) in a mixture of acetic acid and acetic anhydride. The resultant mixture was heated at 70^oC for 4 hours. It was cooled, poured into water and extracted with ethyl acetate. The organic extract was washed with aqueous sodium bisulphite, aqueous ferrous sulphate and water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was triturated with ether and filtered to give 4-[4-bromo-3-fluoro-2-(methylsulphonyl)-benzoyl]-5-cyclopropylisoxazole (compound 31, 0.85 g) as a white solid, m.p. 144-145°C.

Reference Example 1

A mixture of 3-cyclopropyl-1-[3,4-difluoro-2-(methylsulphonyl) phenyl]propane-1,3-dione (0.85g) and triethyl orthoformate (1.04g) in acetic anhydride was stirred and heated at reflux for 4 hours. It was evaporated to dryness and the residue was treated with toluene and re-evaporated to give 3-cyclopropyl-1-[3,4-difluoro-2-(methylsulphonyl)phenyl]-2-ethoxymethylenepropane-1,3-dione (1.13g) as a brown oil which was not purified further.

By proceeding in a similar manner the following compounds were prepared from the appropriately substituted starting materials;



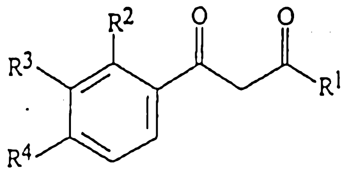
R^1	R^2	R^3	R^4
Cyclopropyl	SMe	Cl	Cl
Cyclopropyl	SMe	OMe	Br
Cyclopropyl	SO_2Me	OMe	Br
Cyclopropyl	SMe	OMe	Cl
Cyclopropyl	SMe	Me	Cl
Cyclopropyl	SMe	F	Cl
Cyclopropyl	SMe	CO_2Me	CF_3
Cyclopropyl	SMe	CO_2Me	Cl

R^1	R^2	R^3	R^4
Cyclopropyl	SMe	Cl	Br
Cyclopropyl	SMe	Cl	CF_3
Cyclopropyl	SMe	F	Br
Cyclopropyl	SMe	$C(CH_3)=CH_2$	Cl
Cyclopropyl	SMe	Me	SMe

Reference Example 2

Magnesium (0.17g) was suspended in methanol containing carbon tetrachloride (approximately 0.1 ml) and the mixture was warmed to initiate the reaction. t-Butyl 3-cyclopropyl-3-oxopropionate (1.32g) was added and the mixture was stirred for 1 hour. The mixture was evaporated to dryness and the residue was dissolved in toluene and re-evaporated. The residue was dissolved in acetonitrile and 3,4-difluoro-2-(methylsulphonyl)benzoyl chloride (1.83g) was added. The mixture was stirred at room temperature for 4 hours and left to stand overnight. The mixture was evaporated to dryness and the residue was partitioned between toluene and hydrochloric acid (2M). The layers were separated and the organic layer was washed with water then dried by azeotropic removal of water. 4-Toluene sulphonic acid (0.5g) was added to the mixture which was heated at reflux for 4 hours. After cooling it was washed with water, dried (anhydrous $MgSO_4$) and filtered. The filtrate was evaporated to dryness to give 3-cyclopropyl-1-[3,4-difluoro-2-(methylsulphonyl)phenyl]propane-1,3-dione (0.86g) as a brown solid which was not purified further.

By proceeding in a similar manner the following compounds were prepared from the appropriately substituted starting materials. In all cases the acetonitrile is replaced by toluene



R^1	R^2	R^3	R^4	m.p/NMR
Cp	SMe	Cl	Cl	57-58.5°C
Cp	SMe	OMe	Br	a
Cp	SO_2Me	OMe	Br	-
Cp	SMe	OMe	Cl	b
Cp	SMe	F	Cl	Not purified further
Cp	SMe	CO_2Me	CF_3	Not purified further
Cp	SMe	CO_2Me	Cl	Not purified further
Cp	SMe	Cl	Br	c
Cp	SMe	Cl	CF_3	Not purified further
Cp	SMe	F	Br	d
Cp	SMe	$C(CH_3)=CH_2$	Cl	61-63°C

Note: Cp = Cyclopropyl

a = NMR ($CDCl_3$): 0.9-1.4(m,4H), 1.7-1.9(m,1H), 2.5(s,3H), 3.95(s,3H), 5.9(s,1H), 7.0(d,1H), 7.4(d,1H).

b = NMR ($CDCl_3$) 0.8-1.4(m,4H), 1.5-1.9(m,1H), 2.45(s,3H), 4.0(s,3H), 6.0(s,1H), 7.15(d,1H), 7.4(d,1H).

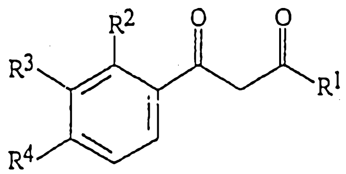
c = NMR ($CDCl_3$): 1.0(m,2H), 1.2(m,2H), 1.75(m,1H), 2.5(s,3H), 5.95(s,1H), 7.2(d,1H), 7.65(d,1H) 15.7-16.1(bs,1H).

d = NMR ($CDCl_3$): 1.0(m,2H), 1.25(m,2H), 1.75(m,1H), 2.5(s,3H), 6.0(s,1H), 7.2(d,1H) 7.55(dd,1H) 15.7-16.0(bs,1H).

Reference Example 3

A mixture of methyl 4-chloro-3-methyl-2-(methylsulphenyl)benzoate (19.5g) and cyclopropyl methyl ketone (13.4 g) in dry tetrahydrofuran was added to a stirred heated suspension of sodium hydride (80% oil dispersion, 4.8 g) in dry tetrahydrofuran. The mixture was stirred and heated at reflux for 2 hours. It was cooled and hydrochloric acid (2ml) was added. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water, saturated aqueous sodium bicarbonate, water, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give 1-[4-chloro-3-methyl-2-(methylsulphenyl)phenyl]-3-cyclopropylpropan-1,3-dione (20.19 g) as a yellow oil, NMR($CDCl_3$) 0.9(m,2H), 1.2 (m,2H), 1.7(m,1H), 2.3(s,3H), 2.65(s,3H), 5,85 (s,1H), 7.15(d,1H), 7.3(d,1H), 15.7-16.0(bs,1H).

By proceeding in a similar manner the following compound was prepared from the appropriately substituted starting material;



R^1	R^2	R^3	R^4	m.p/NMR
Cp	SMe	Me	SMe	a

a = NMR ($CDCl_3$) 1.0(m,2H), 1.2(m,2H), 1.75(m,1H), 2.3(s,3H), 2.5(s,3H), 2.6(s,3H), 6.0(s,1H), 7.1(d,1H), 7.3(d,1H), 15.8-16.1(bs,1H)

Benzoyl chlorides were prepared by heating the appropriately substituted benzoic acids at reflux with thionyl chloride for 3 hours. The excess thionyl chloride was removed by evaporation and the benzoyl chlorides were used directly without further purification.

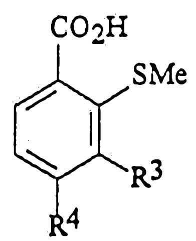
Reference Example 4

Hydrogen peroxide (11ml) was added with stirring to a cooled solution of 3,4-difluoro-2-(methylsulphenyl)benzoic acid (3.0g) and acetic anhydride (2.1ml) in acetic acid while maintaining the temperature below 5°C. The mixture was stirred at 0°C for 0.5 hours then warmed to room temperature. Further acetic acid was added and the mixture was stirred at room temperature for 0.5 hours and at 65°C for 2.5 hours. After cooling to room temperature water was added and the mixture was extracted with ethyl acetate, washed with water, aqueous ferrous sulphate solution and water, dried (anhydrous $MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was recrystallised from a mixture of cyclohexane and ether to give 3,4-difluoro-2-(methylsulphonyl)benzoic acid (2.0g) as a white solid, m.p. 194°C.

Reference Example 5

n-Butyllithium (2.5m in hexane, 35ml) was added with cooling to a solution of 3,4-difluorobenzoic acid (5.5g) in dry tetrahydrofuran while maintaining the temperature below -70°C. The mixture was stirred for 2 hours at -70°C. A solution of dimethyl disulphide (19.8g) in tetrahydrofuran was added and the mixture was stirred at -70°C for 1.5 hours. It was allowed to warm to room temperature, diluted with ether and washed with water. The aqueous layer was acidified to pH 1 and extracted with ether, washed with water, dried (anhydrous $MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was recrystallised from a mixture of cyclohexane and ether to give 3,4-difluoro-2-(methylsulphenyl)benzoic acid (5.9g) as a white solid, m.p. 149.2-149.6°C.

