

PATENT SPECIFICATION

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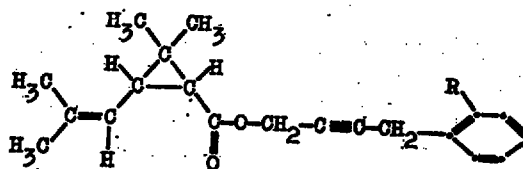


(54) NOVEL CHRYSANTHEMIC ACID ESTERS AND THE MANUFACTURE THEREOF

(71) We, ROCHE PRODUCTS LIMITED, a British Company of Broadwater Road, Welwyn Garden City, Hertfordshire, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with novel chrysanthemic acid esters and the manufacture thereof.

The chrysanthemic acid esters provided by the invention can be generically formulated thus:

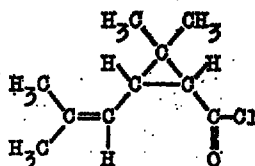


(I)

wherein R represents a hydrogen atom or the methyl group and the broken line denotes an optional bond. They are useful as insecticides.

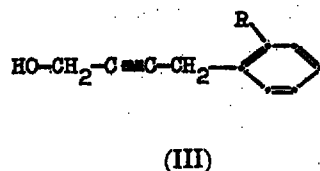
Examples of esters provided by the invention in which R represents a hydrogen atom are 4 - phenyl - 2 - butynyl - ($\pm$) - *cis/trans* - 2,2 - dimethyl - 3 - (2 - methyl - propenyl) - cyclopropane carboxylate and *trans* - 4 - phenyl - 2 - butenyl ($\pm$) - *cis/trans* - 2 - dimethyl - 3 - (2 - methyl - propenyl) - cyclopropane carboxylate. An example of an ester provided by the invention in which R represents the methyl group is 4 - (2 - methyl - phenyl) - 2 - butynyl ($\pm$) - *cis/trans* - 2,2 - dimethyl - 3 - (2 - methyl - propenyl) - cyclopropane carboxylate.

The chrysanthemic acid esters aforesaid can be manufactured according to the invention by reacting an acid chloride of the general formula



(II)

with an alcohol of the general formula



wherein R and the broken line have the significance given earlier.

The acid chloride starting materials of formula II are known substances and can be prepared by chlorinating the corresponding carboxylic acids (e.g. using thionyl chloride).

The acetylenic alcohol starting materials of formula III can be prepared, for example, by reacting propargyl alcohol with an alkyl-magnesium halide (e.g. ethyl-magnesium bromide), treating the resulting GRIGNARD complex with cuprous chloride or cuprous cyanide, treating the resulting mixture with a halide of the general formula

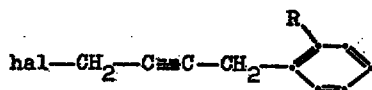


, wherein R has the significance given earlier and X represents a chlorine or bromine atom, and decomposing the product by conventional techniques such as by treatment with aqueous ammonium chloride. They may also be prepared, for example, by reacting the appropriate aryl-magnesium halide (e.g. phenyl-magnesium bromide) with 4-chloro-2-butyne-1-ol and decomposing the product by conventional techniques such as by treatment with aqueous ammonium chloride.

The olefinic alcohol starting materials of formula III can be prepared, for example, by reducing a corresponding acetylenic alcohol starting material either with an alkali-metal aluminium hydride or with hydrogen in the presence of a partially deactivated palladium catalyst. The reduction of an acetylenic alcohol with an alkali-metal aluminium hydride (e.g. lithium aluminium hydride) yields an olefinic alcohol starting material of formula III having a *trans* configuration at the 2,3-position and is conveniently carried out in an inert organic solvent (e.g. an ether such as diethyl ether) at an elevated temperature (e.g. the reflux temperature of the reduction mixture). On the other hand, the reduction with hydrogen in the presence of a partially deactivated palladium catalyst yields an olefinic alcohol starting material of formula III having a *cis* configuration at the 2,3-position. This reduction is suitably carried out in the presence of a palladium catalyst which has been partially deactivated with lead with the addition of quinoline and in the presence of an inert organic solvent such as petroleum ether at room temperature and atmospheric pressure.

