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(19)

(54) ISOINDOLINE COMPOUNDS

(71) We, CARLO ERBA, S.p.A., an Italian Body Corporate of Via Carlo Imbonati 24, Milan, Italy, 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.

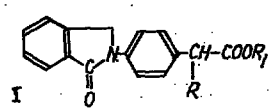
The present invention relates to certain isoindoline compounds having analgesic and anti-inflammatory activity, to a process for their preparation and to pharmaceutical compositions containing them.

In recent years, the search for substances with analgesic and anti-inflammatory activity has shifted from the cortisone derivatives (still endowed with hormonal actions) and morphine narcotics to other classes of chemical compounds.

While products with undeniable pharmacological activity have been obtained, the problem is far from completely solved, because many of these products are quite toxic and poorly tolerated, causing as they do, among other things, ulcerations, gastrointestinal disturbances and nausea; furthermore, they cause harmful secondary effects.

Certain isoindoline compounds have now been found to be characterised by negligible toxicity and to be tolerated well.

The compounds have the general formula



I

wherein R is hydrogen or lower alkyl, and R_1 is hydrogen, lower alkyl or a group of formula

$$-(CH_2)_n-NR_2R_3,$$

wherein n is 1 or 2 and each of R_2 and R_3, which may be the same or different, is hydrogen or lower alkyl; or, when R_1 is hydrogen or the group

$$-(CH_2)_nNR_2R_3,$$

a physiologically acceptable salt thereof.

When R_1 is hydrogen, the salts are with physiologically acceptable organic or inorganic bases, in particular with 2-(dimethylamino) ethanol. When R_1 is the group

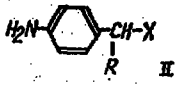
$$-(CH_2)_n-NR_2R_3,$$

the salts are with physiologically acceptable organic or inorganic acids.

The term "lower alkyl" as used herein refers to those groups having 1 to 4 carbon atoms.

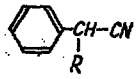
The compounds of general formula (I) may be prepared by:

(a) reacting o-cyano-benzyl bromide (which may be prepared by reacting o-cyano-toluene with bromine at above 150° C) with a compound of general formula (II)

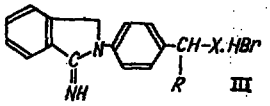


II

wherein X is a carboxy, carbethoxy or cyano group, and R is as defined above [which may be prepared from the corresponding nitro-compound by reduction with iron and ammonium chloride or by catalytic hydrogenation, the nitro-compound being obtainable in known manner by nitration of a compound of general formula

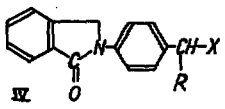


(Bull. Soc. Chim. France, 1960, p 866)] preferably at 75—85° C and in a polar solvent (e.g. ethanol or methanol), to give a compound of general formula (III)



wherein R and X are as defined above, which is subsequently reacted with a suitable base (e.g. potassium hydroxide or carbonate) or acid (e.g. concentrated sulphuric acid) preferably at 75—180° C, to give a compound of general formula (I), wherein R_1 is hydrogen, and subsequently, if desired, esterifying in known manner (preferably at 60—120° C) the compound of general formula (I) thus obtained; or

(b) reacting phthalide with a compound of general formula (II) wherein X is a carboethoxy or cyano group, preferably at 150—300° C, to give a compound of formula (IV)

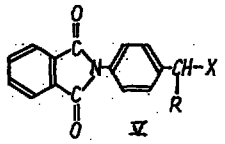


wherein R is as defined above and X is a carboethoxy or cyano group, which if desired is subsequently saponified with an appropriate base or acid, to give a compound of general formula (I), wherein R_1 is hydrogen and subsequently, if desired, esterifying as described above the compound of general formula (I), thus obtained; or

(c) reacting thiophthalide (see Prey and Kondler, Monat. für Chemie, 1958, *89*, 505) with a compound of formula (II) wherein X is a carbethoxy or cyano group, preferably at 150—280° C and in a sealed tube, to give a compound of formula (IV) which if desired is subsequently saponified to give a compound of general formula (I), wherein R_1 is hydrogen, which, if desired, is esterified as described above; or

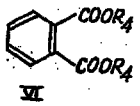
(d) reacting phthalic aldehyde with a compound of formula (II) wherein X is a carbethoxy or cyano group, preferably at 50—150° C and in a polar solvent (e.g. dimethyl formamide or dimethyl sulphoxide), to give a compound of formula (IV), which if desired is subsequently saponified to give a compound of general formula (I), wherein R_1 is hydrogen, which, if desired is esterified as described above; or

(e) reacting phthalic anhydride with a compound of formula (II) wherein X is a carbethoxy or cyano group, preferably at 60—150° C, to give a compound of formula (V)



wherein X is a carbethoxy or cyano group and R is as defined above, which is subsequently reduced, with for example zinc and acetic acid and preferably at 60 to 150° C, to give a compound of formula (IV), which if desired is subsequently saponified to give a compound of general formula (I), wherein R_1 is hydrogen, which, if desired, is esterified as described above; or

(f) reacting a compound of general formula (VI)



wherein the groups R_4 are both hydrogen, both methyl groups, or both ethyl groups, with a compound of formula (II) wherein X is a carbethoxy or cyano group preferably at 80 to 280° C and in the presence or absence of a solvent, to give a compound of formula (V), wherein X is a carbethoxy or cyano group and R is as defined above, which is subsequently reduced to give a compound of formula (IV), which if desired is then saponified to give a compound of general formula (I), wherein R_1 is a hydrogen, which, if desired, is esterified as described above; and if desired reacting the compound of general formula (I), wherein R_1 is hydrogen obtained in steps (a) to (f), with an appropriate base to give a physiologically acceptable salt, or reacting the compound of general formula (I), wherein R_1 is the group

$$-(CH_2)_n-NR_2R_3,$$

obtained in steps (a) to (f) with an appropriate acid to give a physiologically acceptable salt.

If compounds of general formula (I), wherein R_1 is an ethyl group, are desired, processes (b, (c), (d), (e) and (f) may be stopped, when the compounds of general formula (IV), wherein X is a carbethoxy group, have been obtained.

As described above, the optional esterification of the compounds of general formula (I) wherein R_1 is hydrogen, to give compounds of general formula (I), wherein R_1 is different from hydrogen, is performed in known manner. For example, the esters with 2-(dimethylamino)ethanol may be prepared by treatment of said compounds with thionyl chloride at 60 to 90° C in the presence or absence of a solvent, and then reacting the acid chlorides so obtained, with 2-(dimethylamino)ethanol at room temperature in a polar solvent, for example, dioxan, or benzene.