By proceeding in a similar manner the following compounds were prepared from the appropriately substituted starting materials;



R^3	R^4	Reaction temp	m.p.
F	Cl	-40°C	145-146°C
Cl	CF_3	-40°C	97-100°C

Reference Example 6

A solution of sodium nitrite (4.53g) in water was added to a stirred suspension of 3,4-dichloroanthranillic acid (15g) in acetic acid and concentrated hydrochloric acid while maintaining the temperature below 5°C. The mixture was stirred at below 5°C for 2 hours then poured into a solution of dimethyl disulphide (8.4g) and copper powder (0.1g) in acetic acid. The mixture was stirred at room temperature for 1 hour and poured into water. The solid was filtered off, dried and recrystallized from cyclohexane to give 3,4-dichloro-2-(methylsulphenyl)benzoic acid (12.02g) as a pale yellow solid, NMR (DMSO - D_6) 2.4(s,3H), 7.5(d,1H), 7.7(d,1H), 13.5(bs,1H).

Reference Example 7

A solution of potassium hydroxide (2.0g) in water was added to a solution of ethyl 4-bromo-3-methoxy-2-(methylsulphenyl)benzoate (4.5g) in ethanol. The resulting solution was stirred and heated at reflux for 3 hours. After cooling, the mixture was evaporated to dryness and the residue was dissolved in water and washed with ethyl acetate. The aqueous solution was acidified to pH 1 and extracted with ethyl acetate, dried (anhydrous $MgSO_4$) and filtered. The filtrate was evaporated to dryness to give 4-bromo-3-methoxy-2-(methylsulphenyl)benzoic acid as a white solid, NMR ($CDCl_3$) 2.5(s,3H), 3.9(s,3H), 7.4(s,2H), 10.9(bs,1H).

By proceeding in a similar manner the following compound was prepared from the appropriately substituted starting material:

4-Bromo-3-methoxy-2-(methylsulphonyl)benzoic acid NMR ($CDCl_3$) 3.3(s,3H), 4.1(s,3H), 7.1(d,1H), 7.75(d,1H), 8.2(bs,1H).

Reference Example 8

A solution of methanethiol (47ml) in dimethyl formamide was added to a mixture of ethyl 2,4-dibromo-3-methoxybenzoate (105g) and potassium carbonate (131g) in dimethyl formamide and the resultant suspension was stirred at room temperature overnight. Water was added and the mixture was extracted into ether, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by column chromatography eluted with a mixture of ethyl acetate and cyclohexane to give as the minor component ethyl 4-bromo-3-methoxy-2-(methylsulphenyl)-benzoate (4.5g) as a white solid, NMR ($CDCl_3$) 1.5(t,3H), 2.6(s,3H), 4.05(s,3H), 4.5(q,2H), 7.35 (m,2H).

Reference Example 9

Hydrogen peroxide (11.3ml) was added to a cooled solution of ethyl 4-bromo-3-methoxy-2-(methylsulphenyl)benzoate (3.7g) and acetic anhydride (2.0ml) in acetic acid at $0^{o}C$. The mixture was stirred at $0^{o}C$ for 1 hour then warmed to room temperature and heated at $85^{o}C$ for 3 hours. After cooling to room temperature the mixture was diluted with ethyl acetate and washed with water, aqueous ferrous sulphate solution, water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give ethyl 4-bromo-3-methoxy-2-(methylsulphonyl)benzoate (3.6g) as a yellow oil, NMR ($CDCl_3$) 1.6(t,3H), 3.5(s,3H), 4.3(s,3H), 4.55(q,2H), 7.2(d,1H), 7.95(d,1H).

Reference Example 10

A mixture of 2-[4-chloro-3-methoxy-2-(methylsulphenyl)phenyl]-4,4-dimethyloxazoline (9.0g) and hydrochloric acid (5M) was stirred and heated at reflux for 5 hours. After cooling, the mixture was diluted with water and extracted with dichloromethane. It was dried ($MgSO_4$) filtered and the filtrate was evaporated to dryness to give 4-chloro-3-methoxy-2-(methylsulphenyl) benzoic acid as a white solid, m.p. 98-99°C.

Reference Example 11

n-Butyllithium (2.5M in hexane, 54ml) was added with cooling to a stirred solution of 2-(4-chloro-3-methoxyphenyl)-4,4-dimethyloxazoline (27.0g) in tetrahydrofuran while maintaining the temperature below -40°C. The mixture was stirred at -78°C overnight. A solution of dimethyl disulphide (26.5g) in tetrahydrofuran was added dropwise and the mixture was stirred at -40°C overnight. After allowing to warm to room temperature the mixture was treated with hydrochloric acid (2M). The organic layer was washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by dry column flash chromatography eluted with a mixture of ethyl acetate and n-hexane to give 2-[4-chloro-3-methoxy-2-(methylsulphenyl) phenyl]-4,4-dimethyloxazoline (11.1g) as a white solid, m.p. 50-52°C.

Reference Example 12

n-Butyllithium (2.5M in hexane, 63ml) was added to a solution of diisopropylamine in dry tetrahydrofuran while maintaining the temperature at 0°C. Once addition was complete the cooling bath was removed and the mixture stirred for 30 minutes at room temperature. The resulting solution of lithium di-isopropylamide (LDA) was then added to a solution of 4-bromo-3-fluorobenzoic acid (14.6g) in tetrahydrofuran while maintaining the temperature at -50°C. The mixture was then stirred for 5 hours at -30°C. A solution of dimethyl disulphide (21g) in tetrahydrofuran was then added and the cooling bath was removed and the mixture allowed to stir at room temperature overnight. The mixture was diluted with ether and washed with water. The aqueous layer was acidified to pH 1 with 2M hydrochloric acid and extracted with ether, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue triturated with petroleum spirit (b.p. 60-80°C) to give 4-bromo-3-fluoro-2-(methylsulphenyl)benzoic acid (14g) as a white solid, m.p. 152-154°C.

By proceeding in a similar manner from the appropriately substituted starting material 4-bromo-3-chloro-2-(methylsulphenyl)benzoic acid was prepared, m.p. 126-129°C.

Reference Example 13

A solution of 4-bromo-3-fluorotoluene (35g) and sodium hydroxide (7.7g) in pyridine and water was stirred and heated to reflux. Potassium permanganate (123g) was added to the mixture over 2 hours. The resulting suspension was heated at reflux for a further 3 hours. The mixture was filtered hot through hyflo. The hyflo was washed with boiling water, followed by ethyl acetate. The cooled aqueous layer was acidified to pH 1 with concentrated hydrochloric aci and extracted with ethyl acetate. The organic extract was washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue triturated with petroleum spirit (bp 60-80°C) to give 4-bromo-3-fluorobenzoic acid as a white solid (21.25g), m.p. 213-215°C.

Reference Example 14

Lithium hydroxide monohydrate (1.87 g) was added to a solution of methyl 3-methoxycarbonyl-2-(methylsulphenyl)-4-trifluoromethylbenzoate (13.71 g) in methanol and water. The mixture was stirred at room temperature overnight and the methanol was removed by evaporation. The residual aqueous solution was acidified to pH 1 and extracted with ether, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give 3-methoxycarbonyl-2-(methylsulphenyl)-4-trifluoromethylbenzoic acid (10.85 g) as an off-white solid, NMR ($CDCl_3$) 2.45(s, 3H), 3.95(s,3H), 5.45-6.1(bs,1H), 7.2(d,1H), 7.95(d,1H).

By proceeding in a similar manner the following compound was prepared from the appropriately substituted starting material:

4-chloro-3-methoxycarbonyl-2-(methylsulphenyl)benzoic acid, NMR ($CDCl_3$) 2.5 (s,3H), 4.0 (s, 3H), 7.55(d,1H), 8.0(d,1H).

