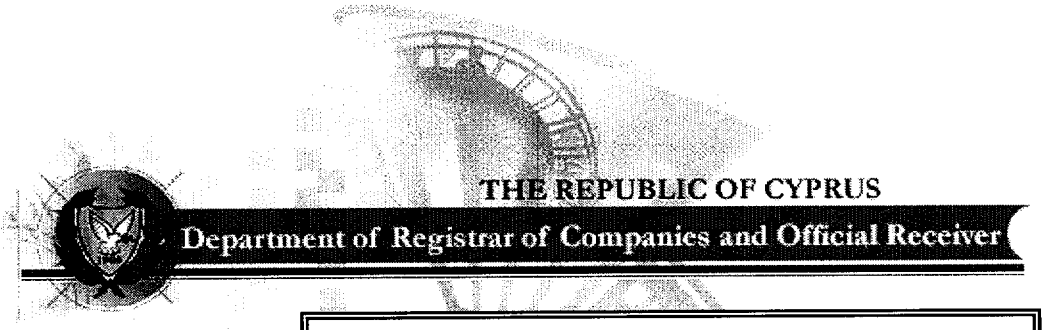

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

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PUBLICATION NUMBER

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Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

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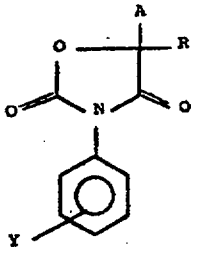
(54) Derivatives of N-phenyl-1,3-oxazolidine-2,4-diones

(57) N-Aryl-1,3-oxazolidine-2,4-diones, useful as fungicides, have the general formula:



in which:

R represents a hydrogen atom or a C_{1-5} alkyl group;

Y represents a hydrogen or halogen atom or 3,4-dichloro, 3,5-dichloro, 3,5-dibromo, 3,5-dimethyl, 3,5-dimethoxy or 3,5-bis-trifluoromethyl;

A represents CN or

in which R^1 represents OH, OR, NH—NHR or $N(R)_2$ in which R is as defined above.

Certain of the chemical formulae appearing in the printed specification were submitted in formal form after the date of filing.

GB 2 015 506A

SPECIFICATION

Derivatives of N-phenyl-1,3-oxazolidine-2,4-diones

This invention relates to derivatives of N-phenyl-1,3-oxazolidine-2,4-diones which possess a fungicidal action. In particular the invention relates to N-aryl-1,3-oxazolidine-2,4-diones substituted in the 5-position, to their preparation and to their use as fungicides.

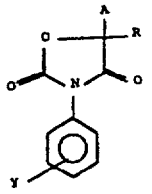
Derivatives of N-(3,5-dichlorophenyl)-1,3-oxazolidine-2,4-dione substituted in the 5-position with two alkyl groups or with a hydrogen and an alkyl group are disclosed in Dutch Patent Application No. 68/17249 as having fungicidal activity. French Patent Application No. 2 172 295 refers to those compounds as having only a weak fungicidal activity and discloses derivatives of N-(3,5-dichlorophenyl)-1,3-oxazolidine-2,4-dione having in the 5-position two substituents, one of which is hydrogen or an alkyl group and the other is an alkenyl group or both together represent a methylene group.

One particular compounds among those disclosed in Dutch Patent Application No. 68/17249, i.e. N-(3,5-dichlorophenyl)-5,5-dimethyl-1,3-oxazolidine-2,4-dione, is commercially available under the trade name Sclex, and this has been found to possess prejudicial secondary effects on man.

The compound N-(3,5-dichlorophenyl)-5-methyl-5-vinyl-1,3-oxazolidine-2,4-dione in accordance with French Patent Specification No. 2 172 295 is commercially available under the trade name Vinchlozoline and exhibits some difficulties in its synthesis, particularly with regard to the preparation of the required β—γ unsaturated lactate.

The necessity of finding new compounds economically advantageous and efficient in defending important agrarian cultures from the attack of pathogenous fungi is the main reason for a continuous and intense research work in the field of the N-aryloxazolidiones. It is an object of this invention to provide new compounds having fungicidal properties.

Therefore according to the invention there is provided an N-aryl-1,3-oxazolidine-2,4-dione of the general formula:



in which:

R represents a hydrogen atom or an alkyl group containing 1 to 5 carbon atoms,

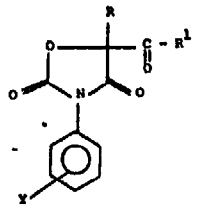
Y represents a hydrogen or halogen atom or 3,4-dichloro, 3,5-dichloro, 3,5-dibromo, 3,5-dimethyl, 3,5-dimethoxy or 3,5-bis-trifluoromethyl;

A represents CN or

in which R^1 represents OH, OR, NH—NHR or $N(R)_2$ in which R is as defined above.

