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

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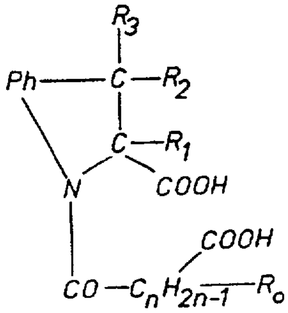
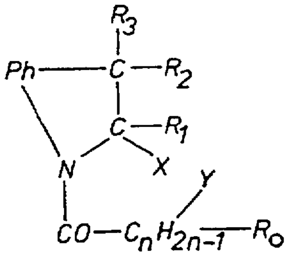
(54) 1-Carboxyalkanoylindoline-2-carboxylic acids, process for their manufacture, pharmaceutical preparations containing these compounds and their therapeutic application.

(57) The invention concerns hypotensive, antihypertensive and bradycardic compounds of the formula I



(I)

wherein Ph is unsubstituted 1,2-phenylene, or 1,2-phenylene substituted by one to three identical or different members selected from lower alkyl, lower alkoxy, lower alkylenedioxy, hydroxy, halogeno and trifluoromethyl; R_o is hydrogen or HPh; each of R_1, R_2 and R_3 is hydrogen or lower alkyl; and n is an integer from 1 to 10; the amides, mono- or di-lower alkylamides, lower alkyl esters, (amino, mono- or di-lower alkylamino, carboxy or carbo lower alkoxy)-lower alkyl esters, or salts thereof. They can be prepared, for example, by hydrolysing a compound of the general formula



wherein at least one of X and Y is cyano, and the other is said free, amidized or esterified carboxy group.

GB 2 085 880 A

Certain of the chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

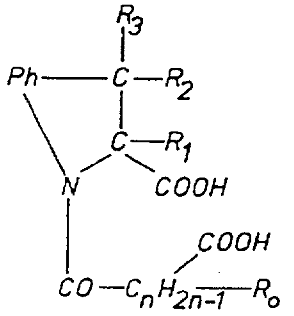
SPECIFICATION

1-Carboxyalkanoylindoline-2-carboxylic acids, process for their manufacture, pharmaceutical preparations containing these compounds and their therapeutic application

1-Alkanoylindoline-2-carboxylic acids and their 5,6-dihydroxy-derivatives, i.e., N-acylated Cyclodopa-derivatives, are described in Nippon Kagaku Zasshi *87*, 760 (1966) and US-Patent 3,796,723 or Helv. Chim. Acta *53*, 1701 (1970) respectively, e.g., as synthetical examples of O- and/or N-acylations. Also, 1-carboxyacyl-(azetidine, pyrrolidine or piperidine)-2-carboxylic acids and their functional derivatives are known, e.g., according to US-Patent 4,052,511, as possessing anti-hypertensive activity.

Surprisingly it was found that either by introduction of a carboxy group into the former indolines, or by extension of the latter pyrrolidines t the indoline ring-system, superior antihypertensive agents are obtained.

The present invention provides therefore the new 1-carboxy-(alkanoyl or aralkanoyl)-indoline-2-carboxylic acids of the general formula I



(I)

wherein Ph is unsubstituted 1,2-phenylene, or 1,2-phenylene substituted by one to three identical or different members selected from lower alkyl, lower alkoxy, lower alkylenedioxy, hydroxy, halogeno and trifluoromethyl; R_o is hydrogen or HPh; each of R_1, R_2 and R_3 is hydrogen or lower alkyl; and n is an integer from 1 to 10; the amides, mono- or di-lower alkylamides, lower alkyl ester, (amino, mono- or di-lower alkylamino, carboxy or carbo lower alkoxy)-lower alkyl esters, or salts, especially pharmaceutically acceptable salts thereof; process for their manufacture, pharmaceutical preparations containing these compounds and their therapeutic application.

The 1,2-phenylene group Ph and/or the phenyl group HPh, are peferably unsubstituted or monosubstituted, and their substituents are illustrated by the following groups; lower alkyl, e.g., methyl, ethyl, n- or i-propyl or -butyl; lower alkoxy, e.g., methoxy, ethoxy, n- or i-propoxy or -butoxy; lower alkylenedioxy, e.g., methylenedioxy, 1,1- or 1,2-ethylenedioxy; hydroxy; halogeno, e.g., fluoro, chloro or bromo; or trifluoromethyl.

Each of R_1, R_2 and R_3 is preferably hydrogen, but also lower alkyl, advantageously methyl, or another of those mentioned previously.

The term "lower", referred to above and hereinafter in connection with organic radicals or compounds respectively, defines such with up to 7, preferably up to 4, and advantageously but one or two carbon atoms.

The alkylene or aralkylene moiety $C_nH_{\overline{2n-1}}$ R_o is either straight, or preferably branched, and contains advantageously up to 8 chain-carbon atoms. Thus, it represents for example, in case R_0 = H, ethylene, 1,2- or 1,3-propylene, 2-methyl-1,2- or 1,3-propylene, 1,2-, 1,3-, 2,3- or 1,4-butylene, 1,2-, 1,3-, 1,4-, 2,4- or 1,5-pentylene; or in case R_o = phenyl, ω-phenyl-(1,2-, 1,3- or 2,3-propylene, -butylene or -pentylene, 1,3-, 2,3- or 2,4-butylene, -pentylene or -hexylene, or 3,5-heptylene or -octylene).

Said functional derivatives, wherein either one or both carboxy groups are esterified or amidized, are preferably the mono- or bis-lower alkyl esters, e.g. the methyl, ethyl, n- or i-propyl or -butyl esters; the mono- or bis-amide, or the correspondingly N-alkylated amides, e.g. mono- or dimethylamide, or said substituted lower alkyl esters, preferably the half-esters with a free indoline-2-carboxy group, e.g. the ω-(amino, mono- or dimethylamino, carboxy or carbethoxy)-(ethyl, propyl or butyl) esters.

Salts are preferably pharmaceutically acceptable salts, e.g. metal or ammonium salts or said acids, more particularly alkali or alkaline earth metal salts, e.g., the sodium, potassium, magnesium or calcium salt; or advantageously easily crystallizing ammonium salts derived from ammonia or organic amines, such as mono, di- or tri-lower (alkyl, cycloalkyl or hydroxyalkyl)-amines, lower alkylenediamines or (hydroxy-lower alkyl or aryl lower alkyl)-lower alkylammonium bases, e.g., methylamine, diethylamine, triethylamine, dicyclohexylamine, triethanolamine, ethylenediamine, tris-(hydroxymethyl)-aminomethane or benzyltrimethylammonium hydroxide. Said basic (amino, mono- or di-lower alkyl-amino)-lower alkyl esters form also acid addition salts, which are preferably such of therapeutically acceptable inorganic or organic acids, for example hydrohalic, e.g. hydrochloric or hydrobromic acid; sulfuric, phoshoric, nitric or perchloric acid; aliphatic or aromatic carboxylic or sulfonic acids, e.g. formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, maleic, fumaric, hydroxymaleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-amino-salicylic, pamoic, nicotinic; methanesulfonic, ethanesulfonic, hydroxy-ethanesulfonic, ethylenesulfonic, halogenbenzenesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; or ascorbic acid.

The compounds of this invention exhibit valuable pharmacological properties, primarily hypotensive, antihypertensive and caridoactive effects, inter alia due to their angiotensin converting enzyme inhibitory activity. These pharmacological properties are demonstrable by in vivo or in vitro or in vitro animal tests, using advantageously mammals, e.g., rats, cats, dogs or isolated organs thereof, as test objects. The animals may either be normotensive or hypertensive e.g., genetically hypertensive rats, or renal hypertensive rats and dogs, and sodium-depleted dogs. Said compounds can be applied to them enterally or parenterally, advantageously orally or intravenously, for example within gelatin capsules or in the form of starchy suspensions or aqueous solutions respectively. The applied dosage may range between about 0.01 and 50 mg/kg/day, preferably between about 0.1 and 25 mg/kg/day, advantageously between about 1 and 10 mg/kg/day.

The in vivo lowering effect on the blood pressure is recorded either directly by means of a catheter, for example placed in the dog's femoral artery, or indirectly by sphygmomanometry at the rat's tail, and a transducer, expressing the blood pressure prior and after dosing in mm Hg. Thus, for example, the representative members of the compounds of this invention, illustrated by the Examples herein, are very effective in hypertensive rats and dogs at p.o.-doses as low or lower than 10 mg/kg/day.

The also inhibit the angiotensin I pressure response of normotensive rats. The enzyme renin normally causes specific hydrolysis of the circulating renin-substrate-protein. This hydrolysis generates angiotensin I, which is further hydrolyzed by the action of said converting enzyme to the potent vasoconstrictor angiotensin II. The inhibition of said anzyme prevents the generation of angiotensin II from I and, therefore, attenuates any pressure response following an angiotensin I challenge.

The corresponding in vivo test is performed with male, normotensive rats, which are anesthetized with 100-120 mg/kg i.p. of sodium ethyl-(1-methylpropyl)-malonylthiourea. A femoral artery and saphenous vein are cannulated for direct blood pressure measurement and i.v. administration of angiotensin I and compound of this invention. After the basal blood pressure is stablized, pressor response to 3 challanges of 0.33 μg/kg of angiotensin I i.v., in 5 minutes intervals, are obtained. Pressure responses are again obtained 5, 10, 15, 30 and 60 minutes after either i.v., or p.o. administration (stomach tube) of the compounds to be tested, and compared with the initial responses. Any observed decrease of said pressor response is an indication of angiotensin I converting enzyme inhibition, ranging up to 80% after 10 mg/kg i.v., or 50 mg/kg p.o. doses, which decrease may be sustained up to 60 minutes.

