

PATENT SPECIFICATION

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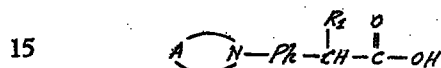
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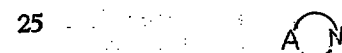
(54) TERTIARY AMINOACIDS, PROCESS FOR THEIR MANUFACTURE AND COMPOSITIONS CONTAINING SAME

(71) We, CIBA-GEIGY AG (formerly Ciba Limited), a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, 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:—

10 Patent Specification No. 1 268 831 relates to α - (aminophenyl) - aliphatic carboxylic acids, in which the amino group is a cyclic *tert* - amino group. It describes, *inter alia*, compounds of the formula



20 in which R_1 represents a hydrogen atom, a lower (up to C_7) alkyl group or a 3 to 7 ring-membered cycloalkyl; Ph represents a 1,3- or 1,4 - phenylene radical that is unsubstituted or substituted by a lower alkyl, lower alkoxy, trifluoromethyl, di - lower alkyl - amino or lower alkylene - amino group or by 1 or 2 halogen atoms; and the group of the formula



is a lower alkylene - amino or hydroxy - lower alkylene - amino, or a lower alkenyl-

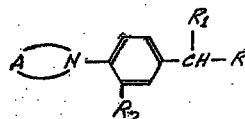
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ene - amino group; provided that R_1 represents a 3 to 7 ring-membered cycloalkyl group and/or



represents a lower alkylene - amino group; and lower alkyl esters, amides, mono - lower alkyl- and di - lower alkyl - amides, and ammonium, alkali metal and alkaline earth metal salts, and physiologically tolerable acid addition salts of such compounds. These compounds show anti-inflammation properties and can be used accordingly.

It has now been found that compounds of the formula



(I)

wherein R is a free, esterified, amidated, thio-amidated or salified carboxyl group or a cyano group, R_1 represents hydrogen, lower alkyl or cyclopropyl, R_2 denotes a hydrogen atom, halogen or trifluoromethyl, and



represents a 3 - pyrrolin - 1 - yl or 1,2,5,6 - tetrahydro - 1 - pyridyl radical, as well as acid addition salts and N - oxides thereof, possess particularly pronounced anti-inflammation properties (better than those generally possessed by other members of the broader group mentioned above) or can in a simple manner be converted into corresponding pharmacologically active compounds.

The term "lower" as used herein in qualifying organic radicals, groups or compounds refers to such radicals, groups or compounds having up to 4 carbon atoms.

Halogen is primarily fluoro and above all chloro.

An esterified carboxyl group R is especially an optionally substituted carbo - lower alkoxy group. Amidated or thioamidated carboxyl groups are optionally monosubstituted or disubstituted, for example by optionally substituted lower alkyl groups, by lower alkylene groups optionally possessing hetero - atoms as chain members or by hydroxyl groups; salified carboxyl groups are, for example, in the metal or ammonium salt form.

A lower alkyl group contains up to 4 carbon atoms and is, for example, methyl, ethyl, *n* - propyl, isopropyl, *n* - butyl, isobutyl, *sec* - butyl or *tert* - butyl.

A substituted lower alkyl radical contains hydroxyl, lower alkoxy or optionally substituted, preferably tertiary, amino groups as substituents, with such substituents preferably being removed by at least one carbon atom from the linkage carbon atom of the lower alkyl radical.

A lower alkoxy group contains up to 4 carbon atoms and is, for example, methoxy, ethoxy, *n* - propoxy, isopropoxy or *n* - butyloxy.

An optionally substituted amino group contains, for example, lower alkyl, lower alkylene, lower oxaalkylene or lower azaalkylene radicals as substituents and is, for example, a lower alkylamino or di - lower alkylamino group, (for example methylamino, dimethylamino, ethylamino or diethylamino), an alkyleneamino group with 3 to 7 ring members, for example pyrrolidino or piperidino, morpholino or a piperazino group which may be substituted in the 4-position, for example, by a lower alkyl radical. The above-mentioned optionally substituted amino groups can also form the nitrogen part of amide or thioamide groupings.

The anti-inflammatory properties of the compounds of the invention can be demonstrated by means of animal experiments, with mammals, for example, rats, preferably being used as experimental animals. Following the experimental method described, for example, by Winter et al., *Proc. Soc. Exptl. Biol. & Med.*, Volume 111 page 544 (1962), the com-

pounds of the present invention are administered in the form of aqueous solutions or suspensions, which, for example, contain carboxymethylcellulose or polyethylene glycol as solubilizing agents, with the aid of stomach tubes to adult male and female rats. About one hour later, a 1% strength suspension of carrageenine in an aqueous physiological saline solution is injected into the left hind paw of the experimental animal. After 3—4 hours, the volume and/or weight of the oedemic left hind paw are compared with those of the right hind paw. The difference between the two extremities is compared with that in untreated control animals; this comparison serves as a measure of the anti-inflammatory effect of the experimental compounds.

Following the adjuvant - arthritis test developed by Newbould, *Brit. J. Pharmacol. Chemotherap.*, Vol 21, p. 127 (1963), rats are sensitized under an ether anaesthesia by administering a 1% aqueous carrageenine suspension to all 4 paws. After 24 hours a 1% suspension of *Mycobacterium butyricum* is injected between the tail skin. After 7 days the experimental compounds are administered in the above-mentioned manner with the aid of stomach tubes over the course of 14 days. The rats are weighed once a week and the number and strength of secondary arthritic lesions are determined three times weekly.

The compounds of the present invention can, therefore, be used as anti-inflammation agents in the treatment of arthritic and dermatopathological symptoms, and also as intermediates in the manufacture of other valuable, for example, pharmacologically active, compounds.

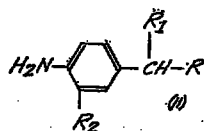
Particularly pronounced pharmacological properties, especially anti-inflammatory properties, are exhibited by compounds of the formula I, in which R is carboxyl, R₁ represents hydrogen, methyl or cyclopropyl, R₂ is hydrogen or chloro, and



is 3 - pyrrolin - 1 - yl, or salts, particularly pharmaceutically acceptable, non-toxic alkali metal, alkaline earth metal or ammonium salts, thereof, and above all by [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid and its salts, especially its pharmaceutically acceptable, non-toxic alkali metal, alkaline earth metal and ammonium salts, which show excellent anti-inflammatory properties in the test systems described above.

The compounds of the present invention can be manufactured according to processes

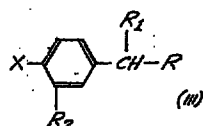
which are in themselves known, for example,
(a) by reacting a compound of the formula



5 with a reactive ester of a compound of the formula



or (b) splitting off in a compound of the formula

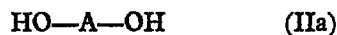


10 wherein X represents an alkyleneamino group that corresponds to the group



and contains in the β - or γ -position a substituted hydrazono group capable of being
15 cleaved off by pyrolysis while introducing a double bond into such alkyleneamino group, the group capable of being cleaved off, and, if desired, converting a resulting compound
20 within the framework of the definition into another compound of the invention.

According to process modification a) a reactive ester of the glycol of the formula



25 is, for example, the corresponding dihalide, *e.g.* dichloride or dibromide. This reaction is preferably carried out in the presence of water- or an acid-binding agent, for example, an alkali metal or a corresponding alcoholate or carbonate.

30 A substituted hydrazono group contains, for example, sulfonyl groups as substituents, for example, N' -lower alkylsulfonyl- or N' -arylsulfonyl-hydrazono groups, *e.g.* N' -phenylsulfonyl-hydrazono, N' -4-methylphenylsulfonyl-hydrazono or N' -4-bromophenylsulfonylhydrazono. Such groups
35 are cleaved off by pyrolysis, advantageously in the absence of a solvent or in the presence of a high-boiling diluent, if desired, under
40 reduced pressure.

Resulting compounds can be converted into one another in a manner which is in itself known. Thus, for example, resulting free acids can be esterified using alcohols in the presence of esterification agents, for
45 example strong acids, for example hydrochloric acid, sulfuric acid or *p*-toluenesulfonic acid, as well as dicyclohexylcarbodiimide, or diazo compounds, and can also be converted into acid halides by treatment with
50 thionyl halides, for example thionyl chloride, or phosphorus halides or oxyhalides, for example phosphorus chloride or oxychloride.

Resulting esters can be hydrolyzed to free acids, for example, by treatment with suitable basic agents for example aqueous alkali metal hydroxides, or can be trans-esterified into other esters by treatment with alcohols in the presence of acid or alkaline agents,
60 for example mineral acids or complex heavy metal acids, as well as alkali metal carbonates or alkali metal alcoholates esters can be converted into amides by treatment with ammonia or appropriate amines.

Resulting acid halides can, on treatment with alcohols, as well as ammonia or amines, be converted into esters and amides, respectively, and resulting metal salts of the acids can, by means of alcohols or the corresponding
70 halides, for example chlorides or bromides, or of suitable organic halogenosulfites, for example lower alkyl chlorosulfites, also be converted into esters. Resulting metal salts, upon treatment with thionyl halides, for example thionyl chloride, phosphorus
75 halides, for example phosphorus pentachloride, or phosphorus oxyhalides, for example phosphorus oxychloride, furnish the corresponding acid halides, whereas by treating resulting ammonium salts with dehydrating reagents, for example phosphorus
80 pentoxide, thionyl halides, phosphorus halides or phosphorus oxyhalides, amides and nitriles can be formed. Sulfur-containing compounds, for example thioamides, may be obtained
85 from the oxygen analogs, for example by treatment with sulfur or phosphorus pentasulfide.

