

1 387 733

## PATENT SPECIFICATION

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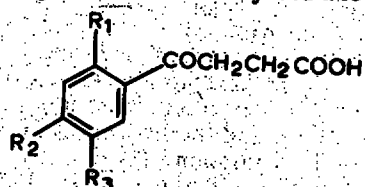
(54) 3-(TRISUBSTITUTED BENZOYL)-PROPIONIC ACID AND A  
 METHOD FOR THE PRODUCTION THEREOF

(71) We TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA also known as Takeda Chemical Industries Ltd of 27 Doshomachi 2-chome, Higashi-ku, Osaka, Japan, a body corporate organised under the laws of Japan 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:—

This invention relates to a novel 3-(trisubstituted benzoyl)-propionic acid and the production thereof.

Heretofore, there has been no report that benzoyl propionic acid derivatives have a spasmolytic or relaxing action on the gall bladder, the common biliary duct, especially Oddi's sphincter.

We have found that a compound represented by the following formula (I) has a strong spasmolytic or relaxing action on the gall bladder, the common biliary duct, especially Oddi's sphincter as well as a strong choleric activity and a low toxicity:



(I)

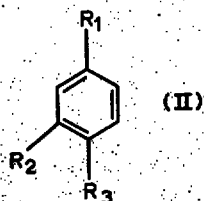
wherein R<sub>1</sub> is an alkyl group of 1 to 4 carbons, an alkoxy group of 1 to 4 carbons or hydroxyl, and R<sub>2</sub> and R<sub>3</sub> are the same or different and represent an alkyl group of 1

to 4 carbons, an alkoxy group of 1 to 4 carbons, hydroxyl, halogen or an alkylthio group of 1 to 4 carbons, or together constitute an alkylendioxy group of 1 to 3 carbons, with the proviso that when R<sub>1</sub> is an alkoxy group, at least one of R<sub>2</sub> and R<sub>3</sub> is alkoxy or alkylthio group or R<sub>2</sub> and R<sub>3</sub> together constitute alkylendioxy, when R<sub>1</sub> is alkyl or hydroxyl, R<sub>2</sub> and R<sub>3</sub> which are the same or different, represent alkoxy or alkylthio group or together constitute alkylendioxy, when R<sub>2</sub> and R<sub>3</sub> are methoxy, R<sub>1</sub> is an alkyl group of 2 or 3 carbons, an alkoxy group of 2 to 4 carbons or hydroxyl and when R<sub>2</sub> is methyl and R<sub>3</sub> is methoxy, R<sub>1</sub> is an alkoxy group of 2 to 4 carbons.

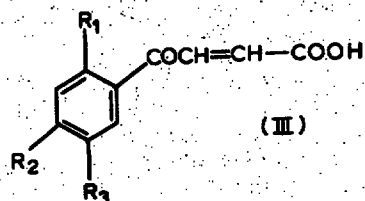
Referring to the formula (I), the alkyl group of R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub> may be exemplified by methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, sec. butyl and tert. butyl, the alkoxy group of R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub> may be exemplified by methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, sec. butoxy and tert. butoxy, the halogen atom of R<sub>2</sub> or R<sub>3</sub> may be exemplified by chlorine, bromine, iodine and fluorine, the alkylthio group of R<sub>2</sub> or R<sub>3</sub> may be exemplified by methylthio, ethylthio, *n*-propylthio, isopropylthio, *n*-butylthio, sec. butylthio and tert. butylthio and the alkylendioxy group formed by connection of R<sub>2</sub> and R<sub>3</sub> may be exemplified by methylenedioxy, ethylenedioxy and propylenedioxy.

The compound of the formula (I) can be produced by, for example:

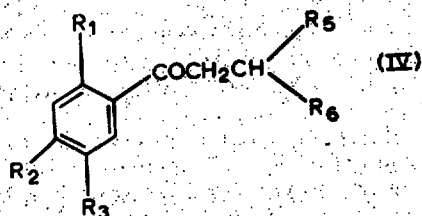
(1) reacting a compound of the formula (II)



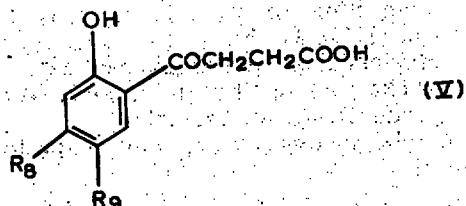
- wherein  $R_1$ ,  $R_2$  and  $R_3$  have the same meaning as defined above with a reactive derivative of succinic anhydride, succinic acid half-ester half-halide, succinic acid half-ester half nitrile or succinic acid half-ester and hydrolysing the resulting product, if necessary;
- 5 (2) subjecting a compound of the formula (III);



- wherein  $R_1$ ,  $R_2$  and  $R_3$  have the same meaning as defined above to hydrogenation; and
- 15 (3) treating a compound of the formula (IV)

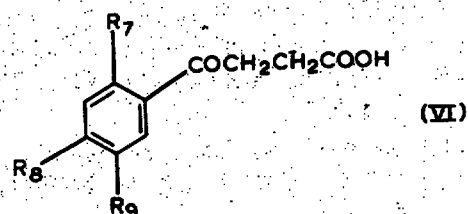


- wherein  $R_1$ ,  $R_2$  and  $R_3$  have the same meaning as defined above and  $R_5$  and  $R_6$  are the same as or different from each other, esterified carboxyl group or cyano or one of  $R_5$  and  $R_6$  is hydrogen and the other is cyano with an acid or an alkali.
- 20 The compound (I) wherein  $R_1$  is hydroxyl, namely the compound of the formula:



- wherein  $R_8$  and  $R_9$  are the same as or different from each other, an alkoxy group of 1 to 4 carbons or an alkylthio group of 1 to 4 carbons, or together constitute an
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alkylene-dioxy group of 1 to 3 carbons can be produced by, for example, subjecting a compound of the formula (VI):



where  $R_7$  is an alkoxy group and  $R_8$  and  $R_9$  have the same meaning as above to ether cleavage.

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The esterified carboxyl group of  $R_2$  and  $R_3$  may be exemplified by alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), aralkoxycarbonyl (e.g. benzoylcarbonyl or phenethyloxy-carbonyl) and aryloxycarbonyl (e.g. phenoxycarbonyl or tolyloxy-carbonyl).

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An alkoxy group of  $R_7$ ,  $R_8$  and  $R_9$ , an alkylthio group and an alkylendioxy group of  $R_8$  and  $R_9$  may be exemplified in the same way as in the case of  $R_1$ ,  $R_2$  and  $R_3$ .