The reaction of an acid chloride starting material of formula II with an alcohol starting material of formula III is conveniently carried out in the presence of an acid-binding agent. Suitable acid-binding agents include alkali-metal carbonates (e.g. sodium carbonate), alkali-metal bicarbonates (e.g. sodium bicarbonate) and tertiary organic amines (e.g. triethyl amine and pyridine). Pyridine is the preferred acid-binding agent. The reaction may suitably be carried out in the presence of an inert solvent such as a hydrocarbon (e.g. benzene, toluene or xylene), an ether (e.g. diethyl ether or dioxan), or a halogenated hydrocarbon (e.g. methylene chloride or chloroform). Suitably, the reaction is carried out at a temperature within the approximate range of from 0°C to 30°C (preferably at ca 20°C) under the atmosphere of an inert gas such as nitrogen or argon.

The chrysanthemic acid esters of formula I can also be manufactured in accordance with the invention by reacting an alkali-metal salt, silver salt or tri(lower alkyl) amine salt of a chrysanthemum carboxylic acid with a halide of the formula



(V)

wherein R and the broken line have the significance given earlier and *hal* stands for a halogen atom.

The alkali-metal salts and tri(lower alkyl) amine salts referred to earlier can be prepared, for example, by treating a chrysanthemum carboxylic acid in an inert solvent such as a lower-alkanol (e.g. ethanol) with the calculated amount of an alkali-metal hydroxide solution or a tri(lower alkyl) amine. The preferred alkali-metal salts are the sodium and potassium salts and the preferred tri(lower alkyl) amine salts are the triethyl amine salts. The silver salts can be prepared by treating an alkali-metal salt such as the sodium salt in an aqueous solution with silver nitrate.

The halide starting materials of formula V can be prepared, for example, by treating an alcohol of formula III with a suitable halogenating agent (e.g. thionyl chloride or phosphorus tribromide in pyridine). The preferred halide starting materials of formula V are the chloride and bromides.

The reaction of an alkali-metal salt, a silver salt or a tri(lower alkyl) amine salt of a chrysanthemum carboxylic acid with a halide of formula V is suitably carried out in an inert organic solvent. Any suitable inert organic solvent can be used, but it is preferred to use a ketone such as acetone or methyl ethyl ketone or diglyme. The reaction is preferably carried out at an elevated temperature, suitably at the reflux temperature of the reaction mixture. It is also advantageous to carry out the reaction under the atmosphere of an inert gas such as nitrogen or argon.

It will be appreciated that the chrysanthemic acid moiety of formula I can show both geometric isomerism and optical isomerism. The alcohol moiety can also show geometric isomerism when a double-bond is present in the 2,3-position. It will accordingly be understood that the esters provided by this invention include all of the various geometrical and optical isomers as well as mixtures thereof. One type of mixture is obtained by using an acid chloride starting material mixture, an alkali-metal salt starting material mixture, a silver salt starting material mixture or a tri(lower alkyl) amine salt starting material mixture obtained from a commercial carboxylic acid which is a racemic *cis/trans* mixture containing a *cis/trans* ratio of ca 30:70%.

As mentioned earlier, the esters provided by the invention are useful as insecticides. They are active against a variety of insects (particularly against *Musca domestica*) and have been found to be particularly effective when they are synergised with well-known pyrethrin synergists such as piperonyl butoxide and (1,2-methylenedioxy)-4-[2-(octylsulphonyl)-propyl]-benzene. Furthermore, they have been found to have a very low mammalian toxicity. For example, 4-phenyl-2-butyryl ($\pm$)-*cis/trans*-2,2-dimethyl-3-(2-methyl-propenyl)-cyclopropane carboxylate has an LD₅₀ of 16000 mg/kg p.o. in mice and has been shown to have an activity against *Musca domestica* in the order of pyrethrin extract and DDT. It also shows an activity against bean aphids, codlin moth and colorado beetle.