The compounds of general formula (I) wherein R_1 is hydrogen, may also be converted, if desired, in known manner into their salts with physiologically acceptable inorganic bases, for example sodium or calcium hydroxide, or organic bases, for example 2-(dimethylamino)ethanol. For example, the salts of the compounds of general formula (I) wherein R_1 is hydrogen, with 2-(dimethylamino)-ethanol may be obtained by reacting, at room temperature, these compounds with an aqueous solution containing a stoichiometric quantity of 2-(dimethylamino)ethanol and then lyophilizing the product. The compounds of general formula (I), wherein R_1 is the group

$$-(CH_2)_n-NR_2R_3,$$

may also be converted, if desired, in known manner into their salts with physiologically acceptable organic or inorganic acids.

The compounds of the present invention possess good analgesic and anti-inflammatory activity, as shown by the data reported in the Table 1 below, where phenylbutazone (the analgesic and anti-inflammatory activity of which has been given the conventional value of 1) is listed as a reference compound.

TABLE 1

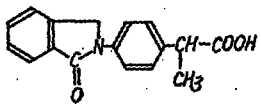
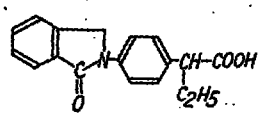
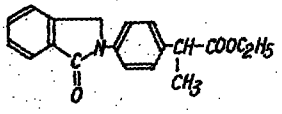
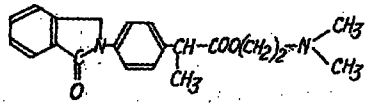
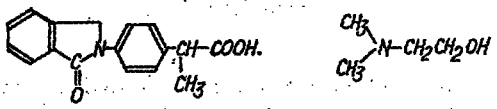
Compound	Analgesic activity	Anti-inflammatory activity
	100	20
	32	8
	40	13
	33	11

TABLE 1 (Continued)

Compound	Analgesic activity	Anti-inflammatory activity
	54	42
Phenylbutazone	1	1

The analgesic activity was assessed by means of the phenylquinone test in mice [Siegmund *et al.*, Proc. Soc. Exper. Biol. Med., *95*, 729 (1957)].

The anti-inflammatory activity was assessed by means of the carrageenin-induced oedema test in rats [Winter *et al.*, Proc. Soc. Exper. Biol. Med., *111*, 544 (1962) and J. Pharmac. Exp. Therap., *141*, 369 (1963)].

Table 2 shows the anti-inflammatory activity of 1 - oxo - 2 - {p - [(α - methyl) - carboxymethyl] - phenyl} - isoindoline (I) in comparison with α - [3 - chloro - 4 - (1 - oxo - 2 - isoindolinyl) - phenyl] - propionic acid (II), described in Belgian Patent Specification No. 753,600.

TABLE 2

Test	Potency ratio I/II	Limits for P = 0.05
Carrageenin-induced oedema in rat paw	5.27	2.84 — 10.78
Granuloma pouch test in the rat	12.66	6.60 — 58.58

In Table 2, the anti-inflammatory activity was determined by employing both Winter's method, as previously indicated, and the granuloma pouch technique [Boris and Stevenson, Arch. Int. Pharmacodyn., *153*, 205 (1965)]. The potency ratios were estimated following the parallel line biological assay method [Finney, Statistical Method in Biological Assay—Griffin—London (1952)].

As shown by the data reported in Table 2, it was surprisingly found that the anti-inflammatory activity of 1 - oxo - 2 - {p - [(α - methyl) - carboxymethyl] - phenyl} - isoindoline is much higher than that of α - [3 - chloro - 4 - (1 - oxo - 2 - isoindolinyl) - phenyl] - propionic acid.

The pharmacological data reported above have been confirmed by clinical trials performed on man.

The compounds of the present invention are preferably administered orally, but they can also be administered by the parenteral or topical route.

The pharmaceutical compositions containing the compounds of this invention can therefore be in the form of capsules, tablets, pills, syrups, vials, suppositories or ointments.

Examples of the substances which can serve as pharmacological carriers or diluents for the pharmaceutical compositions are talc, gelatin, lactose, starch, magnesium stearate, polyvinylpyrrolidone, as well as other non-toxic compatible substances used in pharmaceutical formulations.

The invention therefore also provides a pharmaceutical composition comprising a compound of general formula (I) and a pharmaceutically acceptable carrier or diluent.

The invention is illustrated by the following Examples.

Example 1.

A mixture of ethyl p - amino - (α - methyl)-phenylacetate (24.15 g.; 0.125 moles) and o - cyano - benzyl bromide (24.5 g.; 0.125 moles) in 99.9% ethanol (400 ml) is heated under a reflux for 6 hours, treated with charcoal and filtered while hot. The filtrate is concentrated to about one third and then poured in diethyl ether (1500 ml). The precipitate is filtered and washed again with diethyl ether (100 ml) to obtain 1 - imino - 2 - {p-[(α - methyl) - carboethoxymethyl] - phenyl}-isoindoline. HBr (44.8 g., yield = 92%), m.p. 203—204° C.

In the same way, and by reacting o - cyano-benzyl bromide with the appropriate amino acid esters, the following compounds are obtained:

1 - imino - 2 - [2 - (carboethoxymethyl)-phenyl] - isoindoline. HBr, m.p. 204—206° C.

1 - imino - 2 - {p - [(α - ethyl) - carboethoxymethyl] - phenyl} -isoindoline. HBr, m.p. 157—159° C.

1 - imino - 2 - {p - [(α - propyl) - carboethoxymethyl] - phenyl} - isoindoline. HBr, m.p. 158—160° C.

1 - imino - 2 - {p - [(α - butyl) - carboethoxymethyl] - phenyl} isoindoline. HBr, m.p. 140—142° C.

Example 2.

1 - imino - 2 - {p - [(α - methyl) - carboethoxymethyl] - phenyl} - isoindoline HBr, (9.73 g.; 0.025 moles) dissolved in 95% ethanol (65 ml) is added to potassium carbonate (13.82 g.; 0.1 moles) dissolved in water (100 ml). The mixture of the reagents is heated under reflux while stirring for 18 hours thus obtaining complete solution. Ethyl alcohol is evaporated under vacuum, the insoluble residue is filtered off and the filtrate is acidified with 8% hydrochloric acid (about 60 ml).