Resulting amides or thioamides can be hydrolyzed under acid or alkaline conditions, for example, by treatment with aqueous mineral acids and/or carboxylic acids, or alkali metal hydroxides, as well as alcoholized or trans-aminated; furthermore, they can be desulfurized, for example, by treatment with
90 mercury-II oxide and lower alkyl halides, followed by hydrolysis.

Resulting nitriles can be hydrolyzed or alcoholized, for example, by treatment with concentrated aqueous or alcoholic acids or with alkaline agents, for example alkali metal hydroxides and alkaline hydrogen peroxide.

Resulting esters, salts or nitriles, in which the group R_1 represents hydrogen, can be metallized in the α -position to the function-
105

ally modified carboxyl group, for example, by treatment with alkali metals or derivatives thereof, for example organic alkali metal compounds, for example, phenyl - lithium or triphenylmethyl - sodium, or with alkali metal, for example sodium, hydrides, amides or alcoholates, and can then be reacted with a reactive ester of an alcohol of the formula



- 10 for example a corresponding halide, an organic group R_1 thus being introduced into the α - position.

- 15 A resulting free acid can be converted into a salt in a manner which is in itself known, for example by reaction with an approximately stoichiometric amount of a suitable salt-forming agent, for example ammonia, an amine or an alkali metal or alkaline earth metal hydroxide, carbonate or hydrogen carbonate. Resulting ammonium or metal salts of this type can be converted into the free compound by treatment with an acid, for example hydrochloric acid, sulfuric acid or acetic acid, until the requisite pH-value is reached.

- 25 A resulting basic compound can be converted into an acid addition salt, for example by reaction with an inorganic or organic acid or an appropriate anion exchange preparation, and isolation of the resulting salt. A resulting acid addition salt can be converted into the free compound by treatment with a base, for example an alkali metal hydroxide, ammonia or a hydroxyl ion exchange preparation. Acid addition salts, for example pharmaceutically acceptable, non-toxic acid addition salts, are, for example, those with inorganic acids, for example hydrochloric, hydrobromic, sulfuric, phosphoric, nitric or perchloric acid, or with organic acids, especially organic carboxylic or sulfonic acids, for example formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenyl-acetic, benzoic, 4 - aminobenzoic, anthranilic, 4 - hydroxybenzoic, salicylic, aminosalicilic, embonic or nicotinic acid, as well as methane-sulfonic, ethanesulfonic, 2 - hydroxyethane-sulfonic, ethylenesulfonic, benzenesulfonic, 4 - chlorobenzenesulfonic, 4 - toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexyl-sulfamic acid.

- These and other salts, for example the picrates, can also be used for the purification of the free compounds or for identification purposes; thus, free compounds can be converted into their salts, these salts separated from the crude mixture, and the free compounds then obtained from the isolated salts.

- 60 In view of the close relationships between the compounds of the invention in the free form and in the form of their salts, whenever free compounds or salts are referred to

in the preceding and following context, the corresponding salts and free compounds, respectively, are also intended provided such is possible or appropriate under the circumstances.

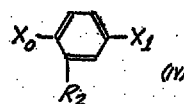
N - oxides may be obtained according to *per se* known procedures, for example by treating the resulting compounds with hydrogen peroxide or an inorganic or organic peracid, particularly percarboxylic acid, e.g. peracetic, trifluoroperacetic or perbenzoic acid.

Resulting isomer mixtures can be resolved into the individual isomers in a manner which is in itself known, for example by fractional distillation or crystallization and/or by chromatography. Racemic products can be resolved into the optical antipodes, for example by resolution, for example fractional crystallization, of mixtures of diastereo - isomeric salts, for example with *d* - or *l* - tartaric acid or with *d* - α - phenylethylamine, *d* - α - (1 - naphthyl) - ethylamine or *l* - cinchonidine, and, if desired, by liberation of the free antipodes from the salts.

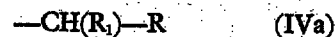
The above reactions are carried out according to methods which are in themselves known, for example in the absence or presence of diluents, preferably those which are inert towards the reagents and are capable of dissolving them, if necessary, in the presence of catalysts, condensation reagents or neutralizing agents, in an inert gas atmosphere, for example a nitrogen atmosphere, with cooling or warming and/or under elevated pressure.

According to the present process, those starting materials are preferably employed that lead to the formation of those compounds of the invention that are described above as being particularly preferred.

The starting materials are known or, if new, can be manufactured in a manner which is in itself known, for example by converting in a compound of the formula



in which X_0 is an amino group or the group X or a residue capable of being converted into an amino group or into the group X, for example a nitro group, and X_1 is a group capable of being converted into a group of the formula



the group X_1 into the group IVa according to *per se* known procedures, and, if necessary, converting a group X_0 that is capable of

being converted into an amino group or into the group X_1 into an amino group or into the group X_1 .

In a compound of the formula IV the group X_1 can be replaced by the entire grouping of the formula IVa or a part thereof, especially the carboxyl portion, or the grouping of the formula IVa may be liberated from a suitable radical which already contains the requisite number of carbon atoms, for example by conversion of a potential carboxyl group or of an alkylidene radical.

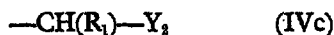
Thus, X_1 can denote a hydrogen atom, a metallic grouping or a reactive esterified hydroxyl group. A metallic grouping is, for example, an alkali metal atom, for example a lithium atom, or a substituted alkaline earth metal, zinc or cadmium atom, a halogenomagnesium group, a lower alkyl - zinc or lower alkyl - cadmium group, for example a chloro-, bromo- or iodo- magnesium group, a methyl- or ethyl - zinc or methyl- or ethyl - cadmium group. A reactive esterified hydroxyl group is preferably a hydroxyl group esterified by a strong mineral acid or an organic sulfonic acid, for example a hydrohalic, sulfuric, lower alkanesulfonic or benzenesulfonic acid, for example hydrochloric, hydrobromic, methanesulfonic, ethanesulfonic, benzenesulfonic or *p* - toluenesulfonic acid. The corresponding starting material of the formula IV is reacted with a compound of the formula



in which R has the above meaning, but is especially a carboxyl group in salt form, an esterified or amidated carboxyl group or a cyano group. In the above compounds of the formulae IV and IVb, one of the radicals X_1 and Y_1 denotes a metallic grouping and the other a reactive esterified hydroxyl group, or X_1 represents a hydrogen atom and Y_1 a free or reactive esterified hydroxyl group.

The above reaction can be carried out according to the Grignard or Friedel-Crafts reaction, in which a new carbon-carbon bond is formed from two different reagents. The Friedel-Crafts reaction is carried out in the presence of a Lewis acid, for example an aluminum salt, or a boron, antimony-V, iron-III or zinc salt, especially chloride, or of hydrofluoric, sulfuric or preferably polyphosphoric acid, with the latter primarily being used with compounds of the formula IVb or derivatives thereof in which Y_1 represents a hydroxyl group.

The radical X_1 in compounds of formula IV can also represent a grouping of the formula



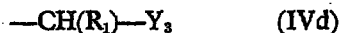
wherein Y_2 denotes a metallic radical, for

example one of those mentioned above, or an ammonium group, for example a tri - lower alkyl - ammonium or di - lower alkyl - aryl - lower alkyl - ammonium group, for example trimethylammonium or dimethylbenzylammonium group, or a free or reactive, functionally converted, such as esterified or etherified, as well as salified, hydroxyl group, for example, a hydroxyl group esterified as mentioned-above, or a hydroxyl group etherified with a lower alkanol or an aryl - lower alkanol, or a hydroxyl group in the form of a corresponding salt grouping, the cation portion being an alkali or alkaline earth metal, for example sodium, potassium or calcium.

Such a metal, ester, ether or alcoholate compound of the formula IV can be reacted with a reactive derivative of carbonic or formic acid, with only one of the two reagents containing a metallic grouping. A metal compound or Grignard compound of the formula IV can be reacted with a suitable metal-free carbonic acid or formic acid derivative, preferably with carbon dioxide, but also with an appropriate carbonate or halogenoformic acid ester, for example diethyl carbonate, orthoformic acid lower alkyl ester, for example orthoformic acid ethyl ester or propyl ester, or halogenoformic acid lower alkyl, phenyl or phenyl - lower alkyl ester, wherein a lower alkyl, phenyl or phenyl - lower alkyl radical may optionally be substituted, for example chloroformic acid ethyl ester, *tert* - butyl ester, allyl ester, 2 - methoxyethyl ester, phenyl ester or benzyl ester, or with a cyanogen halide or carbamoyl halide, for example cyanogen bromide or diethylcarbamoyl chloride.

A starting material of the formula IV having a grouping of formula IVc, wherein Y_2 denotes an ammonium group or a free or reactive, functionally modified, especially esterified, or etherified hydroxyl group, is preferably reacted with a metal cyanide, for example an alkali metal cyanide, *e.g.* sodium or potassium cyanide. A starting material, wherein Y_2 in a group of the formula IVc represents a free, esterified or salified hydroxyl group, or a corresponding dehydrated compound of formula IV, wherein X_1 represents a 1 - lower alkenyl radical, can also be reacted with carbon monoxide. The latter is used under neutral or basic, especially acid conditions, for example in the presence of sulfuric acid, and under high pressures and/or temperatures, for example at up to 400 atmospheres and 300°C, preferably in the presence of a heavy metal catalyst, for example a nickel or cobalt salt or a carbonyl derivative thereof. Carbon monoxide can also be formed from suitable reagents, for example formic acid in the presence of high-boiling mineral acids, *e.g.* sulfuric acid or phosphoric acid.