The esters of the invention can be used in the form of conventional insecticidal compositions which contain them in association with a compatible carrier material. The compositions can be made up, for example, as concentrates or with carriers as premixes or as sprays, aerosols or dusts. In certain cases it may be desirable that the carrier materials include emulsions, solutions or organic solvents. Solid carriers which may be used include, for example, talc, silica and similar powders which do not bring about decomposition of the esters. The insecticidal compositions may, if desired, contain conventional additives such as emulsifying agents or wetting agents and may also contain other compatible insecticides and/or synergists.

The following Examples illustrate the invention. The chrysanthemum monocarboxylic acid chloride mentioned therein was obtained from the commercial ($\pm$) carboxylic acid consisting of a *cis/trans* mixture in the ratio of ca 30:70.

EXAMPLE 1

A) The preparation of the starting material:

(i) Ethyl magnesium bromide was prepared from 97.2 of magnesium and 436 g of ethyl bromide in 300 ml of dry ether and 500 ml of dry tetrahydro-furan and

the resulting solution was decanted free of unreacted magnesium. All subsequent operations were performed under an atmosphere of nitrogen. 112.8 g of redistilled propargyl alcohol were added over a period of 0.5 hour, then the mixture was heated under reflux for 2 hours and partially cooled. 12.0 g of cuprous cyanide were added followed, over a period of 0.5 hour, by 275 g of benzyl bromide. The mixture was then heated under reflux for 92 hours, treated with excess saturated aqueous ammonium chloride solution and extracted with ether. The ether extract was dried over anhydrous sodium sulphate, filtered and evaporated. The residue was distilled and subsequently refractionated (to remove any traces of benzyl bromide) to yield 95.5 g of 4-phenyl-2-butyne-1-ol of boiling point 116°C/0.2 mm Hg.

(ii) A suspension of 12.2 g of dry magnesium in 120 ml of dry ether was treated with a crystal of iodine and 78.5 g of bromo-benzene were added dropwise thereto over a period of 0.75 hour with stirring and cooling. The resulting mixture was stirred for a further 0.25 hour at 0°—10°C. The resulting GRIGNARD solution was decanted from unreacted magnesium, 20 ml of dry ether being used to assist transfer. A solution of 26.3 g of 4-chloro-2-butyne-1-ol in 20 ml of dry ether was added to the stirred GRIGNARD solution over a period of 20 minutes at 20°C. The resulting mixture was stirred at 20°C for a further 0.75 hour, then heated under gentle reflux for 80 minutes, cooled, poured into a mixture of saturated aqueous ammonium chloride solution and ice, and extracted three times with ether. The ether extracts were washed twice with brine, dried over anhydrous sodium sulphate, filtered and evaporated. The residue was distilled to yield 24.7 g of 4-phenyl-2-butyne-1-ol of boiling point 143°—150°C/15 mm Hg; $n_D^{20}=1.5581$.

B) The process:

A solution of 14.0 g of chrysanthemum monocarboxylic acid chloride in 50 ml of dry benzene was added dropwise over a period of 0.25 hour at 20°C under a nitrogen atmosphere to a stirred solution of 12.0 g of 4-phenyl-2-butyne-1-ol and 11.85 g of dry pyridine in 120 ml of dry benzene. The resulting mixture was stirred at 20°C for a further 16 hours, then the precipitated pyridine hydrochloride was filtered off and washed with benzene. The combined filtrate and washings were washed successively with dilute aqueous hydrochloric acid, 2-N aqueous sodium hydroxide solution, dilute aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous sodium sulphate, filtered and evaporated. The residue was distilled to yield 19.5 g of 4-phenyl-2-butyne-1-ol (±) *cis/trans*-2,2-dimethyl-3-(2-methyl-propenyl)-cyclopropane carboxylic of boiling point 172°—174°C/0.65 mm Hg; $n_D^{20}=1.5277$.

EXAMPLE 2

By a procedure analogous to that described in Example 1B, from 8.8 g of 4-(2-methyl-phenyl)-2-butyne-1-ol and 9.33 g of chrysanthemum monocarboxylic acid chloride there were obtained 12.9 g of 4-(2-methyl-phenyl)-2-butyne-1-ol (±) *cis/trans*-2,2-dimethyl-3-(2-methyl-propenyl)-cyclopropane carboxylate of boiling point 190°—200°C/0.9 mm Hg.