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The production of the compound (I) by the reaction between the compound (II) and the reactive derivative of succinic acid varies with the kinds of reactive derivatives of succinic acid. Typical modes are as follows:

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(I—A) The reaction between the compound (II) and succinic anhydride gives directly the compound (I).

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(I—B) The reaction between the compound (II) and the succinic acid half-ester half-halide such as  $\beta$  methoxycarbopropionyl chloride and  $\beta$  ethoxycarbopropionyl chloride or succinic acid half-acid half-ester half-nitrile such as methyl  $\beta$ -cyanopropionate and ethyl  $\beta$  cyanopropionate gives the ester corresponding to the compound (I) and the hydrolysis of the ester gives the compound (I).

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(I—C) The reaction between the compound (II) and a succinic acid half-ester such as monomethyl succinate and monoethyl succinate in the presence of polyphosphoric acid or polyphosphoric acid ester gives the ester corresponding to the compound (I), and the hydrolysis of the ester gives the compound (I).

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The reaction of the above (I—A) or (I—B) is advantageously carried out in a suitable inert solvent such as an aromatic hydrocarbon or its derivative (e.g. benzene, toluene, xylene or nitrobenzene), a halogeno aliphatic hydrocarbon (e.g. methylene chloride, chloroform, carbon tetrachloride, ethylene dichloride or ethylene tetrachloride), ether (e.g. ethyl ether, propyl ether, isopropyl ether, ethyleneglycol dimethylether, ethylene-

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glycol diethylether or carbon disulfide and mixtures of two or more of them. It is desirable to carry out the reaction under anhydrous conditions and in the presence of a metal chloride such as anhydrous aluminium chloride, stannic chloride, zinc chloride and titanium tetrachloride and mixtures of two or more of them. The reaction temperature is, in general, from  $-70^{\circ}\text{C}$  to  $200^{\circ}\text{C}$ . and desirably from  $-10^{\circ}\text{C}$  to  $100^{\circ}\text{C}$ . The introduction of dry hydrogen chloride to the reaction system can serve to accelerate the desired reaction.

The reaction of the above (1—C) may conveniently be carried out in the absence of a solvent. In this reaction, any polyphosphoric acid or polyphosphoric acid ester can be employed, and it may be used in an amount of, in general, from 2 to 20 times, preferably from 5 to 10 times as much as the compound (II). The reaction temperature is, in general, from  $0^{\circ}\text{C}$ . to  $250^{\circ}\text{C}$ . desirably from  $30^{\circ}\text{C}$ . to  $100^{\circ}\text{C}$ . The other conditions may be the same as those of the reaction (1—A) or (1—B).

The reactions of (1—B) and (1—C) give the ester corresponding to the compound (I). The ester, in the reaction mixture or isolated from the reaction mixture is subjected to hydrolysis. The hydrolysis is carried out under acidic or alkaline conditions. In case of alkaline conditions, the hydrolysis may conveniently be carried out in the presence of water or a mixture of water and a lower alcohol having from 1 to 4 carbon atoms such as methanol or ethanol, in the presence of an alkaline substance such as sodium hydroxide or potassium hydroxide, sodium bicarbonate, sodium carbonate or potassium carbonate at a temperature ranging from  $-10^{\circ}\text{C}$ . to  $150^{\circ}\text{C}$ . In the case of acidic conditions, the hydrolysis may conveniently be carried out in water or a mixture of water and a lower alcohol having from 1 to 4 carbon atoms such as methanol or ethanol, an ether such as tetrahydrofuran or dioxane or an organic acid such as formic acid or acetic acid in the presence of a mineral acid such as hydrochloric acid, sulfuric acid or phosphoric acid at a temperature ranging from  $-10^{\circ}\text{C}$ . to  $150^{\circ}\text{C}$ . In the reaction of (1—C), after condensation reaction between the compound (II) and the succinic acid half-ester is completed, the polyphosphoric acid or polyphosphoric acid ester in the reaction mixture is hydrolysed by the addition of water and the hydrolysis of the ester of the compound (I) is easily carried out by the addition of an aqueous organic solvent and heating the reaction mixture.

Hydrogenation of the reaction (2) mentioned above may be carried out in conventional ways such as catalytic reduction, a reduction using an acid with a metal

such as zinc, iron or tin, or an amalgam such as sodium amalgam. Catalytic reduction is, in general, carried out in a suitable solvent such as a lower alcohol having from 1 to 4 carbon atoms (e.g. methanol or ethanol), an ether (e.g. dioxane, tetrahydrofuran, isopropyl-ether), acetic acid, ethyl acetate or water, or a mixture of two or more of them, in the presence of catalyst such as palladium, platinum, rhodium or nickel.

The compound (III) is a novel compound and it may be produced by reacting the compound (II) with a reactive derivative of maleic acid, for instance, maleic anhydride, in a manner similar to that of (1A), (1—B) or (1—C).

Treatment of the compound (IV) with an acid or an alkali can be carried out in conditions similar to those of hydrolysis of the ester in the reaction (1—B) or (1—C).

Ether cleavage of the compound (VI) is carried out in the presence of an inorganic acid e.g. hydriodic acid, hydrobromic acid or hydrochloric acid, a mixture of potassium iodide and a polyphosphoric acid, an organic acid such as formic acid, acetic acid or trifluoroacetic acid or a mixture of the organic acid and sodium iodide or potassium iodide. In addition to the acid, a suitable solvent such as water, a lower alcohol having from 1 to 4 carbon atoms, a phenol, an organic acid or an ether such as dioxane or tetrahydrofuran may be employed. The reaction temperature ranges, in general, from  $0^{\circ}\text{C}$ . to  $200^{\circ}\text{C}$ ., desirably from  $70^{\circ}\text{C}$ . to  $160^{\circ}\text{C}$ .

In order to isolate the desired compound (I) from any of the reaction mixtures among those described above, various conventional treatments may be employed. For example, steam distillation, extraction with a solvent or an alkaline solution, distillation or chromatography is advantageously employed.

The compound (I) may be obtained in the form of a pharmaceutically acceptable salt, such as a metal salt of e.g. sodium, calcium, magnesium or lithium or an ammonium salt or an amine salt.

The compound (I) thus produced is novel and has a strong spasmolytic or relaxing action on the smooth muscles of the gall bladder, the common biliary duct, especially Oddi's sphincter as well as a strong choleretic activity and low toxicity and therefore it is very useful as a therapeutic agent for cholestytopathy, especially biliary dyskinesia and cholelithiasis, or cholagogus.