__Reference Example 15__

Sodium thiomethoxide (6.83 g) was added to a solution of methyl 2-fluoro-3-methoxycarbonyl-4-trifluoromethylbenzoate (24.85 g) in xylene. After stirring for 0.5 hours lithium hydroxide monohydrate (4.10 g) was added and the mixture was stirred for 48 hours. Hydrochloric acid (2M) was added. It was extracted with ether, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was triturated with cyclohexane. The solid was filtered off and the filtrate was evaporated to dryness to give methyl 3-methoxycarbonyl-2-(methylsulphenyl)-4-trifluoromethylbenzoate (13.71g) as a yellow oil NMR ($CDCl_3$) 2.4(s,3H), 3.95 (s,6H), 7.65 (s,2H).

By proceeding in a similar manner methyl 4-chloro-3-methoxycarbonyl-2-(methylsulphenyl)benzoate was prepared from the appropriately substituted starting material.

__Reference Example 16__

A solution of 2-fluoro-3-methoxycarbonyl-4-trifluoromethylbenzoic acid (23.43 g) in thionyl chloride was stirred and heated at reflux for 2 hours, cooled and evaporated to dryness. The residue was dissolved in methanol and the resultant solution was stirred and heated at reflux overnight. It was cooled and evaporated to dryness. The residue was purified by chromatography eluted with a mixture of ether and cyclohexane to give methyl 2-fluoro-3-methoxycarbonyl-4-trifluoromethylbenzoate (25.85 g) as a yellow oil, NMR ($CDCl_3$) 4.0(s, 6H), 7.55(d,1H), 8.15(t,1H).

By proceeding in a similar manner the following compounds were prepared from the appropriately substituted starting material:

methyl 4-chloro-2-fluoro-3-methoxycarbonylbenzoate NMR ($CDCl_3$) 3.9(s,3H), 4.0(s,3H), 7.3(d,1H), 7.95(t,1H);

methyl 4-chloro-2-fluoro-3-methylbenzoate NMR ($CDCl_3$) 2.35(d,3H), 3.95(s,3H), 7.2(d,1H) 7.7(t.1H);

methyl 4-chloro-2-fluoro-3-isopropenylbenzoate NMR ($CDCl_3$) 2.1(s,3H), 3.95(s,3H), 5.0(s,1H) 5.45(s,1H) 7.3(d,1H) 7.8(t,1H).

Reference Example 17

A solution of lithium diisopropyl amide in dry tetrahydrofuran (prepared from diisopropylamine (17.0 ml) and n-butylithium (48.4 ml) in dry tetrahydrofuran)was added to a solution of methyl 2-fluoro-6-trifluoromethylbenzoate (22.39 g) in dry tetrahydrofuran while maintaining the temperature below -70^{o}C. The mixture was stirred at -78^{o}C for 3 hours. The solution was poured onto solid carbon dioxide pellets and stirred until it had warmed to room temperature. The mixture was evaporated and treated with hydrochloric acid (2M). It was extracted with ether, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give 2-fluoro-3-methoxycarbonyl-4-trifluoromethylbenzoic acid (24.43 g) as an off-white solid NMR ($CDCl_3$) 3.95(s,3H), 7.55(d,1H), 8.15(t,1H).

By proceeding in a similar manner the following compound was prepared from the appropriately substituted starting material:

4-chloro-2-fluoro-3-methoxycarbonylbenzoic acid NMR ($CDCl_3$) 4.0(s,3H), 7.4(d,1H), 8.1(t,1H).

Reference Example 18

Potassium carbonate (48.37 g) was added to a solution of methanethiol (16.84 g) in dry dimethyl formamide. Methyl 4-chloro-2-fluoro-3-methylbenzoate (35.45 g) was added to the resulting suspension. The mixture was stirred for 60 hours. It was poured into water, extracted with ether, washed with water, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was separated by chromatography eluted with a mixture of ether and hexane to give methyl 4-chloro-3-methyl-2-(methylsulphenyl)benzoate (19.53 g) as a clear oil, NMR ($CDCl_3$) 2.35(s,3H), 2.7(s,3H), 3.95(s,3H), 7.25(d,1H), 7.4(d,1H), and methyl 3-methyl-2, 4-bis(methylsulphenyl)benzoate (9.29 g) as a yellow solid NMR ($CDCl_3$) 2.3 (s,3H), 2.5 (s,3H), 2.6 (s,3H), 3.95 (s,3H), 7.1 (d,1H), 7.4 (d,1H).

Reference Example 19

n-Butyllithium (2.5 M in hexane, 100 ml) was added to a cooled solution of 2-chloro-6-fluorotoluene (36.1 g) in dry tetrahydrofuran while maintaining the temperature below -60^{o}C. The mixture was stirred at -78^{o}C overnight then poured onto solid carbon dioxide pellets. The mixture was stirred and allowed to warm to room temperature. It was acidified to pH 1 and extracted with ether. The organic layer was extracted into aqueous sodium hydroxide solution (2M) and water. The combined aqueous extracts were acidified to pH 1 and the solid formed was filtered off and washed with water and n-hexane to give 4-chloro-2-fluoro-3-methylbenzoic acid (40.35 g) as a white solid, NMR (DMSO-d_6) 2.3(d,3H), 7.4(d,1H) 7.7(t,1H).

By proceeding in a similar manner the following compound was prepared from the appropriately substituted starting material:

4-chloro-2-fluoro-3-isopropenylbenzoic acid m.p. 201-202°C.

Reference Example 20

A solution of sodium hydroxide (7.0 g) in water was added to methyl 4-chloro-3-isopropenyl-2-(methylsulphenyl)benzoate (7.3 g) and the resulting mixture was heated at reflux for 2 hours. Ethanol was added and the mixture was heated at reflux for 1 hour. The ethanol was removed by evaporation and the aqueous residue was acidified to pH 1. It was extracted with ethyl acetate, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give 4-chloro-3-isopropenyl-2-(methylsulphenyl)benzoic acid (6.15 g) NMR ($CDCl_3$) 2.05 (s,3H), 2.4 (s,3H), 4.85 (s,1H), 5.35 (s,1H), 7.45 (d,1H), 7.85 (d,1H).

Reference Example 21

A mixture of methyl 4-chloro-2-fluoro-3-isopropenylbenzoate (8.6 g) and sodium thiomethoxide (3.15 g) in dimethyl formamide was heated at 50°C for 3 hours and stirred at room temperature overnight. Ether was added and the mixture was washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography eluted with a mixture of ethyl acetate and hexane to give methyl 4-chloro-3-isopropenyl-2-(methylsulphenyl)benzoate (5.95 g) as a clear oil NMR ($CDCl_3$) 2.1(s,3H), 2.35(s,3H), 3.95(s,3H), 4.9(s,1H), 5.4(s,1H), 7.45(s,2H).

Reference Example 22

A mixture of 2-(2-chloro-6-fluorophenyl)propan-2-ol (19.0g), concentrated sulphuric acid and water was heated at reflux for 2 hours. It was cooled and extracted with ether, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography eluted with hexane to give 2-(2-chloro-6-fluorophenyl)-propene (11.6 g) as a clear oil, NMR ($CDCl_3$) 1.95(s,3H) 4.95(s,1H), 5.85(s,1H), 6.85-7.0(m,1H), 7.05-7.2(m,2H).

Reference Example 23

A solution of methyl 2-chloro-6-fluorobenzoate (40.0g) in ether was added to a solution of methyl magnesium iodide in ether (prepared from methyl iodide (120.0g) and magnesium turnings (20.6g) in ether). The resulting solution was stirred and heated at reflux for 5 hours, poured onto a mixture of ice and concentrated sulphuric acid and the layers separated. The organic layer was washed with water, saturated aqueous sodium bisulphite, water, dried (anhydrous magnesium sulphate) and filtered. The filtrate was evaporated to dryness to give 2-(2-chloro-6-fluorophenyl)propan-2-ol (36.8g) as an orange oil, NMR ($CDCl_3$) 1.8(d,6H), 3.5-3.7(bs,1H), 6.9-7.05(m,1H), 7.1-7.25(m,2H).

According to a feature of the present invention, there is provided a method for controlling the growth of weeds (i.e. undesired vegetation) at a locus which comprises applying to the locus a herbicidally effective amount of at least one isoxazole derivative of general formula (I). For this purpose, the isoxazole derivatives are normally used in the form of herbicidal compositions (i.e. in association with compatible diluents or carriers and/or surface active agents suitable for use in herbicidal compositions), for example as hereinafter described.

The compounds of general formula (I) show herbicidal activity against dicotyledonous (i.e. broad-leafed) and monocotyledonous (i.e. grass) weeds by pre- and/or post-emergence application.