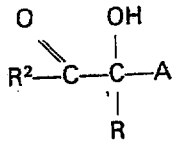
Examples of compounds which have been prepared in accordance with the invention are recorded in Table 1.

TABLE 1



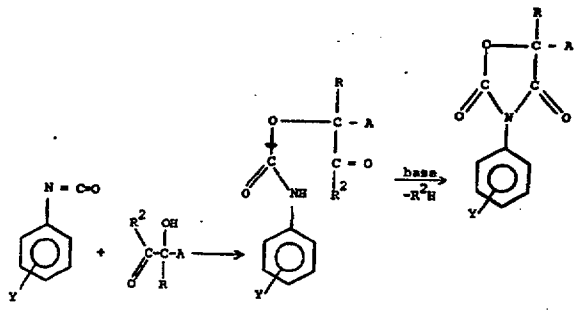
Compound No.	Substituents			Melting point °C	Crystallization solvent	Elemental Analysis					
						C%		H%		N%	
	Y	R	R^1			calc.	found	calc.	found	calc.	found
1	H	CH_3	OC_2H_5	103–6	ethanol	59.31	58.63	4.98	4.90	5.32	5.24
2	3-Cl	CH_3	OC_2H_5	88–90	ethanol	52.45	53.62	4.06	4.13	4.70	5.00
3	4-Cl	CH_3	OC_2H_5	94–97	ethanol	52.45	52.65	4.06	4.14	4.70	4.63
4	3,5-Cl_2	CH_3	OC_2H_5	109–10	ethanol	47.01	47.22	3.34	3.32	4.22	4.40
5	3,4-Cl_2	CH_3	OC_2H_5	78–80	ethanol	47.01	47.90	3.34	3.40	4.22	4.20
6	3,5-$(CH_3)_2$	CH_3	OC_2H_5	112–4	ethanol	61.80	62.40	5.90	5.80	4.80	4.80
7	3,5-$(OCH_3)_2$	CH_3	OC_2H_5	110–1	ethanol	55.73	55.64	5.30	5.30	4.33	4.76
8	3,5-$(CF_3)_2$	CH_3	OC_2H_5	115–7						3.51	3.45
9	3,5-Cl_2	C_2H_5	OC_2H_5	90–4	ethanol	48.58	48.68	3.78	3.69	4.05	4.11
10	3,5-Cl_2	CH_3	OC_3H_7n	75–9	ethanol	48.58	49.39	3.78	4.14	4.05	3.88
11	3,5-Cl_2	CH_3	OC_3H_7iso	95–8	ethanol	48.58	48.44	3.78	3.89	4.05	4.10
12	3,5-$(CH_3)_2$	H	OC_2H_5	62–4	methanol	60.64	60.64	5.45	5.57	5.05	4.93
13	3,5-$(OCH_3)_2$	H	OC_2H_5			54.37	54.41	4.89	5.34	4.53	4.40
14	3,5-$(CF_3)_2$	H	OC_2H_5	118–20	ethanol					3.64	3.56
15	3,5-Cl_2	H	OC_2H_5	90–92	ethanol	45.31	45.70	2.85	2.88	4.40	4.34
16	3,5-Cl_2	CH_3	OCH_3	127–9	ethanol	45.31	45.86	2.85	2.94	4.40	4.45

The compounds of the invention may be prepared by reacting α-hydroxy-esters or analogues thereof having the general formula:



(II)

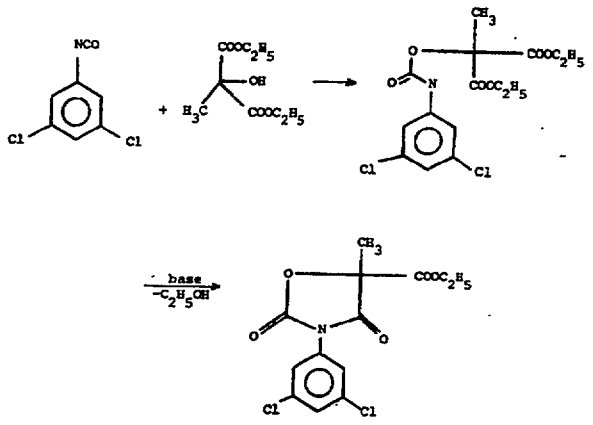
in which A and R are as defined above and R^2 represents OH, OR or NH_2, in which R is as defined above,
with an aryl-isocyanate in the presence of a tertiary base, which favours the ring-closing of the intermediate carbamate. The reaction scheme is as follows:



The α-hydroxy-esters of type II are derivatives readily obtainable from inexpensive raw materials.
The compounds of formula I are endowed with a high fungicidal action, which is superior to that of known N-(3,5-dichlorophenyl)-1,3-oxazolidine-2,4-diones as will be illustrated hereinafter. The compounds may be applied to plants in an amount from 0.37% upwards.
The invention will be illustrated by the following Examples.