The compound (I) can be administered orally in the form of tablets, granules or powder, or by way of injection.

A typical effective daily dose of the compound (I) is, usually 20 to 1000 mg, desirably, 50 to 300 mg. when administered intravenously to adult humans. Of course,

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an increased or reduced dose is also effective depending on symptoms.

The following examples, the relationship between parts by weight and parts by volume corresponds to the relationship between grams and milliliters.

#### Example 1

To a mixture of 7.5 parts by weight of 1,2,4-triethoxy-benzene, 40 parts by volume of tetrachloroethane and 7.5 parts by weight of succinic anhydride is added 23 parts by weight of anhydrous aluminium chloride and the mixture is stirred for 1 hour at 25°C. then for another 2 hours at 60°C. After the

addition of 50 parts by weight of ice and 50 parts by volume of concentrated hydrochloric acid, the reaction mixture is subjected to steam distillation. After cooling crystals separated from the remaining liquid are collected by filtration and recrystallised from aqueous ethanol, whereby 2.5 parts by weight of 3-(2', 4', 5'-triethoxybenzoyl)-propionic acid are obtained as colourless needles, m.p. 105° - 151°C.

#### Examples 2 to 4

In the manner similar to that of Example 1, the following compounds are obtained.

| Example No. | Compound                                                        | mp. (°C) |
|-------------|-----------------------------------------------------------------|----------|
| 2           | 3-(2'-ethoxy-4'-5'-dimethoxy-benzoyl)-propionic acid            | 156—158  |
| 3           | 3-(2'- <i>n</i> -butoxy-4',5'-dimethoxy-benzoyl)-propionic acid | 156—157  |
| 4           | 3-(2',4',5'-tri- <i>n</i> -butoxybenzoyl)-propionic acid        | 117—118  |

#### Example 5

To the mixture of 9.0 parts by weight of 3,4-diethoxy-toluene, 6.0 parts by weight of succinic anhydride and 100 parts by volume of carbon tetrachloride is added 27 parts by weight of anhydrous aluminium chloride. The mixture is stirred for 1 hour at 25°C. and mildly refluxed for 2 hours. After cooling, 70 parts by weight of ice and 70 parts by volume of concentrated hydrochloric acid are added to the mixture, methylenedichloride is added and the whole mixture is shaken. The organic sol-

vent layer is separated and extracted with a 2N-aqueous solution of sodium carbonate. The aqueous solution is adjusted with dilute hydrochloric acid to pH 2.5, whereby 3-(2'-methyl-4', 5'-diethoxybenzoyl)-propionic acid is obtained as crystals. Recrystallisation of the crystals gives 10.0 parts by weight of colourless plates melting at 116° - 117°C.

#### Examples 6 - 14

In a similar manner to that of Example 5, the following compounds are produced.

| Example No. | Compound                                                                         | mp. (°) |
|-------------|----------------------------------------------------------------------------------|---------|
| 6           | 3-(2',4'-dimethoxy-5'-chloro-benzoyl)-propionic acid                             | 185—187 |
| 7           | 3-(2'- <i>n</i> -propyl-4',5'-dimethoxy-benzoyl)-propionic acid                  | 95—96   |
| 8           | 3-(2'- <i>n</i> -propyl-4'-methoxy-5'-ethoxy-benzoyl)-propionic acid             | 93      |
| 9           | 3-(2'- <i>n</i> -propyl-4'-methoxy-5'- <i>n</i> -propoxy-benzoyl)-propionic acid | 70      |
| 10          | 3-(2'- <i>n</i> -propyl-4'-methoxy-5'- <i>n</i> -butoxy-benzoyl)-propionic acid  | 85—86   |
| 11          | 3-(2',4'-diethoxy-5'-chlorobenzoyl)-propionic acid                               | 172—173 |
| 12          | 3-(2'-methoxy-4'- <i>t</i> -butyl-5'-ethoxy-benzoyl)-propionic acid              | 135—137 |
| 13          | 3-(2',4'-diethoxy-5'-ethyl-benzoyl)-propionic acid                               | 153—155 |
| 14          | 3-(2'-methoxy-4'-chloro-5'-methoxy-benzoyl)-propionic acid                       | 186—188 |

#### Example 15

To the mixture of 13.6 parts by weight of 1-ethoxy-3, 4-dimethoxybenzene, 12 parts by weight of  $\beta$ -ethoxycarbopropionyl chloride and 65 parts by volume of benzene are added 18 parts by weight of anhydrous stannic chloride over 25 minutes, and the mixture is stirred at 25°C. for 1 hour. The mixture is cooled at 5°C. and 130 parts by volume of 20% hydrochloric acid are added thereto on stirring. To the mixture is added 250 parts by volume of methylene chloride and the mixture is shaken. The methylene chloride layer is separated and extracted with a 5% aqueous solution of sodium bicarbonate twice and then washed with water twice. After drying with anhydrous calcium chloride, the solvent is distilled off.

To the residue are added 120 parts by volume of methanol and 95 parts by volume of 1*N*-methanolic potassium hydroxide. The mixture is stirred at 60°C. for 1 hour. After removal of methanol by distillation under reduced pressure, to the residue are added 150 parts by volume of water and 100 parts by volume of methylene chloride, and the mixture is shaken. The aqueous layer is separated and adjusted to pH 2.5 with concentrated hydrochloric acid, whereby 14 parts by weight of 3-(2'-ethoxy-4', 5'-dimethoxybenzoyl)-propionic acid are obtained as pale yellow crystals. m.p. 156°—158°C.

#### Examples 16—23

In a manner similar to that of Example 15, the following compounds are obtained.

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| Example No. | Compound                                                                        | mp. (°C) |
|-------------|---------------------------------------------------------------------------------|----------|
| 16          | 3-(2',4'-5'-triethoxybenzoyl)-propionic acid                                    | 150—151  |
| 17          | 3-(2'- <i>n</i> -butoxy-4',5'-dimethoxybenzoyl)-propionic acid                  | 156—157  |
| 18          | 3-(2'-methoxy-4',5'-methylene-dioxy-benzoyl)-propionic acid                     | 140—141  |
| 19          | 3-(2'- <i>n</i> -propyl-4',5'-methylene-dioxy-benzoyl)-propionic acid           | 138—139  |
| 20          | 3-(2'- <i>n</i> -propyl-4'-methoxy-5'- <i>n</i> -butoxy-benzoyl)-propionic acid | 85—86    |
| 21          | 3-(2'-ethoxy-4'-methyl-5'-methylthio-benzoyl)-propionic acid                    | 117—118  |
| 22          | 3-(2'-methoxy-4'-chloro-5'-methoxybenzoyl)-propionic acid                       | 186—188  |
| 23          | 3-(2'-methoxy-4'- <i>t</i> -butyl-5'-ethoxybenzoyl)-propionic acid              | 135—137  |