By the term "pre-emergence application" is meant application to the soil in which the weed seeds or seedlings are present before emergence of the weeds above the surface of the soil. By the term "post-emergence application" is meant application to the aerial or exposed portions of the weeds which have emerged above the surface of the soil. For example, the compounds of general formula (I) may be used to control the growth of:

broad-leafed weeds, for example, Abutilon theophrasti, Amaranthus retroflexus, Bidens pilosa, Chenopodium album, Galium aparine, Ipomoea spp. e.g. Ipomoea purpurea, Sesbania exaltata, Sinapis arvensis, Solanum nigrum and Xanthium strumarium, and

grass weeds, for example Alopecurus myosuroides, Avena fatua, Digitaria sanguinalis, Echinochloa crus-galli, Sorghum bicolor, Eleusine indica and Setaria spp, e.g. Setaria faberii or Setaria viridis, and

sedges, for example, Cyperus esculentus.

The amounts of compounds of general formula (I) applied vary with the nature of the weeds, the compositions used, the time of application, the climatic and edaphic conditions and (when used to control the growth of weeds in crop-growing areas) the nature of the crops. When applied to a crop-growing area, the rate of application should be sufficient to control the growth of weeds without causing substantial permanent damage to the crop. In general, taking these factors into account, application rates between 0.01kg and 5kg of active material per hectare give good results. However, it is to be understood that higher or lower application rates may be used, depending upon the particular problem of weed control encountered.

The compounds of general formula (I) may be used to control selectively the growth of weeds, for example to control the growth of those species hereinbefore mentioned, by pre- or post-emergence application in a directional or non-directional fashion, e.g. by directional or non-directional spraying, to a locus of weed infestation which is an area used, or to be used, for growing crops, for example cereals, e.g. wheat, barley, oats, maize and rice, soya beans, field and dwarf beans, peas, lucerne, cotton, peanuts, flax, onions, carrots, cabbage, oilseed rape, sunflower, sugar beet, and permanent or sown grassland before or after sowing of the crop or before or after emergence of the crop. For the selective control of weeds at a locus of weed infestation which is an area used, or to be used, for growing of crops, e.g. the crops hereinbefore mentioned, application rates between 0.01kg and 4.0kg, and preferably between 0.01kg and 2.0kg, of active material per hectare are particularly suitable.

The compounds of general formula (I) may also be used to control the growth of weeds, especially those indicated above, by pre- or post-emergence application in established orchards and other tree-growing areas, for example forests, woods and parks, and plantations, e.g. sugar cane, oil palm and rubber plantations. For this purpose they may be applied in a directional or non-directional fashion (e.g. by directional or non-directional spraying) to the weeds or to the soil in which they are expected to appear, before or after planting of the trees or plantations at application rates between 0.25kg and 5.0kg, and preferably between 0.5kg and 4.0kg of active material per hectare.

The compounds of general formula (I) may also be used to control the growth of weeds, especially those indicated above, at loci which are not crop-growing areas but in which the control of weeds is nevertheless desirable.

Examples of such non-crop-growing areas include airfields, industrial sites, railways, roadside verges, the verges of rivers, irrigation and other waterways, scrublands and fallow or uncultivated land, in particular where it is desired to control the growth of weeds in order to reduce fire risks. When used for such purposes in which a total herbicidal effect is frequently desired, the active compounds are normally applied at dosage rates higher than those used in crop-growing areas as hereinbefore described. The precise dosage will depend upon the nature of the vegetation treated and the effect sought.

Pre- or post-emergence application, and preferably pre-emergence application, in a directional or non-directional fashion (e.g. by directional or non-directional spraying) at application rates between 1.0kg and 20.0kg, and preferably between 5.0 and 10.0kg, of active material per hectare are particularly suitable for this purpose.

When used to control the growth of weeds by pre-emergence application, the compounds of general formula (I) may be incorporated into the soil in which the weeds are expected to emerge. It will be appreciated that when the compounds of general formula (I) are used to control the growth of weeds by post-emergence application, i.e. by application to the aerial or exposed portions of emerged weeds, the compounds of general formula (I) will also normally come into contact with the soil and may also then exercise a pre-emergence control on later-germinating weeds in the soil.

Where especially prolonged weed control is required, the application of the compounds of general formula (I) may be repeated if required.

According to a further feature of the present invention, there are provided compositions suitable for herbicidal use comprising one or more of the isoxazole derivatives of general formula (I), in association with, and preferably homogeneously dispersed in, one or more compatible agriculturally- acceptable diluents or carriers and/or surface active agents [i.e. diluents or carriers and/or surface active agents of the type generally accepted in the art as being suitable for use in herbicidal compositions and which are compatible with compounds of general formula (I)]. The term "homogeneously dispersed" is used to include compositions in which the compounds of general formula (I) are dissolved in other components. The term "herbicidal compositions" is used in a broad sense to include not only compositions which are ready for use as herbicides but also concentrates which must be diluted before use. Preferably, the compositions contain from 0.05 to 90% by weight of one or more compounds of general formula (I).

The herbicidal compositions may contain both a diluent or carrier and surface-active (e.g. wetting, dispersing, or emulsifying) agent. Surface-active agents which may be present in herbicidal compositions of the present invention may be of the ionic or non-ionic types, for example sulphoricinoleates, quaternary ammonium derivatives, products based on condensates of ethylene oxide with alkyl and polyaryl phenols, e.g. nonyl- or octyl-phenols, or carboxylic acid esters of anhydrosorbitols which have been rendered soluble by etherification of the free hydroxy groups by condensation with ethylene oxide, alkali and alkaline earth metal salts of sulphuric acid esters and sulphonic acids such as dinonyl- and dioctyl-sodium sulphonosuccinates and alkali and alkaline earth metal salts of high molecular weight sulphonic acid derivatives such as sodium and calcium lignosulphonates and sodium and calcium alkylbenzene sulphonates.

Suitably, the herbicidal compositions according to the present invention may comprise up to 10% by weight, e.g. from 0.05% to 10% by weight, of surface-active agent but, if desired, herbicidal compositions according to the present invention may comprise higher proportions of surface-active agent, for example up to 15% by weight in liquid emulsifiable suspension concentrates and up to 25% by weight in liquid water soluble concentrates.

Examples of suitable solid diluents or carriers are aluminium silicate, talc, calcined magnesia, kieselguhr, tricalcium phosphate, powdered cork, adsorbent carbon black and clays such as kaolin and bentonite. The solid compositions (which may take the form of dusts, granules or wettable powders) are preferably prepared by grinding the compounds of general formula (I) with solid diluents or by impregnating the solid diluents or carriers with solutions of the compounds of general formula (I) in volatile solvents, evaporating the solvents and, if necessary, grinding the products so as to obtain powders. Granular formulations may be prepared by absorbing the compounds of general formula (I) (dissolved in suitable solvents, which may, if desired, be volatile) onto the solid diluents or carriers in granular form and, if desired, evaporating the solvents, or by granulating compositions in powder form obtained as described above. Solid herbicidal compositions, particularly wettable powders and granules, may contain wetting or dispersing agents (for example of the types described above), which may also, when solid, serve as diluents or carriers.

Liquid compositions according to the invention may take the form of aqueous, organic or aqueous-organic solutions, suspensions and emulsions which may incorporate a surface-active agent. Suitable liquid diluents for incorporation in the liquid compositions include water, glycols, tetrahydrofurfuryl alcohol, acetophenone, cyclohexanone, isophorone, toluene, xylene, mineral, animal and vegetable oils and light aromatic and naphthenic fractions of petroleum (and mixtures of these diluents). Surface-active agents, which may be present in the liquid compositions, may be ionic or non-ionic (for example of the types described above) and may, when liquid, also serve as diluents or carriers.

Powders, dispersible granules and liquid compositions in the form of concentrates may be diluted with water or other suitable diluents, for example mineral or vegetable oils, particularly in the case of liquid concentrates in which the diluent or carrier is an oil, to give compositions ready for use.

When desired, liquid compositions of the compound of general formula (I) may be used in the form of self-emulsifying concentrates containing the active substances dissolved in the emulsifying agents or in solvents containing emulsifying agents compatible with the active substances, the simple addition of water to such concentrates producing compositions ready for use.

Liquid concentrates in which the diluent or carrier is an oil may be used without further dilution using the electrostatic spray technique.