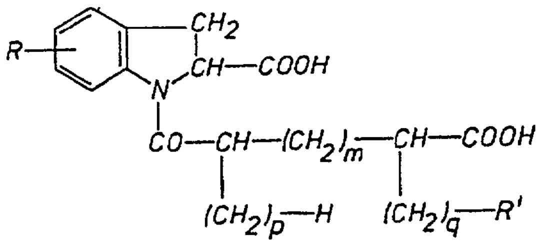
The in vitro inhibition of the angiotensin-converting enzyme by the compounds of this invention can be demonstrated analogous to Biochim. Biophys. Acta *293*, 451 (1973). According to this method said compounds are dissolved at about 1 mM concentrations in phosphate buffer, externally cooled with ice. To these solutions various μl amounts of 1 mM of histidyl-leucine in phosphate buffer are added, followed by 100 μl of 5 mM hippuryl-histidyl-leucine in phosphate buffer and 50 μl of the angiotensin-converting enzyme, which is freshly prepared from lungs of adult male rabbits in Tris buffer, containing potassium and magnesium chloride, as well as sucrose. Said solutions are incubated at 37° for 30 minutes and combined with 0.75 ml of 0.6 N aqueous sodium hydroxide to stop further reaction. Then 100 μl of o-phthalaldehyde are added at room temperature, and 10 minutes later 100 μl of 6N hydrochloric acid. These samples are read against water in a spectrophotometer set at 360 nm, and the optical densities thereof estimated. They are corrected for the standard curve via a conversion factor expressing nanomoles of histidyl-leucine formed during said 30 minute incubation period. The results are plotted against drug concentration to determine the IC_{50}, i.e., the drug concentration which gives half the activity of the control sample containing no drug. Again, said representative members of the compounds of this invention are very effective in this in vitro test system, down to IC_{50} values as low or lower than 39 nM.

Accordingly, the compounds of this invention are valuable antihypertensive agents, especially useful for ameliorating hypertension (regardless of etiology) and/or heart-conditions, such as congestive heart failure, and/or other edemic or ascitic diseases, e.g. hepatic cirrhosis. They are also useful intermediates in the preparation of other valuable products, especially of corresponding pharmaceutical compositions.

Particularly useful are those compounds of Formula I, wherein Ph is unsubstituted 1,2-phenylene, or 1,2-phenylene, or 1,2-phenylene substituted by one or two identical or different members selected from lower alkyl, lower alkoxy, hydroxy and halogeno, or 1,2-phenylene substituted by one lower alkylenedioxy or trifluoromethyl group; R_o is hydrogen or HPh; each of R_1, R_2 and R_3 is hydrogen or lower alkyl; and n is an integer from 1 to 10; the amides, mono- or di-lower alkylamides, lower alkyl esters, (amino, mono-or di-lower alkylamino, carboxy or carbo-lower alkoxy)-lower alkyl esters, or salts especially pharmaceutically acceptable alkali metal, alkaline earth metal or ammonium salts of said acids, or acid addition salts of said aminoalkyl esters.

More preferred are those compounds of Formula I, wherein pH is 1,2-phenylene, unsubstituted or mono-substituted by lower alkyl, lower alkoxy, lower alkylenedioxy, hydroxy, halogeno or trifluoromethyl; R_o is hydrogen or HPh; each of R_1, R_2 and R_3 is hydrogen of methyl; and n is an integer from 2 to 8; the amides, mono- or di-lower alkyl-amides, lower alkyl esters, (amino, mono- or di-lower alkylamino, carboxy or carbo-lower alkoxy)-lower alkyl esters, or salts, especially pharmaceutically acceptable alkali metal, alkaline earth metal or ammonium salts of said acids, or acid addition salts of said aminoalkyl esters.

Especially valuable compounds are those of the general Formula II



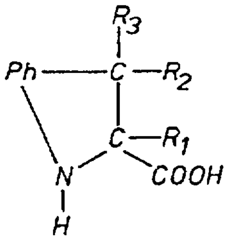
(II)

more specifically the indoline-2S-chiral epimers thereof, wherein R is hydrogen, alkyl or alkoxy with up to 4 carbon atoms, halogeno or trifluoromethyl m is the integer 0 or 1; each of p and q is an integer from 0 to 2; and R′ is hydrogen or R-phenyl; the mono- or bis-amide, the mono- or bis-(lower alkyl or ω-amino-lower alkyl) esters, and salts, especially pharmaceutically acceptable alkali metal or ammonium salts of said acids or acid addition salts of said aminoalkyl esters.

The most preferred compounds are those of Formula II, wherein R is hydrogen, methyl, methoxy, fluoro, chloro or trifluoromethyl, advantageously in the 5-position, each of m and p is the integer 1, q is the integer 1 or 2, and R′ is hydrogen or phenyl, the mono- or bis-amide, the mono- or bis-(lower alkyl or ω-amino-lower alkyl) esters, and salts especially pharmaceutically acceptable alkali metal or ammonium salts of said acids or acid addition salts of said aminoalkyl esters.

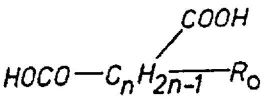
The compounds of this invention are prepared according to conventional methods, advantageously by:

1) condensing a compound of the general Formula III



(III)

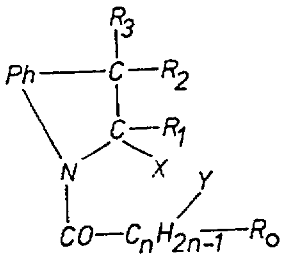
or said acid or amino derivatives thereof, with a reactive functional derivative of a compound of the general Formula IV



$$HOCO-C_nH_{2n-1}(COOH)-R_o$$

(IV); or

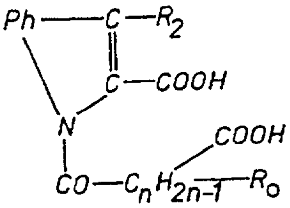
2) hydrolysing or alcoholyzing a compound of the general Formula V



(V)

wherein at least one of X and Y is cyano, and the other is said free, amidized or esterified carboxy group; or

3) hydrogenating in a compound of the general Formula VI



(VI)

or said acid or amino derivatives thereof, the indole moiety to the indoline moiety; and, if desired, converting any resulting compound into another compound of this invention.

Reactive functional derivatives of compounds IV are preferably esterhalides, simple or mixed anhydrides, such as the lower alkyl half esters of said acid chlorides, the cyclic anhydride, or mixed acetic or cyanoacetic anhydrides. Said condensation of compounds III and IV occurs either spontaneously, or in the presence of condensing agents, such as organic or inorganic bases, e.g. said salt-forming amines or alkali metal carbonates, or disubstituted carbodiimides.

Said hydrolysis of the nitriles V to the corresponding acids or amides is advantageously carried out with inorganic acids, such as hydrohalic acids, in known manner; and said alcoholysis is analogously performed in the presence of both said acids and the corresponding unsubstituted or substituted lower alkanols.

Finally, said hydrogenation of the indoles VI to the indolines I is also performed according to conventional hydrogenations of 1-acyl-indoles, for example, with catalytically activated or nascent hydrogen, e.g. hydrogen in the presence of platinum, palladium, rodium or nickel catalysts, or hydrogen generated electrolytically, or by the action of metals on acids or alcohols. Also reducing agents may be used, such as simple or complex light metal hydrides, e.g. boranes, or advantageously alkali metal borohydrides or cyanoborohydrides. Preferred is the asymmetric hydrogenation to the indoline-2S-carboxylic acids, or said derivatives thereof, with chiral catalysts, as, for example, prepared from a rhodium salt with (R)-1,2-bis-(diphenyl-phosphino)-propane or (R)-1,2-bis(o-anisylphenylphosphino)-ethane and 1,5-cyclooctadiene.

The compounds of the invention so obtained, can be converted into each other according to conventional methods. Thus, for example, resulting amides or esters may be further hydrolyzed or alcoholyzed (transesterified) according to process 2), or with aqueous alkalies, such as alkali metal carbonates or hydroxides, respectively. Resulting free acids may be esterified with said unsubstituted or substituted lower alkanols or diazolalkanes, or converted into said metal, ammonium or acid addition salts in conventional manner.

Thus, for example, any resulting free acid or base can be converted into a corresponding metal, ammonium or acid addition salt respectively, by reacting it with an equivalent amount of the corresponding base, basic salt, acid or ion exchange preparation, e.g. said acids with alkali or ammonium hydroxides or carbonates, or said aminoalkyl esters with said inorganic or organic acids respectively. Any resulting salt may also be converted into the free compound, by liberating the latter with stronger acids or bases respectively.

In view of the close relationship between the free compounds, and the salts thereof, whenever a compound of the invention, or intermediate thereof, is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The starting materials of Formulae III and IV are known or if new, they may be obtained according to methods known per se, for example analogously to the methods described in the examples herein. The new starting materials also constitute an object of the invention.

Starting compounds of Formula V, are also obtained according to conventional methods, e.g., by condensing the nitriles corresponding to the Formulae III and/or IV according to said process 1.

Starting materials of Formula VI are obtained according to methods known per se, for example, by introducing a corresponding acyl radical into an indol-2-carboxylic acid lower alkyl ester.

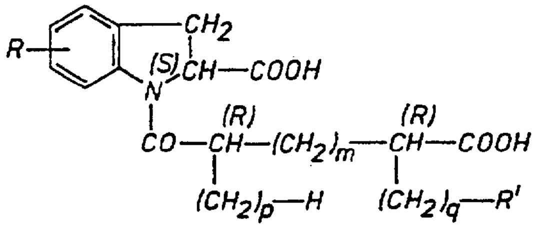
In case mixtures of geometrical or optical isomers of the above compounds of Formulae I to VI are obtained, these can be separated into the single isomers by methods in themselves known, e.g., by fractional distillation, crystallization and/or chromatography.