EXAMPLE 1

N-(3,5-dichlorophenyl)-5-methyl-5-carboethoxy-1,3-oxazolidine-2,4-dione. (Compound No. 4 — Table 1)



37.6 g of 3,5-dichlorophenyl-isocyanate and 38 g of diethylic methyl-tartronate (diethyl esther of the 2-methyl-2-hydroxy-malonic acid) were dissolved in 1 litre of benzene. The resulting solution was stirred at room temperature for 3 hours, additioned with 1 ml of triethylamine and thereafter was heated under reflux for 12 hours.
The resulting mixture was filtered and the solvent was evaporated under reduced pressure. The solid residue was re-crystallized from ethyl alcohol to yield 45 g of the product in the form of white needles, having a melting point of 109 to 110°C.
By an analogous procedure, the remaining compounds indicated in Table 1 were synthesized.

EXAMPLE 2

Biological activity of the compounds of the invention

a) Activity in vitro.

The activity was determined by evaluating the percentage in growth of the fungi cultivated in an earth containing increasing amounts of the compounds being tested. The compounds were introduced into the cultural medium in the form of dispersions with dimethyl-sulphoxide and Tween 20, so as to have a final concentration of 0.5% in dimethyl-sulphoxide and of 0.01% in Tween 20.

For the species of fungi such as *Botrytis cinerea, Monilia fructigena, Penicillium italicum* and *Aspergillus parassiticum,* 1 drop of a suspension of spores and mycelium was put in the centre of Petri dishes containing agar-treated soil (PD Agar Difco), so obtaining a circular inoculum. After a 4-day growth at 25°C, the diameters of the colonies which had developed, were measured, and the percentages of growth inhibition in respect of the untreated checks were calculated. For the species *Helminthosporium Maydis, Helminthosporium oryzae* and *Alternaria tenuis,* 100 μl of a suspension of spores and mycelium were introduced into tubes containing 10 cc of potato broth (Difco), which were kept horizontally and in incubation for 7 days at 25°C. After such a period and after intense agitation, the percentage of growth inhibition of the fungi was calculated by placing the tubes vertically and close to one another.

The results obtained are recorded in Table 2.

TABLE 2

Compound No.	Fungus	Botrytis c.	Monilia fric.	Penicillium lt.	Aspergillus par.	Helminthosporium Maydis	Helminthosporium oryzae	Alternaris tenuis
	dose	5 ppm	5 ppm	25 ppm	25 ppm	25 ppm	25 ppm	50 ppm
16		100	100	100	100	100	100	100
4		100	100	100	100	100	100	100
9		100	100	100	100	100	100	100
10		100	100	100	100	100	100	100
Sclex (*)		100	100	80	70	60	70	30
Vinchloz-oline (**)		100	100	100	100	100	100	80

(*) N-(3,5-dichlorophenyl)-5,5-dimethyl-oxazolidine-2,4-dione ,(active principle of the commercial product "Sclex")

(**) N-(3,5-dichlorophenyl)-5,5-dimethyl-oxazolidine-2,4-dione (active principle of the commercial product "Vinchlozoline")

b) Preventive activity against *Botrytis cinerea* on tomato plants

Both leaf faces of tomato plants cv. Marmande, cultivated in pots in a conditioned environment at 25°C and 60% relative humidity, were sprayed with a hydroacetonic solution at 20% of acetone (vol./vol.) of the products being tested.

After one day the artificial infection was effected by inoculating a suspension of *Botrytis cinerea* in carrot broth (1,000,000 of spores/cc) into both leaf faces. After a 24-hour residence period in a humidity-saturated environment at 26°C, the plants were transferred into an environment at 26°C and 70% relative humidity for the duration of the incubation period (6 days).

Finally, the degree of the infection was visually evaluated according to indexes of a scale of measure ranging from 100 (sound plant) to 0 (thoroughly infected plant).

The results obtained are recorded in Table 3.