Herbicidal compositions according to the present invention may also contain, if desired, conventional adjuvants such as adhesives, protective colloids, thickeners, penetrating agents, stabilisers, sequestering agents, anti-caking agents, colour[illegible]gents and corrosion inhibitors. These adjuvants may also serve as carriers [illegible]uents.

Unless otherwise specified, the following percentages are by weight. Preferred herbicidal compositions according to the present invention are

aqueous suspension concentrates which comprise from 10 to 70% of one or more compounds of general formula (I), from 2 to 10% of surface-active agent, from 0.1 to 5% of thickener and from 15 to 87.9% of water;

wettable powders which comprise from 10 to 90% of one or more compounds of general formula (I), from 2 to 10% of surface-active agent and from 8 to 88% of solid diluent or carrier;

water soluble or water dispersible powders which comprise from 10 to 90% of one or more compounds of general formula (I), from 2 to 40% of sodium carbonate and from 0 to 88% of solid diluent;

liquid water soluble concentrates which comprise from 5 to 50%, e.g. 10 to 30%, of one or more compounds of general formula (I), from 5 to 25% of surface-active agent and from 25 to 90%, e.g. 45 to 85%, of water miscible solvent, e.g. dimethylformamide, or a mixture of water-miscible solvent and water;

liquid emulsifiable suspension concentrates which comprise from 10 to 70% of one or more compounds of general formula (I), from 5 to 15% of surface-active agent, from 0.1 to 5% of thickener and from 10 to 84.9% of organic solvent;

granules which comprise from 1 to 90%, e.g. 2 to 10% of one or more compounds of general formula (I), from 0.5 to 7%, e.g. 0.5 to 2%, of surface-active agent and from 3 to 98.5%, e.g. 88 to 97.5%, of granular carrier and

emulsifiable concentrates which comprise 0.05 to 90%, and preferably from 1 to 60% of one or more compounds of general formula (I), from 0.01 to 10%, and preferably from 1 to 10%, of surface-active agent and from 9.99 to 99.94%, and preferably from 39 to 98.99%, of organic solvent.

Herbicidal compositions according to the present invention may also comprise the compounds of general formula (I) in association with, and preferably homogeneously dispersed in, one or more other pesticidally active compounds and, if desired, one or more compatible pesticidally acceptable diluents or carriers, surface-active agents and conventional adjuvants as hereinbefore described. Examples of other pesticidally active compounds which may be included in, or used in conjunction with, the herbicidal compositions of the present invention include herbicides, for example to increase the range of weed species controlled for example alachlor [2-chloro-2,6'-diethyl-N-(methoxy-methyl)-acetanilide], atrazine [2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine], bromoxynil [3,5-dibromo-4-hydroxybenzonitrile], chlortoluron [N'-(3-chloro-4-methylphenyl)-N,N-dimethylurea], cyanazine [2-chloro-4-(1-cyano-1- methylethylamino)-6-ethylamino-1,3,5-triazine], 2,4-D [2,4-dichlorophenoxy-acetic acid], dicamba [3,6-dichloro-2-methoxybenzoic acid], difenzoquat [1,2- dimethyl-3,5-diphenyl-pyrazolium salts], flampropmethyl [methyl N-2-(N- benzoyl-3-chloro-4-fluoroanilino)-propionate], fluometuron [N'-(3-trifluoro- methylphenyl)-N,N-dimethylurea], isoproturon [N'-(4-isopropylphenyl)-N,N-dimethylurea], insecticides, e.g. synthetic pyrethroids, e.g. permethrin and cypermethrin, and fungicides, e.g. carbamates, e.g. methyl N-(1-butyl-carbamoyl- benzimidazol-2-yl)carbamate, and triazoles e.g. 1-(4-chloro-phenoxy)-3,3- dimethyl-1-(1,2,4-triazol-1-yl)-butan-2-one.

Pesticidally active compounds and other biologically active materials which may be included in, or used in conjunction with, the herbicidal compositions of the present invention, for example those hereinbefore mentioned, and which are acids, may, if desired, be utilized in the form of conventional derivatives,.for example alkali metal and amine salts and esters.

According to a further feature of the present invention there is provided an article of manufacture comprising at least one of the isoxazole derivatives of general formula (I) or, as is preferred, a herbicidal composition as hereinbefore described, and preferably a herbicidal concentrate which must be diluted before use, comprising at least one of the isoxazole derivatives of general formula (I) within a container for the aforesaid derivative or derivatives of general formula (I), or a said herbicidal composition, and instructions physically associated with the aforesaid container setting out the manner in which the aforesaid derivative or derivatives of general formula (I) or herbicidal composition contained therein is to be used to control the growth of weeds. The containers will normally be of the types conventionally used for the storage of chemical substances which are solid at normal ambient temperatures and herbicidal compositions particularly in the form of concentrates, for example cans and drums of metal, which may be internally lacquered, and plastics materials, bottles or glass and plastics materials and, when the contents of the container is a solid, for example granular, herbicidal compositions, boxes, for example of cardboard, plastics materials and metal, or sacks. The containers will normally be of sufficient capacity to contain amounts of the isoxazole derivative or herbicidal compositions sufficient to treat at least one acre of ground to control the growth of weeds therein but will not exceed a size which is convenient for conventional methods of handling. The instructions will be physically associated with the container, for example by being printed directly thereon or on a label or tag affixed thereto. The directions will normally indicate that the contents of the container, after dilution if necessary, are to be applied to control the growth of weeds at rates of application between 0.01kg and 20kg of active material per hectare in the manner and for the purposes hereinbefore described.

The following Examples illustrate herbicidal compositions according to the present invention:

EXAMPLE C1

A soluble concentrate is formed from :

Active ingredient (compound 1)	20% w/v
Potassium hydroxide solution 33% w/v	10% v/v
Tetrahydrofurfuryl alcohol (THFA)	10% v/v
Water	to 100 volumes.

by stirring THFA, active ingredient (compound 1) and 90% volume of water and slowly adding the potassium hydroxide solution until a steady pH 7-8 is obtained then making up to volume with water.

Similar soluble concentrates may be prepared as described above by replacing the isoxazole (compound 1) with other compounds of general formula (I).

EXAMPLE C2

A wettable powder is formed from :

Active ingredient (compound 1)	50%	w/w
Sodium dodecylbenzene sulphonate	3%	w/w
Sodium lignosulphate	5%	w/w
Sodium formaldehyde alkylnaphthalene sulphonate	2%	w/w
Microfine silicon dioxide	3%	w/w and
China clay	37%	w/w

by blending the above ingredients together and grinding the mixture in an air jet mill.

Similar wettable powders may be prepared as described above by replacing the isoxazole (compound 1) with other compounds of general formula (I).

EXAMPLE C3

A water soluble powder is formed from :

Active ingredient (compound 1)	50%	w/w
Sodium dodecylbenzenesulphonate	1%	w/w
Microfine silicon dioxide	2%	w/w
Sodium bicarbonate	47%	w/w

by mixing the above ingredients and grinding the above mixture in a hammer mill.

Similar water soluble powders may be prepared as described above by replacing the isoxazole (compound 1) with other compounds of general formula (I).

The compounds of the invention have been used in herbicidal applications according to the following procedures.

METHOD OF USE OF HERBICIDAL COMPOUNDS:

a) General

Appropriate quantities of the compounds used to treat the plants were dissolved in acetone to give solutions equivalent to application rates of up to 4000g test compound per hectare (g/ha). These solutions were applied from a standard laboratory herbicide sprayer delivering the equivalent of 290 litres of spray fluid per hectare.

b) Weed control : Pre-emergence

The seeds were sown in 70 mm square, 75 mm deep plastic pots in non-sterile soil . The quantities of seed per pot were as follows:-

Weed species	Approx number of seeds/pot
1) Broad-leafed weeds	
Abutilon theophrasti	10
Amaranthus retroflexus	20
Galium aparine	10
Ipomoea purpurea	10
Sinapis arvensis	15
Xanthium strumarium	2.
2) Grass weeds	
Alopecurus myosuroides	15
Avena fatua	10
Echinochloa crus-galli	15
Setaria viridis	20.
3) Sedges	
Cyperus esculentus	3.

Crop	
1) Broad-leafed	
Cotton	3
Soya	3.

2) Grass	Approx number of seeds/pot
Maize	2
Rice	6
Wheat	6.