Racemic products can likewise be resolved into the optical antipodes, for example, by separation of diastereomeric salts thereof, such as according to J. Org. Chem. *43*, 3803 (1978), e.g., by the fractional crystallization of d- or ℓ-(tartrates, mandelates, camphorsulfonates, or 1-naphthyl-1-ethylisocyanates), or of d- or ℓ-(α-methylbenzyl-ammonium, cinchonidine, cinchonine, quinine, quinidine, ephedrine, dehydroabietylamine, brucine or strychnine)-salts. The preferred starting material of Formula III is the 2S-optical isomer (epimer) thereof.

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, alkaline or acidic condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures, preferably at the boiling point of the solvents used, at atmospheric or superatmospheric pressure.

The invention further includes any variant of said processes, in which an intermediate product obtainable at any stage of the process is used as a starting material and any remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed under the reaction conditions, or in which the reaction components are used in the form or their salts or optically pure antipodes.

Mainly those starting materials should be used in said reactions, that lead to the formation of those compounds indicated above as being especially valuable, e.g., those of Formula II, and being the following chiral isomers:



(IIa)

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients suitable for either enteral or parenteral administration. Preferred are tablets and gelatin capsules comprising the active ingredient together with diluents, e.g., lactose, dexrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, and lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol, for tablets, also binders, e.g., magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethyl-cellulose and/or polyvinylpyrrolidone, if desired, disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures and/or adsorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as peserving stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said pharmaceutical compositions are prepared according to conventional mixing, granulating or coating methods respectively, and contain about 0.1 to 75 %, preferably about 1 to 50 % of the active ingredient. A unit dosage for a mammal of about 50-70 kg weight may contain between about 5 and 100 mg of the active ingredient.

The following Examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centigrade, and all parts wherever given are parts by weight. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mmHg.

Example 1:

To the suspension of 5.0 g of indoline-2S-carboxylic acid ethyl ester hydrochloride, 9.1 g of powdered potassium carbonate and 45 ml of methylene chloride, 3.61 g of methyl glutaroyl chloride in 5 ml of methylene chloride are added while stirring at room temperature. The mixture is stirred overnight at room temperature, cooled with ice, and 100 ml of water are added. The organic layer is separated, washed with N-hydrochloric acid and water, dried and evaporated, to yield the 1-(4-carbomethoxybutanoyl)-indoline-2S-carboxylic acid ethyl ester melting at 88-90°.

The starting material is prepared as follows: 120 g of 1-acetyl-indoline-2-carboxylic acid [Nippon Kagaku Zasshi *87*, 760 (1966)] and 172 g of ℓ-cinchonidine are dissolved in 1,200 ml of hot ethanol. The solution is allowed to stand at room temperature overnight and then at 0° for 4 days. The white crystalline salt is filtered off and discarded. The filtrate is evaporated, 1,000 ml of water are added and the solution is adjusted to pH = 1 with concentrated hydrochloric After 15 minutes the product is collected by filtration and washed thrice with 250 ml of 2N aqueous hydrochloric acid, twice with 500 ml of water and twice with 100 ml of ethanol, to give the 1-acetylindoline-2S-carboxylic acid melting at 214-215°; $[\alpha]_D = -133.3°$ (c = 1.165 in ethanol).

The suspension of 37.5 g thereof in 380 ml of 2N aqueous hydrochloric acid is deoxygenated by bubbling nitrogen through it for 5 minutes, followed by refluxing for 2 hours. It is cooled to room temperature, filtered through infusorial earth, the filtrate evaporated and the residue crystallized from diethyl ether-isopropanol, to yield the indoline-2S-carboxylic acid hydrochloride melting at 133° (decomposition); $[\alpha]_D = -70.4°$ (c = 1 in ethanol).

The solution of 34 g thereof in 350 ml of ethanol is saturated with dry hydrogen chloride without external cooling. The mixture is stirred for 2 hours at room temperature and the solvent removed until crystallization begins. The concentrate is poured into 400 ml of diethyl ether, cooled at 0° for 1 hour and filtered, to yield the indoline-2S-carboxylic acid ethyl ester hydrochloride melting at 179-181°; $[\alpha]_D = -63°$ (c = 1.385 in ethanol).

Example 2

To the suspension of 5.0 g of 1-(4-carbomethoxybutanoyl)-indoline-2S-carboxylic acid ethyl easter in 47 ml of methanol is added 47 ml of N aqueous sodium hydroxide and the mixture is stirred at room temperature for 4 hours. It is concentrated at room temperature and reduced pressure, the aqueous solution acidified with concentrated hydrochloric acid while cooling, the resulting precipitate collected, washed with water and dried, to yield the 1-(4-carboxybutanoyl)-indoline-2S-carboxylic acid melting at 175-177°; $[\alpha]_D = -97.8°$ (c = 1.0 in ethanol).

Example 3

To the solution of 11 g of indoline-2S-carboxylic acid hydrochloride in 75 ml of pyridine, 8.25 g of 4-carbomethoxy-2-methylbutanoyl chloride are added and the mixture is stirred at room temperature overnight. The pyridine is distilled off at room temperature and reduced pressure, the residue is cooled, acidified with 3N hydrochloric acid and extracted with methylene chloride. The extract is evaporated, the residue dissolved in 125 ml diethyl ether and the solution combined with that of 10 ml of dicyclohexylamine in 125 ml of hexane. The precipitate is collected, washed with hot ethyl acetate and suspended in acetone overnight, to yield the dicyclohexylammonium 1-(4-carbomethoxy-2-methylbutanoyl)-indoline-2S-carboxylate, melting at 203-205°; the corresponding free 2S-acid melts at 97-99°C.

The first starting material is described as intermediate in Example 1, and the second may be prepared as follows:

9.64 g of oxalyl chloride are added to the solution of 6.1 g of 4-carbomethoxy-2-methylbutanoic acid (US-Patent 4,052,511) in 50 ml of methylene chloride. The mixture is refluxed for two hours and evaporated, to yield the 4-carbomethoxy-2-methylbutanoyl chloride, which is used as such without further purification.

Example 4

The solution of 2.03 g of indoline-2S-carboxylic acid ethyl ester and 2.5 g of 2-(2-penethyl)-glutaric acid anhydride in 75 ml of toluene, is heated to 70° overnight under nitrogen. It is evaporated, the residue dissolved in diethyl ether, the solution washed with N hydrochloric acid and extracted with saturated aqueous sodium bicarbonate. The extract is cooled, acidified with hydrochloric acid and re-extracted with methylene chloride. The organic extract is evaporated, the residue dissolved in diethyl ether and the solution combined with that of 1.2 ml of dicyclohexylamine in 25 ml of hexane. The resulting precipitate is filtered off and washed with hexane, to yield the dicyclohexylammonium 1-[4-carboxy-4-(2-phenethyl)-butanoyl]-indoline-2S-carboxylic acid ethyl ester, melting at 132-134°. It may be re-converted to the free acid with N hydrochloric acid.

The starting material is prepared as follows: 29.8 g of indoline-2S-carboxylic acid ethyl ester hydrochloride are partitioned between 300 ml of saturated aqueous sodium bicarbonate and 100 ml of methylene chloride. The aqueous layer is extracted twice with additional 200 ml of methylene chloride, the combined organic layers washed with saturated aqueous sodium chloride and evaporated, to yield the indoline-2S-carboxylic acid ethyl easter as an oil, showing the major IR-band at 1730 cm^{-1}.

The solution of 12 g of 2-(2-phenethyl)-glutaric acid [J. Chem, Soc. *1950*, 1683] in 75 ml of acetic acid anhydride is refluxed for 4 hours and evaporated. The residue is crystallized from diethyl ether, to yield the corresponding anhydride melting at 78-80°C.

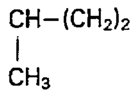
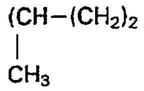
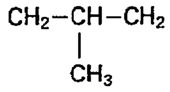
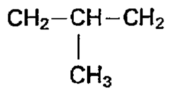
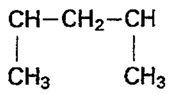
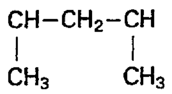
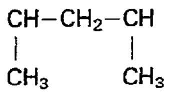
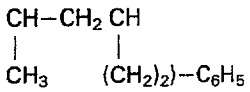
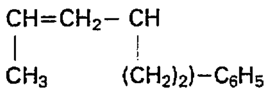
Example 5

The solution of 2.4 g of 1-[4-carboxy-4-(2-phenethyl)-butanoyl]-indoline-2S carboxylic acid ethyl ester in 17.6 ml of methanol and 17.6 ml of N aqueous sodium hydroxide is stirred at room temperature for 2.5 hours. It is concentrated at room temperature under reduced pressure, the aqueous solution filtered, acidified with hydrocholric acid and extracted with methylene chloride. The extract is evaporated and the residue crystallized from petroleum ether, to yield the 1-[4-carboxy-4-(2-phenethyl)-butanoyl]-indoline-2S-carboxylic acid melting at 136-138°C.