The precipitate thus obtained is filtered, washed with water (100 ml), with 8% hydrochloric acid (30 ml), and again with water (50 ml) to obtain, after crystallization from 95% ethanol, 1 - oxo - 2 - {p - [(α - methyl)-carboxymethyl] - phenyl} - isoindoline (6 g., yield = 85%), m.p. 213—214° C.

In the same way, and by employing the compounds prepared according to Example 1, the following compounds are obtained:

1 - oxo - 2 - [p - (carboxymethyl) - phenyl]-isoindoline, m.p. 208—209° C.

1 - oxo - 2 - {p - [(α - ethyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 180—182° C.

1 - oxo - 2 - {p - [(α - propyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 160—162° C.

1 - oxo 2 - {p - [(α - butyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 145—147° C.

Example 3.

A mixture of o - cyano - benzyl bromide (3.92 g.; 0.02 moles) and p - amino - (α-methyl) - phenylacetic acid (3.3 g.; 0.02 moles) in 99.9% ethanol (80 ml) is heated under reflux for 6 hours, evaporated to small volume (about 30 ml) under vacuum and then poured in diethyl ether (about 400 ml). The separated solid is crystallized from ethanol diethyl ether to obtain 1 - imino - 2 - {p-[(α - methyl) - carboxymethyl] - phenyl}-isoindoline. HBr (5.77 g. yield = 80%), m.p. 264—266° C (dec.).

This product dissolved in 95% ethanol (60 ml) is added to potassium carbonate (6.91 g.; 0.05 moles) dissolved in water (50 ml). The mixture of the reagents is refluxed for 12 hours to obtain complete solution. Ethyl alcohol is evaporated under vacuum, the undissolved residue is filtered and the filtrate is acidified with 8% hydrochloric acid (about 30 ml). The precipitate thus formed is filtered, washed with water (80 ml), with 8% hydrochloric acid (15 ml) and again with water (40 ml), to obtain, after crystallization from 95% ethanol, 1 - oxo - 2 - {p - [(- methyl)-carboxymethyl] - phenyl} - isoindoline (4.7 g., yield = 84%), m.p. 213—214° C.

In the same way, and by reacting o-cyano-benzylbromide with the appropriate amino acids, the following compounds are obtained:

1 - oxo - 2 - [p - (carboxymethyl) - phenyl-isoindoline, m.p. 208—209° C.

1 - oxo - 2 - {p - [(α- ethyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 180—182° C.

1 - oxo - 2 - {p - [(α - propyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 160—162° C.

1 - oxo - 2 - {p - [(α - butyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 145—147° C.

Example 4.

Phthalide (2.7 g.; 0.02 moles) and ethyl p - amino (α - methyl) - phenylacetate (11.6 g.; 0.06 moles) are heated to 280° for 4 hours in a sealed tube, then cooled, treated with water (100 ml), acidified with 8% hydrochloric acid (40 ml), and extracted with ethyl acetate (200 ml). The organic layer is washed with water (80 ml), dried and evaporated to dryness *in vacuo*. The oily residue is crystallized from ligroin to obtain 1 - oxo - 2 - {p - [(α-methyl) - carboethoxymethyl] - phenyl}-isoindoline (4.32 g., yield = 70%), m.p. 99—101° C.

In the same way, and by reacting phthalide with the appropriate amino acid esters, the following compounds are obtained:

1 - oxo - 2 - [p - (carboethoxymethyl)-phenyl] - isoindoline, m.p. 122—124° C.

1 - oxo - 2 - {p - [(α - ethyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 107—109° C.

1 - oxo - 2 - {p - [(α - propyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 105—106° C.

1 - oxo - 2 - {p - [(α - butyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 106—107° C.

Example 5.

Thiophthalide (1.5 g.; 0.01 moles) and ethyl p - amino - (α - methyl) - phenylacetate (5.8 g.; 0.03 moles) are heated to 190—200° for 3 hours in a sealed tube, then cooled, treated with water (50 ml), acidified with 8% hydrochloric acid (20 ml), and extracted with ethyl acetate (50 ml). The organic layer is washed with water (40 ml), dried and evaporated to dryness *in vacuo*. The residue is crystallized from ligroin to obtain 1 - oxo - 2-{p - [(α - methyl) - carboethoxymethyl]-phenyl} - isoindoline (2.32 g., yield = 75%), m.p. 99—101° C.

In the same way, and by reacting thiophthalide with the appropriate amino acid esters, the following compounds are obtained:

1 - oxo - 2[p - (carboethoxymethyl)-phenyl] - isoindoline, m.p. 122—124° C.

1 - oxo - 2 - {p - [(α - ethyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 107—109° C.

1 - oxo - 2 - {p - [(α - propyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 105—106° C.

1 - oxo 2 - {p - [(α - butyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 106—107° C.

Example 6.

A solution of phthalic aldehyde (2.94g.; 0.022 moles) suspended in dimethylformamide (200 ml), heated to 60°, was treated with ethyl p - amino - (α - methyl) - phenylacetate (3.86 g.; 0.02 moles), dissolved in dimethylformamide (150 ml), over an hour. The mixture is stirred again for 2 hours at 60°, and the solvent is evaporated under vacuum. The oily residue is dissolved in ethyl acetate (80 ml), washed with 8% hydrochloric acid (15 ml) and with water (30 ml). The organic layer is dried, evaporated to dryness under vacuum, and the residue is crystallized from ligroin to obtain 1 - oxo - 2 - {p - [(α-methyl) - carboethoxymethyl] - phenyl}-isoindoline (5.25 g., yield = 85%), m.p. 99—101° C.

In the same way, and by reacting phthalic aldehyde with the appropriate amino acid esters, the following compounds are obtained:

1 - oxo 2 - [p - (carboethoxymethyl)-phenyl] - isoindoline, m.p. 122—124° C.

1 - oxo - 2 - {p - [(α - ethyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 107—109° C.

1 - oxo - 2 - {p - [(α - propyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 105—106° C.

1 - oxo - 2 - {p - [(α - butyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 106—107° C.

Example 7.