The compounds of the invention were applied to the soil surface, containing the seeds, as described in (a). A single pot of each crop and each weed was allocated to each treatment, with unsprayed controls and controls sprayed with acetone alone.

After treatment the pots were placed on capillary matting kept in a glass house, and watered overhead . Visual assessment of crop damage was made 20-24 days after spraying. The results were expressed as the percentage reduction in growth or damage to the crop or weeds, in comparison with the plants in the control pots.

c) Weed control : Post-emergence

The weeds and crops were sown directly into John Innes potting compost in 75 mm deep, 70 mm square pots except for Amaranthus which was pricked out at the seedling stage and transferred to the pots one week before spraying. The plants were then grown in the greenhouse until ready for spraying with the compounds used to treat the plants. The number of plants per pot were as follows :-

1) Broad leafed weeds

Weed species	Number of plants per pot	Growth stage
Abutilon theophrasti	3	1-2 leaves
Amaranthus retroflexus	4	1-2 leaves
Galium aparine	3	1st whorl
Ipomoea purpurea	3	1-2 leaves
Sinapis arvensis	4	2 leaves
Xanthium strumarium	1	2-3 leaves.

2) Grass weeds

Weed species	Number of plants per pot	Growth stage
Alopecurus myosuroides	8-12	1-2 leaves
Avena fatua	12-18	1-2 leaves
Echinochloa crus-galli	4	2-3 leaves
Setaria viridis	15-25	1-2 leaves.

3) Sedges

Weed species	Number of plants per pot	Growth stage
Cyperus esculentus	3	3 leaves.

1) Broad leafed

Crops	Number of plants per pot	Growth stage
Cotton	2	1 leaf
Soya	2	2 leaves.

2) Grass

Crops	Number of plants per pot	Growth stage
Maize	2	2-3 leaves
Rice	4	2-3 leaves
Wheat	5	2-3 leaves.

The compounds used to treat the plants were applied to the plants as described in (a). A single pot of each crop and weed species was allocated to each treatment, with unsprayed controls and controls sprayed with acetone alone.

After treatment the pots were placed on capillary matting in a glass house, and watered overhead once after 24 hours and then by controlled sub-irrigation. Visual assessment of crop damage and weed control was made 20-24 days after spraying. The results were expressed as the percentage reduction in growth or damage to the crop or weeds, in comparison with the plants in the control pots.

The compounds of the invention have shown an excellent level of herbicidal activity together with crop tolerance on the weeds used in the foregoing experiments.

When applied pre- or post-emergence at 1000g/ha compounds 1 to 35 gave at least 90% reduction in growth of one or more of the weed species.

The following comparative examples compare the activity of compounds of the formula (I) with prior art compounds and illustrate the remarkable and unexpected improvement in herbicide activity over the closest prior art compounds:

COMPARATIVE EXAMPLE 1

Table 1 compares the activity of a compound of formula (I), 4-[4-chloro-3-ethoxy-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole "Compound A", with prior art compounds 52 and 56 of EP-A-0418175. These compounds differ from Compound A because the 2- and 4- substituents of the phenyl ring are inverted, ie:

Compound A =	2-SO_2Me	3-OEt 2-Cl
Compounds 52 & 56 =	3-OEt	4-SO_2Me

Post-emergence against Setaria viridis compound A was 4 times more active than compound 52 and 6.5 times more active than prior art compound 56. Post-emergence against Echinochloa crus-galli compound A was greater than 1.75 times more active than compound 52 and greater than 1.9 times more active than prior art compound 56.

COMPARATIVE EXAMPLE 2

In a similar manner, Table 2 compares the activity of compound 4 of the instant application with prior art compounds 16, 20 and 21 of EP-A-0418175.

Compound 4 =	2-SO_2Me, 3-Cl, 2-Cl
Prior art Compounds 16, 20 and 21 =	2-Cl, 3-Cl, 4-SO_2Me

Post-emergence against Setaria viridis compound 4 was greater than 3.8 times more active than compounds 16 and 20 and 3.3 times more active than prior art compound 21.

Post-emergence against Echinochloa crus-galli compound 4 was greater than 62 times more active than compounds 16 and 20 and greater than 29 times more active than prior art compound 21.

COMPARATIVE EXAMPLE 3

Table 3 provides data comparing the properties of the other compounds of formula (I) with the other 2,3-4-trisubstituted compounds disclosed in EP-A-0418175 (these compounds are indicated with a "P" before their compound number in EP-A-0418175). Additional representative compounds of the invention are included in this Table (numbered 36 to 79). In nearly all cases the compounds of the invention were more active than all the prior art compounds against Setaria viridis, and that over 90% of the compounds were more active than all the prior art compounds against Echinochloa crus-galli.

Comparative Data

Note:

(1) In the Tables the following abbreviations are used:

Cp = Cyclopropyl

Setvi = Setaria viridis

Echcg = Echinochloa crus-galli

(2) The Prior art compounds of EP-A-0418175 are indicated with a P before their compound number (e.g. P52 is compound 52 of EP-A-0418175).

In each case the compounds were screened against the weed species according to the procedure described in the instant application.

Table 1

Post Emergence ED90 values (in g/ha)

Cpd	R	R^1	R^2	R^3	R^4	SETVI	ECHCG
P52	H	Me	Cl	OEt	SO_2Me	368	28
P56	H	Cp	Cl	OEt	SO_2Me	591	31
A	H	Cp	SO_2Me	OEt	Cl	**208**	**<16**

Table 2

Post Emergence ED90 values (in g/ha)

Cpd	R	R^1	R^2	R^3	R^4	SETVI	ECHCG
P16	H	Me	Cl	Cl	SO_2Me	>1000	>1000
P20	H	iPr	Cl	Cl	SO_2Me	>1000	961
P21	H	Cp	Cl	Cl	SO_2Me	852	462
4	H	Cp	SO_2Me	Cl	Cl	261	<16

Table 3

Comparison of Activity of Compounds of Australian Patent Appln. No. 32819/93 With Prior art in EP-A-0418175

Post Emergence ED90 values (in g/ha)

Cpd	R	R1	R2	R3	R4	SETVI	ECHCG
1	H	Cp	SO2Me	F	F	342	24
2	H	Cp	SMe	Cl	Cl	36	<16
3	H	Cp	SOMe	Cl	Cl	101	<16
5	H	Cp	SMe	MeO	Br	266	16
6	H	Cp	SO2Me	MeO	Br	302	<16
7	H	Cp	SOMe	MeO	Br	977	<16
8	CO2Et	Cp	SMe	Cl	Cl	594	<16
9	CO2Et	Cp	SOMe	Cl	Cl	759	16
10	H	Cp	SMe	MeO	Cl	288	16
11	CO2Et	Cp	SO2Me	Cl	Cl	925	69
12	H	Cp	SOMe	MeO	Cl	293	16
13	H	Cp	SO2Me	MeO	Cl	194	<16
14	H	Cp	SMe	Me	Cl	>1000	338
15	H	Cp	SMe	F	Cl	322	16
16	H	Cp	SOMe	F	Cl	1050	<16
17	H	Cp	SO2Me	F	Cl	>1000	<16
18	H	Cp	SOMe	Me	Cl	>1000	31
19	H	Cp	SO2Me	Me	Cl	>1000	16
20	H	Cp	SMe	CO2Me	CF3	540	207
21	H	Cp	SMe	CO2Me	Cl	375	44
22	H	Cp	SMe	Cl	Br	28	<16
23	H	Cp	SOMe	Cl	Br	67	<16
24	H	Cp	SO2Me	Cl	Br	147	<16
25	H	Cp	SOMe	CO2Me	Cl	>1000	54
26	H	Cp	SO2Me	CO2Me	Cl	759	<16
27	H	Cp	SMe	Cl	CF3	456	69
28	H	Cp	SO2Me	Cl	CF3	393	24
29	H	Cp	SMe	F	Br	97	<16
30	H	Cp	SOMe	F	Br	375	<16
31	H	Cp	SO2Me	F	Br	357	<16

Table 3 (Cont.)