A further group X_1 can also be a grouping of the formula



wherein Y_3 represents a radical capable of being converted into a free or functionally modified carboxyl group; the desired conversion of Y_3 into an optionally functionally converted carboxyl group can be effected by oxidation or rearrangement. A group Y_3 capable of being converted by oxidation is, for example, a methyl hydroxymethyl, borylmethyl, hydroxyiminomethyl or formyl group, as well as a 1 - lower alkenyl or 1 - lower alkynyl group, a 1,2 - dihydroxy - lower alkyl group, or an acyl, for example a lower alkanoyl, lower alkenoyl or a free or functionally modified, for example esterified, carboxycarbonyl group.

In a corresponding starting material of the formula IV having a grouping of the formula IVd, wherein Y_3 represents an oxidatively convertible, potential carboxyl group, Y_3 can be converted into a free or functionally modified carboxyl group with the aid of standard oxidation methods, for example by treatment with oxygen (either in pure form or in the form of air), preferably in the presence of a suitable catalyst, for example a silver, manganese, iron or cobalt catalyst, or with oxidizing agents, for example hydrogen peroxide or a nitrogen oxide, or oxidizing acids or salts thereof, for example hypohalous acids, periodic acid, nitric acid or percarboxylic acids or corresponding salts, for example alkali metal salts thereof, e.g. sodium hypochlorite or sodium periodate, peracetic acid, perbenzoic acid or monoperphthalic acid, heavy metal salts or oxides, for example alkali metal, for example sodium or potassium, chromates or permanganates, chromium-III or copper-II salts, for example halides or sulfates, or silver, mercury, vanadium-V, chromium-VI or manganese-IV oxides, in an acid or alkaline medium. Usually, in the above oxidation methods free acids or salts thereof are obtained as products.

If on the other hand, for example, a starting material of formula IV with a group X_1 of the formula IVd, in which Y_3 is a hydroxyiminomethyl group, that is to say an oxime, is used and the Beckmann rearrangement is carried out, for example, by treatment with sulfuric acid, *p* - toluenesulfonyl chloride or phosphorus pentachloride, or an oxidation is carried out, for example with hydrogen peroxide or one of the above percarboxylic acids, or if a compound having a formyl or acyl group Y_3 in a grouping of the formula IVd, that is to say an aldehyde or ketone, is employed and treated with hydrazoic acid according to the Schmidt reaction, for example in the presence of sulfuric acid, or

if a compound having a formyl group Y_3 is treated with a sulfonyl - hydroxamate or nitrohydroxamate, a nitrile, an amide or a hydroxamic acid, respectively, is obtained.

A starting material of the formula IV having the above group of the formula IVd, wherein Y_3 is an optionally functionally modified, especially esterified, carboxycarbonyl group, for example a carbo - lower alkoxy carbonyl group, can be converted into the desired compound of the formula I either by oxidation, for example with hydrogen peroxide in an acid medium, for example in the presence of a mineral acid, or by decarbonylation, primarily by pyrolysis, preferably in the presence of copper or glass powder.

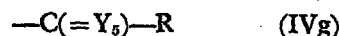
A group X_1 in a starting material of the formula IV can also represent a radical which above all yields the grouping of the formula



Such a radical is, for example, a group of the formula



or of the formula



wherein the radical Y_4 can be converted into hydrogen, for example by reduction, decarbonylation, deacylation or desulfurization, and the radical Y_5 is converted by reduction into the group R_1 together with hydrogen.

Thus, the radical Y_4 can represent a free or reactive esterified or etherified hydroxyl or mercapto group, for example one of the above-mentioned corresponding groups, or the appropriate mercapto equivalents, for example a hydroxyl or a mercapto group, chloro, bromo or iodo, a benzyloxy or benzylmercapto group, furthermore a disubstituted amino group, for example di - lower alkylamino group, for example dimethylamino or diethylamino. Y_5 can denote a lower alkylidene or cyclopropylidene group or an optionally ketalized oxo or thiono group. Starting materials with such groups or corresponding quaternary *o*- or *p*-quinone methides thereof, which can be obtained by splitting off the elements of a compound of the formula Y_4-H from a starting material of the formula IV with a grouping of the formula IVf, for example on treatment with strong mineral acids or alkali metal hydroxides, can be converted in the desired manner by reduction, for example by treatment with catalytically activated hydrogen, for example hydrogen in the presence of a nickel, palladium or platinum catalyst, with electrolytically generated hydrogen or with a chemical reducing agent (nascent hydrogen), for example reducing metals, preferably in the presence

of a hydrogen - furnishing agent, for example an acid, a base, *e.g.* an alkali metal hydroxide, or an alcohol, for example with zinc, amalgamated zinc, iron or tin, preferably in the presence of aqueous mineral acids or organic carboxylic acids, for example hydrochloric acid or acetic acid, with zinc - nickel or aluminum - nickel alloys, preferably in the presence of an aqueous alkali metal hydroxide, or with an alkali metal, for example sodium or potassium, or a corresponding amalgam, in the presence of a lower alkanol.

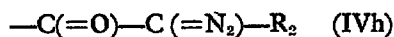
In the reduction of a starting material having a mercapto group or a free or ketalized thiono group, desulfurizing agents, for example mercury or copper oxide, or Raney nickel, are preferably used.

If Y_4 represents a free hydroxyl group, it is also possible to use an aqueous suspension of phosphorus and iodine, hydriodic acid, tin(II) chloride or an alkali metal, for example sodium, sulfite or dithionite, as the reducing agent, and if Y_4 denotes an esterified hydroxyl group, for example halogeno, it is also possible to use a lower alkyl or cyclopropyl metal compound, for example the corresponding lithium or Grignard compound, as the reducing agent. The above metal compounds are also suitable for the reduction of the above-mentioned quinone methide compounds.

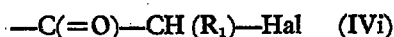
If Y_6 represents an oxo group, the Clemmensen or Wolff-Kishner reduction (including the Huang-Minlon modification) can be used for its removal, a chemical reducing agent (nascent hydrogen) or hydrazine being used, the latter preferably, in the presence of a strong alkali metal hydroxide, for example sodium or potassium hydroxide, for example in an aqueous or high-boiling glycol medium.

If Y_4 represents a carboxyl group and the starting material stands primarily for a corresponding malonic acid derivative, such a starting material can be decarboxylated by pyrolysis, preferably in an acid medium. If Y_4 represents an acyl group, but not a carboxyl group, for example a lower alkanoyl, aryl or aryl - lower alkanoyl, *e.g.* acetyl or benzoyl group, the corresponding β - keto - acid starting material can be subjected to acid splitting by the action of a strongly alkaline agent, for example an alkali metal hydroxide, *e.g.* one of those mentioned above.

A further substituent X_1 , which also yields the above-mentioned grouping of formula IVe, is an optionally substituted acetyl group, substituted acetyl groups being, for example, groups of the formulae



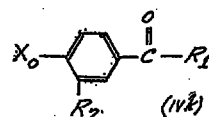
or



in which Hal denotes a halogen atom. An acetyl starting material can be converted into compounds of the present invention in accordance with the Willgerodt-Kindler reaction, for example by treatment with sulfur in the presence of ammonia or of a primary or secondary amine, especially of morpholine, and preferably of an acid, for example a sulfonic acid, for example *p* - toluenesulfonic acid, the resulting product being a thioamide or an amide (the latter when the reaction is carried out in an aqueous medium). A corresponding α - diazoacetyl starting material can be converted into compounds of the present invention according to the Wolff reaction (Arndt-Eistert), for example by hydrolysis, alcoholysis, ammonolysis or aminolysis, preferably with irradiation or heating in the presence of heavy metal catalyst, for example copper or silver catalyst. An α - halogenoacetyl starting material can be converted into compounds of the present invention according to the Favorskii-(Wallach) rearrangement, for example by treatment with a strong alkaline reagent, for example an alkali metal hydroxide, or a soluble silver salt, for example silver nitrate.

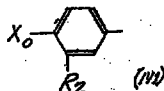
Intermediates used for the manufacture of the above starting materials are obtained according to known methods. Thus, if X_1 , for example, represents a reactive esterified hydroxyl group, then this group can be introduced by halogenation or by nitration, followed by reduction, diazotization and Sandmeyer reaction. The resulting starting material can subsequently be converted into a metallic compound, for example by reaction with an alkali or alkaline earth metal, for example lithium or magnesium, or with a di - lower alkyl - zinc or -cadmium.

Starting materials in which Y_2 represents a metallic group can be manufactured in an analogous manner, for example by treating the reactive ester of a corresponding benzyl alcohol compound with an alkali or alkaline earth metal or a di - lower alkyl - zinc or -cadmium. On the other hand, it is possible, for example, to reduce compounds of the formula



which can be manufactured in a simple manner according to the Friedel-Crafts reaction, with lithium aluminum hydride, or, if R_1 represents hydrogen, with an organic magnesium halide compound in which the organic radical represents one of the appropriate radicals R_1 , or to react Grignard com-

pounds having the radical of the formula



with an aldehyde of formula



- 5 the corresponding benzyl alcohol compounds being thus formed.

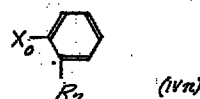
In the latter, the hydroxyl group can be converted into a reactive esterified hydroxyl group or into a salified hydroxyl group in a manner which is in itself known, for example by treatment with a phosphorus halide, thionyl halide or sulfonyl halide and an alkali metal or alkaline earth metal, respectively. Resulting esters or salts can be converted into ethers by treatment with alcohols or alcoholates or reactive esters of alcohols. Starting materials in which Y_2 represents an ammonium group can be obtained from the above reactive esters by reaction with tertiary amines or with secondary amines, followed by quaternization of the resulting tertiary amines according to the usual methods, for example by treatment with lower alkyl halides or aryl - lower alkyl halides.