#### Example 24

In 30 parts by volume of dried ethylether are dissolved 3.0 parts by weight of 1,2,4-triethoxybenzene and 3.0 parts by weight of methyl- $\beta$ -cyanopropionate. To the solution are added 2.0 parts by weight of anhydrous zinc chloride and 2.0 parts by weight of anhydrous aluminium chloride. Hydrogen chloride gas is passed through the mixture over 30 minutes. The mixture is left standing at 15°C. for 15 hours and 100 parts by volume of ethylether are added thereto. After removal of the upper layer, the residue is mixed with 100 parts by volume of 20% hydrochloric acid and refluxed for 30 minutes, whereby pale yellow crystals are separated. After cooling, the crystals are collected by filtration (yield: 4.3 parts).

20. The crystals thus obtained are mixed with 30 parts by volume of methanol and 50 parts by volume of 1N-methanolic potassium hydroxide and heated for 40 minutes. After removal of the solvent, the remaining liquid is dissolved in 70 parts by volume of water and neutralised with concentrated hydrochloric acid, whereby 3.0 parts by weight of 3-(2', 4', 5'-triethoxybenzoyl)-propionic acid are obtained as crystals melting at 150°—151°C.

#### Example 25

In a similar manner to that of Example

24, 3-(2', 4', 5'-tri-*n*-butoxybenzoyl)-propionic acid is obtained as colourless crystals melting at 117°—118°C.

#### Example 26

A mixture of 12 parts by weight of 3,4-diethoxytoluene, 10 parts by weight of succinic acid monoethyl ester and 100 parts by weight of polyphosphoric acid is heated at 50°C. for 1 hour. To the mixture is added 200 parts by volume of ice-water and the mixture is extracted with diethylether. By distilling off the solvent, 15 parts by weight of ethyl 3-(2'-methyl-4', 5'-diethoxybenzoyl)-propionate are obtained as crystals melting at 81° - 82°C.

The crystals are added to a mixture of 70 parts by volume of methanol and 70 parts by volume of 1N-methanolic potassium hydroxide and heated at 50°C. for 1 hour. After removal of methanol, the remaining liquid is dissolved in water and neutralised with concentrated hydrochloric acid, whereby 3(2'-methyl-4', 5'-diethoxybenzoyl)-propionic acid is obtained as crystals. Recrystallisation from aqueous methanol gives 12 parts by weight of colourless platelets melting at 116° - 117°C.

#### Example 27—32

In a similar manner to that of Example 26, the following compounds are obtained

16

| Example No. | Compound                                                                       | mp. (°C) |
|-------------|--------------------------------------------------------------------------------|----------|
| 27          | 3-(2'-methoxy-4'-t.-butyl-5'-ethoxybenzoyl)-propionic acid                     | 135—137  |
| 28          | 3-(2- <i>n</i> -propyl-4'-methoxy-5'- <i>n</i> -propoxybenzoyl)-propionic acid | 70       |
| 29          | 3-(2',4',5'-tri- <i>n</i> -butoxybenzoyl)-propionic acid                       | 117—118  |
| 30          | 3-(2'-methoxy-4',5-methylene-dioxy-benzoyl)-propionic acid                     | 140—141  |
| 31          | 3-(2'- <i>n</i> -butoxy-4',5-dimethoxy-benzoyl)-propionic acid                 | 156—157  |
| 32          | 3-(2',5'-diethoxy-4'-methyl-benzoyl)-propionic acid                            | 128—129  |

**Example 33**

To a 50% (weight/volume) chloroform solution of polyphosphoric acid ester are added 5 parts by weight of 1, 2, 4-triethoxybenzene and 3 parts by weight of succinic acid half-methyl ester. The mixture is heated at 50°C. for 1 hour and mixed with 50 parts by volume of ice-water and 30 parts by volume of chloroform and then stirred for 40 minutes at 26°C.

The chloroform layer is separated and washed with water and dried. The solvent is distilled off. To the residue is added 30 parts by volume of methanol and 30 parts by volume of 1*N*-methanolic potassium hydroxide. The mixture is stirred for 40 minutes at 50°C. and the solvent is distilled off. The residue is dissolved in 100 parts by volume of water and washed with 30 parts by volume of diethylether. The pH of the mixture is adjusted to 2.5 with concentrated hydrochloric acid, whereby 3-(2', 4', 5'-triethoxybenzoyl)-propionic acid is obtained as crystals. Recrystallisation of the crystals from aqueous acetone gives 4.1 parts by weight of colourless plates melting at 150° - 151°C.

**Example 34**

To a mixture of 2.1 parts by weight of 1, 2, 4-triethoxybenzene, 1.2 parts by weight of maleic anhydride and 30 parts by volume of carbon tetrachloride are added 5.2 parts by

weight of anhydrous aluminium chloride. The mixture is stirred for 1 hour and heated at 50°C. for another hour. After cooling, concentrated hydrochloric acid and ice are added to the mixture. The mixture is extracted with methylenechloride and the methylene chloride layer is washed with water and dried over anhydrous sodium sulfate. Upon removing the solvent by distillation, 3-(2', 4', 5'-triethoxybenzoyl)-trans-acrylic acid is obtained as crystals. Recrystallisation from a mixture of ethanol and benzene gives yellow needles melting at 192° - 194°C.

A mixture of 1.0 part by weight of 3-(2', 4', 5'-triethoxy-benzoyl)-trans-acrylic acid, 50 parts by volume of methanol and 0.2 part by weight of 5% palladium-charcoal is subjected to catalytic reduction at 25°C. under atmospheric pressure for 1 hour. After removal of the catalyst by filtration, the filtrate is evaporated and the residue is recrystallised from aqueous ethanol to give 0.85 part by weight of 3-(2', 4', 5'-triethoxybenzoyl)-propionic acid as pale yellow needles melting at 150 - 151°C.