A mixture of phthalic anhydride (14.8 g.; 0.1 moles) and ethyl p - amino - (α - methyl)-phenylacetate (19.3 g.; 0.1 moles) in glacial acetic acid (70 ml) is heated under reflux for 4 hours, hen cooled at abolt 40°, and diluted with water (50 ml). The oily precipitate, which formed, solidifies after rubbing, is then cooled at 0°, filtered and washed with water (40 ml), to obtain, after crystallization from 99.9% ethanol, N - {4 - [(α - methyl) - carboethoxymethyl] - phenyl} - phthalimide (30 g., yield = 93%), m.p. 113—114° C. In the same way, and by reacting phthalic anhydride with the appropriate amino acid esters, the following compounds are obtained:

N - [4 - (carboethoxymethyl) - phenyl]-phthalimide, m.p. 150—152° C.

N - {4 - [(α - ethyl) - carboethoxymethyl]-phenyl} - phthalimide, m.p. 108—109° C.

N - {4 - [(α - propyl) - carboethoxymethyl] - phenyl} - phthalimide, m.p. 119—121° C.

N - {4 - [(α - butyl) - carboethoxymethyl]-phenyl} - phthalimide, m.p. 80—82° C.

Example 8.

A mixture of phthalic acid (16.6 g.; 0.1 moles) and ethyl p - amino - (α - methyl)-phenyl - acetate (20 g.; 0.103 moles) is heated in an oil bath at 200—210° for an hour and a quarter, then cooled, to obtain, after crystallization from 99% ethanol, N - {4 - [(α-methyl) - carboethoxymethyl] - phenyl}-phthalimide (31 g., yield = 96%), m.p. 113—114° C. In the same way, and by reacting phthalic acid with the appropriate amino acid esters, the following compounds are obtained:

N - [4 - (carboethoxymethyl) - phenyl]-phthalimide, m.p. 150—152° C.

N - {4 - [(α - ethyl) - carboethoxymethyl]-phenyl} - phthalimide, m.p. 108—109° C.

N - {4 - [(α - propyl) - carboethoxymethyl] - phenyl} - phthalimide, m.p. 119—121° C.

N - {4 - [(α - butyl) - carboethoxymethyl]-phenyl} - phthalimide, m.p. 80—82° C.

Example 9.

Diethyl phthalate (4.44 g.; 0.02 moles) and ethyl p - amino - (α - methyl) - phenylacetate (3.86 g.; 0.02 moles) suspended in anhydrous dimethylformamide (100 ml) are heated under reflux for 4 hours. The mixture

is evaporated to dryness under vacuum, the residue is redissolved in ethyl acetate (100 ml), then washed with 8% hydrochloric acid (15 ml), with water (40 ml), dried and evaporated to dryness under vacuum, to obtain, after crystallization from 99% ethanol, N - {4-[(α - methyl) - carboethoxymethyl] - phenyl}-phthalimide (4.52 g.; yield = 70%), m.p. 113—114° C.

In the same way, and by reacting ethyl phthalate with the appropriate amino acid esters, the following compounds are obtained:

N - [4 - (carboethoxymethyl) - phenyl]-phthalimide, m.p. 150—152° C.

N - {4 - [(α - ethyl) - carboethoxymethyl]-phenyl} - phthalimide, m.p. 108—109° C.

N - {4 - [(α - propyl) - carboethoxymethyl] - phenyl} - phthalimide, m.p. 119—121° C.

N - {4 - [(α - butyl) - carboethoxymethyl]-phenyl} - phthalimide, m.p. 80—82° C.

Example 10.

To a solution of N - {4 - [(α - methyl)-carboethoxymethyl] - phenyl} - phthalimide (16.1 g.; 0.05 moles) suspended in acetic acid (200 ml), zinc in powder form (19.6 g.; 0.3 moles) is added under stirring. The mixture is heated under reflux for 4 hours, filtered, and the residue is then washed with warm acetic acid (40 ml). The filtrate is evaporated to dryness under vacuum, the residue is redissolved in water (100 ml) and neutralized (pH 7) with sodium bicarbonate. The solid, thus formed, is filtered to obtain, after crystallization from ligroin, 1 - oxo - 2 - {p-[(α - methyl) - carboethoxymethyl] - phenyl}-isoindoline (13.9 g., yield = 90%), m.p. 99—101° C.

In the same way, and starting from the phthalimides prepared according to Examples 7, 8 and 9, the following compounds are obtained:

1 - oxo - 2 - [p - (carboxyethoxymethyl)-phenyl] - isoindoline, m.p. 122—124° C.

1 - oxo - 2 - {p - [(α - ethyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 107—109° C.

1 - oxo 2 - {p - [(α - propyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 105—106° C.

1 - oxo - 2 - {p - [(α - butyl) - carboethoxymethyl] - phenyl} - isoindoline, m.p. 106—107° C.

Example 11.

A mixture of 1 - oxo - 2 - {p - [(α-methyl) - carboethoxymethyl] - phenyl}-isoindoline (12.36 g.; 0.04 moles) and potassium carbonate (12.36 g.) in 95% ethanol (280 ml) and water (182 ml) is heated under reflux for 8 hours to obtain a complete solution. Ethyl alcohol is evaporated under vacuum, the aqueous solution is acidified with 8% hydrochloric acid (55 ml), and the precipitate, thus formed, is filtered, washed with water (55 ml), to obtain, after crystallization from 95% ethanol, 1 - oxo - 2 - {p - [p-methyl) - carboxymethyl] - phenyl} - isoindoline (9.1 g., yield = 81%, m.p. 213—214° C.

In the same way, and starting from the derivatives prepared according to Examples 4, 5, and 6, the following compounds are obtained:

1 - oxo - 2 - [p - (carboxymethyl)-phenyl] - isoindoline, m.p. 208—209° C.

1 - oxo - 2 - {p - [(α - ethyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 180—182° C.

1 - oxo - 2 - {p - [(α - propyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 160—162° C.

1 - oxo 2 - {p - [(α - butyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 145—147° C.

Example 12.

A mixture of o - cyano - benzyl bromide (3.92 g.; 0.02 moles) and p -amino - (α-methyl) - phenyl - acetonitrile (2.92 g.; 0.02 moles) in 99.9% ethanol (80 ml) is heated under reflux for 6 hours and evaporated under vacuum (about 15 mm Hg.) The precipitate, thus formed, is filtered to obtain 1 - imino-2 - {p - [(α - methyl) - cyanomethyl]-phenyl} - isoindoline. HBr (5.47 g.; yield = 80%), m.p. 253—255° C.