25 Starting materials having a group Y_3 can be obtained from the above-mentioned starting materials having a metallic group Y_2 by treatment with a methyl halide, formaldehyde, a formyl halide, a lower alkanal, lower alkenal or hydroxy - lower alkanal, or a lower alkanoyl halide, lower alkenoyl halide or oxalyl halide, particularly chloride, it being possible, if desired, to dehydrate resulting alcohols, for example by treatment with acidic reagents, for example sulfuric acid or phosphorus pentoxide, and thus to convert them to the corresponding unsaturated compounds. The latter, for example methylene compounds, can be reacted with boranes to give borylmethyl compounds, while aldehydes on treatment with hydroxylamine yield the corresponding hydroxyiminomethyl compounds, i.e. oxime compounds. Aldehyde starting materials, in which Y_3 represents a formyl group, can also be formed from ketones of the formula IVk by reaction with dimethylsulfonium methylide or dimethyloxysulfonium methylide (obtained from the corresponding trimethylsulfonium salts) and rearrangement of the resulting ethylene oxides to the corresponding aldehydes by reaction with Lewis acids, for example *p* - toluenesulfonic acid or boron trifluoride. They can also be formed according to the Darzens condensation by treatment of ketones of the formula IVk with α - halogeno - alkanecarboxylic or α - halogeno - alkenecarboxylic acid esters in the

presence of suitable alkali metal alcoholates, e.g. potassium *tert* - butyloxide, saponification of the resulting glycidic acid esters, rearrangement of the resulting acids and decarboxylation of the intermediate products, preferably in an acidic medium, for example with sulfuric acid.

The starting materials having a free, esterified or etherified hydroxyl or mercapto group Y_4 can be obtained according to the cyanohydrin method or analogous syntheses, for example by reaction of a compound of the formula IVk or a thiono-analog thereof with an aqueous alkali metal cyanide, for example potassium cyanide, under acidic conditions and, if desired, conversion of a resulting nitrile into another acid derivative and/or of a resulting hydroxyl compound into a corresponding mercapto compound or into a corresponding reactive ester or ether, or dehydration with the formation of a corresponding unsaturated compound. Starting materials in which Y_4 represents a disubstituted amino group, for example dimethylamino group, can be formed from starting materials of the formula IV in which X_1 represents an acetyl group, for example by treatment with an alkali metal cyanide and ammonium carbonate, followed by a base or acid, and disubstitution of the free amino group, for example with formaldehyde and formic acid.

Compounds wherein Y_5 represents an oxo or thiono group can be formed according to the Friedel-Crafts reaction using compounds of the formula



and oxalyl halides, for example oxalyl chloride. A resulting phenylglyoxylic acid ester can then be reduced by treatment with an R_1 -Grignard compound and dehydrated, if desired. They are also obtained according to the Ando synthesis, for example on treating a compound of the formula IVn with a mesoxalic acid ester in the presence of a Lewis acid, for example tin-IV chloride; in the resulting adduct the hydroxyl group can be removed reductively and the malonic acid ester compound formed can be metallized and then be treated with a reactive ester of an alcohol of formula R_1-OH , or the resulting compound can be saponified and decarboxylated.

Further, it is possible to obtain α - diazo-ketone compounds when a corresponding benzoic acid halide is treated with an R_1 -diazo compound. α - Halogenoketone compounds are, for example, obtained when a

corresponding lower alkanoyl - benzene compound is halogenated or an α - diazoketone compound is reacted with a hydrohalic acid.

A group X_0 capable of being converted into the amino group or the group X may be converted into the latter according to *per se* known methods, a nitro group, for example, by reduction, for example by treatment with catalytically activated hydrogen or with a chemical reducing agents (nascent hydrogen).

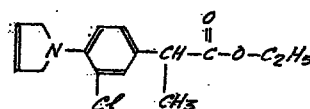
The pharmacologically useful compounds of the present invention can, for example, be used for the manufacture of pharmaceutical preparations, which contain an effective amount of the active substance together with inorganic or organic, solid or liquid, pharmaceutically acceptable excipients, which are suitable for enteral, parenteral or topical administration. Preferably, tablets or gelatine capsules are used which contain the active substance together with diluents, for example lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, and lubricants, for example, silica, talc, stearic acid or salts thereof, for example magnesium or calcium stearate, and/or polyethylene glycol; tablets also contain binders, for example magnesium aluminum silicate, starches, for example corn starch, wheat starch, rice starch or arrowroot starch, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone and, if desired, disintegrating agents, for example starches, agar, alginic acid or sodium alginate, or effervescing mixtures and/or adsorbents, dyestuffs flavors or sweeteners. Injectable preparations are preferably isotonic aqueous solutions or suspensions; suppositories and ointments are primarily fat emulsions or suspensions. The pharmaceutical preparations can be sterilized and/or contain auxiliary substances, for example preservatives, stabilizers, wetting agents, emulsifiers, solubilizers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical preparations are manufactured in a manner which is in itself known, for example by means of conventional mixing, granulating or dragee-making processes, and contain from about 0.1% to about 75%, especially from about 1% to about 50%, of the active substance; if desired, they can contain further pharmacologically valuable substances.

The Examples which follow illustrate the invention; the temperatures are given in degrees centigrade.

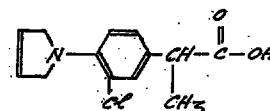
Example 1

A mixture of 85.5 g of ethyl α - (4 - amino - 3 - chlorophenyl) - propionate hydrochloride, 142 g of sodium carbonate and 600 ml of dimethylformamide is mixed dropwise with 107 g of 1,4 - dibromo - 2 - butene while stirring; the mixture is then boiled for 5 hours under reflux and allowed to stand

for 16 hours at room temperature. The reaction mixture is filtered, the filtrate is evaporated under reduced pressure and the residue is triturated with hexane and filtered; the filter residue is washed with petroleum ether. The filtrate is evaporated and the residue, containing α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid ethyl ester of the formula



is treated with 280 ml of a 25% strength aqueous sodium hydroxide solution and boiled for 8 hours under reflux. After cooling, the mixture is diluted with water and washed with ether; the pH of the aqueous phase is adjusted to 5-5.2 by means of hydrochloric acid and the mixture is extracted with ether. The organic extract is dried, filtered and evaporated and the residue is recrystallized from a mixture of benzene and hexane. The resulting α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid of the formula



melts at 94-96°.

The starting material can be manufactured as follows:

A solution of 52 g of 4 - nitrophenyl - acetic acid ethyl ester in 350 ml of a 1:1 mixture of dimethylformamide and toluene is treated with 9.5 g of a 50% strength suspension of sodium hydride in mineral oil, added in portions while stirring and cooling. After stirring at room temperature for 1½ hours, 26 g of methyl iodide are added dropwise and the mixture is stirred for 16 hours at room temperature. Water is carefully added and the mixture is extracted with ether; the organic extract is dried, filtered and evaporated. The residue is taken up in 100 ml of ethanol, and the solution is seeded with a few crystals of starting material and allowed to stand in the cold. The resulting precipitate is filtered off and the filtrate is evaporated; the residue is ethyl α - (4 - nitrophenyl) - propionate.

A mixture of 50 g of ethyl α - (4 - nitrophenyl) - propionate in 200 ml of 95% aqueous ethanol is hydrogenated in the presence of 0.4 g of a palladium-on-charcoal catalyst until hydrogen absorption ceases.

The mixture is filtered and the filtrate is evaporated. The hydrochloride of the resulting ethyl α - (4 - amino - phenyl) - propionate melts at 137—140°.

- 5 A mixture of 25 g of ethyl α - (4 - amino - phenyl) - propionate and 100 ml of acetic acid anhydride, prepared while stirring and cooling, is allowed to stand for 1 hour at room temperature and is then evaporated under reduced pressure. The residue is recrystallized from ether; the ethyl α - (4 - acetylamino - phenyl) - propionate melts at 88—90°.

- 15 Chlorine gas is allowed to bubble through a solution of 25 g of ethyl α - (4 - acetylamino - phenyl) - propionate while stirring and cooling, with the course of the chlorination being followed by means of thin layer chromatography (silica gel; 1:4-mixture of hexane and ether). After no further starting material can be detected, the mixture is evaporated under reduced pressure, the residue is taken up in 150 ml of ethanol, and hydrogen chloride gas is allowed to bubble through the solution for 45 minutes. The mixture is then boiled under reflux for 15 hours and evaporated. The residue is recrystallized from a mixture of ethanol and ether; the resulting ethyl α - (4 - amino - 3 - chlorophenyl) - propionate hydrochloride melts at 164—168°.

The starting material can also be manufactured as follows:

- 35 Dry hydrogen chloride gas is passed for 5½ hours, while stirring, through a mixture of 5000 ml of anhydrous ethanol and 1000 g of 4 - amino - phenylacetic acid boiling under reflux; the mixture is stirred and boiled for a further 4 hours. After cooling at 10° for 16 hours, the mixture is filtered and the filter residue is washed with cold anhydrous ethanol and dissolved in 8000 ml of water. An aqueous sodium hydroxide solution (50%) is added in 50 ml portions while stirring until the mixture is basic; it is then stirred for 1 hour at room temperature. The resulting precipitate is filtered off and washed with water to yield ethyl 4 - amino - phenylacetate, m.p. 47—49°.

- 50 A solution of 200 g of ethyl 4 - amino - phenylacetate in 250 ml of acetic acid anhydride is allowed to stand for 10 minutes and is then poured onto 1500 ml of a mixture of ice and water while stirring. The resulting precipitate is filtered off and washed with water to yield the ethyl 4 - acetylamino - phenylacetate, m.p. 75—78°.