**Examples 35—38**

In a similar manner to that of Example 34, the following starting 3-(trisubstituted benzoyl)-acrylic acids and desired 3-(trisubstituted benzoyl)-propionic acids are obtained.

| Example No. | Starting compound                                                |           | Catalyst   | Objective compound                                           |         |
|-------------|------------------------------------------------------------------|-----------|------------|--------------------------------------------------------------|---------|
|             | Compound                                                         | mp (°C)   |            | Compound                                                     | mp (°C) |
| 35          | 3-(2'-methyl-4',5'-diethoxy-benzoyl)-trans-acrylic acid          | 126—127.5 | Pd—C       | 3-(2'-methyl-4',5'-diethoxy-benzoyl)-propionic acid          | 116—117 |
| 36          | 3-(2',4'-diethoxy-5'-chlorobenzoyl)-trans-acrylic acid           | 198       | Na-amalgam | 3-(2',4'-diethoxy-5'-chlorobenzoyl)-propionic acid           | 172—173 |
| 37          | 3-(2'-n-propyl-4'-methoxy-5'-n-butoxybenzoyl)-trans-acrylic acid | 91—93     | Pd—C       | 3-(2'-n-propyl-4'-methoxy-5'-n-butoxybenzoyl)-propionic acid | 85—86   |
| 38          | 3-(2'-n-propyl-4'-methoxy-5'-n-butoxybenzoyl)-cis-acrylic acid   | 103—106   | Pd—C       | 3-(2'-n-propyl-4'-methoxy-5'-n-butoxybenzoyl)-propionic acid | 85—86   |

#### Example 39

To a mixture of 0.56 part by weight of diethyl malonate, 0.2 part by weight of 50% sodium hydride and 8.0 part by volume of dried tetrahydrofuran is added 1.0 part by weight of 2',4',5'-triethoxyphenacyl chloride little by little at 25°C., and the mixture is stirred for 10 hours. To the mixture are added 8 parts by volume of ethyl acetate and 50 parts by weight of ice water and the result is shaken. The ethyl acetate layer is separated and washed with water and then dried and evaporated. The residue is recrystallised from methanol to give ethyl 3-(2',4',5'-triethoxybenzoyl)-2-ethoxycarboxypropionate as pale yellow plates melting at 97° - 98°C. A mixture of 1.5 parts by weight of ethyl 3-(2',4',5'-triethoxybenzoyl)-2-

#### Example 40

In a similar manner to that of example 39, 2.0 parts by weight of 2',4',5'-triethoxyphenacyl chloride are reacted with 35 0.9 parts by weight of ethyl cyanacetate and 0.34 part by weight of 50% sodium hydride. ethoxycarboxypropionate, 30 parts by volume of dioxane and 30 parts by volume of 30% sulfuric acid is heated at 120°C. for 2 hours. The mixture is diluted with water and extracted with chloroform. The chloroform layer is separated and washed with water and dried. The solvent is distilled off, whereby 1.1 parts by weight of 3-(2',4',5'-triethoxybenzoyl)-propionic acid are obtained. Recrystallisation from aqueous methanol gives pale yellow needles melting at 150° - 151°C.

The reaction mixture is subjected to chromatography with silica gel and eluted with benzene, whereby 0.62 part by weight of 3-(2', 4', 5'-triethoxybenzoyl)-2-ethoxycarbopropionitrile is obtained as crystals. Recrystallisation from methanol gives colourless plates melting at 109°C. - 110°C.

One part by weight of 3-(2', 4', 5'-triethoxybenzoyl)-2-ethoxycarbopropionitrile is treated with 14 parts by volume of 4N-hydrochloric acid and 40 parts by volume of acetic acid at 100° - 110°C. for 2 hours. The reaction mixture is treated in the same manner as that of Example 39 whereby 0.65 part by weight of 3-(2', 4', 5'-triethoxybenzoyl)-propionic acid is obtained. mp. 150 - 151°C.

#### Example 41

To a mixture of 5.0 parts by weight of 3-methoxy-4-*n*-butoxy-*n*-propylbenzene, 4.0 parts by weight of  $\beta$ -chloropropionyl chloride and 20 parts by volume of dried benzene is added dropwise 9.0 parts by weight of stannic chloride dissolved in 5 parts by volume of carbon tetrachloride on cooling below 20°C. After stirring for 2 hours, about 200 parts by volume of ice-water are added to the mixture, 200 parts by volume of benzene are added and the mixture is shaken. The benzene layer is separated and washed with water and dried. The solvent is distilled off and the residue is crystallised from petroleum ether whereby  $\omega$ -chloro (2' - *n* - propyl - 4' - methoxy - 5' - *n* - butoxy)-propiophenone is obtained as colourless prisms. m.p. 42 - 43°C.

To 30 parts by volume of dimethylsulfoxide are added 6.0 parts by weight of  $\omega$ -chloro-2'-*n*-propyl - 4' - methoxy - 5' - *n* - butoxy-propiophenone. To the mixture is added 1.0 parts by weight of sodium cyanide. The mixture is stirred for 2 hours at 80°C. The reac-

tion mixture is mixed with ice-water and extracted with benzene. The benzene layer is washed with water and dried. The solvent is distilled off and the residue is crystallised from aqueous ethanol to give 3-(2'-*n*-propyl-4' - methoxy - 5' - *n* - butoxybenzoyl)-propionitrile which is obtained as colourless needles melting at 76°C.

A mixture of 1 part by weight of 3-(2'-*n*-propyl-4' - methoxy - 5' - *n*-butoxybenzoyl)-propionitrile, 2 parts by volume of concentrated hydrochloric acid, 5 parts by volume of water and 5 parts by volume of acetic acid is stirred for 1.5 hours at 80° - 90°C. The reaction mixture is diluted with water and extracted with methylenechloride and the extract is washed, dried and concentrated. The residue is mixed with *n*-hexane and cooled whereby 0.8 part by weight of 3-(2' - *n* - propyl - 4' - methoxy - 5' - *n* - butoxybenzoyl)-propionic acid is obtained as crystals. Recrystallisation from a mixture of methylenechloride and *n*-hexane gives pale yellow crystals melting at 85° - 86°C.

#### Example 42

A mixture of 2 parts by weight of 3-(2', 4', 5'-triethoxybenzoyl)-propionic acid, 12 parts by weight of potassium iodide and 60 parts by volume of formic acid is refluxed for 3 hours and the solvent is distilled off. The residue is mixed with 50 parts by volume of water and stirred for a while and then insoluble substance is collected by filtration. The substance is washed with water and recrystallised from aqueous ethanol whereby 1.2 parts by weight of 3-(2' - hydroxy - 4', 5' - diethoxybenzoyl)-propionic acid are obtained as colourless crystals melting at 142° - 144°C.