TABLE 3

Preventive fungicidal activity against *Botrytis cinerea* on tomato plants

Dose %	3	1.5	0.75	0.37
Compound No. 4	100	100	100	95
Compound No. 16	100	100	100	
Sclex (PB 50) (reference commercial product)	100	97	96	80
Vinchozoline (PB 50) (reference commercial product)	100	100	95	80

c) Preventive activity against *Plasmopara viticola* on vine plants

The leaves of vine plants cv. Dolcetto, cultivated in pots in a conditioned environment at 25°C and 60% relative humidity were treated by spraying both faces of same with the products being tested in a hydroacetonic solution (20% of acetone vol./vol.). 24 hours after the treatment, the lower faces of the leaves were sprayed with an aqueous suspension of conidia of *Plasmopara viticola* (200,000 conidia/cc); after a 24 hour period of residence in a humidity saturated environment at 21°C, the plants were transferred to 70% relative humidity at 21°C for the incubation period (7 days). Finally the degree of infection was evaluated according to indexes of an evaluation scale range from 100 (sound plant) to 0 (fully infected plant).

The results obtained are recorded in Table 4.

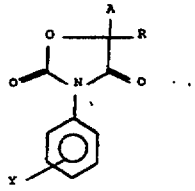
TABLE 4

Preventive fungicidal activity against Plasmopara viticola on vine plants.

Compound No.	Dose % 1	0.5	0.1
2	100	100	100
7	100	100	100
9	100	100	100
10	100	100	100
11	100	100	100
13	100	100	85
Vinchlozoline (PB 50) (commercial product of reference)	100	95	80

CLAIMS

1. An N-aryl-1,3-oxazolidine-2,4-dione of the general formula:



in which:

R represents a hydrogen atom or an alkyl group containing 1 to 5 carbon atoms;

Y represents a hydrogen or halogen atom or 3,4-dichloro, 3,5-dichloro, 3,5-dibromo, 3,5-dimethyl, 3,5-dimethoxy or 3,5-bis-trifluoromethyl;

A represents CN or

in which R^1 represents OH, OR, NH—NHR or $N(R)_2$ in which R is as defined above.

2. N-(3,5-dichlorophenyl)-5-methyl-5-carbomethoxy-1,3-oxazolidine-2,4-dione.

3. N-(3-chlorophenyl)-5-methyl-5-carboethoxy-1,3-oxazolidine-2,4-dione.

4. N-(3,5-dichlorophenyl)-5-methyl-5-carboethoxy-1,4-oxazolidine-2,4-dione.

5. N-(3,5-dimethylphenyl)-5-methyl-5-carboethoxy-1,3-oxazolidine-2,4-dione.

6. N-(3,5-dimethoxyphenyl)-5-methyl-5-carboethoxy-1,3-oxazolidine-2,4-dione.

7. N-[(-3,5-bis-trifluoromethyl)-phenyl]-5-methyl-5-carboethoxy-1,3-oxazolidine-2,4-dione.

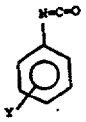
8. N-(3,5-dichlorophenyl)-5-methyl-5-carboethoxy-1,3-oxazolidine-2,4-dione.

9. N-(3,5-dichlorophenyl)-5-methyl-5-(n.propoxycarbonyl)-1,3-oxazolidine-2,4-dione.

10. N-(3,5-dimethylphenyl)-5-carboethoxy-1,3-oxazolidine-2,4-dione.

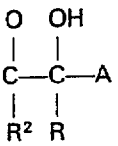
11. An N-aryl-1,3-oxazolidine-2,4-dione substantially as herein described with reference to any one of the Examples.

12. A process for preparing a compound as claimed in Claim 1, comprising reacting a phenyl isocyanate having the formula:



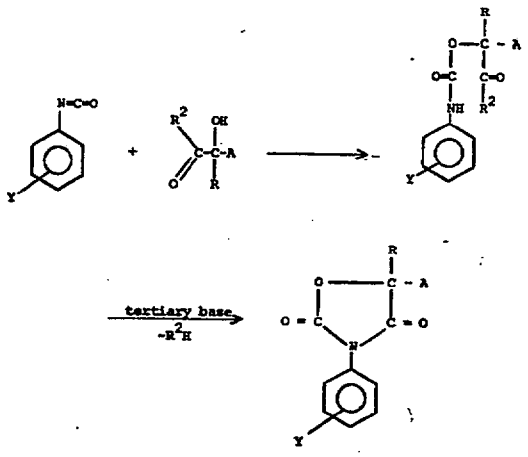
in which Y is as defined in Claim 1,

with an α-hydroxy-ester of the formula:



in which R and A are as defined in Claim 1 and R^2 represents OH, OR or NH_2 in which R is as defined in Claim 1,

and cyclizing the resulting compound in the presence of a tertiary base according to the reaction scheme:



13. A process for the preparation of N-aryl-1,3-oxazolidine-2,4-dione derivatives substantially as herein described with reference to Example 1.

14. A method of fighting the infections due to fungi in plants, comprising treating the plants with one or more of the compounds as claimed in Claim 1, in an amount of at least 0.37%.

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