In the same way, and by reacting o - cyano-benzyl bromide with the appropriate amino-nitrile, the following compounds are obtained:

1 - imino - 2 - [p - (cyanomethyl) - phenyl]-isoindoline. HBr

1 - imino 2 - {p - [(α - ethyl) - cyanomethyl] - phenyl} - isoindoline. HBr

1 - imino 2 - {p - [(α - propyl) - cyanomethyl] - phenyl} - isoindoline. HBr

1 - imino - 2 - {p - [(α - butyl) - cyanomethyl] - phenyl} - isoindoline. HBr

Example 13.

1 - Imino - 2 - {p - [(α - methyl) - cyanomethyl] - phenyl} - isoindoline. HBr (3.42 g.; 0.01 moles) dissolved in 99.9% ethanol (80 ml) was treated with potassium carbonate (5.52 g.) dissolved in water (20 ml). The mixture is heated under reflux for 10 hours and filtered. The residue is washed with water (50 ml) to obtain, after crystallization from 99.9% ethanol, 1 - oxo - 2 - {p - [(α - methyl)-cyanomethyl] - phenyl} - isoindoline (2.22 g., yield = 85%), m.p. 192—194° C.

In the same way, and starting from the derivatives prepared according to Example 12, the following compounds are obtained:

1 - oxo 2 - [p - (cyanomethyl) - phenyl]-isoindoline.

1 - oxo - 2 - {p - [(α - ethyl) - cyanomethyl] - phenyl} - isoindoline.

1 - oxo - 2 - {p - [(α - propyl) - cyanomethyl] - phenyl} - isoindoline.

1 - oxo - 2 - {p - [(α - butyl) - cyanomethyl] - phenyl} - isoindoline.

Example 14.

A mixture of phthalide (2.7 g.; 0.02 moles) and p - amino - (α - methyl) - phenylacetonitrile (8.8 g.; 0.06 moles) is heated to 280° for 4 hours in a sealed tube, cooled, treated with water (100 ml), acidified with 8% hydrochloric acid (40 ml) and extracted with ethyl acetate (200 ml). The organic layer is washed with water (80 ml), dried and evaporated to dryness under vacuum. The residue is crystallized from 99.9% ethanol to obtain 1 - oxo 2 - {p - [(α - methyl) - cyanomethyl] - phenyl} - isoindoline (3.57 g.; yield = 68%), m.p. 192—194° C.

In the same way, and by reacting phthalide with the appropriate amino nitrile, the following compounds are obtained:

1 - oxo - 2 - [p - cyanomethyl) - phenyl]-isoindoline

1 - oxo 2 - {p - [(α - ethyl) - cyanomethyl] - phenyl} - isoindoline

1 - oxo - 2 - {p - [(α - propyl) - cyanomethyl] - phenyl} - isoindoline

1 - oxo 2 - {p - [(α - butyl) - cyanomethyl] - phenyl} - isoindoline

Example 15.

A mixture of thiophthalide (3 g.; 0.02 moles) and p - amino - (α - methyl) - phenylacetonitrile (8.8 g.; 0.06 moles) is heated to 210—220° C for 4 hours in a sealed tube, cooled, redissolved in water (100 ml), acidified with 8% hydrochloric acid (40 ml), and extracted with ethyl acetate (150 ml). The organic layer is washed with water (80 ml), dried and evaporated to dryness under vacuum. The residue is crystallized from 99.9% ethanol to obtain 1 - oxo 2 - {p - [(α - methyl)-cyanomethyl] - phenyl} - isoindoline (3.67 g., yield = 70%), m.p. 192—194° C.

In the same way, and by reacting thiophthalide with the appropriate amino nitrile, the following compounds are obtained:

1 - oxo - 2 - [p - (cyanomethyl) - phenyl]-isoindoline

1 - oxo 2 - {p - [(α - ethyl) - cyanomethyl] - phenyl} - isoindoline

1 - oxo - 2 - {p - [(α - propyl) - cyanomethyl] - phenyl} - isoindoline

1 - oxo 2 - {p - [(α - butyl) - cyanomethyl] - phenyl} - isoindoline

Example 16.

A solution of phthalic aldehyde (2.94 g.; 0.022 moles) suspended in dimethylformamide (200 ml), heated to 60° C, was treated with p - amino - (α - methyl) - phenyl - acetonitrile (2.92 g.; 0.02 moles), dissolved in dimethylformamide (100 ml), over an hour. The mixture is stirred again for 4 hours at 60° C, and the solvent is evaporated under vacuum. The oily residue is dissolved in ethyl acetate (100 ml), washed with 8% hydrochloric acid (15 ml), and then with water (30 ml). The organic layer is dried and evaporated to dryness under vacuum. The residue is crystallized from 99.9% ethanol to obtain 1 - oxo - 2-{p - [(α - methyl) - cyanomethyl] - phenyl}-isoindoline (3.94 g., yield = 75%), m.p. 192—194° C.

In the same way, and by reacting phthalic aldehyde with the appropriate amino nitrile, the following compounds are obtained:

1 - oxo 2 - [p - (cyanomethyl) - phenyl]-isoindoline

1 - oxo 2 - {p - [(α - ethyl) - cyanomethyl] - phenyl} - isoindoline

1 - oxo 2 - {p - [(α - propyl) - cyanomethyl] - phenyl} - isoindoline

1 - oxo 2 - {p - [(α - butyl) - cyanomethyl] - phenyl} - isoindoline

Example 17.

A mixture of phthalic anhydride (17.8 g.; 0.12 moles) and p - amino - (α - methyl)-phenyl - acetonitrile (14.61 g.; 0.1 moles) in glacial acetic acid (90 ml) is heated under reflux for 4 hours to obtain a complete solution. The mixture is then cooled, and the solid which separated is filtered, washed with water and dried to obtain N - {4 - [(α-methyl) - cyanomethyl] - phenyl} - phthalimide (22.1 g., yield = 80%), m.p. 213—215° C.

In the same way, and by reacting phthalic anhydride with the proper amino nitriles, the following compounds are obtained:

N - [4 - (cyanomethyl) - phenyl] - phthalimide

N - {4 - [(α - ethyl) - cyanomethyl]-phenyl} - phthalimide

N - {4 - [(α - propyl) - cyanomethyl]-phenyl} - phthalimide

N - {4 - [(α - butyl) - cyanomethyl]-phenyl} - phthalimide

Example 18.