Post Emergence ED90 values (in g/ha)

Cpd	R	R1	R2	R3	R4	SETVI	ECHCG
32	H	Cp	SMe	C(CH3)=CH2	Cl	>1000	107
33	H	Cp	SMe	Me	SMe	250	16
34	H	Cp	SOMe	C(CH3)=CH2	Cl	>1000	24
35	H	Cp	SO2Me	C(CH3)=CH2	Cl	638	<16
36	H	Cp	SMe	Br	Cl	69	16
37	H	Cp	SOMe	Br	Cl	75	<16
38	H	Cp	SO2Me	Br	Cl	896	<16
39	H	Cp	SMe	Br	Br	136	16
40	H	Cp	SOMe	Br	Br	373	16
41	H	Cp	SO2Me	Br	Br	1048	<16
42	H	Cp	SMe	Cl	F	97	16
43	H	Cp	SOMe	Cl	F	62	<16
44	H	Cp	SO2Me	Cl	F	668	<16
45	H	Cp	SMe	F	F	293	24
46	H	Cp	SOMe	F	F	194	<16
47	H	Cp	SO2Et	Cl	Cl	426	<16
48	H	Cp	SO2Et	Cl	Cl	636	24
49	H	Cp	SOEt	Cl	Cl	896	<16
50	H	Cp	SO2Me	OCH2CF3	Cl	31	<16
51	H	Cp	SO2Me	CH=CH2	Cl	107	<16
52	H	Cp	SEt	Br	Br	290	<16
53	H	Cp	SMe	OEt	SMe	125	<16
54	H	Cp	SEt	Br	Cl	333	16
55	H	Cp	SO2Me	Cl	OCF3	355	<16
56	H	Cp	SOMe	Cl	OCF3	302	24
57	H	Cp	SOEt	Br	Cl	119	<16
58	H	Cp	SO2Me	OCH(CH3)CF3	Cl	90	<16
59	H	Cp	SMe	Cl	CHF2	140	<16
60	H	Cp	SMe	OMe	SMe	123	<16
61	H	Cp	SO2Me	Cl	CHF2	429	<16
62	H	Cp	SOMe	Cl	CHF2	364	<16
63	H	Cp	SO2Me	OCH2CF3	Br	136	<16
64	H	Cp	SO2Me	OCH(CH3)CF3	F	82	<16
65	H	Cp	SO2Me	OCH2CF2CF3	Cl	111	<16

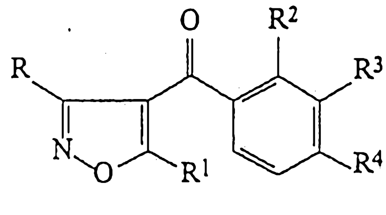
Table 3 (Cont.)

Post Emergence ED90 values (in g/ha)

Cpd	R	R1	R2	R3	R4	SETVI	ECHCG
66	H	Cp	SMe	OEt	Br	328	63
67	CO2Et	Cp	SMe	Br	Cl	36	<16
68	CO2Et	Cp	SOMe	Br	Cl	293	<16
69	CO2Et	Cp	SO2Me	Br	Cl	338	<16
70	CO2Et	Cp	SMe	Cl	Br	62	<16
71	CO2Et	Cp	SOMe	Cl	Br	112	<16
72	CO2Et	Cp	SO2Me	Cl	Br	457	<16
73	CO2Et	Cp	SMe	F	F	763	16
74	CO2iPr	Cp	SMe	Cl	Cl	124	<16
75	CO2Me	Cp	SMe	Cl	Cl	24	<16
76	H	Cp	SMe	CH=CH2	Cl	318	249
77	H	Cp	SOMe	CH=CH2	Cl	686	<16
78	H	Cp	SO2Me	OiPr	Cl	540	16
79	CO2Et	Cp	SOMe	Br	Br	426	<16
P36	H	Me	Cl	Cl	SMe	>1000	>1000
P46	H	Me	Cl	Cl	SOMe	>1000	355
P59	H	Cp	Cl	OEt	SO2Et	>1000	135
P61	H	Me	Me	CO2Me	SO2Me	>1000	>1000
P63	H	Me	Cl	OiPr	SO2Me	>1000	>1000
P64	H	Me	Me	CO2iPr	SO2Me	>1000	1220
P65	H	Cp	Me	CO2iPr	SO2Me	>1000	393

CLAIMS

1. A 4-benzoyl isoxazole derivative of general formula (I)



(I)

wherein:

R represents a hydrogen atom or a group $-CO_2R^5$;

R^1 represents methyl, isopropyl, cyclopropyl or 1-methylcyclopropyl;

R^2 represents $-S(O)_nR^{51}$;

R^3 represents:

a chlorine, bromine or fluorine atom;

a straight- or branched- chain alkyl or alkoxy group containing up to four carbon atoms optionally substituted by one or more halogen atoms;

a straight- or branched chain alkenyl group containing up to six carbon atoms; or

a group $-CO_2R^{52}$;

R^4 represents:

a chlorine, bromine or fluorine atom;

a straight- or branched- chain alkyl group containing up to four carbon atoms optionally substituted by one or more halogen atoms;

an alkoxy group containing up to four carbon atoms substituted by one or more halogen atoms;

$-S(O)_pR^{53}$ or cyano;

R^5 represents a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

R^{51} and R^{53}, which may be the same or different, each represents a straight- or branched- chain alkyl group containing up to four carbon atoms;

R^{52} represents methyl or ethyl;

n represents zero, one or two; and

p represents zero, one or two.

2. A compound according to claim 1 in which R^1 represents cyclopropyl.

3. A compound according to claim 1 or 2 wherein:

R^3 represents a fluorine, chlorine or bromine atom; a methyl or ethyl group; an alkoxy group containing one or two carbon atoms optionally substituted by one or more halogen atoms; an alkenyl group containing from two to four carbon atoms; or $-CO_2R^{52}$;

R^4 represents a fluorine, chlorine or bromine atom; an alkyl group containing one or two carbon atoms substituted by one or more halogen atoms; an alkoxy group containing one or two carbon atoms substituted by one or more halogen atoms; or $-S(O)_pR^{53}$, wherein p represents zero and R^{53} is a methyl or ethyl group; and

R^{51} represents a methyl or ethyl group.

4. A compound according to claim 1, 2 or 3 wherein:

R^3 represents a fluorine, chlorine or bromine atom; a methyl, methoxy or ethoxy group; an alkenyl group containing two or three carbon atoms; or $-CO_2R^{52}$ wherein R^{52} is methyl;

R^4 represents a fluorine, chlorine or bromine atom or a group selected from trifluoromethyl, trifluoromethoxy and $-S(O)_pMe$ wherein p is zero;

R^5 represents a methyl or ethyl group; and

R^{51} represents a methyl or ethyl group.

5. A compound according to any one of the preceding claims wherein:

R^3 represents fluorine, chlorine, bromine, methyl or methoxy;

R^4 represents fluorine, chlorine, bromine or trifluoromethyl;

R^5 represents methyl or ethyl; and

R^{51} represents methyl.

6. A compound according to any one of the preceding claims wherein:

R^3 represents fluorine, chlorine, bromine or methoxy;

R^4 represents fluorine, chlorine, bromine or trifluoromethyl;

R^5 represents methyl or ethyl; and

R^{51} represents methyl.

7. A compound according to any one of the preceding claims wherein:

R^3 represents a chlorine, bromine or fluorine atom;

R^4 represents fluorine, chlorine, bromine or trifluoromethyl;

R^5 represents methyl or ethyl; and

R^{51} represents methyl.