Example 6

According to the methods illustrated by the previous examples, the following 1-(carboxyalkanoyl or -aralkanoyl)-indoline-2S-carboxylic acids of Formula I, with Ph = 1,2-phenylene and $R_1 = R_2 = R_3 = H$, as well as said derivatives thereof, are prepared:

No.	$C_nH_{2n-1}-R_o$	$C_nH_{2n-1}-R_o-$ COOH deriv.	Indoline-2-COOH der.	m.p. °C or NMR
1	$\underset{\substack{\vert \\ CH_3}}{CH}-CH_2$	–	–	122–124°, 83–85° for hemihydrate
2	$(CH_2)_2-\underset{\substack{\vert \\ CH_3}}{CH}$	–	ethyl ester	104–106°
3	$(CH_2)_2-\underset{\substack{\vert \\ CH_3}}{CH}$	–	–	172–174°

No.	$C_nH_{2n-1}-R_o$	$C_nH_{2n-1}-R_o-$ COOH deriv.	Indoline-2-COOH der.	m.p. °C or NMR
4	 $\underset{CH_3}{CH}-(CH_2)_2$	methyl ester	ethyl ester	4.25, 3.65 1.30 ppm
5	 $(\underset{CH_3}{CH}-(CH_2)_2$	–	–	72–74°
6	 $CH_2-\underset{CH_3}{CH}-CH_2$	–	ethyl ester	125–127°
7	 $CH_2-\underset{CH_3}{CH}-CH_2$	–	–	125-127°
8	 $\underset{CH_3}{CH}-CH_2-\underset{CH_3}{CH}$ (erythro)	–	ethyl ester-D	132-134°
9	 $\underset{CH_3}{CH}-CH_2-\underset{CH_3}{CH}$ (erythro)	–	–	58–60°
10	 $\underset{CH_3}{CH}-CH_2-\underset{CH_3}{CH}$ (threo)	–	–	70–72°
11	 $\underset{CH_3}{CH}-CH_2\,\underset{(CH_2)_2)-C_6H_5}{CH}$ (erythro)	–	–	1.17, 1.32 ppm
12	 $\underset{CH_3}{CH}=CH_2-\underset{(CH_2)_2)-C_6H_5}{CH}$ (erythro)	–	–	1.15, 1.25 ppm

D=dicyclohexylammonium salt

The starting materials for said compounds 1, 2, 4, 6, 11 and 12 are the 3-carbomethoxy-2-methylpropanoyl chloride, 2-methylglutaric anhydride, 4-carbomethoxy-2-methylbutanoyl chloride, 3-methylglutaric anhydride and the erythro or threo 4-carbomethoxy-4-(2-phenethyl)-2-methylbutanoyl chloride respectively. That of compounds 8 and 10 may be prepared as follows: The solution of 6.0 g of meso-2,4-dimethylglutaric acid anhydride [J. Am. Chem. Soc. *77*, 1862 (1955)] in 4 ml of methanol is reflexed for one hour and evaporated, to yield the erythro-4-carbomethoxy-2,4-dimethylbutanoic acid. it is converted into the acid chloride by refluxing it with 10.9 g of oxalyl chloride in 50 ml of methylene chloride for 2 hours, and evaporating said mixture.

The corresponding threo-isomer is analogously obtained from the racemic anhydride.

Example 7

The solution of 1 g of 1-(4-carbomethoxy-2-methylbutanoyl)-indoline-2S-carboxylic acid (Example 3) in 10 ml of methanol is saturated with ammonia at 0° and stored in a pressure bottle at room temperature for 4 days. It is evaporated, the residue taken up in water, the mixture acidified with 2N hydrochloric acid at 0° and the addition of a few drops of methylene chloride initiates crystallization. The mixture is filtered and the residue triturated with diethyl ether, to yield the 1-(4-carbamoyl-2-methylbutanoyl)-indoline-2S-carboxylic acid melting at 192-194°.

Example 8

a) To a solution of 1.43 g of indoline-2S-carboxylic acid hydrochloride in 15 ml pyridine at 0°C is added 1.35 g of 4-carboethoxy-2R, 4R-dimethylbutanoyl chloride. The reaction mixture is stirred at room temperature for 3 hours and evaporated under reduced pressure. The residue is treated with 20 ml of 3N hydrochloric acid and extracted three times with 10 ml of methylene chloride and the extract is evaporated to dryness. The 1-(4-carboethoxy-2R, 4R-dimethylbutanoyl)-indoline-2S-carboxylic acid obtained is dissolved in 75 ml of ether and treated with 2.2 ml dicyclohexylamine to yield the crystalline dicyclohexylammonium salt. This is slurried in a mixture of 40 ml of ethyl acetate and 45 ml of 5% aqueous potassium bisulfate solution for 1 hour. The ethyl acetate layer is separated, washed with water, dried over sodium sulfate, and evaporated to dryness. Crystallization from hexane yields 1-(4-carboethoxy-2R,4R-dimethylbutanoyl)-indoline-2S-carboxylic acid, melting at 125-127°, $[\alpha]_D = -159°$ (c = 0.2 ethanol).

b) By using 4-carboethoxy-2R-methylbutanoyl chloride instead of the 4-carboethoxy-2R,4R-dimethylbutanoyl chloride as described above, one obtains 1-(4-carboethoxy-2R-methylbutanoyl)-indoline-2S-carboxylic acid, melting at 133-135°, $[\alpha]_D = -120.5°$ (c = o.2 in ethanol).

c) Similarly prepared is 1-(4-carboethoxy-2R-isopropylbutanoyl)-indoline-2S-carboxylic acid.

d) Prepared similarly are 1-(4-carboethoxy-2R,4R-dimethyl-butanoyl)-indoline-2S-carboxylic acids wherein the 5-position of the indoline nucleus is substituted by either methoxy, chloro or methyl.

The starting materials are prepared as follows:

A solution of 3.7 g of 2R-methylglutaric acid [J. Am. Chem. Soc. *77*, 3383 (1955)] in 10 ml of acetyl chloride is stirred is stirred at 50° for 2 hours. The reaction mixture is evaporated to dryness to yield the 2R-methylglutaric anhydride, melting at 50-52°, $[\alpha]_D = +43.8°$ (c = 1.0 in chloroform). 2R,4R-dimethylglutaric anhydride, melting at 43-45°, $[\alpha]_D = +56.5°$ (c = 1.0 in chloroform) is prepared in identical fashion from 2R, 4R-dimethylglutaric acid [Arkiv Kemi Mineral. Geol. *B14*, 1 (1940), $[\alpha]_D = -35.5°$ (c = 2.0 in ethanol].

Similarly prepared is the 2R-isopropylglutaric anhydride from the corresponding 2R-isopropylglutaric acid [Arkiv Kemi Mineral. Geol. *B23*, 1 (1946)].

A solution of 1.7 g of 2R,4R-dimethylglutaric anhydride in 40 ml of absolute ethanol is heated under reflux overnight and evaporated to dryness to yield 4-carboethoxy-2R,4R-dimethylbutanoic acid as an oil, $[\alpha]_D = -49.4°$ (c = 1.0 in ethanol).

A solution of 2.9 g of 2R-methylglutaric anhydride in 10 ml of ethanol is refluxed for 3 hours and evaporated to dryness. A solution of the oil in 25 ml of ether is treated with 5.0 ml of dicyclohexylamine in 25 ml of hexane to yield the 4-carboethoxy-2R-methylbutanoic acid as the dicyclohexylammonium salt, m.p. 98-100°.

Conversion to the free acid with 1N hydrochloric acid and extraction with ethyl acetate gives 4-carboethoxy-2R-methylbutanoic acid as an oil, $[\alpha]_D = -20.9°$ (c = 1.0 in chloroform).

A solution of 1.27 g of 4-carboethoxy-2R,4R-dimethylbutanoic acid in 15 ml of methylene chloride is treated with 1.7 g of oxalyl chloride, heated under reflux for 3 hours and evaporated to dryness to yield 4-carboethoxy-2R,4R-dimethylbutanoyl chloride, NMR peaks at 1.8, 2.5, 2.8, 4.1 ppm. Similarly prepared are the 4-carboethoxy-2R-methyl-butanoyl chloride (NMR peaks at 2.0, 2.4, 4.3 ppm) and the 4-carboethoxy-2R-isopropylbutanoyl chloride.

5-methoxyindoline-2-carboxylic acid, 5-chloro-indoline-2-carboxylic acid, and 5-methylindoline-2-carboxylic acid can be prepared from the corresponding substituted indole-2-carboxylic acid according to the metod described for Example 1.

Example 9

a) To a solution of 2.63 g of ethyl indoline-2S-carboxylate in 40 ml of methylene chloride containing 4.8 g of anhydrous potassium carbonate is added 2.39 g of 4-carboethoxy-2R,4R-dimethylbutanoyl chloride. The reaction mixture is stirred overnight at room temperature and then extracted with 20 ml of water. The organic layer is washed with 15 ml of 1N hydrochloric acid and 15 ml of water, dried over sodium sulfate and evaporated to give ethyl 1-(4-carboethoxy-2R,4R-dimethylbutanoyl)-indoline-2S-carboxylate as an oil having $[\alpha]_D = -130.10°$ (c = 1.0 in ethanol).

b) Similarly prepared is ethyl 1-(4-carboethoxy-2R-methylbutanoyl)-indoline-2S-carboxylate as an oil having NMR peaks at 1.2, 4.1 to 4.3, 4.9, 6.7 and 7.2 ppm using 4-carboethoxy-2R-methylbutanoyl chloride as the acylating reagent.

Example 10

To a solution of 3.2 g of ethyl indoline-2S-carboxylate hydrochloride and 1.47 g of triethylamine in 60 ml of methylene chloride is added 2.34 g of 4-carboethoxy-2R-methylbutanoic acid followed by 2.97 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reaction mixture is stirred at room temperature for 3 days and poured into water. The organic layer is separated and washed successively with 30 ml of 1N hydrochloric acid, 30 ml of water and 30 ml of 10% aqueous sodium bicarbonate solution. The organic layer is dried over sodium sulfate and evaporated to dryness to yield ethyl 1-(4-carboethoxy-2R-methylbutanoyl)-indoline-2S-carboxylate identical to the compound of example 9b).

Example 11

A solution of 0.45 g of ethyl indoline-2S-carboxylate and 0.30 g of 2R,4R-dimethylglutaric anhydride in 10 ml of toluene is stirred at 70° for 18 hours. The reaction mixture is cooled to room temperature, washed twice with 5 ml of 1N hydrochloric acid and extracted twice with 10 ml of 5% sodium bicarbonate. The combined bicarbonate portions are acidified with 4.0 ml of 12N hydrochloric acid and extracted three times with 10 ml of methylene chloride. The combined methylene chloride portions are dried over sodium sulfate and evaporated to give ethyl 1-(4-carboxy-2R,4R-dimethyl-butanoyl)-indoline-2S-carboxylate as an oil having NMR peaks at 1.0 to 1.3, 4.15, 5.10, 7.2 and 8.4 ppm.