A mixture of phthalic acid (3.32 g.; 0.02 moles) and p - amino - (α - methyl) - phenylacetonitrile (2.96 g.; 0.02 moles) is heated in an oil bath to 220—230° C for 1½ hr., then cooled and redissolved with water and the solid which formed is filtered to obtain N-

{4 - [(α - methyl) - cyanomethyl] - phenyl}-phthalimide (4.68 g.; yield = 85%), m.p. 213—215° C.

In the same way, and by reacting phthalic acid with the appropriate amino nitrile, the following compounds are obtained:

N - [4 - (cyanomethyl) - phenyl] - phthalimide

N - {4 - [(α - ethyl) - cyanomethyl]-phenyl} - phthalimide

N - {4 - [(α - propyl) - cyanomethyl]-phenyl} - phthalimide

N - {4 - [(α - butyl) - cyanomethyl[-phenyl} - phthalimide

Example 19.

A mixture of ethyl phthalate (4.44 g.; 0.02 moles) and p - amino - (α - methyl)-phenyl acetonitrile (2.96 g.; 0.02 moles) suspended in anhydrous dimethylformamide (100 ml) is heated under reflux for 4 hours, evaporated to dryness under vacuum, the residue is then redissolved with ethyl acetate (100 ml), washed with 8% hydrochloric acid (15 ml), then with water (40 ml), subsequently dried and evaporated to dryness under vacuum. The residue is crylstallized from 99% ethanol to obtain N - {4 - [(α - methyl) - cyanomethyl] - phenyl} - phthalimide (4.13 g., yield = 75%), m.p. 213—215° C.

In the same way, and by reacting ethyl phthalate with the appropriate amino nitrile, the following compounds are obtained:

N - [4 - (cyanomethyl) - phenyl] - phthalimide

N - {4 - [(α - ethyl) - cyanomethyl]-phenyl} - phthalimide

N - {4 - [(α - propyl) - cyanomethyl]-phenyl} - phthalimide

N - {4 - [(α - butyl) - cyanomethyl]-phenyl} - phthalimide

Example 20.

A suspension of N - {4 - [(α - methyl)-cyanomethyl] - phenyl} - pthalimide (2.76 g.; 0.01 moles) in glacial acetic acid (50 ml), heated to 70° C. was gradually treated with zinc in powder form (4 g.). The mixture is then heated under reflux for 14 hours. The inorganic layer is filtered, the filtrate is cooled, and the solid product which formed is filtered, treated with water, then with 8% sodium bicarbonate (50 ml), and filtered again. The residue is crystallized from 99.9% ethanol to obtain 1 - oxo - 2 - {p - [(α - methyl)-cyanomethyl] - phenyl} - isoindoline (1.83 g., yield = 70%), m.p. 192—194° C. In the same way, and starting from the derivatives prepared according to Example 17, 18 and 19, the following compounds are obtained:

1 - oxo - 2 - [p - (cyanomethyl) - phenyl]-isoindoline

1 - oxo 2 - {p - [(α - ethyl) -cyanomethyl]-phenyl} - isoindoline

1 - oxo - 2 - {p - [(α - propyl) - cyanomethyl] - phenyl} - isoindoline

1 - oxo - 2 - {p - [α - butyl) - cyanomethyl] - phenyl} - isoindoline

Example 21.

A suspension of 1 - oxo - 2 - {p-[(α - methyl) - cyanomethyl] - phenyl}-isoindoline (2.62 g.; 0.01 moles) in concentrated sulphuric acid (2.42 ml) and water (7.4 ml) is heated under reflux for 16 hours, and then poured into cold water (100 ml). The solid which separated is filtered, and then treated with 8% sodium hydroxide (30 ml). The insoluble residue is filtered and the filtrate is acidified with 8% hydrochloric acid (30 ml); the solid is filtered and crystallized from 95% ethanol to obtain 1 - oxo - 2 - {p - [(α-methyl) - carboxymethyl] - phenyl} - isoindoline (2.39 g., yield = 85%), m.p. 213—214° C.

In the same way, and starting from the derivatives prepared according to Example 14, 15 and 20, the following compounds are obtained:

1 - oxo - 2 - [p - (carboxymethyl) - phenyl]-isoindoline, m.p. 208—209° C.

1 - oxo - 2 - {p - [(α - ethyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 180—182° C.

1 - oxo - 2 - {p - [(α - propyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 160—162° C.

1 - oxo - 2 - {p - [α - butyl) - carboxymethyl] - phenyl} - isoindoline, m.p. 145—147° C.

Example 22.

A solution of 1 - oxo - 2 - {p - [(α-methyl) - carboxymethyl] - phenyl} - isoindoline (15.4 g.; 0.055 moles) and concentrated sulphuric acid (6 ml) in anhydrous methyl alcohol (180 ml) is heated under reflux for 6 hours, then cooled and filtered, and the precipitate is washed with 2% sodium bicarbonate (100 ml) to obtain, after crystallization from methyl alcohol, 1 - oxo-2 - {p - [(α - methyl) - carbomethoxymethyl] - phenyl} - isoindoline (15.5 g., yield = 96%), m.p. 124—126° C.

In the same way, and by reacting methyl alcohol with the appropriate isoindoline, the following compounds are obtained:

1 - oxo 2 - [p - carbomethoxy - methyl)-phenyl] - isoindoline

1 - oxo 2 - {p - [(α - ethyl) - carbomethoxymethyl] - phenyl} - isoindoline

1 - oxo - 2 - {p - [(α - propyl) - carbomethoxy - methyl] - phenyl} - isoindoline

1 - oxo - 2 - {p - [(α - butyl) - carbomethoxy - methyl] - phenyl } - isoindoline

Example 23.

A solution of 1 - oxo - 2 - {p - [(α-methyl) - carboxymethyl] - phenyl} - isoindoline (20 g.; 0.0714 moles) and thionyl chloride (120 ml) is heated under reflux for 3 hours, the excess thionyl chloride is distilled off, then anhydrous benzene (150 ml) is added, and after evaporation to dryness, and treatment with petroleum ether, the solid which formed is filtered; crystallization of the solid from a mixture of benzene and petroleum ether gives the acid chloride of 1 - oxo - 2-{p - [(α - methyl) carboxymethyl] - phenyl}-isoindoline (18.5 g., yield = 85%), m.p. 132—134° C.