#### Examples 43-45

According to a similar manner to that of Example 42, the following compounds are obtained.

| Example No. | Compound                                                     | mp (°C) |
|-------------|--------------------------------------------------------------|---------|
| 43          | 3-(2'-hydroxy-4',5'-dimethoxybenzoyl)-propionic acid         | 162-163 |
| 44          | 3-(2'-hydroxy-4',5'-methylenedioxybenzoyl)-propionic acid    | 180-182 |
| 45          | 3-(2'-hydroxy-4',5'- <i>n</i> -butoxybenzoyl)-propionic acid | 127     |

#### Example 46

In 50 parts by volume of ethyl acetate are dissolved 9 parts by weight of 2-methyl-4,5-diethoxy-acetophenone and 12 parts by weight of cupric bromide and the mixture is refluxed for 30 minutes. After removal of white inorganic substance by filtration, the filtrate is washed with water and dried over

anhydrous sodium sulfate and the solvent is distilled off. The residue is recrystallised from petroleum ether to give 8.6 parts by weight of 2'-methyl-4', 5'-diethoxyphenacylbromide as colourless crystals.

To a mixture of 15 parts by volume of dry tetrahydrofuran, 0.6 part by weight of

10 diethyl malonate and 0.22 part by weight of sodium hydride is added 0.7 parts by weight of 2'-methyl-4',5'-diethoxyphenacylbromide and the mixture and the mixture is stirred for 12 hours. The reaction mixture is poured into water and acidified with diluted hydrochloric acid and extracted with ethyl acetate. The extract is washed with water, dried over anhydrous sodium sulfate, and the solvent is distilled off, whereby 0.68 part by weight of ethyl 3-(2'-methyl-4',5'-diethoxybenzoyl)-2-ethoxycarbopropionate is obtained as an oily substance. The substance shows the following IR absorption and NMR spectrum.

15 IR absorption:  $\nu_{\text{max}}^{\text{film}} \text{ cm}^{-1}$  1750-1715 (ester), 1665 (ketone)  
NMR spectrum (60 MC, in  $\text{CDCl}_3$ ,  $\delta$  p.p.m.):

20

1. 1—1.6 (12H, triplet,  $-\text{CH}_2-\text{CH}_2-$ ), 2.42 (3H, singlet, aromatic  $\text{CH}_3$ ), 3.35 (2H, doublet,  $-\text{COCH}_2-$ ), 3.6—4.4 (9H, quartet and multiplet,  $-\text{CH}_2-\text{CH}_2-$  and  $-\text{CH}(\text{COOC}_2\text{H}_5)_2$ ), 6.62 (1H, singlet,  $\text{C}_6-\text{H}$ ), 7.28 (1H, singlet,  $\text{C}_6-\text{H}$ ).  
In a similar manner to that of Example 39, 3-(2'-methyl-4',5'-diethoxybenzoyl)-propionic acid is obtained from ethyl 3-(2'-methyl-4'-5'-diethoxybenzoyl)-2-ethoxycarbopropionate.

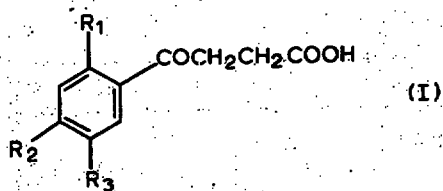
#### Examples 47—49

In a similar manner to that of Example 41, the following starting 3-(trisubstituted benzoyl)-propionitriles and desired 3-(trisubstituted benzoyl)-propionic acids are obtained.

| Example No. | Starting compound                                           |                           | Objective compound                                           |                           |
|-------------|-------------------------------------------------------------|---------------------------|--------------------------------------------------------------|---------------------------|
|             | Compound                                                    | mp ( $^{\circ}\text{C}$ ) | Compound                                                     | mp ( $^{\circ}\text{C}$ ) |
| 47          | 3-(2',4',5'-triethoxybenzoyl)-propionitrile                 | 117—118                   | 3-(2',4',5'-triethoxybenzoyl)-propionic acid                 | 150—151                   |
| 48          | 3-(2',4'-diethoxy-5'-chlorobenzoyl)-propionitrile           | 141—142                   | 3-(2',4'-diethoxy-5'-chlorobenzoyl)-propionic acid           | 172—173                   |
| 49          | 3-(2'-ethoxy-4'-methyl-5'-methylthio-benzoyl)-propionitrile | 99—100                    | 3-(2'-ethoxy-4'-methyl-5'-methylthio-benzoyl)-propionic acid | 117—118                   |

#### WHAT WE CLAIM IS:—

- 40 1. A compound of the formula (I):



45 wherein  $\text{R}_1$  is an alkyl group of 1 to 4 carbons, an alkoxy group of 1 to 4 carbons or hydroxyl, and  $\text{R}_2$  and  $\text{R}_3$  are the same or different, and represent an alkyl group of 1 to 4 carbons, an alkoxy group of 1 to 4 carbons hydroxyl, halogen or an alkylthio group of 1 to 4 carbons, or together constitute an alkylendioxy group of 1 to 3 carbons, with the proviso that, when  $\text{R}_1$  is the alkoxy group, at least one of  $\text{R}_2$  and  $\text{R}_3$  is an alkoxy group or alkylthio group, or  $\text{R}_2$  and  $\text{R}_3$  together constitute alkylendioxy, when  $\text{R}_1$  is the alkyl or hydroxyl,  $\text{R}_2$  and  $\text{R}_3$  which may be the same or different represent alkoxy or alkylthio or together constitute alkylendioxy, and that, when  $\text{R}_2$  and  $\text{R}_3$  are

methoxy  $\text{R}_1$  is an alkyl group of 2 or 3 carbons, an alkoxy group of 2 to 4 carbons or hydroxyl and when  $\text{R}_2$  is methyl and  $\text{R}_3$  is methoxy,  $\text{R}_1$  is an alkoxy group of 2 to 4 carbons, or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein  $\text{R}_1$ ,  $\text{R}_2$  and  $\text{R}_3$  which may be the same or different represent alkoxy.

3. 3-(2'-ethoxy-4',5'-dimethoxybenzoyl)-propionic acid.

4. 3-(2',4',5'-triethoxybenzoyl)-propionic acid.

5. 3-(2'-butoxy-4',5'-dimethoxybenzoyl)-propionic acid.

6. A compound as claimed in claim 1, wherein  $\text{R}_1$  is alkyl group and  $\text{R}_2$  and  $\text{R}_3$  which may be the same or different, represent alkoxy, or together constitute alkylendioxy.

7. 3-(2'-methyl-4',5'-diethoxybenzoyl)-propionic acid.

8. 3-(2'-n-propyl-4',5'-dimethoxybenzoyl)-propionic acid.

9. 3-(2'-n-propyl-4'-methoxy-5'-ethoxybenzoyl)-propionic acid.