- 55 A solution of 170 g of ethyl 4 - acetylamino - phenylacetate in 25 ml of ether is added over the course of 25 minutes, while stirring, to a mixture of 20.38 g of sodium, 2000 ml of anhydrous ammonia and a few crystals of iron-III nitrate nonahydrate. A mixture of 120.28 g of methyl iodide and 50 ml of ether is then added dropwise over the

course of 20 minutes; the mixture is stirred for 1 hour, then treated with 50 g of ammonium chloride and evaporated. The residue is taken up in ether and a dilute aqueous sodium hydroxide solution. The basic solution is extracted with ether and the combined organic solutions are evaporated to yield the ethyl α - (4 - acetylamino - phenyl) - propionate, m.p. 84—86°. The material, which is approximately 90% pure, is distilled in a short path distillation apparatus; the fraction boiling at 170—183°/0.15 mm Hg is collected.

A solution of 72 g of ethyl α - (4 - acetylamino - phenyl) - propionate in 200 ml of acetic acid is treated with gaseous chlorine which is allowed to bubble through the solution while stirring at a temperature of 15—20°. The course of the reaction is followed by means of thin layer chromatography, using a 4:1-mixture of ether and hexane as the mobile phase, in which the product has an Rf-value of 0.8 and the starting material an Rf-value of 0.51. After completion of the chlorination, the mixture is evaporated and the residue is distilled. The fraction boiling at 155—160°/10.7 mm Hg is ethyl α - (4 - acetylamino - 3 - chloro - phenyl) - propionate.

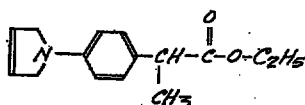
A mixture of 60 g of ethyl α - (4 - acetylamino - 3 - chlorophenyl) - propionate and 200 ml of ethanol is saturated with gaseous hydrogen chloride and boiled for 1 hour under reflux, and is then evaporated under reduced pressure. The residue is taken up in an aqueous sodium hydroxide solution and the mixture is extracted with ether. The organic extract is evaporated and the residue is chromatographed on aluminum oxide, eluting with a 95:5 mixture of cyclohexane and ethyl acetate. The resulting ethyl α - (4 - amino - 3 - chloro - phenyl) - propionate melts at 168—170°.

Example 2

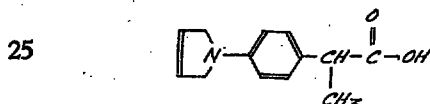
A mixture of 25.1 of *d,l* - α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid, obtainable according to the process of Example 1, in 450 ml of ether is mixed with 17.1 g of *d* - α - (1 - naphthyl) - ethylamine while stirring; the mixture is evaporated under reduced pressure and the residue is recrystallized seven times from a mixture of ethanol and ether. A solution of 5 g of the resulting salt, m.p. 133—135°, in a minimum amount of a 5% aqueous sodium hydroxide solution is washed with ether, the pH-value is adjusted to 5.5 with hydrochloric acid, and the mixture is extracted with ether. The organic extract is dried, filtered and evaporated to yield *d* - α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid, $[\alpha]_D^{25} = +34.8^\circ$ (ethanol).

Example 3

A mixture of 11.3 g of *cis* - 1,4 - dichloro - 2 - butene, 15.7 g of ethyl α - (4 - amino - phenyl) - propionate, 100 ml of dimethylformamide and 10.6 g of sodium carbonate is boiled for 5 hours under reflux while stirring and is then allowed to stand for 16 hours at room temperature. The mixture is filtered; the filtrate is evaporated under reduced pressure and the residue, containing ethyl α - [4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionate of the formula



is taken up in 260 ml of a 25% aqueous sodium hydroxide solution and boiled for 8 hours under reflux. After cooling, the mixture is diluted with water and washed with ether, and the pH-value is adjusted to about 5 with hydrochloric acid. The mixture is extracted with ether; the organic extract is dried and evaporated and the residue is recrystallized from ethanol. The resulting α - [4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid of the formula



melts at 197—199°.

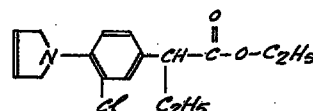
The starting material is prepared as follows:

To a solution of 52 g of ethyl 4 - nitro - phenylacetate in 350 ml of a 1:1-mixture of dimethyl formamide and toluene, 9.5 g of a 50% suspension of sodium hydride in mineral oil are added portionwise while stirring and cooling. After stirring at room temperature for 1½ hours, 26 g of methyl iodide are added dropwise and the mixture is stirred for 16 hours at room temperature. The mixture is carefully combined with water and extracted with diethyl ether; the organic extract is dried, filtered and evaporated. The residue is taken up in 100 ml of ethanol, the solution is seeded with a few crystals of starting material and allowed to stand in the cold. The resulting precipitate is filtered off and the filtrate is evaporated to yield ethyl α - (4 - nitro - phenyl) - propionate.

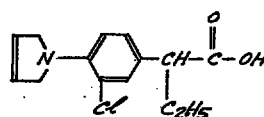
A mixture of 50 g of ethyl α - (4 - nitro - phenyl) - propionate in 200 ml of 95% aqueous ethanol is hydrogenated in the presence of 0.4 g of palladium-on-charcoal until the hydrogen uptake ceases. The mixture is filtered and the filtrate is evaporated to yield ethyl α - (4 - amino - phenyl) - propionate; its hydrochloride melts at 137—140°.

Example 4

A mixture of 24 g of ethyl α - (4 - amino - 3 - chlorophenyl) - butyrate, 21 g of sodium carbonate and 25 g of *cis* - 1,4 - dichloro - 2 - butene in 250 ml of dimethylformamide is refluxed for 12 hours. After cooling, it is diluted with diethyl ether, filtered and the filtrate is evaporated. A total of 11 g of the residue, containing ethyl α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - butyrate of the formula



is taken up in 100 ml of ethanol and 20 ml of 25% aqueous sodium hydroxide solution; the mixture is refluxed for 6 hours and evaporated under reduced pressure. The residue is taken up in water, the solution is washed with diethyl ether, its pH value is adjusted to 5.5 with hydrochloric acid and it is extracted with diethyl ether. The organic extract is dried and evaporated and the residue is recrystallized from hexane to yield α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - butyric acid of the formula



m.p. 103—105°.

The starting material is prepared as follows: To a mixture of 104 g of ethyl 4 - nitrophenyl - acetate in 350 ml of dimethylformamide and 350 ml of toluene, 19 g of a 50% suspension of sodium hydride in mineral oil are added during ¾ hour at 10° while stirring. After 1½ hours, 78 g of ethyl iodide are added during 1 hour while stirring and again after 1½ hours, a small amount of water is added dropwise. The mixture is then acidified with 10% hydrochloric acid and extracted with diethyl ether. The organic extract is dried and evaporated to yield ethyl α - (4 - nitrophenyl) - butyrate.

A mixture of 115 g of ethyl α - (4 - nitrophenyl) - butyrate, 400 ml of 95% ethanol and 1.5 g of palladium-on-charcoal is hydrogenated under an initial pressure of 3 atmospheres and at room temperature. After the hydrogen uptake has ceased, the mixture is filtered, the filtrate is evaporated and the residue is taken up in 2N hydrochloric acid. The solution is washed with diethyl ether, made basic with an aqueous sodium hydroxide solution and extracted with diethyl ether. The organic extract is evaporated to yield ethyl α - (4 - aminophenyl) - butyrate.

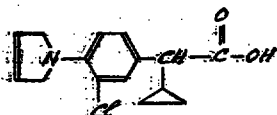
A mixture of 35 g of ethyl α - (4 - amino-phenyl) - butyrate and 100 ml of acetic acid anhydride is stirred for 1 hour on the steam bath and evaporated to yield ethyl α - (4 - acetylamino - phenyl) - butyrate.

Chlorine gas is bubbled through a solution of 35 g of ethyl α - (4 - acetylamino - phenyl) - butyrate in 200 ml of acetic acid while stirring and keeping the temperature at 15–20°; the course of the reaction is followed by thin layer chromatography on silica gel in a 1:4-mixture of hexane and diethyl ether. After the starting material has been consumed, the reaction mixture is evaporated, to yield ethyl α - (4 - acetyl-amino - 3 - chloro - phenyl) - butyrate hydrochloride.

Hydrogen chloride gas is bubbled through a solution of 36 g of ethyl α - (4 - acetyl-amino - 3 - chloro - phenyl) - butyrate hydrochloride in 200 ml of ethanol for 45 minutes while stirring. The mixture is refluxed for 20 hours, then allowed to stand for 24 hours at room temperature and evaporated. The residue is taken up in water, the solution made basic with an aqueous sodium hydroxide solution and extracted with diethyl ether. The organic extract is dried and evaporated, and the residue is distilled; the fraction boiling at 130–132°/0.4 mm Hg contains ethyl α - (4 - amino - 3 - chloro - phenyl) - butyrate.

Example 5

A mixture of 0.63 g of methyl α - (4 - amino - 3 - chlorophenyl) - α - cyclopropyl - acetate hydrochloride, 0.55 g of cis - 1,4 - dichloro - 2 - butene, 0.7 g of sodium carbonate and 50 ml of dimethylformamide is refluxed under nitrogen for 10 hours and stirred at room temperature for 2 days, then filtered. The filtrate is evaporated, the residue is taken up in water, the mixture is extracted with diethyl ether and the extract is evaporated under reduced pressure. The residue is taken up in 35 ml of ethanol, 0.5 ml of water and 0.28 g of potassium hydroxide are added, and the mixture is refluxed for 2 hours and evaporated under reduced pressure. The residue is taken up in water, the solution is washed with diethyl ether, the pH is adjusted to 4–4.5 with hydrochloric acid and the mixture is extracted with ethyl acetate. The organic extract is dried and evaporated, and the residue is recrystallized from diethyl ether to yield α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - α - cyclopropyl - acetic acid of the formula



m.p. 152–156°.