Example 12

a) To a solution of 3.4 g of ethyl 1-(4-carboethoxy-2R,4R-dimethyl-butanoyl)-indoline-2S-carboxylate in 30 ml of ethanol is added 28.2 ml of 1N aqueous sodium hydroxide solution. The reaction mixture is stirred at room temperature for 4 hours, evaporated to remove ethanol and acidified with 3.5 ml of concentrated hydrochloric acid. The mixture is extracted four times with 10 ml of methylene chloride. The combined extract is dried over sodium sulfate and evaporated to dryness and the residue is recrystallized from ether-petroleum ether to give 1-(4-carboxy-2R,4R-dimethyl butanoyl)-indoline-2S-carboxylic acid melting at 132-134°, $[\alpha]_D = -144°$ (c = 1.0 in ethanol).

Similar hydrolysis of 0.46 of ethyl 1-(4-carboxy-2R,4R-dimethyl-butanoyl)-indoline-2S-carboxylate (Example 10) and crystallization of the product from water yields the 1-(4-carboxy-2R,4R-dimethyl-butanoyl)-indoline-2S-carboxylic acid hydrate having a melting point of 93-95°, $[\alpha]_D = -142.8°$ (c = 1.0 in ethanol).

b) Similarly, hydrolysis of ethyl 1-(4-carboethoxy-2R-methylbutanoyl)-indoline-2S-carboxylate yields 1-(4-carboxy-2R-methylbutanoyl)-indoline-2S-carboxylic acid, crystallized from ether and melting at 147-149°, $[\alpha]_D = -125°$ (c = 0.2 in ethanol). Similarly, hydrolysis of 1-(4-carboethoxy-2R-methylbutanoyl)-indoline-2S-carboxylic acid yields the diacid identical to the 1-(4-carboxy-2R-methylbutanoyl)-indoline-2S-carboxylic acid isolated above.

Example 13

A solution of 90 mg of indoline-2S-carboxylic acid hydrochloride is treated with 92 mg of 4-carboethoxy-2R-methyl-4R-phenethylbutanoyl chloride in pyridine by the analogous process described in detail for Example 8 to yield 1-(4-carboethoxy-2R-methyl-4R-phenethylbutanoyl)-indoline-2S-carboxylic acid as the dicyclohexylamine salt melting at 146-149°. The salt is converted to the free acid (by general procedure as described e.g. in Example 8) to yield 1-(4-carboethoxy-2R-methyl-4R-phenylethyl-butanoyl)-indoline-2S-carboxylic acid melting at 95-98°, $[\alpha]_D = -117,5°$ (c = 0.88 in chloroform).

The starting material is prepared in part according to the general process described in Tetrahedron Letters *1980*, 4233-6, as follows:

25 ml of 1N aqueous sodium hydroxide solution are added to a solution of 2.0 g of L-prolinol (US patent 3,935,280) in 50 ml of methylene chloride. After cooling the reaction mixture to 0°, 4.0 g of 4-phenylbutyric acid chloride is added and the reaction mixture is stirred vigorously for 4 hours at 0°C, followed by 1 hour at room temperature. The reaction mixture is diluted with an equal volume of methylene chloride and the layers separated. The organic phase is washed with 30 ml of water and dried over sodium sulfate/potassium carbonate. The solvent is evaporated to yield the N-(4-phenylbutanoyl)-L-prolinol having IR peaks at 3280 and 1605 cm^{-1}, $[\alpha]_D^{25} = -40.3°$ (c = 1.42 in methanol). 20.5 g of N-methyl-N,N'-dicyclohexylcarbodiimidium iodide [Angew. Chem., Int. Ed. *11*, 229 (1972)] are added to a solution of 5.3 g of R-(−)-3-benzyloxy-2-methylpropanol [Helv. Chim. Acta *60*, 925 (1977)] in 200 ml dry tetrahydrofuran under nitrogen and the reaction mixture is stirred at room temperature for 14 hours. The solvent is evaporated and 20 ml of ether and 5 ml of pentane are added. The resulting yellow solid is collected and the mother liquors are chromatographed on 200 g of silica gel with pentane to yield the S-(+)-3-benzyloxy-2-methylpropyl iodide having Rf = 0.60 (9:1 of pentane: ether/silica gel), $[\alpha]_D^{25} = +11.1°$ (c = 1.11 in methanol). 1.75 g of N-(4-phenylbutanoyl)-L-prolinol is dissolved in 2 ml of dry tetrahydrofuran and added dropwise to a solution

of lithium diisopropylamide (15. 6 m moles) in 50 ml of tetrahydrofuran at 0° under nitrogen. After 30 minutes at 0°, 2.03 g of S-(+)-3-benzyloxy-2-methylpropyl iodide is added dropwise in 2 ml of dry tetrahydrofuran. The reaction mixture is stirred at 0° for 5 hours, at −15° for 15 hours and quenched at 0° with excess saturated aqueous ammonium chloride solution. The reaction mixture is diluted with 20 ml of ether. The layers are evporated and the organic phase is washed with 16 ml of 1N hydrochloric acid, 15 ml of saturated aqueous sodium chloride solution, 15 ml of saturated aqueous sodium bicarbonate solution and dried over sodium sulfate.

Evaporation of solvent yields an oil which is filtered through 60 g of silica gel with ethyl acetate to yield the N-(R,R-5-benzyloxy-4-methyl-2-phenethylpentanoyl)-L-prolinol having Rf = 0.51 (ethyl acetate/silica gel).

A solution of 2.0 g of N-(R,R-5-benzyloxy-4-methyl-2-phenethyl pentanoyl)-L-prolinol in 50 ml of 1N ethanolic hydrochloric acid is refluxed under nitrogen for 15 hours. The solvent is evaporated and the residue is chromatographed on 60 g of silica gel with pentane: ether (2:1) to yield the ethyl R,R-5-benzyloxy-4-methyl-2-phenethyl-pentaoate having Rf 0.37 (9:1 of pentane: ether/SiO_2), $[\alpha]_D^{25} = +2.85°$ (c = 1.10 in ethanol).

A solution of 0.6 g of ethyl R,R-5-benzyloxy-4-methyl-2-phenethyl-pentanoate in 50 ml of anhydrous ethanol is hydrogenated at 2.7 atmospheres for 3 hours at room temperature with 0.5 g of 5% palladium on charcoal catalyst. The catalyst is then removed by filtering and the solvent is evaporated to yield the ethyl R,R-5-hydroxy-4-methyl-2-phenethylpentanoate having Rf = 0.36 (1:1 of pentane-ether).

Ethyl R,R-5-hydroxy-4-methyl-2-phenethylpentanoate (0.35 g) is dissolved in 15 ml of dry dimethylformamide at room temperature under nitrogen. Pyridinium dichromate (2.5 g) is added and the reaction mixture is stirred for 15 hours at room temperature before being poured into 150 ml of water. The aqueous solution is extracted with ether (4 × 40 ml). the etheral extracts are washed with 30 ml of water and then three times with 20 ml of a 1:1 solution of sodium bicarbonate: potassium carbonate (pH = 10.5). The basic wash is acidified to pH = 2 with concentrated sulfuric acid, while keeping the temperature between 5 and 10°C, and extracted with ether (4 × 20 ml),. The etheral extracts are washed with 20 ml of saturated aqueous sodium chloride solution and dried over sodium sulfate/magnesium sulfate. Evaporation of the solvent yields the 4-carboethoxy-2R-methyl-4R-(phenethyl)-butanoic acid, having Rf = 0.50 (99:1:100 of ether: acetic acid: hexane), $[\alpha]_D^{25} = -4.91°$ (c = 1.24 in ethanol).

Treatment of 4-carboethoxy-2R-methyl-4R-(phenethyl)-butanoic acid with oxalyl chloride in methylene chloride yields 4-carboethoxy-2R-methyl-4R-phenethyl-butanoyl chloride, which is used without further purification.

Example 14

According to the process described for Example 10, 79 mg of ethyl indoline-2S-carboxylate hydrochloride is reacted with 96.5 mg of 4-carboethoxy-2R-methyl-4R-(phenethyl)-butanoic acid (See Example 13) in the presence of 0.05 ml of triethylamine and 66.5 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride to yield ethyl 1-(4-carboethoxy-2R-methyl-4R-phenethylbutanoyl)-indoline-2S-carboxylate having Rf = 0.6 (9:1 chloroform-methanol/SiO_2).

To a solution of 87 mg of the above diester in 4 ml of methanol at room temperature is added 0.2 ml of 2.2 N aqueous potassium hydroxide, 1.5 ml of water and the reaction mixture is stirred at room temperature for 2 hours. The reaction mixture is worked up in the usual manner (see Example 12) to yield 1-(4-carboethoxy-2R-methyl-4R-phenethylbutanoyl)-indoline-2S-carboxylic acid purified as the dicyclohexylamine salt melting at 145-8° and identical to compound of Example 13.

To a solution of 0.28 g of 1-(4-carboethoxy-2R-methyl-4R-phenethylbutanoyl)-indoline-2S-carboxylic acid in 3ml of methanol are added 2 ml of 1N aqueous lithium hydroxide. The reaction mixture is stirred at 55° for 6 hours and then evaporated. The residue in 30 ml of water is washed with 15 ml of diethyl ether. The aqueous layer is acidified to pH 2 with 1N aqueous hydrochloric acid and extracted with 3 × 25 ml of methylene chloride. These combined organic portions are dried over magnesium sulfate and evaporated. The residue is crystallized from pentane to give 1-(4-carboxy-2R-methyl-4R-phenethylbutanoyl)-indoline-2S-carboxylic acid melting at 137-139°, $[\alpha]_D = -62°$ (c = 0.25 in chloroform).