10. 3-(2'-n-propyl-4'-methoxy-5'-n-pro-

diethyl malonate and 0.22 part by weight of sodium hydride is added 0.7 parts by weight of 2' - methyl - 4',5'-diethoxyphenacylbromide and the mixture and the mixture is stirred for 12 hours. The reaction mixture is poured into water and acidified with diluted hydrochloric acid and extracted with ethyl acetate. The extract is washed with water, dried over anhydrous sodium sulfate, and the solvent is distilled off, whereby 0.68 part by weight of ethyl 3-(2'-methyl-4', 5'-diethoxybenzoyl)-2-ethoxycarboxpropionate is obtained as an oily substance. The substance shows the following IR absorption and NMR spectrum.

IR absorption:  $\nu_{\text{max}}^{\text{film}} \text{ cm}^{-1}$  1750-1715 (ester), 1665 (keytone)

NMR spectrum (60 MC, in  $\text{CDCl}_3$ ,  $\delta$  p.p.m.):

1. 1—1.6 (12H, triplet,  $-\text{CH}_2-\text{CH}_2-$ ), 2.42 (3H, singlet, aromatic  $\text{CH}_3$ ), 3.35 (2H, doublet,  $-\text{COCH}_2-$ ), 3.6—4.4 (9H, quartet and multiplet,  $-\text{CH}_2-\text{CH}_2-$  and  $-\text{CH}(\text{COOC}_2\text{H}_5)_2$ ); 6.62 (1H, singlet,  $\text{C}_6-\text{H}$ ), 7.28 (1H, singlet,  $\text{C}_6-\text{H}$ ).

In a similar manner to that of Example 39, 3 - (2' - methyl - 4',5' - diethoxybenzoyl)-propionic acid is obtained from ethyl 3-(2'-methyl - 4' - 5' - diethoxybenzoyl)-2-ethoxycarboxpropionate.

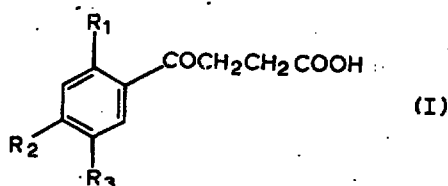
Examples 47—49

In a similar manner to that of Example 41, the following starting 3-(trisubstituted benzoyl)-propionitriles and desired 3-(trisubstituted benzoyl)-propionic acids are obtained.

| Example No. | Starting compound                                           |                           | Objective compound                                   |                           |
|-------------|-------------------------------------------------------------|---------------------------|------------------------------------------------------|---------------------------|
|             | Compound                                                    | mp ( $^{\circ}\text{C}$ ) | Compound                                             | mp ( $^{\circ}\text{C}$ ) |
| 47          | 3-(2',4',5'-triethoxybenzoyl)-propionitrile                 | 117—118                   | 3-(2',4',5'-triethoxybenzoyl)-propionic acid         | 150—151                   |
| 48          | 3-(2',4'-diethoxy-5'-chlorobenzoyl)-propionitrile           | 141—142                   | 3-(2',4'-diethoxy-5'-chlorobenzoyl)-propionic acid   | 172—173                   |
| 49          | 3-(2'-ethoxy-4'-methyl-5'-methylthio-benzoyl)-propionitrile | 99—100                    | 3-(2'-ethoxy-4'-methyl-5'-methylthio)-propionic acid | 117—118                   |

#### WHAT WE CLAIM IS:—

1. A compound of the formula (I):



wherein  $\text{R}_1$  is an alkyl group of 1 to 4 carbons, an alkoxy group of 1 to 4 carbons or hydroxyl, and  $\text{R}_2$  and  $\text{R}_3$  are the same or different, and represent an alkyl group of 1 to 4 carbons, an alkoxy group of 1 to 4 carbons, hydroxyl, halogen or an alkylthio group of 1 to 4 carbons, or together constitute an alkylendioxy group of 1 to 3 carbons, with the proviso that, when  $\text{R}_1$  is the alkoxy group, at least one of  $\text{R}_2$  and  $\text{R}_3$  is an alkoxy group or alkylthio group, or  $\text{R}_2$  and  $\text{R}_3$  together constitute alkylendioxy, when  $\text{R}_1$  is the alkyl or hydroxyl,  $\text{R}_2$  and  $\text{R}_3$  which may be the same or different represent alkoxy or alkylthio or together constitute alkylendioxy, and that, when  $\text{R}_2$  and  $\text{R}_3$  are

methoxy  $\text{R}_1$  is an alkyl group of 2 or 3 carbons, an alkoxy group of 2 to 4 carbons or hydroxyl and when  $\text{R}_2$  is methyl and  $\text{R}_3$  is methoxy,  $\text{R}_1$  is an alkoxy group of 2 to 4 carbons, or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein  $\text{R}_1$ ,  $\text{R}_2$  and  $\text{R}_3$  which may be the same or different represent alkoxy.

3. 3-(2'-ethoxy-4',5'-dimethoxybenzoyl)-propionic acid.

4. 3-(2',4',5'-triethoxybenzoyl)-propionic acid.

5. 3-(2'-butoxy-4',5'-dimethoxybenzoyl)-propionic acid.

6. A compound as claimed in claim 1, wherein  $\text{R}_1$  is alkyl group and  $\text{R}_2$  and  $\text{R}_3$  which may be the same or different, represent alkoxy, or together constitute alkylendioxy.

7. 3 - (2'-methyl - 4',5' - diethoxybenzoyl)-propionic acid.

8. 3 - (2'-n - propyl - 4',5'-dimethoxybenzoyl)-propionic acid.

9. 3-(2'-n-propyl-4'-methoxy-5'-ethoxybenzoyl)-propionic acid.

10. 3-(2'-n - propyl-4' - methoxy-5'-n-pro-



poxybenzoyl)-propionic acid.

11. 3-(2'-*n*-propyl-4'-5'-methylenedioxybenzoyl)-propionic acid.

12. A compound as claimed in claim 1, wherein  $R_1$  is alkoxy and one of  $R_2$  and  $R_3$  is alkoxy whilst the other is chlorine.

13. 3-(2',4'-diethoxy-5'-chlorobenzoyl)-propionic acid.

14. 3-(2',4'-dimethoxy-5'-chlorobenzoyl)-propionic acid.

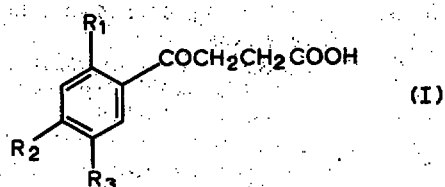
15. 3-(2',5'-dimethoxy-4'-chlorobenzoyl)-propionic acid.