The acid chloride (12 g.) is now dissolved in anhydrous dioxan (200 ml), and this solution is added dropwise, with effective agitation, to a solution of 2-(dimethylamino)ethanol (12 ml) in anhydrous dioxan (200 ml) to produce a slightly exothermic reaction. The mixture is agitated for 3 hours at room temperature and then allowed to stand overnight. The precipitate thus formed is then filtered, and the filtrate is evaporated under vacuum to give an oily residue. This residue is dissolved in chloroform (150 ml), the chloroform solution is washed with 2% sodium bicarbonate (100 ml), dried over anhydrous sodium sulphate and evaporated to dryness under vacuum. The residue is then extracted with hot hexane, and subsequently cooled to obtain the 2-(dimethylamino)-ethanol ester of 1 - oxo - 2-{p - [(α - methyl) - carboxymethyl]-phenyl} - isoindoline (11.3 g., yield = 80%), m.p. 61—63° C.

In the same way, and by reacting N,N-dimethylaminoethanol with the acid chlorides of the appropriate isoindoline, the following compounds are obtained:

2 - (dimethylamino)ethanol ester of 1 - oxo-2 - [p - (carboxymethyl) - phenyl] - isoindoline

2 - (dimethylamino)ethanol ester of 1-oxo - 2 - {p - [(α - ethyl) - carboxymethyl]-phenyl} isoindoline

2 - (dimethylamino)ethanol ester of 1 - oxo-2 - {p - [(α - propyl) - carboxymethyl]-phenyl} - isoindoline

2 - (dimethylamino)ethanol ester of 1 - oxo-2 - {p - [(α - butyl) - carboxymethyl]-phenyl} - isoindoline.

Example 24.

2-(Dimethylamino)ethanol (1 ml) is added to 1 - oxo - 2 - {p [(α - methyl) - carboxymethyl] - phenyl} - isoindoline (2.8 g.; 0.01 moles), suspended in water (100 ml). The solution is then lyophilized to obtain the 2-(dimethylamino)ethanol salt of 1 - oxo - 2-{p - [(α - methyl) - carboxymethyl]-phenyl} - isoindoline (3.7 g., yield = 100%).

In the same way, and by reacting 2-(dimethylamino)ethanol with the appropriate isoindoline, the following compounds are obtained:

2 - (dimethylamino)ethanol salt of 1 - oxo-2 - [p - (carboxymethyl) - phenyl] - isoindoline

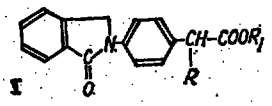
2 - (dimethylamino)ethanol salt of 1 - oxo-2 - {p - [(α - ethyl) - carboxymethyl]-phenyl} - isoindoline

2 - (dimethylamino)ethanol salt of 1 - oxo-2 - {p - [(α - propyl) - carboxymethyl]-phenyl} - isoindoline

2 - (dimethylamino)ethanol salt of 1 - oxo-2 - {p - [(α - butyl) - carboxymethyl]-phenyl} - isoindoline.

WHAT WE CLAIM IS:—

1. A compound of general formula (I)



wherein R is hydrogen or lower alkyl, and R_1 is hydrogen, lower alkyl or a group of formula

$$—(CH_2)_n—NR_2R_3,$$

wherein n is 1 or 2 and each of R_2 and R_3, which may be the same or different, is hydrogen or lower alkyl; or, when R_1 is hydrogen or the group

$$—(CH_2)_nNR_2R_3,$$

a physiologically acceptable salt thereof.

2. 1 - Oxo - 2 - {p - [(α - methyl) - carboxymethyl] - phenyl} - isoindoline.

3. 1 - Oxo - 2 - {p -[(α - ethyl) - carboxymethyl] - phenyl} - isoindoline.

4. 1 - Oxo - 2 - {p - [(α - propyl) - carboxymethyl] - phenyl} - isoindoline.

5. 1 - Oxo - 2 - {p - [(α - butyl) - carboxymethyl] - phenyl} - isoindoline.

6. 1 - Oxo - 2 - {p - [(α - methyl) - carboethoxymethyl] - phenyl} - isoindoline.

7. 2 - (dimethylamino)ethanol ester of 1 - oxo - 2 - {p - [(α - methyl) - carboxymethyl] - phenyl} - isoindoline.

8. 2 - (dimethylamino)ethanol salt of 1 - oxo - 2 - {p - [(α - methyl) - carboxymethyl] - phenyl} - isoindoline.

9. A compound according to claim 1 specifically named herein.

10. A process for the preparation of a compound according to any one of the preceding claims, the process comprising:

(a) reacting o-cyano-benzyl bromide with a compound of general formula (II)

Example 23.

A solution of 1 - oxo - 2 - {p - [(α-methyl) - carboxymethyl] - phenyl} - isoindoline (20 g.; 0.0714 moles) and thionyl chloride (120 ml) is heated under reflux for 3 hours, the excess thionyl chloride is distilled off, then anhydrous benzene (150 ml) is added, and after evaporation to dryness, and treatment with petroleum ether, the solid which formed is filtered; crystallization of the solid from a mixture of benzene and petroleum ether gives the acid chloride of 1 - oxo - 2-{p - [(α - methyl) carboxymethyl] - phenyl}-isoindoline (18.5 g., yield = 85%), m.p. 132—134° C.

The acid chloride (12 g.) is now dissolved in anhydrous dioxan (200 ml), and this solution is added dropwise, with effective agitation, to a solution of 2-(dimethylamino)ethanol (12 ml) in anhydrous dioxan (200 ml) to produce a slightly exothermic reaction. The mixture is agitated for 3 hours at room temperature and then allowed to stand overnight. The precipitate thus formed is then filtered, and the filtrate is evaporated under vacuum to give an oily residue. This residue is dissolved in chloroform (150 ml), the chloroform solution is washed with 2% sodium bicarbonate (100 ml), dried over anhydrous sodium sulphate and evaporated to dryness under vacuum. The residue is then extracted with hot hexane, and subsequently cooled to obtain the 2-(dimethylamino)-ethanol ester of 1 - oxo - 2-{p - [(α - methyl) - carboxymethyl]-phenyl} - isoindoline (11.3 g., yield = 80%), m.p. 61—63° C.

In the same way, and by reacting N,N-dimethylaminoethanol with the acid chlorides of the appropriate isoindoline, the following compounds are obtained:

2 - (dimethylamino)ethanol ester of 1 - oxo-2 - [p - (carboxymethyl) - phenyl] - isoindoline

2 - (dimethylamino)ethanol ester of 1-oxo - 2 - {p - [(α - ethyl) - carboxymethyl]-phenyl} isoindoline

2 - (dimethylamino)ethanol ester of 1 - oxo-2 - {p - [(α - propyl) - carboxymethyl]-phenyl} - isoindoline

2 - (dimethylamino)ethanol ester of 1 - oxo-2 - {p - [(α - butyl) - carboxymethyl]-phenyl} - isoindoline.