Example 15

Preparation of 10,000 tablets each containing 5 mg of the active ingredient:

Formula:

1-[4-carboxy-4-(2-phenethyl)-butanoyl]-indoline-2S-carboxylic acid	50 g
Lactose	1,157 g
Corn starch	75 g
Polyethylene glycol 6,000	75 g
Talcum powder	5 g
Magnesium stearate	18 g
Purified water	q.s.

Procedure

All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance, lactose, talcum, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 40 ml of water and the suspension added to the boiling solution of the polyethylene glycol in 150 ml of water. The paste formed is added to the powders which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35°, broken on a screen with 1.2 mm openings and compressed into tablets using concave punches with 6.4 mm diameter, uppers bisected.

Example 16

Preparation of 10,000 capsules each containing 10 mg of the active ingredient:

Formula

1-(4-carboethoxy-2R,4R-dimethylbutanoyl)-indoline-2S-carboxylic acid	100 g
Lactose	1,800 g
Talcum powder	100 g

Procedure

All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance is placed in a suitable mixer and mixed first with the talcum, then with the lactose until homogenous. No. 3 capsules are filled with 200 mg, using a capsule filling machine.

Analogously tablets or capsules are prepared from the remaining compounds of the invention, e.g., those illustrated by the other Examples herein.

Example 17

To a solution of 0.78 g of ethyl indoline-2S-carboxylate hydrochloric, 0.90 g of 4R-carboethoxy-6-phenylhexanoic acid, and 0.48 ml of triethylamine in 40 ml of methylene chloride are added 0.72 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reaction mixture is stirred at room temperature for 4 days. 300 ml of diethyl ether is added and the mixture is washed with 25 ml of water, 25 ml of 2N aqueous hydrochloric acid and 25 ml of saturated aqueous sodium bicarbonate solution. The organic layer is dried over magnesium sulfate and evaporated to give ethyl 1-(4-carboethoxy-4R-phenethylbutanoyl)-indoline-2S-carboxylate with $[\alpha]_D = -64.3°$ (c = 0.85 in chloroform).

The starting material for the above procedures is prepared as follows:

8.10 g of N-(4-phenylbutanoyl)-L-prolinol in 50 ml of tetrahydrofuran are added to 71 mMol of lithium diisopropylamide in 270 ml of tetrahydrofuran at −20°. After 1 hour 3.1 ml of allyl bromide are added. After 1 hour at −20° the reaction mixture is diluted with 250 ml of diethyl ether. The layers are separated and the organic phase is washed with 200 ml of 0.5N aqueous hydrochloric acid and 200 ml of saturated aqueous sodium cholride solution, dried over sodium sulfate, and evaporated to give the N-(2R-allyl-4-phenylbutanoyl)-L-prolinol having $[\alpha]_D = -23.5°$ (c = 1 in methanol).

A solution of 7.65 g of N-(2R-allyl-4-phenyl-butanoyl)-L-prolinol in 350 ml of 10% ethanolic sulfuric acid is refluxed for 10 hours. The solvent is evaporated and the residue is partitioned between 100 ml of water and 200 ml of diethyl ether. The layers are separated and the organic phase is washed with 50 ml of saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and evaporated to give the ethyl 2R-allyl-4-phenyl-butyrate having $R_f = 0.42$ (9:1 hexane:ether/SiO_2).

The 22.2 ml of 1M borane in tetrahydrofuran at 0°C is added 3.1 g of 2-methyl-2-butene. After 2 hours at 0°, 4.7 g of ethyl 2R-allyl-4- phenyl-butyrate are added. After 2 hours 7.3 ml of 3N aqueous sodium hydroxide solution and 7.3 ml of 30% aqueous hydrogen peroxide are added 30 minutes the reaction mixture is diluted with 75 ml of diethyl ether. The layers are separated and the aqueous layer is extracted with 2 × 25 ml of diethyl ether. The combined ether extracts are washed with 25 ml of 1% aqueous sodium carbonate solution and 25 ml of saturated aqueous sodium sulfite solution. The organic phase is dried over magnesium sulfate and evaporated to give ethyl 5-hydroxy-2R-phenethyl-pentanoate with NMR peaks at 7.3, 4.25, 3.61, 1.55-2.78 and 1.27 ppm.

To 4.97 g of ethyl 5-hydroxy-2R-phenethyl-pentanoate in 100 ml of dimethylformamide is added 27.4 g of pyridinium dichromate. The reaction mixture is stirred overnight at room temperature and then poured into 300 ml of ice water. The mixture is extracted with 5 × 100 ml of diethyl ether. The combined organic portions are washed with 100 ml of 5% aqueous sodium carbonate solution. The aqueous phase is acidified with concentrated sulfuric acid to pH 2 and extracted with 3 × 100 ml of diethyl ether. These ether extracts and dried over magnesium sulfate and evaporated to give 4R-carboethoxy-6-phenyl-hexanoic acid with $[\alpha]_D = +4.32°$ (c = 1 in methanol).

Example 18

To 1.10 g of ethyl 1-(4-carboethoxy-4R-phenethylbutanoyl)-indoline-2S-carboxylate in 5 ml of ethanol are added 1.07 ml of 2.21N aqueous potassium hydroxide solution. The reaction mixture is stirred at room temperature for 1 hour and then evaporated. The residue in 20 ml of saturated aqueous sodium bicarbonate solution is washed with 20 ml of diethyl ether. The aqueous layer is adjusted to pH = with 2N aqueous hydrochloric acid and extracted with 2 × 25 ml of methylene chloride. The combined methylene chloride portions are dried over magnesium sulfate and evaporated to give 1-(4-carboethoxy-4R-phenethyl-butanoyl)-indoline-2S-carboxylic acid melting at 100-102°, $[\alpha]_D = -83.4°$ (c = 1.13 in chloroform).

Example 19

To 0.67 g of 1-(4-carboethoxy-4R-phenethylbutanoyl)-indoline-2S-carboxylic acid in 8 ml of methanol are added 4.9 ml of 1N aqueous lithium hydroxide solution. The reaction mixture is stirred at 55° for 8 hours and then evaporated. The residue in 30 ml of saturated aqueous sodium bicarbonate solution is washed with 25 ml of diethyl ether. The aqueous layer is acidified with 2N aqueous hydrochlic acid and extracted with 2 × 25 ml of methylene chloride. The combined methylene chloride portions and dried over magnesium sulfate and evaporated. The residue is crystallized from pentane to give 1-(4-carboxy-4R-phenethylbutanoyl)-indoline-2S-carboxylic acid melting at 132-135°, $[\alpha]_D = -79.1°$ (c = 0.81 in chloroform).

Example 20

To a solution of 5.0 g of ethyl indoline-2S-carboxylate hydrochloride and 2.2 g of triethylamine in 40 ml of toluene are added 3.1 g of (2R, 4R)-dimethylglutaric anhydride. The reaction mixture is stirred at 80° for 4 hours, then cooled to room temperature and washed with 10 ml of 1N hydrochloric acid and 10 ml of water. The organic layer is dried over sodium sulfate and evaporated. The residue is crystallized from diethyl ether-hexane to give ethyl 1-(4-carboxy-2R,4R-dimethylbutanoyl)-indoline-2S-carboxylate melting at 110-112°, $[\alpha]_D = -156.5°$ (c = 0.2 in ethanol).

Example 21

To a solution of 6.5 g of ethyl 1-(4-carboethoxy-2-isopropyl-butanoyl)-indoline-2S-carboxylate in 50 ml of methanol are added 52 ml of 1N aqueous sodium hydroxide solution. The reaction mixture is stirred 2 hours at room temperature and then the methanol is evaporated. The aqueous residue is acidified with 5 ml of concentrated hydrochloric acid and extracted with 3 × 25 ml of methylene chloride. The combined organic portions are drived over sodium sulfate and evaporated. The residue is crystallized from diethyl ether to give 1-(4-carboxy-2-isopropylbutanoyl)-indoline-2S-carboxylic acid melting at 184-186°, $[\alpha]_D = -81°$ (c = 0.2 in ethanol).

The starting material is prepared as follows:

A solution of 14.0 g of 2-isopropylglutaric acid in 80 ml of acetyl chloride is stirred at 50° for 2 hours and then evaporated to give 2-isoporpylglutaric anhydride with NMR peaks at 0.98, 1.89, 2.43 and 2.85 ppm.

A solution of 4.0 g of 2-isopropylglutaric anhydride in 20 ml of ethanol is refluxed for 3 hours and then evaporated to give 4-carboethoxy-2-isopropylbutyric acid with NMR peaks at 4.76, 2.31, 1.84, 1.21, and 0.95 ppm.

To a solution of 5.62 g of ethyl indoline-2S-carboxylate hydrochloride, 5,0 g of 4-carboethoxy-2-isopropylbutyric acid and 2.5 g of triethylamine in 80 ml of methylene chloride are added 5.21 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reaction mixture is stirred overnight at room temperature. The reaction mixture is washed with 40 ml of water, 30 ml of 1N hydrochloric acid and 30 ml of saturated aqueous soidum bicarbonate solution, dried and evaporated, to give ethyl 1-(4-carboethoxy-

2-isopropyl-butanoyl)-indoline-2S-carboxylate with NMR peaks at 7.16, 6.78, 5.11, 4.22, 3.31, 2.31, 1.98, 1.22 and 0.95 ppm.