16. 3-(2'-hydroxy-4',5'-dimethoxybenzoyl)-propionic acid.

17. 3-(2'-ethoxy-4'-methyl-5'-methylthiobenzoyl)-propionic acid.

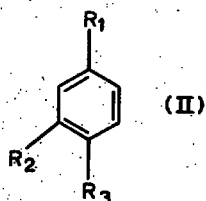
18. 3-(2'-hydroxy-4'-5'-diethoxybenzoyl)-propionic acid.

19. A method of producing a compound of the formula (I):



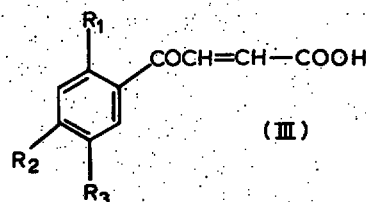
wherein  $R_1$  is an alkyl group of 1 to 4 carbons or an alkoxy group of 1 to 4 carbons of hydroxyl, and  $R_2$  and  $R_3$  which may be the same or different, represent an alkyl group of 1 to 4 carbons, hydroxyl, halogen or an alkylthio group of 1 to 4 carbons, or together constitute an alkylenedioxy group of 1 to 3 carbons, with the proviso that, when  $R_1$  is alkoxy, at least one of  $R_2$  and  $R_3$  is alkoxy or alkylthio group, or  $R_2$  and  $R_3$  together constitute alkylenedioxy, when  $R_1$  is alkyl or hydroxyl,  $R_2$  and  $R_3$  which may be the same or different, represent alkoxy or alkylthio group, or together constitute alkylenedioxy, and that when  $R_2$  and  $R_3$  are methoxy,  $R_1$  is an alkyl group of 2 or 3 carbons, an alkoxy group of 2 to 4 carbons or hydroxyl, and when  $R_2$  is methyl and  $R_3$  is methoxy,  $R_1$  is an alkoxy group of 2 to 4 carbons or hydroxyl which method comprises:

(1) reacting a compound of the formula (II):

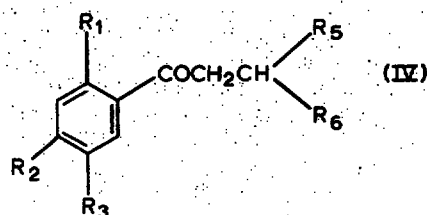


wherein  $R_1$ ,  $R_2$  and  $R_3$  have the same meaning as above, with a reactive derivative of succinic acid, and hydrolysing the resulting product, if necessary:

(2) subjecting a compound of the formula (III):

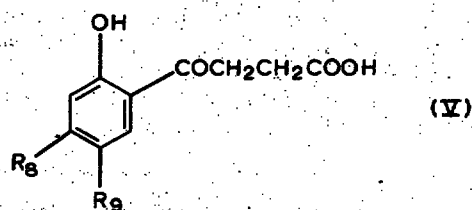


wherein  $R_1$ ,  $R_2$  and  $R_3$  have the same meaning as above to hydrogenation; or  
(3) treating a compound of the formula (IV):

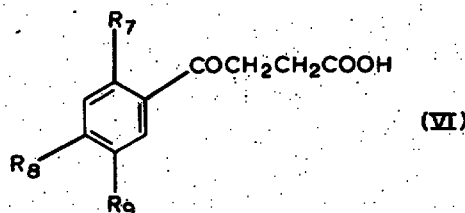


wherein  $R_1$ ,  $R_2$  and  $R_3$  have the same meaning as above and  $R_5$  and  $R_6$ , which may be the same or different, represent esterified carboxyl or cyano, or one of  $R_5$  and  $R_6$  is hydrogen and the other is cyano with an acid or an alkali and optionally converting the compound (I) to a pharmaceutically acceptable salt thereof.

20. A method for producing a compound of the formula (V):



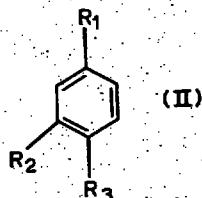
wherein  $R_8$  and  $R_9$  which may be the same or different, represent an alkoxy group of 1 to 4 carbons or an alkylthio group of 1 to 4 carbons, or together constitute an alkylenedioxy group of 1 to 3 carbons which method comprises subjecting a compound of the formula (VI):



wherein  $R_7$  is an alkoxy and  $R_8$  and  $R_9$  have the same meaning as above to an ether cleavage reaction.



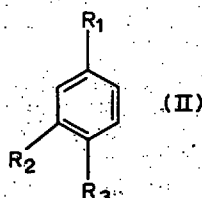
21. A method as claimed in claim 19, in which a compound of the formula (II):



5 wherein  $R_1$ ,  $R_2$  and  $R_3$  have the same meaning as above is reacted with succinic anhydride.

22. A method as claimed in claim 21, wherein  $R_1$  is alkyl group and  $R_2$  and  $R_3$  which may be the same or different represents an alkoxy group, or together constitute an alkylenedioxy group.

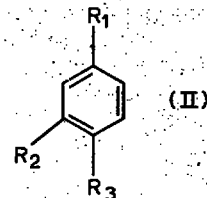
23. A method as claimed in claim 19, in which a compound of the formula (II):



15 wherein  $R_1$ ,  $R_2$  and  $R_3$  have the same meaning as above is reacted with succinic acid half-ester of half-halide or a succinic acid half-ester, half-nitrile, and the resulting product is subjected to hydrolysis.

20 24. A method as claimed in claim 23, wherein  $R_1$  is alkyl group and  $R_2$  and  $R_3$  which may be the same or different represent alkoxy group, or together constitute an alkylenedioxy group.

25. A method as claimed in claim 19, in which a compound of the formula (II):



wherein  $R_1$ ,  $R_2$  and  $R_3$  have the same meaning as above is reacted with a succinic acid half-ester in the presence of polyphosphoric acid or polyphosphoric acid ester, and the resulting product is treated with an acid or alkali.

26. A method as claimed in claim 25, wherein  $R_1$  is alkyl and  $R_2$  and  $R_3$  which may be the same or different, represent alkoxy group, or together constitute an alkylenedioxy group.

27. A method as claimed in claim 19 substantially as herein described with reference to any of the specific examples.

28. A compound of formula (I) as defined in claim 1 or pharmaceutically acceptable salt thereof when made by a method as claimed in any of claims 19—27.

29. A compound of formula (I) as defined in claim 1 or pharmaceutically acceptable salts thereof substantially as herein described with reference to any of the specific examples.

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