8. A compound according to claim 1 or 2 which is

5-cyclopropyl-4-[3,4-difluoro-2-(methylsulphonyl)benzoyl]isoxazole;

5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphenyl) benzoyl]isoxazole;

5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphinyl)benzoyl]isoxazole;

5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphonyl)benzoyl]isoxazole;

5-cyclopropyl-4-[4-bromo-3-methoxy-2-(methylsulphenyl)benzoyl]isoxazole;

5-cyclopropyl-4-[4-bromo-3-methoxy-2-(methylsulphonyl)benzoyl]isoxazole;

5-cyclopropyl-4-[4-bromo-3-methoxy-2-(methylsulphinyl)benzoyl]isoxazole;

~~ethyl 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphenyl)benzoyl]isoxazole-3-carboxylate;~~

ethyl 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphinyl) benzoyl]isoxazole-3-carboxylate;

4-[4-chloro-3-methoxy-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

ethyl 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphonyl)benzoyl]-isoxazole-3-carboxylate;

4-[4-chloro-3-methoxy-2-(methylsulphinyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-chloro-3-methoxy-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-chloro-3-methyl-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-chloro-3-fluoro-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-chloro-3-fluoro-2-(methylsulphinyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-chloro-3-fluoro-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-chloro-3-methyl-2-(methylsulphinyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-chloro-3-methyl-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole;

5-cyclopropyl-4-[3-methoxycarbonyl-2-(methylsulphenyl)-4-trifluoromethyl-benzoyl]isoxazole;

4-[4-chloro-3-methoxycarbonyl-2-(methylsulphenyl)benzoyl]-5-cyclopropyl-isoxazole;

4-[4-bromo-3-chloro-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-bromo-3-chloro-2-(methylsulphinyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-bromo-3-chloro-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-chloro-3-methoxycarbonyl-2-(methylsulphinyl)benzoyl]-5-cyclopropyl-isoxazole;

4-[4-chloro-3-methoxycarbonyl-2-(methylsulphonyl)benzoyl]-5-cyclopropyl-isoxazole;

4-[3-chloro-2-(methylsulphenyl)-4-trifluoromethylbenzoyl]-5-cyclopropyl-isoxazole;

4-[3-chloro-2-(methylsulphonyl)-4-trifluoromethylbenzoyl]-5-cyclopropyl-isoxazole;

4-[4-bromo-3-fluoro-2-(methylsulphenyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-bromo-3-fluoro-2-(methylsulphinyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-bromo-3-fluoro-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole;

4-[4-chloro-3-isopropenyl-2-(methylsulphenyl)-benzoyl]-5-cyclopropyl-isoxazole;

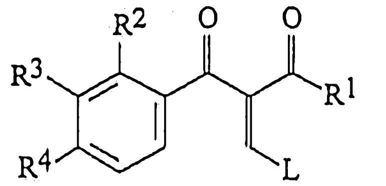
5-cyclopropyl-4-[3-methyl-2,4-bis(methylsulphenyl)-benzoyl]isoxazole;

4-[4-chloro-3-isopropenyl-2-(methylsulphinyl)-benzoyl]-5-cyclopropylisoxazole; or

4-[4-chloro-3-isopropenyl-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole.

9. A process for the preparation of a compound of general formula (I) as defined in claim 1 which comprises:

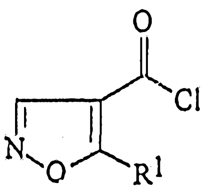
a) the reaction of a compound of general formula (II):



(II)

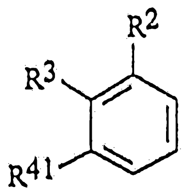
wherein R^1, R^2, R^3 and R^4 are as defined in claim 1 and L is a leaving group, with a salt of hydroxylamine;

b) where R represents hydrogen, R^2 represents a group $-SR^{51}$ and R^4 represents a group R^{41} which is as defined for R^4 provided that p is zero, the reaction of a compound of general formula (III):



(III)

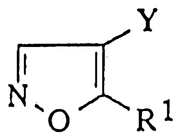
wherein R^1 is as defined in claim 1, with a compound of general formula (IV):



(IV)

wherein R^2 represents a group $-SR^{51}$, R^3 is as defined in claim 1 and R^{41} is as defined above;

c) when R is hydrogen, the reaction of a compound of general formula (V):

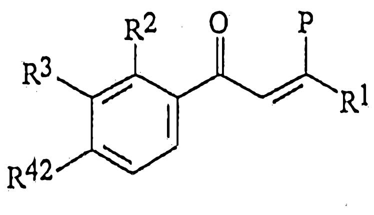


(V)

wherein R^1 is as defined in claim 1 and Y represents a carboxy group or a reactive derivative thereof, or a cyano group, with an appropriate organometallic reagent;

d) where n is one or two and/or p is one or two the oxidation of the sulphur atom of the corresponding compound of general formula (I) in which n is zero or one and/or p is zero or one.

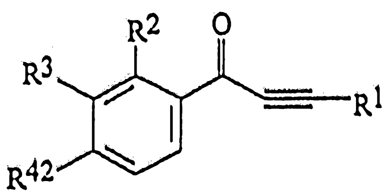
e) where R represents a group $-CO_2R^5$, n is zero or two and R^4 represents a group R^{42} which is as defined for R^4 provided that p is 0 or 2, the reaction of a compound of general formula (VI):



(VI)

wherein R^1, R^2, R^3 are as defined in claim 1, n is zero or two, R^{42} is as defined above and P is a leaving group, with a compound of general formula $R^5O_2CC(X)=NOH$ wherein R^5 is as defined in claim 1 and X is a halogen atom;

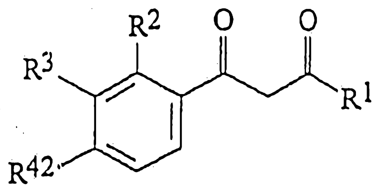
f) where R represents a group $-CO_2R^5$, n is zero or two and R^4 represents a group R^{42}, the reaction of a compound of general formula (VII):



(VII)

wherein R^1, R^2 and R^3 are as defined in claim 1, n is 0 or 2 and R^{42} is as defined above, with a compound of general formula $R^5O_2CC(X)=NOH$, wherein R^5 is as defined in claim 1 and X is a halogen atom; or

g) where R represents $-CO_2R^5$, n is zero or two and R^4 represents a group R^{42}, the reaction of a salt of a compound of general formula (VIII):



(VIII)

wherein R^1, R^2 and R^3 are as defined in claim 1, n is 0 or 2 and R^{42} is as defined above, with a compound of general formula $R^5O_2CC(X)=NOH$ wherein R^5 is as defined in claim 1 and X is a halogen atom.

10. A herbicidal composition which comprises as active ingredient a herbicidally effective amount of an isoxazole derivative of general formula (I) as defined in any one of claims 1 to 8 in association with an agriculturally acceptable diluent or carrier and/or surface active agent.

11. A herbicidal composition according to claim 10 which comprises 0.05 to 90% by weight of active ingredient.

12. A herbicidal composition according to claim 10 which is in liquid form and contains from 0.05 to 25% of surface-active agent.

13. A herbicidal composition according to claim 10 in the form of an aqueous suspension concentrate, a wettable powder, a water soluble or water dispersible powder, a liquid water soluble concentrate, a liquid emulsifiable suspension concentrate, a granule or an emulsifiable concentrate.

14. A method for controlling the growth of weeds at a locus which comprises applying to the locus a herbicidally effective amount of an isoxazole derivative of general formula (I) as defined in any one of claims 1 to 8.

15. A method according to claim 14 in which the locus is an area used, or to be used, for growing crops and the compound is applied at an application rate from 0.01 kg to 4.0 kg per hectare.

16. A method according to claim 14 in which the locus is an area which is not a crop-growing area and the compound is applied at an application rate of from 1.0 kg to 20.0 kg per hectare.

17. The compound according to claim 1 which is ethyl 5-cyclopropyl-4-[3,4-dichloro-2-(methylsulphenyl)benzoyl]isoxazole-3-carboxylate.

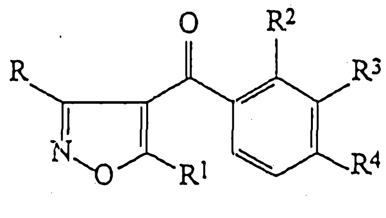
18. A compound according to claim 1 or a composition comprising the same or a method of use thereof substantially as hereinbefore described with reference to any one of the examples.

DATED this 18th day of August, 1995.

RHONE-POULENC AGRICULTURE LIMITED
By Their Patent Attorneys:
CALLINAN LAWRIE

ABSTRACT

4-Benzoyl isoxazole derivatives of general formula (I):



(I)

wherein

R represents a hydrogen atom or a group $-CO_2R^5$;

R^1 represents methyl, isopropyl, cyclopropyl or 1-methylcyclopropyl;

R^2 represents $-S(O)_nR^{51}$;

R^3 represents a chlorine, bromine or fluorine atom, a straight- or branched- chain alkyl, alkoxy, haloalkyl or haloalkoxy group, an alkenyl group or a methyl or ethyl ester group;

R^4 represents a chlorine, bromine or fluorine atom; an alkyl, alkoxy haloalkyl, haloalkoxy, $-S(O)_pR^{53}$ or cyano group;

R^5 represents an alkyl or haloalkyl group;

R^{51} and R^{53} independently represent an alkyl group, and

n and p independently represent zero one or two,

and their use as herbicides is described.