Example 22

To a solution of 4.0 g of indoline-2S-carboxylic acid hydrochloride and 2.0 g of triethylamine in 40 ml of toluene are added 2.84 g of 3,3-dimethylglutaric anhydride. The reaction mixture is stirred at 80° for hours and then evaporated. The residue is partitioned between 25 ml of 1N hydrochloric acid and 25 ml of methylene chloride. The organic layer is separated and washed with 20 ml of water and extracted with 2 × 20 ml of saturated aqueous sodium bicarbonate solution. The bicarbonate extracts and acidified with 5 ml of concentrated hydrochloric acid and extracted with 2 × 25 ml of methylene chloride. The organic layer is dried over sodium sulfate and evaporated. The residue is crystallized from ether hexane to give 1-(4-carboxy-3,3-dimethylbutanoyl)-indoline-2S-carboxylic acid melting at 132-133°, $[\alpha]_D = -151°$ (c = 0.2 in ethanol).

Example 23

To a solution of 1.0 g of 5-chloroindoline-2-carboxylic acid hydrochloride and 0.43 g of triethylamine in 15 ml of toluene are added 0.55 g of 2R,4R-dimethylglutaric anhydride. The reaction mixture is stirred at 80° for 3.5 hours and then evaporated. The residue is partitioned between 20 ml of 1N hydrochloric acid and 20 ml of methylene chloride. The methylene chloride layer is washed with 10 ml of water and then extracted with 2 × 10 ml of saturated aqueous sodium bicarbonate solution. The bicarbonate extracts are acidified with 2.5 ml of concentrated hydrochloric acid and extracted with 3 × 10 ml of methylene chloride. These organic extracts are dried over sodium sulfate and evaporated. The residue is dissolved in 7 ml of diethyl ether and 0.4 g of dicyclohexylamine. The product is filtered and recrystallized from ethyl acetate to give 1-(4-carboxy-2R,4R-dimethylbutanoyl)-5-chloroindoline-2-carboxylic acid bis-dicyclohexylammonium salt melting at 185-187°. $[\alpha]_D = -26.50°$ (c = 0.2 in ethanol).

Similarly prepared is 1-(4-carboxy-2R,4R-dimethylbutanoyl)-5-methyl indoline-2-carboxylic acid bis-dicyclohexylammonium salt melting at 198-200°, $[\alpha]_D = +0.9°$ (c = 0.2 in ethanol).

Also similarly prepared is 1-(4-carboxy-2R,4R-dimethylbutanoyl)-5-methoxyindoline-2S-carboxylic acid melting at 150–152°, $[\alpha]_D = -130°$ (c = 0.2 in ethanol).

The starting material is prepared as follows:

The mixture of 20 g of 5-methoxyindole-2-carboxylic acid (J. Chem. Soc., *1970*, 865) and 200 ml of acetic anhydride is refluxed for 2 hours and allowed to cool to room temperature. It is filtered, the filtrate evaporated and the residue is stirred in 300 ml of water. Excess sodium bicarbonate is added, the mixture stirred for 3 hours and then washed with 200 ml of diethyl ether. The aqueous layer is acidified to pH = 1 with concentrated hydrochloric acid and filtration yields the 1-acetyl-5-methoxyindole-2-carboxylic acid melting at 173-175°.

The solution of 16.5 g thereof in 250 ml of ethanol is hydrogenated at one atmosphere in the presence of 1.0 g of platinum oxide. After 2 hours the mixture is filtered and the filtrate concentrated to 100 ml. After standing at 0° overnight it is filtered, to give the colorless crystalline 1-acetyl-5-methoxyindoline-2-carboxylic acid melting at 164-167°C.

6.0 g thereof are refluxed in 60 ml of 2N aqueous hydrochloric acid for 2 hours and the mixture is evaporated. The residue is dissolved in 50 ml of isopropanol and diethyl ether is added until the solution becomes turbid. After cooling at 0° the precipitate is filtered off, to yield the 5-methoxyindoline-2-carboxylic acid hydrochloride melting at 90-92° (decomposition).

Other substituted indoline-2-carboxylic acids are similarly prepared i.e., 5-chloroindoline-2-carboxylic acid hydrochloride melting at 165-167° and 5-methylindoline-2-carboxylic acid hydrochloride melting at 171-173°.

Example 24

To a solution of 1.5 g of 4-cyanobutryic acid, 3.0 g of ethyl indoline-2S-carboxylate hydrochloride and 1.35 g of triethylamine in 75 ml of methylene chloride are added 3.8 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reaction mixture is stirred at room temperature for 3 days. The reaction mixture is washed with 50 ml of water, 50 ml of 2N hydrochloric acid and 50 ml of saturated aqeuous sodium bicarbonate solution. The organic layer is dried over magnesium sulfate and evaporated to give the ethyl 1-(4-cyanobutanoyl)-indoline-2S-carboxylate, showing major IR-bands at 2240, 1730 and 1660 cm^{-1}.

To 2.3 g of ethyl 1-(4-cyanobutanoyl)-indoline-2S-carboxylate in 30 ml of tetrahydrofuran and 10 ml of water are added 8.8 ml of 1N aqueous lithium hydroxide solution. The reaction mixture is stirred overnight at room temperature. The reaction mixture is diluted with 50 ml of water and washed with 50 ml of diethyl ether. The aqueous layer is acidified with 10 ml of 2N hydrochloric acid and extracted with 2 × 50 ml of diethyl ether. These extracts are dried over magnesium sulfate and evaporated to give 1-(4-cyanobutanoyl)-indoline-2S-carboxylic acid melting at 98-100°, $[\alpha]_D = -112.6°$ (c = 0.9 in ethanol).

A solution of 2.6 g of 1-(4-cyanobutanoyl)-indoline-2S-carboxylic acid in 50 ml of ethanol and 50 ml of ether at 0° is saturated with hydrogen chloride gas. The reaction mixture is then stirred at room temperature for 1 hour. The reaction mixture is cooled to 0° and 50 ml of water is added. After 10 minutes the reaction mixture is concentrated under reduced pressure and the residue is taken up in 50 ml of water and extracted with 2 × 50 ml of ether. The combined ether portions are dried over magnesium sulfate and evaporated. Crystallization of the residue from ether-hexane gives ethyl 1-(4-carboethoxybutanoyl)-indoline-2S-carboxylate melting at 72-73°, $[\alpha]_D = -81.7°$ (c = 0.35 in ethanol).

Cardiovascular pharmacology of compounds of the invention

Testing of compounds is carried out by methods for evaluation of the inhibition of the angiotensin converting-enzyme (ACE). Biochemical assessment of in vitro ACE inhibition (ACEI) gauges the inhibition of peptidolytic acitivity of a compound in rabbit lung tissue. In in vivo studies angiotensin I (AI) pressor response inhibition of the compounds are conducted in rats.

Biochemical testing methodology

A rabbit lung tissue preparation [Das and Saffer, J. Biol. Chem. *250*: 6762, (1975)] was used for assessment of ACE by the method of Cheung and Cushman [Cheung and Cushman, Biochim, Biophys. Acta *293*: 451, (1973)]. This test system incorporates spectrophotometric evaluation of the amount of histidyl-leucine liberated from a synthetic substrate after 30 min. of 37°C incubation. IC_{50} values for ACE inhibition were determined graphically as the concentration of test drug required to reduce the amount of histidyl-leucine formed to 50% of that generated in the absence of the test compound.

Methodology of angiotensin I (AI) pressor response inhibition following intravenous administration of test compounds (% AI)

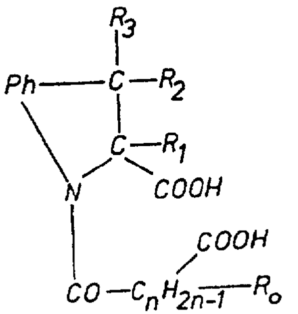
In these studies catheters were placed in a femoral artery and a saphenous vein of anesthetized rats as described above. Arterial pressure was continuously recorded from the arterial catheter, while AI and the test compounds were injected through the venous catheter. AI pressor response inhibition was expressed as tabulated as the average inhibition recorded through 30 min. after test at several doses appropriate to determine the ID_{50} (i.v.) for AI pressor response inhibition.

Results:

Compound of Example	*In vitro ACEI IC_{50}(M)*	*Angiotensin I pressor response inhibition*	
		i.v. Dose (mg/kg)	*% AI inhibition*
2	3×10^{-7}	10	77
6/5	6×10^{-8}	10	70
5	4×10^{-8}	10	71
12/a	3×10^{-8}	ID_{50} : 0.23 mg/kg	
8/a	6×10^{-5}	ID_{50} : 0.29 mg/kg	
12/b	4×10^{-8}	1.0	95
		0.1	37
8/b	1×10^{-5}	0.1	32
6/1	3×10^{-7}		
13	1×10^{-5}	0.1	80
14/c	5×10^{-9}	0.1	61
21	5×10^{-8}	1.0	80
23/c	1×10^{-7}		
23/b	5×10^{-7}		
23/a	4×10^{-6}		

CLAIMS

1. A compound of the general formula I

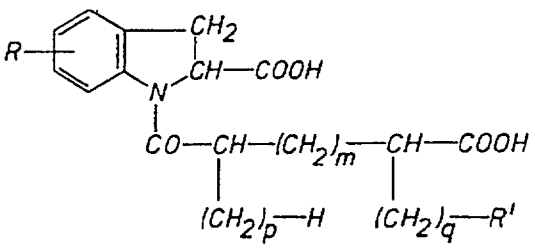


wherein Ph is unsubstituted 1,2-phenylene, or 1,2-phenylene substituted by one to three identical or different members selected from lower alkyl, lower alkoxy, lower alkylenedioxy, hydroxy, halogeno and trifluoromethyl; R_o is hydrogen or HPh; each of R_1, R_2 and R_3 is hydrogen or lower alkyl; and n is an integer from 1 to 10; the amides, mono- or di-lower alkylamides, loer alkyl esters, (amino, mono- or di-lower alkylamino, carboxy or carbo lower alkoxy)-lower alkyl esters thereof.