The starting material is prepared as follows: To a solution of 200 g of α - cyclopropyl - phenyl - acetic acid in 1200 ml of trifluoroacetic acid, the mixture of 73 ml of 70% aqueous nitric acid and 9.1 ml of 96% aqueous sulfuric acid is added dropwise while stirring and cooling to about 3°. After 14 hours, the temperature is allowed to rise to room temperature and the mixture is stirred for an additional three hours, then poured over 3200 g of ice and 300 ml of water while stirring. The mixture is filtered, the filter residue is washed with 6000 ml of water and dried to yield an about 2:1-mixture of α - cyclopropyl - α - (4 - nitro - phenyl) - acetic acid and α - cyclopropyl - α - (2 - nitrophenyl) - acetic acid.

A mixture of 50 g of the above 2:1-mixture of α - cyclopropyl - α - (4 - nitro - phenyl) - acetic acid and α - cyclopropyl - α - (2 - nitrophenyl) - acetic acid, 5 g of 10% palladium-on-charcoal and 550 ml of 95% aqueous ethanol is hydrogenated under atmospheric pressure until 15900 ml of hydrogen have been absorbed. After filtration, the filtrate is concentrated, the precipitate formed in the cold is separated and recrystallized once from ethanol, to yield α - (4 - amino - phenyl) - α - cyclopropyl - acetic acid.

To a mixture of 10 g of α - (4 - amino - phenyl) - α - cyclopropyl - acetic acid and 75 ml of methanol, 75 ml of a saturated solution of hydrogen chloride in methanol are added while stirring and cooling in an ice bath. After 30 minutes, the mixture is warmed to 38° for one hour and stirred at room temperature for 16 hours, then cooled and combined with 100 ml of water. A total of 105 ml of 20% aqueous sodium hydroxide are added while cooling and stirring. The resulting precipitate is filtered off, washed with water and dried to yield methyl α - (4 - amino - phenyl) - α - cyclopropyl - acetate, m.p. 68–69°.

A mixture of 12 g of methyl α - (4 - aminophenyl) - α - cyclopropyl - acetate and 100 ml of acetic acid anhydride is stirred for one hour on the steam bath and then evaporated. The residue is taken up in benzene and the mixture is again evaporated to yield methyl α - (4 - acetylamino-phenyl) - α - cyclopropyl - acetate, m.p. 159–162°.

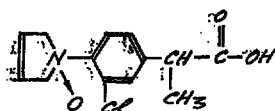
To a solution of 1.6 g of methyl α - (4 - acetylamino - phenyl) - α - cyclopropyl - acetate in 50 ml of acetic acid, 30 ml of a saturated solution of chlorine in acetic acid is added dropwise while stirring. The mixture is then evaporated under reduced pressure and the residue is taken up in twice the volume of benzene. The mixture is evaporated to yield the methyl α - (4 - acetyl-amino - 3 - chloro - phenyl) - α - cyclopropyl - acetate.

Through a solution of 1.6 g of methyl

α - (4 - acetylamino - 3 - chloro - phenyl) - α - cyclopropyl - acetate in 200 ml of methanol, hydrogen chloride is bubbled for 15 minutes; the mixture is then refluxed for 21 hours and evaporated under reduced pressure. The residue is taken up in 6N hydrochloric acid, the mixture is washed with diethyl ether, made basic with an aqueous solution of sodium hydroxide and extracted with diethyl ether. The organic extract is dried and evaporated, the residue is taken up in diethyl ether and acidified with an ether solution of hydrogen chloride. The resulting precipitate is filter off to yield methyl α - (4 - amino - 3 - chloro - phenyl) - α - cyclopropyl - acetate hydrochloride, m.p. 164—169°.

Example 6

To a mixture of 5 g of α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid, 200 ml of 1,2 - dichloroethane and 42.6 g anhydrous disodium phosphate, a solution of trifluoroacetic acid (prepared from 2.1 ml of 90% aqueous hydrogen peroxide and 12.6 ml of trifluoroacetic anhydride in 50 ml of 1,2 - dichloroethane) is added during 40 minutes while stirring at -5 to 0°. After 2 hours, 300 g of ice are added, the organic phase is separated and the aqueous layer is extracted with methylene chloride. The combined organic solutions are dried, filtered and concentrated to yield the α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid N - oxide of the formula



m.p. 140—142°.

Example 7

By replacing in the procedure of Examples 1 and 3 the 1,4 - dibromo - 2 - butene and the *cis* - 1,4 - dichloro - 2 - butene by 1,5 - dibromo - 2 - pentene, and reacting the latter with ethyl α - (4 - amino - 3 - chloro - phenyl) - propionate and ethyl α - (4 - aminophenyl) - propionate, respectively, ethyl α - [3 - chloro - 4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenyl] - propionate and ethyl α - [4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenyl] - propionate, respectively, are obtained. Upon hydrolysis, e.g. as illustrated in Examples 1 and 3, i.e. by treatment with a 25% aqueous sodium hydroxide solution, these esters yield α - [3 - chloro - 4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenyl] - propionic acid and α - [4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenyl] - propionic acid, respectively.

Example 8

To a mixture of 5.5 g of ethyl 4 - (3 - pyrrolin - 1 - yl) - phenylacetate, 100 ml of dimethylformamide and 100 ml of toluene are added portionwise while stirring 1.25 g of a 54% suspension of sodium hydride in mineral oil; stirring is continued for 1½ hour at room temperature. Then, a solution of 6.8 g of methyl iodide in 25 ml of toluene is added dropwise within 20 minutes and the mixture is stirred for 16 hours at room temperature, then evaporated under reduced pressure. The residue, containing ethyl α - [4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionate, is taken up in 75 ml of a 10% aqueous potassium hydroxide solution and the mixture is heated on the steam bath for 2 hours, then cooled, adjusted to pH 5 with hydrochloric acid and extracted with diethyl ether. The organic extract is dried and concentrated, the concentrate is diluted with petroleum ether, and the resulting precipitate is filtered off, to yield α - [4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid, m.p. 197—199° after recrystallization from ethanol.

The starting material is prepared as follows:

A mixture of 10.8 g of ethyl 4 - amino - phenylacetate hydrochloride, 32.4 g of 1,4 - dibromo - 2 - butene, 84 g of sodium hydrogen carbonate and 500 ml of dimethylformamide is refluxed for 6 hours while stirring and filtered hot. The filtrate is evaporated under reduced pressure to yield ethyl 4 - (3 - pyrrolin - 1 - yl) - phenyl - acetate, which is used without further purification.

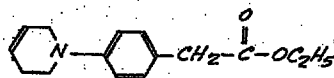
Example 9

To a suspension of 4.37 g of α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid in 30 ml of water, a 50% aqueous sodium hydroxide solution is added dropwise until dissolution occurs; the pH is about 12.5. The solution is evaporated under a pressure of 0.8 mm Hg, the residue is taken up in isopropanol, the mixture is filtered and the filtrate is concentrated. The precipitate formed upon cooling and seeding is filtered off, dried for 16 hours at 90°/0.8 mm Hg and yields the sodium α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionate, m.p. 207—209°.

Example 10

A total of 3 g of the lithium salt of 4 - tolylsulfonylhydrazone of ethyl 4 - (4 - oxo - piperidino) - phenylacetate is slowly heated, first to about 30—40°/0.3 mm Hg to effect a final drying, then to 80—145°/0.3 mm Hg for 45 minutes. The residue is taken up in the minimum amount of ethanol, the solution is poured onto a small column with silica gel and eluted with benzene. The first eluate is evaporated and yields ethyl 4 -

(1,2,5,6 - tetrahydro - 1 - pyridyl) - phenylacetate of the formula



showing in the infrared absorption spectrum characteristic bands at 5.86 μ and 6.08 μ .

Upon hydrolysis, for example, as described in Example 1, the ethyl 4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenylacetate furnishes 4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenylacetic acid.

The starting material is prepared as follows:

A mixture of 89.6 g of ethyl 4 - amino - phenylacetate, 400 g of ethyl acrylate and 100 ml of acetic acid is refluxed for 19 hours and concentrated under reduced pressure. The concentrate is poured onto 500 ml of ice-water; the mixture is made basic with an aqueous sodium hydroxide solution and extracted with diethyl ether. The organic extract is dried, filtered and evaporated and the residue distilled the fraction boiling at 211—213°/0.6 mm Hg contains ethyl 4 - (N,N - bis - carboethoxyethyl - amino) - phenyl - acetate.

To a solution of 38 g of ethyl 4 - (N,N - bis - carboethoxyethyl - amino) - phenyl - acetate in 100 ml of ethanol, a solution of 3.4 g of sodium in 100 ml of ethanol is added dropwise; the mixture is refluxed for 7 hours, then evaporated under reduced pressure. The residue is taken up in water, the mixture extracted with diethyl ether, and the organic extract dried, filtered and evaporated to yield ethyl 4 - (3 - carboethoxy - 4 - oxo - piperidino) - phenyl - acetate.

A mixture of 30.5 g of ethyl 4 - (3 - carboethoxy - 4 - oxo - piperidino) - phenyl - acetate and 300 ml of a 50% aqueous sodium hydroxide solution is heated on the steam bath for 12 hours, then cooled, and acidified with concentrated hydrochloric acid. The mixture is heated for 6 hours and evaporated under reduced pressure; the residue is taken up in an ethanol solution of hydrogen chloride, the mixture is again evaporated and the residue is taken up in water. The aqueous mixture is made basic with an aqueous sodium hydroxide solution and extracted with diethyl ether; the organic extract is dried and evaporated to yield ethyl 4 - (4 - oxo - piperidino) - phenylacetate.