EXAMPLE 3

By a procedure analogous to that described in Example 1B, from 10.5 g of *trans*-4-phenyl-2-buten-1-ol (containing a trace of hydroquinone) and 12.5 g of chrysanthemum monocarboxylic acid chloride there were obtained 15.5 g of *trans*-4-phenyl-2-butenyl (±) *cis/trans*-2,2-dimethyl-3-(2-methyl-propenyl)-cyclopropane carboxylate in the form of a colourless syrup of boiling point 168°—170°C/1.4 mm Hg; $n_D^{20}=1.5200$.

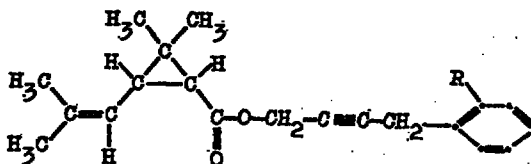
EXAMPLE 4

7.2 g of the sodium salt of chrysanthemum monocarboxylic acid were finely powdered and suspended in 400 ml of diglyme. A solution of 6.3 g of 1-chloro-4-phenyl-2-butyne in 50 ml of diglyme was added and the mixture was stirred and heated in an oil bath at 140°C under a nitrogen atmosphere for 100 hours. The precipitated sodium chloride was filtered off and the diglyme was removed under reduced pressure. The residue was treated with water and extracted three times with 150 ml of ether each time. The ether extracts were combined, washed successively with 2-N sodium hydroxide solution, water and sodium chloride solution and then dried over sodium sulphate. The solution was then filtered, evaporated and the residue distilled. 5.1 g of a product of boiling range 112°—150°C/1.0—0.8 mm Hg (bath temperature 185°C) were obtained. Purification of this product by chromatography on aluminium

oxide using petroleum ether (boiling range 40°—60°C) as the eluant yielded 3.3 g of 4 - phenyl - 2 - butynyl ($\pm$) - *cis/trans* - 2,2 - dimethyl - 3 - (2 - methyl - propenyl) - cyclopropane carboxylate; $n_D^{20}=1.5285$.

WHAT WE CLAIM IS:—

1. Chrysanthemic acid esters of the general formula



wherein R represents a hydrogen atom or the methyl group and the broken line denotes an optional bond.

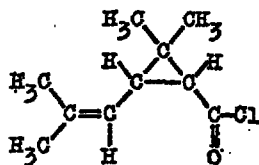
2. 4 - Phenyl - 2 - butynyl ($\pm$) - *cis/trans* - 2,2 - dimethyl - 3 - (2 - methyl - propenyl) - cyclopropane carboxylate.

3. *trans* - 4 - Phenyl - 2 - butenyl ($\pm$) - *cis/trans* - 2,2 - dimethyl - 3 - (2 - methyl - propenyl) - cyclopropane carboxylate.

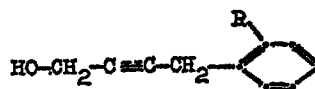
4. 4 - (2 - Methyl - phenyl) - 2 - butynyl ($\pm$) - *cis/trans* - 2,2 - dimethyl - propenyl) - cyclopropane carboxylate.

5. An insecticidal composition containing as an essential active ingredient an ester as set forth in claim 1 in association with a compatible carrier material.

6. A process for the manufacture of the esters claimed in claim 1, which process comprises reacting an acid chloride of the general formula



with an alcohol of the general formula



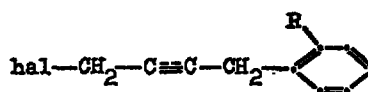
wherein R and the broken line have the significance given earlier.

7. A process as set forth in claim 6, wherein the reaction is carried out in the presence of an acid-binding agent.

8. A process as set forth in claim 7, wherein said acid-binding agent is an alkali-metal carbonate, an alkali-metal bicarbonate or a tertiary organic amine.