2. A compound of the formula I as claimed in claim 1, wherein Ph is unsubstituted 1,2-phenylene, or 1,2-phenylene substituted by one or two identical or different members selected from lower alkyl, lower alkoxy, hydroxy and halogeno, or 1,2-phenylene substituted by one lower alkylenedioxy or trifluoromethyl group; R_o is hydrogen or HPh; each of R_1, R_2 and R_3 is hydrogen or lower alkyl; and n is an integer from 1 to 10; the amides, mono- or di-lower alkylamides, lower alkyl esters, (amino, mono- or di-lower alkylamino, carboxy or carbo-lower alkoxy)-lower alkyl esters thereof.

3. A compound of the formula I as claimed in claim 1, wherein Ph is 1,2-phenylene, unsubstituted or mono-substituted by lower alkyl, lower alkoxy, lower alkylenedioxy, hydroxy, halogeno or trifluoromethyl; R_o is hydrogen or HPh; each of R_1, R_2 and R_3 is hydrogen or methyl; and n is an integer from 2 to 8; the amides, mono- or di-lower alkyl-amides, lower alkyl esters, (amino, mono- or di-lower alkylamino, carboxy or carbo-lower alkoxy)-lower alkyl esters thereof.

4. A compound of the general formula II



wherein R is hydrogen, alkyl or alkoxy with up to 4 carbon atoms, halogeno or trifluoromethyl m is the integer 0 or 1; each of p and q is an integer from 0 to 2; and R' is hydrogen or R-phenyl; the mono- or bis-amide, the mono- or bis-(lower alkyl or ω-amino-lower alkyl) esters thereof.

5. A compound of the formula II as claimed in claim 4, wherein R is hydrogen, methyl, fluoro, chloro or trifluoromethyl, each of m and p is the integer 1, q is the integer 1 or 2, and R' is hydrogen or phenyl, the mono- or bis-amide, the mono- or bis-(lower alkyl or ω-amino-lower alkyl) esters thereof.

6. A compound as claimed in claim 5 wherein R is in the 5-position.

7. A compound as claimed in claim 4, in the form of its 2S-carboxy-indoline chiral epimer.

8. A compound of the formula I as claimed in claim 1, and as defined in the Example 6, under a number from 1 to 12.

9. 1-(4-carbomethoxybutanoyl)-indoline-2S-carboxylic acid ethyl ester.

10. 1-(4-carboxybutanoyl)-indoline-2S-carboxylic acid.

11. 1-(4-carbomethoxy-2-methylbutanoyl)-indoline-2S-carboxylic acid.

12. 1-[4-carboxy-4-(2-phenethyl)-butanoyl]-indoline-2S-carboxylic acid ethyl ester.

13. 1-[4-carboxy-4-(2-phenethyl)-butanoyl]-indoline-2S-carboxylic acid.

14. 1-(4-carbamoyl-2-methylbutanoyl)-indoline-2S-carboxylic acid.

15. 1-(4-carboethoxy-2R,4R-dimethylbutanoyl)-indoline-2S-carboxylic acid.

16. 1-(4-carboethoxy-2R-methylbutanoyl)-indoline-2S-carboxylic acid.

17. 1-(4-carboethoxy-2R-isopropylbutanoyl)-indoline-2S-carboxylic acid.

18. 1-(4-carboethoxy-2R,4R-dimethyl-butanoyl)-5-methoxyindoline-2S-carboxylic acid.

19. 1-(4-carboethoxy-2R,4R-dimethyl-butanoyl)-5-chloroindoline-2S-carboxylic acid.

20. 1-(4-carboethoxy-2R,4R-dimethyl-butanoyl)-5-methylindoline-2S-carboxylic acid.
21. ethyl 1-(4-carboethoxy-2R,4R-dimethylbutanoyl)-indoline-2S-carboxylate.
22. ethyl 1-(4-carboethoxy-2R-methylbutanoyl)-indoline-2S-carboxylate.
23. ethyl 1-(4-carboxy-2R,4R-dimethylbutanoyl)-indoline-2S-carboxylate.
24. 1-(4-carboxy-2R,4R-dimethylbutanoyl)-indoline-2S-carboxylic acid.
25. 1-(4-carboxy-2R,4R-dimethylbutanoyl)-indoline-2S-carboxylic acid hydrate.
26. 1-(4-carboxy-2R-methylbutanoyl)-indoline-2S-carboxylic acid.
27. 1-(4-carboethoxy-2R-methyl-4R-phenylethyl-butanoyl)-indoline-2S-carboxylic acid.
28. ethyl 1-(4-carboethoxy-2R-methyl-4R-phenethylbutanoyl)-indoline-2S-carboxylate.
29. 1-(4-carboxy-2R-methyl-4R-phenethylbutanoyl)-indoline-2S-carboxylic acid.
30. ethyl 1-(4-carboethoxy-4R-phenethylbutanoyl)-indoline-2S-carboxylate.
31. 1-(4-carboethoxy-4R-phenethylbutanoyl)-indoline-2S-carboxylic acid.
32. 1-(4-carboxy-4R-phenethylbutanoyl)-indoline-2S-carboxylic acid.
33. 1-(4-carboxy-2-isoproylbutanoyl)-indoline-2S-carboxylic acid.
34. 1-(4-carboxy-3,3-dimethylbutanoyl)-indoline-2S-carboxylic acid.
35. 1-(4-carboxy-2R,4R-dimethylbutanoyl)-5-chloroindoline-2-carboxylic acid.
36. 1-(4-carboxy-2R,4R-dimethylbutanoyl)-5-methyl-indoline-2-carboxylic acid.
37. 1-(4-carboxy-2R,4R-dimethylbutanoyl)-5-methyl-indoline-2-carboxylic acid.
38. ethyl 1-(4-carboethoxybutanoyl)-indoline-2S-carboxylate.
39. A salt of compound having a salt forming group, as claimed in any of claims 1-14.
40. A salt of a compound having a salt forming group, as claimed in any of claims 15 - 19.
41. A salt of a compound having a salt forming group, as claimed in any of claims 30-38.

42. A pharmaceutically acceptable salt of a compound having a salt forming group, as claimed in any of claims 1-14.

43. A pharmaceutically acceptabe salt of a compound having a salt forming group, as claimed in any of claims 15-29.

44. A pharmaceutically acceptable salt of a compound having a salt forming group, as claimed in any of claims 30-38.

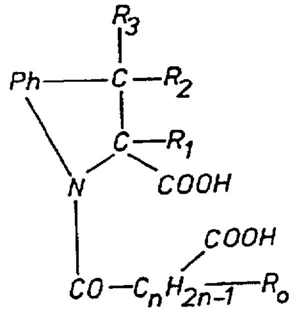
45. A compound of formula I as claimed in claim 1 substantially as described with reference to any of Examples 1 to 14 and 17 to 24.

46. A pharmaceutical preparation comprising a compound claimed in any of claims 1-14 and 42, in admixture or conjunction with a pharmaceutically suitable carrier.

47. A pharmaceutical preparation comprising a compound claimed in an of claims 15-29 and 43, in admixture or conjunction with a pharmaceutically suitable carrier.

48. A pharmaceutical preparation comprising a compound claimed in any of claims 30-38 and 44, in admixture or conjunction with a pharmaceutically suitable carrier.

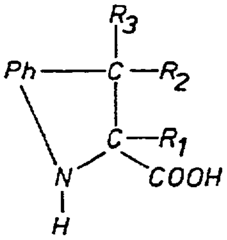
49. Process for the manufacture of 1-carboxy-(alkanoyl or aralkanoyl)-indoline-2-carboxylic acids of the general formula I



(I)

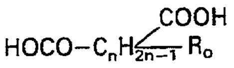
wherein Ph is unsubstituted 1,2-phenylene, or 1,2-phenylene substituted by one to three identical or different members selected from lower alkyl, lower alkoxy, lower alkylenedioxy, hydroxy, halogeno and trifluoromethyl; R_o is hydrogen or HPh; each of R_1, R_2 and R_3 is hydrogen or lower alkyl; and n is an integer from 1 to 10; the amides, mono- or di-lower alkylamides, lower alkyl esters, (amino, mono- or di-lower alkylamino, carboxy or carbo lower alkoxy)-lower alkyl esters, or salts thereof, which consists in

1) condensing a compound of the general formula III



(III)

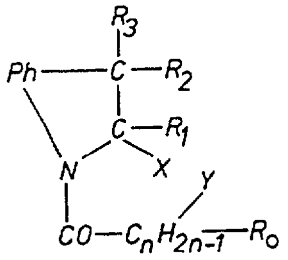
or said acid or amino derivatives thereof, with a reactive functional derivative of a compound of the general Formula IV



$$HOCO-C_nH_{2n-1}(COOH)R_o$$

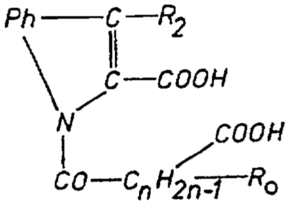
(IV); or

2) hydrolysing or alcoholyzing a compound of the general Formula V



(V)

wherein at least one of X and Y is cyano, and the other is said free, amidized or esterified carboxy group; or
3) hydrogenating in a compound of the general Formula VI



(VI)

or said acid or amino derivatives thereof, the indole moiety to the indoline moiety; and, if desired, converting any resulting compound into another compound of the invention, and/or, if required, converting a resulting free compound into a salt or a resulting salt into the free compound or into another salt, and, if required, resolving a mixture of isomers or racemates obtained into the single isomers or racemates, and, if required, resolving a racemate obtained into the optical antipodes.

50. A process for the preparation of compounds of formula I substantially as described with reference to any of Examples 1-7.

51. A process for the preparation of compounds of formula I substantially as described with reference to any of Examples 8-14.

52. A process for the preparation of compounds of formula I substantially as described with reference to any of Examples 17-24.

53. The compounds of formula I when prepared according to either of claims 49 and 50.

54. The compounds of formula I when prepared according to claim 51.

55. The compounds of formula I when prepared according to claim 52.

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