A mixture of 5.2 g of ethyl 4 - (4 - oxo - piperidino) - phenyl - acetate, 2.1 g of 4 - tolylsulfonyl - hydrazide, 3 ml of glacial acetic acid and 50 ml of ethanol is refluxed for 30 minutes, then cooled. The resulting precipitate is filtered off and taken up in the minimum amount of tetrahydrofuran. To the solution, 13 ml of a 1.6N solution of

n - butyl lithium in hexane are added dropwise under a nitrogen atmosphere while keeping the temperature at 0—5°. After 30 minutes, the mixture is evaporated at a temperature below 35° to yield the lithium salt of the 4 - tolylsulfonyl hydrazone of ethyl 4 - (4 - oxo - piperidino) - phenylacetate, which is used without further purification.

Example 11

Tablets, each containing 0.025 g of the active substance, can be manufactured as follows:

Composition (for 10,000 tablets):

α - [3 - Chloro - 4 - 3 - pyrrolin - 1 - yl) - phenyl] - propionic acid	250 g	75
Lactose	1956 g	
Corn starch	90 g	
Polyethylene glycol 6000	90 g	80
Talc powder	90 g	
Magnesium stearate	24 g	
Purified water	q.s.	

The pulverulent constituents are forced through a sieve of 0.6 mm sieve size. The α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid, the lactose, the talc, the magnesium stearate and half of the corn starch are mixed in a suitable mixer. The other half of the corn starch is suspended in 45 ml of water and the suspension is added to the boiling solution of polyethylene glycol in 180 ml of water. The resulting paste is used to granulate the powder mixture, adding a further amount of water, if necessary. The granules are dried for 16 hours at 35°C, comminuted on a sieve of sieve size 1.2 mm, and processed into tablets using concave punches of 7.1 mm diameter, uppers bisected.

Example 12

The starting material used in Example 1 can also be prepared as follows:

A total of 4.8 g of a 50% dispersion of sodium hydride in mineral oil are added to 100 ml of hexamethylphosphoramide while stirring under a nitrogen atmosphere, followed by 17.1 g of diethyl α - methylmalonate. The mixture is slowly heated to 100° and then treated dropwise with a solution of 19.2 g of 2,4 - dichloro - nitrobenzene in 20 ml of hexamethylphosphoramide, which is added within 30 minutes; the temperature is kept at 100° for 7 hours. After cooling, the mixture is diluted with water and evaporated under reduced pressure, the residue is taken up in water and extracted with benzene. The organic extract is washed with water, dried, filtered and evaporated and the residue is distilled; the fraction boiling at 147—148°/0.25 mm Hg contains diethyl α - (3 - chloro - 4 - nitrophenyl) - α - methylmalonate; the corresponding diethyl α - (3 -

chloro - 4 - nitro - phenyl) - α - ethyl - malonate boils at 170—174°/1 mm Hg.

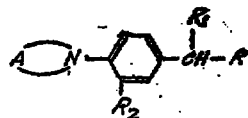
Through a solution of 4 g of diethyl α - (3 - chloro - 4 - nitro - phenyl) - α - methyl - malonate in 50 ml of anhydrous ethanol, hydrogen chloride is bubbled for 5 minutes. Then, 0.5 g of a 10% palladium-on-charcoal catalyst is added and the mixture is hydrogenated for 10 minutes under an initial pressure of 3 at, then filtered. The filtrate is evaporated under reduced pressure, the residue is taken up in a 5% aqueous sodium hydroxide solution, and the mixture is extracted with diethyl ether. The organic extract is dried, filtered and evaporated to yield diethyl α - (4 - amino - 3 - chloro - phenyl) - α - methyl - malonate, which in the infrared absorption spectrum shows characteristic bands at 1720, 3370 and 3460 cm^{-1} .

A mixture of 75 g of diethyl α - (4 - amino - 3 - chloro - phenyl) - α - methyl - malonate and 150 ml of a 50% aqueous sodium hydroxide solution is refluxed for 16 hours, cooled, diluted with water and washed with diethyl ether, then acidified with concentrated hydrochloric acid. The mixture is again refluxed for 16 hours and evaporated under reduced pressure. The residue is taken up in an anhydrous solution of hydrogen chloride in ethanol, the mixture is refluxed for 6 hours and evaporated, and the residue is recrystallized from a mixture of ethanol and diethyl ether to yield ethyl α - (4 - amino - 3 - chloro - phenyl) - propionate hydrochloride, m.p. 164—168°.

We make no claim herein to 4 - (3 - pyrrolin - 1 - yl) - phenylacetic acid or its ethyl ester, or salts of these compounds, pharmaceutical preparations comprising such compounds or processes for preparing such compounds.

Subject to the foregoing disclaimer,
WHAT WE CLAIM IS:—

1. α - (Aminophenyl) - aliphatic carboxylic acid compounds of the formula



(I)

in which R represents a free, esterified, amidated, thioamidated or salified carboxyl group or a cyano group, R_1 stands for a hydrogen atom or a lower alkyl or the cyclopropyl group, R_2 represents hydrogen, halogeno or trifluoromethyl, and

stands for a 3 - pyrrolin - 1 - yl or 1,2,5,6 - tetrahydro - yl - pyridyl radical.

2. Acid addition salts and N - oxides of compounds according to claim 1.

3. α - (Aminophenyl) - aliphatic carboxylic acid compounds of formula I according to claim 1, in which



R_1 , R_2 and R have the meanings given in claim 1, with the proviso that in compounds in which R represents the free carboxyl group or the carbethoxy group and each of R_1 and R_2 represents a hydrogen atom, and



stands for a 1,2,5,6 - tetrahydro - 1 - pyridyl group.

4. Salts of compounds according to claim 3.

5. α - (Aminophenyl) - aliphatic carboxylic acid compounds of formula I according to claim 1, in which



has the meaning given in claim 1, R_1 stands for a hydrogen atom or a methyl or cyclopropyl group, R_2 represents a hydrogen atom or chloro, and R stands for a free or esterified carboxyl group, with the proviso that in a compound in which each of R_1 and R_2 represents a hydrogen atom, and R represents a free carboxyl group or the carbethoxy group, the group



stands for a 1,2,5,6 - tetrahydro - 1 - pyridyl group with 6 ring members.

6. Salts of compounds according to claim 5.

7. α - (Aminophenyl) - aliphatic carboxylic acid compounds of formula I according to claim 1, in which



stands for the 3 - pyrrolin - 1 - yl group, R_1 represents a hydrogen atom or the methyl or cyclopropyl group, R_2 stands for a hydrogen atom or chloro, and R represents the free carboxyl or the carbomethoxy or carbethoxy group.

chloro - 4 - nitro - phenyl) - α - ethyl - malonate boils at 170—174°/1 mm Hg.

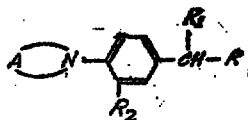
Through a solution of 4 g of diethyl α - (3 - chloro - 4 - nitro - phenyl) - α - methyl - malonate in 50 ml of anhydrous ethanol, hydrogen chloride is bubbled for 5 minutes. Then, 0.5 g of a 10% palladium-on-charcoal catalyst is added and the mixture is hydrogenated for 10 minutes under an initial pressure of 3 at, then filtered. The filtrate is evaporated under reduced pressure, the residue is taken up in a 5% aqueous sodium hydroxide solution, and the mixture is extracted with diethyl ether. The organic extract is dried, filtered and evaporated to yield diethyl α - (4 - amino - 3 - chloro - phenyl) - α - methyl - malonate, which in the infrared absorption spectrum shows characteristic bands at 1720, 3370 and 3460 cm^{-1} .

A mixture of 75 g of diethyl α - (4 - amino - 3 - chloro - phenyl) - α - methyl - malonate and 150 ml of a 50% aqueous sodium hydroxide solution is refluxed for 16 hours, cooled, diluted with water and washed with diethyl ether, then acidified with concentrated hydrochloric acid. The mixture is again refluxed for 16 hours and evaporated under reduced pressure. The residue is taken up in an anhydrous solution of hydrogen chloride in ethanol, the mixture is refluxed for 6 hours and evaporated, and the residue is recrystallized from a mixture of ethanol and diethyl ether to yield ethyl α - (4 - amino - 3 - chloro - phenyl) - propionate hydrochloride, m.p. 164—168°.

We make no claim herein to 4 - (3 - pyrrolin - 1 - yl) - phenylacetic acid or its ethyl ester, or salts of these compounds, pharmaceutical preparations comprising such compounds or processes for preparing such compounds.

Subject to the foregoing disclaimer,
WHAT WE CLAIM IS:—

1. α - (Aminophenyl) - aliphatic carboxylic acid compounds of the formula



(I)

in which R represents a free, esterified, amidated, thioamidated or salfified carboxyl group or a cyano group, R_1 stands for a hydrogen atom or a lower alkyl or the cyclopropyl group, R_2 represents hydrogen, halogeno or trifluoromethyl, and

stands for a 3 - pyrrolin - 1 - yl or 1,2,5,6 - tetrahydro - yl - pyridyl radical.

2. Acid addition salts and N - oxides of compounds according to claim 1.

3. α - (Aminophenyl) - aliphatic carboxylic acid compounds of formula I according to claim 1, in which



R_1 , R_2 and R have the meanings given in claim 1, with the proviso that in compounds in which R represents the free carboxyl group or the carbethoxy group and each of R_1 and R_2 represents a hydrogen atom, and



stands for a 1,2,5,6 - tetrahydro - 1 - pyridyl group.