9. A process as set forth in claim 8, wherein pyridine is used as the acid-binding agent.

10. A process for the manufacture of the esters claimed in claim 1, which process comprises reacting an alkali-metal salt, a silver salt or a tri(lower alkyl) amine salt of a chrysanthemum carboxylic acid with a halide of the formula



wherein R and the broken line have the significance given in claim 1 and *hal* stands for a halogen atom.



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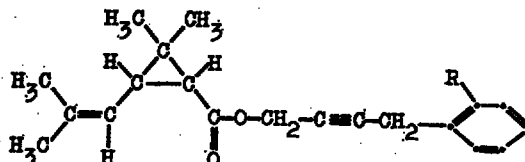
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oxide using petroleum ether (boiling range 40°—60°C) as the eluant yielded 3.3 g of 4 - phenyl - 2 - butynyl (±) - *cis/trans* - 2,2 - dimethyl - 3 - (2 - methyl - propenyl) - cyclopropane carboxylate; $n_D^{20}=1.5285$.

WHAT WE CLAIM IS:—

1. Chrysanthemic acid esters of the general formula



wherein R represents a hydrogen atom or the methyl group and the broken line denotes an optional bond.

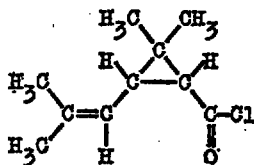
2. 4 - Phenyl - 2 - butynyl (±) - *cis/trans* - 2,2 - dimethyl - 3 - (2 - methyl - propenyl) - cyclopropane carboxylate.

3. *trans* - 4 - Phenyl - 2 - butenyl (±) - *cis/trans* - 2,2 - dimethyl - 3 - (2 - methyl - propenyl) - cyclopropane carboxylate.

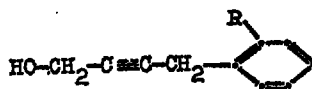
4. 4 - (2 - Methyl - phenyl) - 2 - butynyl (±) - *cis/trans* - 2,2 - dimethyl - propenyl) - cyclopropane carboxylate.

5. An insecticidal composition containing as an essential active ingredient an ester as set forth in claim 1 in association with a compatible carrier material.

6. A process for the manufacture of the esters claimed in claim 1, which process comprises reacting an acid chloride of the general formula



with an alcohol of the general formula



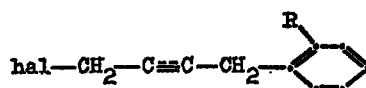
wherein R and the broken line have the significance given earlier.

7. A process as set forth in claim 6, wherein the reaction is carried out in the presence of an acid-binding agent.

8. A process as set forth in claim 7, wherein said acid-binding agent is an alkali-metal carbonate, an alkali-metal bicarbonate or a tertiary organic amine.

9. A process as set forth in claim 8, wherein pyridine is used as the acid-binding agent.

10. A process for the manufacture of the esters claimed in claim 1, which process comprises reacting an alkali-metal salt, a silver salt or a tri(lower alkyl) amine salt of a chrysanthemum carboxylic acid with a halide of the formula



wherein R and the broken line have the significance given in claim 1 and *hal* stands for a halogen atom.

11. A process as set forth in claim 10, wherein an alkali-metal salt of a chrysanthemum carboxylic acid is used.
12. A process as set forth in claim 11, wherein said salt is the sodium or potassium salt.
- 5 13. A process as set forth in claim 10, claim 11 or claim 12, wherein the halide used is a chloride or bromide. 5
14. A process as set forth in any one of claims 6 to 9 inclusive, wherein the acid chloride starting material is reacted with 4-phenyl-2-butyne-1-ol.
- 10 15. A process as set forth in any one of claims 6 to 9 inclusive, wherein the acid chloride starting material is reacted with *trans*-4-phenyl-2-buten-1-ol. 10
16. A process as set forth in any one of claims 6 to 9 inclusive, wherein the acid chloride starting material is reacted with 4-(2-methyl-phenyl)-2-butyne-1-ol.
17. A process for the manufacture of the esters set forth in claim 1, substantially as described with reference to the Examples.
- 15 18. Esters as set forth in claim 1, when manufactured by the process claimed in any one of claims 6 to 17 inclusive. 15

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