Example 24.

2-(Dimethylamino)ethanol (1 ml) is added to 1 - oxo - 2 - {p [(α - methyl) - carboxymethyl] - phenyl} - isoindoline (2.8 g.; 0.01 moles), suspended in water (100 ml). The solution is then lyophilized to obtain the 2-(dimethylamino)ethanol salt of 1 - oxo - 2-{p - [(α - methyl) - carboxymethyl]-phenyl} - isoindoline (3.7 g., yield = 100%).

In the same way, and by reacting 2-(dimethylamino)ethanol with the appropriate isoindoline, the following compounds are obtained:

2 - (dimethylamino)ethanol salt of 1 - oxo-2 - [p - (carboxymethyl) - phenyl] - isoindoline

2 - (dimethylamino)ethanol salt of 1 - oxo-2 - {p - [(α - ethyl) - carboxymethyl]-phenyl} - isoindoline

2 - (dimethylamino)ethanol salt of 1 - oxo-2 - {p - [(α - propyl) - carboxymethyl]-phenyl} - isoindoline

2 - (dimethylamino)ethanol salt of 1 - oxo-2 - {p - [(α - butyl) - carboxymethyl]-phenyl} - isoindoline.

WHAT WE CLAIM IS:—

1. A compound of general formula (I)

wherein R is hydrogen or lower alkyl, and R_1 is hydrogen, lower alkyl or a group of formula

$$—(CH_2)_n—NR_2R_3,$$

wherein n is 1 or 2 and each of R_2 and R_3, which may be the same or different, is hydrogen or lower alkyl; or, when R_1 is hydrogen or the group

$$—(CH_2)_nNR_2R_3,$$

a physiologically acceptable salt thereof.

2. 1 - Oxo - 2 - {p - [(α - methyl) - carboxymethyl] - phenyl} - isoindoline.

3. 1 - Oxo - 2 - {p -[(α - ethyl) - carboxymethyl] - phenyl} - isoindoline.

4. 1 - Oxo - 2 - {p - [(α - propyl) - carboxymethyl] - phenyl} - isoindoline.

5. 1 - Oxo - 2 - {p - [(α - butyl) - carboxymethyl] - phenyl} - isoindoline.

6. 1 - Oxo - 2 - {p - [(α - methyl) - carboethoxymethyl] - phenyl} - isoindoline.

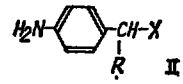
7. 2 - (dimethylamino)ethanol ester of 1 - oxo - 2 - {p - [(α - methyl) - carboxymethyl] - phenyl} - isoindoline.

8. 2 - (dimethylamino)ethanol salt of 1 - oxo - 2 - {p - [(α - methyl) - carboxymethyl] - phenyl} - isoindoline.

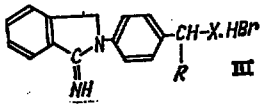
9. A compound according to claim 1 specifically named herein.

10. A process for the preparation of a compound according to any one of the preceding claims, the process comprising:

(a) reacting o-cyano-benzyl bromide with a compound of general formula (II)

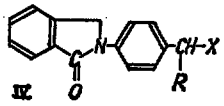


wherein X is a carboxy, carbethoxy or cyano group, and R is as defined in claim 1, to give a compound of general formula (III)



wherein X is as defined above and R is as defined in claim 1, which is subsequently reacted with a suitable base or acid, to give a compound of general formula (I), wherein R_1 is hydrogen, and subsequently, if desired, esterifying the compound of general formula (I) thus obtained; or

(b) reacting phthalide with a compound of general formula (II), wherein X is a carbethoxy or cyano group, to give a compound of formula (IV)

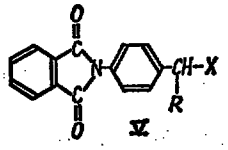


wherein R is as defined in claim 1 and X is a carbethoxy or cyano group, which if desired is subsequently saponified with an appropriate base or acid, to give a compound of general formula (I), wherein R_1 is hydrogen, and subsequently, if desired, esterifying the compound of general formula (I), thus obtained; or

(c) reacting thiophthalide with a compound of formula (II) wherein X is a carbethoxy or cyano group to give a compound of formula (IV) which if desired is subsequently saponified to give a compound of general formula (I), wherein R_1 is hydrogen, which, if desired, is esterified as in process (a); or

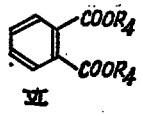
(d) reacting phthalic aldehyde with a compound of formula (II) wherein X is a carbethoxy or cyano group to give a compound of formula (IV), which if desired is subsequently saponified to give a compound of general formula (I), wherein R_1 is hydrogen, which, if desired is esterified as in process (a); or

(e) reacting phthalic anhydride with a compound of formula (II) wherein X is a carbethoxy or cyano group, to give a compound of formula (V)



wherein X is a carbethoxy or cyano group and R is as defined in claim 1, which is subsequently reduced, to give a compound of formula (IV), which if desired is subsequently saponified to give a compound of general formula (I), wherein R_1 is hydrogen, which, if desired, is esterified as in process (a); or

(f) reacting a compound of general formula (VI)



wherein the groups R_4 are both hydrogen, both methyl groups or both ethyl groups, with a compound of formula (II) wherein X is a carbethoxy or cyano group, to give a compound of formula (V), wherein X is a carbethoxy or cyano group and R is as defined in claim 1, which is subsequently reduced to give a compound of formula (IV), which if desired is then saponified to give a compound of general formula (I), wherein R_1 is hydrogen, which, if desired, is esterified as in process (a); and if desired reacting the compound of general formula (I), wherein R_1 is hydrogen, obtained in steps (a) to (f), with an appropriate base to give a physiologically acceptable salt, or reacting the compound of general formula (I), wherein R_1 is the group

$$-(CH_2)_n-NR_2R_3,$$

obtained in steps (a) to (f) with an appropriate acid to give a physiologically acceptable salt.

11. A process according to claim 10 substantially as described in any one of the Examples.

12. A compound of general formula (I) prepared by a process according to claim 10 or 11.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier or diluent.

14. A pharmaceutical composition comprising a compound according to claim 9 or 12 and a pharmaceutically acceptable carrier or diluent.

15. A composition according to claim 13 or 14 substantially as described herein.

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