4. Salts of compounds according to claim 3.

5. α - (Aminophenyl) - aliphatic carboxylic acid compounds of formula I according to claim 1, in which



has the meaning given in claim 1, R_1 stands for a hydrogen atom or a methyl or cyclopropyl group, R_2 represents a hydrogen atom or chloro, and R stands for a free or esterified carboxyl group, with the proviso that in a compound in which each of R_1 and R_2 represents a hydrogen atom, and R represents a free carboxyl group or the carbethoxy group, the group



stands for a 1,2,5,6 - tetrahydro - 1 - pyridyl group with 6 ring members.

6. Salts of compounds according to claim 5.

7. α - (Aminophenyl) - aliphatic carboxylic acid compounds of formula I according to claim 1, in which



stands for the 3 - pyrrolin - 1 - yl group, R_1 represents a hydrogen atom or the methyl or cyclopropyl group, R_2 stands for a hydrogen atom or chloro, and R represents the free carboxyl or the carbomethoxy or carbethoxy group.



8. Ammonium, sodium and potassium salts and pharmaceutically acceptable acid addition salts of compounds according to claim 7.

- 5 9. α - (Aminophenyl) - aliphatic carboxylic acid compounds of formula I according to claim 1, in which



stands for the 3 - pyrrolin - 1 - yl radical, R_1 represents a hydrogen atom or the methyl or cyclopropyl group, R_2 stands for a hydrogen atom or chloro, and R represents the carboxy group.

- 10 10. Salts of compounds according to claim 9.

11. Ethyl 4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenylacetate.

12. Ethyl α - [4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionate.

20 13. Ethyl α - [4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenyl] - propionate.

14. Ethyl α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - acetate.

25 15. Ethyl α - [3 - chloro - 4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenyl] - acetate.

16. Ethyl α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionate.

30 17. Ethyl α - [3 - chloro - 4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenyl] - propionate.

18. α - [3 - Chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid.

19. α - [3 - Chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid.

35 20. α - [4 - (3 - Pyrrolin - 1 - yl) - phenyl] - propionic acid.

21. α - [3 - Chloro - 4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenyl] - propionic acid.

40 22. α - [4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenyl] - propionic acid.

23. Ethyl α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - butyrate.

45 24. α - [3 - Chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - butyric acid.

25. Ethyl α - [3 - chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - α - cyclopropyl - acetate.

50 26. α - [3 - Chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - α - cyclopropyl - acetic acid.

27. α - [3 - Chloro - 4 - (3 - pyrrolin - 1 - yl) - phenyl] - propionic acid N - oxide.

55 28. 4 - (1,2,5,6 - tetrahydro - 1 - pyridyl) - phenylacetic acid.

29. Salts of compounds of any one of claims 10 to 16.

60 30. Salts of compounds of any one of claims 17 to 19.

31. Salts of compounds of claim 20 or 21.

32. Salts of compounds of any one of claims 22 to 27.

33. Pharmaceutically acceptable salts of compounds of any one of claims 10 to 16.

34. Pharmaceutically acceptable salts of compounds of any one of claims 1, 2 and 17 to 19.

35. Pharmaceutically acceptable salts of compounds of any one of claims 3, 5, 20 and 21.

36. Pharmaceutically acceptable salts of compounds of any one of claims 9 and 22 to 27.

37. Pharmaceutical preparations comprising a compound as claimed in any one of claims 10 to 16 and 33, together with a pharmaceutically acceptable carrier.

38. Pharmaceutical preparations comprising a compound as claimed in any one of claims 1, 2, 7, 17 to 19 and 24, together with a pharmaceutically acceptable carrier.

39. Pharmaceutical preparations comprising a compound as claimed in any one of claims 3, 5, 17, 18 and 35, together with a pharmaceutically acceptable carrier.

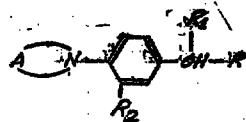
40. Pharmaceutical preparations comprising a compound as claimed in any one of claims 9, 19 to 24 and 36, together with a pharmaceutically acceptable carrier.

41. The compounds of claims 5 and 6 as described in any one of Examples 1 to 3.

42. The compounds of claims 3 and 4 as described in Example 7.

43. The compounds of claims 1 and 2 as described in any one of Examples 4 to 6 and 8 to 10.

44. A process for the manufacture of an α - (aminophenyl) - aliphatic carboxylic acid compound of the formula

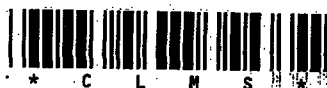


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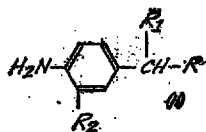
in which R represents an optionally functionally converted carboxyl group, R_1 stands for a hydrogen atom or a lower alkyl or the cyclopropyl group, R_2 represents hydrogen, a halogen atom or the trifluoromethyl group, and



stands for a 3 - pyrrolin - 1 - yl or 1,2,5,6 - tetrahydro - 1 - pyridyl radical, or a functional amine derivative thereof, wherein



a) a compound of the formula

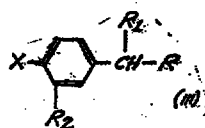


is reacted with a reactive ester of a compound of the formula



or

b) in a compound of the formula



wherein X represents an alkyleneamino group that corresponds to the group



and contains in the β - or γ -position a substituted hydrazono group capable of being cleaved off while introducing a double bond into such alkyleneamino group, the group capable of being cleaved off is split off by pyrolysis, and, if desired, within the defined scope, a resulting compound is converted into another compound of the invention, and/or, if desired, a resulting free compound is converted into a salt or a resulting salt is converted into a free compound or into another salt, and/or, if desired, a resulting mixture of isomers is converted into the single isomers.

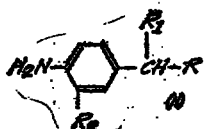
45. Process for the manufacture of an α - (amino - phenyl) - aliphatic carboxylic acid compounds of the formula I according to claim 44, in which



R_1 , R_2 and R have the meaning given in claim 44, with the proviso, that in a compound, in which R_1 and R_2 is hydrogen, and R stands for a free carboxyl or the carboxy group, the group



stands for a 1,2,5,6 - tetrahydro - 1 - pyridyl group, or a salt thereof, wherein a) a compound of the formula



is reacted with a reactive ester of a compound of the formula



and, if desired, within the defined scope, a resulting compound is converted into another compound of the invention, and/or, if desired, a resulting free compound is converted into a salt or a resulting salt is converted into a free compound or into another salt, and/or, if desired, a resulting mixture of isomers is converted into the single isomers.

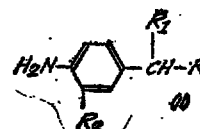
46. Process for the manufacture of an α - (amino - phenyl) - aliphatic carboxylic acid compound of the formula I according to claim 44, in which



has the meaning given in claim 44, R_1 stands for a hydrogen atom or a methyl or cyclopropyl group, R_2 represents a hydrogen atom or chloro, and R stands for a free or esterified carboxyl group, with the proviso, that in a compound, in which R_1 and R_2 is hydrogen, and R stands for a free carboxyl or the carboxy group, the group



stands for a 1,2,5,6 - tetrahydro - 1 - pyridyl group, or a salt thereof, wherein a compound of the formula



is reacted with a reactive ester of a compound of the formula



and, if desired, within the defined scope, a resulting compound is converted into another compound of the invention, and/or, if desired, a resulting free compound is converted into a salt or a resulting salt is converted into a free compound or into another salt, and/or, if desired, a resulting mixture of isomers is converted into the single isomers.

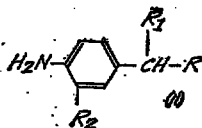
47. Process for the manufacture of an α - (aminophenyl) - aliphatic carboxylic acid compounds of the formula I according to claim 44, in which



has the meaning given in claim 44, R_1 stands for hydrogen or methyl, R_2 is hydrogen or chloro, and R stands for carboxy or, when



each of R_1 and R_2 is hydrogen, for a carboxy group, or a salt thereof, wherein a compound of the formula



5 is reacted with a reactive ester of a compound of the formula



and, if desired, within the defined scope a resulting compound is converted into another compound of the invention, and/or, if desired, a resulting free compound is converted into a salt or a resulting salt is converted into a free compound or into another salt, and/or, if desired, a resulting mixture of isomers is converted into the single isomers.

15 48. Process according to claim 44, wherein a reactive ester of the glycol of the formula IIa is a dihalide thereof.

20 49. A process as claimed in claim 44, wherein a substituted hydrazono group is a sulfonyl-substituted hydrazono group.

50. The process as described in any one of Examples 1 to 3.

51. The process as described in Example

25 7.

52. The process as described in any one of Examples 4 to 6 and 8 to 10.

53. The compounds of claims 1 or 2 substantially as prepared according to the process of any one of claims 44, 48 and 49. 30

54. The compounds of claims 3 or 4 substantially as prepared according to the process of claim 45.

55. The compounds of claims 5 or 6 substantially as prepared according to the process of claim 46. 35

56. The compounds of claims 11 to 17 substantially as prepared according to the process of claim 47. 40

57. The compounds of claims 5 or 6 substantially as prepared according to the procedure substantially as described in any one of Examples 1 to 3.

58. The compounds of claims 3 or 4 substantially as prepared according to the procedure substantially as described in Example 7. 45

59. The compounds of claims 1 or 2 substantially as prepared according to the procedure substantially as described in any one of Examples 4 to 6 and 8 to 10. 50

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