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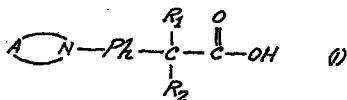
(54) TERTIARY AMINOACIDS, PROCESS FOR THEIR MANUFACTURE AND COMPOSITIONS CONTAINING THEM

(71) We, CIBA GEIGY A.G., 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:—

This invention relates to tertiary amino acids, processes for their manufacture and compositions containing them.

British Patent Specification 1268831 describes α - (amino - phenyl) - aliphatic carboxylic acids (wherein the amino group is a cyclic tert.-amino group) and their acid derivatives. These compounds show anti-inflammatory properties and may be used accordingly.

The present invention provides compounds of the formula



wherein the group



[Price 25p]

represents an unsubstituted or substituted bicyclic alkenyleneamino group with 5 or 6 members in each ring with from 1 to 3 double bonds in the ring system and Ph represents a substituted or unsubstituted phenylene radical, R_1 represents a hydrogen atom or a lower alkyl radical and R_2 represents a hydrogen atom or a lower alkyl radical, a lower alkenyl radical, an unsubstituted or lower alkyl-substituted cycloalkyl or cycloalkenyl radical, a cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl radical, and esters, amides, thioamides, nitriles and hydroxamic acids of such acids and salts thereof. The compounds of the present invention possess pronounced anti-inflammatory properties, as well as analgesic and antifungal effects, or may easily be converted into corresponding pharmacologically active compounds.

The term "lower" used above and below in connection with organic radicals, groups or compounds, denotes such organic radicals, groups or compounds as containing up to 7, preferably up to 4, carbon atoms.

Suitable lower alkyl radicals include, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, secbutyl, tert.-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, n-heptyl and isoheptyl radicals.

Suitable lower alkenyl radicals include, for example, vinyl, allyl, methallyl, 3-butenyl and 1-pentenyl radicals.

Price 33p

A cycloalkyl or cycloalkenyl radical contains preferably from 3 to 7 ring members and may be unsubstituted or substituted by up to 4 lower alkyl groups, which may be the same or different. Suitable cycloalkyl and cycloalkenyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclopropenyl, 1-, 2- and 3-cyclopentenyl and 1-, 2- and 3-cyclohexenyl groups, which may contain up to 4, preferably 1 or 2, of the same or different lower alkyl radicals, especially methyl radicals.

A cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl radical is one of the above-mentioned lower alkyl groups to which is attached in any position, but preferably to the terminal carbon atom, one of the above-mentioned cycloalkyl or cycloalkenyl groups; among such radicals there may be mentioned, for example, cyclopropylmethyl, 2-cyclopentylethyl and 3-cyclopentenylmethyl radicals.

The phenylene radical Ph, to which is attached the group



in the 2-position or preferably the 3-position or more especially the 4-position, is unsubstituted or may be substituted by one or more, preferably 1 or 2, identical or different substituents in the remaining positions. Suitable substituents include for example, lower alkyl radicals, for example those mentioned above, free, etherified and esterified hydroxyl and mercapto radicals, for example, lower alkoxy radicals (for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy and isobutyloxy radicals), lower alkyl-mercapto radicals (for example, methylmercapto and ethylmercapto radicals), halogeno radicals (for example, fluoro, chloro, bromo and iodo radicals), trifluoromethyl radicals, nitro radicals, amino groups, preferably di-lower alkylamino groups (for example, dimethylamino, N-ethyl-N-methylamino, diethylamino, di-n-propylamino, di-isopropylamino, di-n-butylamino and diisobutylamino groups), lower alkylene-amino and lower alkenyleneamino groups (for example, pyrrolidino, piperidino, pyrrolino and piperideino radicals), monoaza-monooxa- and monothiaalkyleneamino radicals, (for example, piperazine, 4-lower alkyl-piperazino, morpholino and thiomorpholino radicals), and lower alkanoylamino radicals, (for example, acetylamino and pivaloylamino radicals), also free or functionally converted carboxyl groups, for example carbo-lower alkoxy radicals, (for example, carbomethoxy and carbethoxy radicals), carbamoyl radicals, unsubstituted or N-substituted, for example, by one or

two of the same or different lower alkyl radicals, (e.g. di-lower alkyl-carbamoyl radicals, for example, the dimethylcarbamoyl radical), cyano radicals and lower alkylsulphonyl radicals (for example, methylsulphonyl and ethylsulphonyl radicals), and free and functionally converted sulpho groups, for example unsubstituted or N-substituted sulphamoyl radicals, (e.g. di-lower alkylsulphamoyl radicals for example, dimethylsulphamoyl radicals). Preferred Ph radicals are 1,3- and 1,4-phenylene, (lower alkyl) - 1,3- and -1,4-phenylene, (lower alkoxy) - 1,3- and -1,4-phenylene, (mono- and di-halogeno) - 1,3- and -1,4-phenylene, (trifluoromethyl) - 1,3- and -1,4-phenylene, (nitro) - 1,3- and -1,4-phenylene, (amino) - 1,3- and -1,4-phenylene, (di-lower alkyl-amino) - 1,3- and -1,4-phenylene and (lower alkylene-amino) - 1,3- and -1,4-phenylene groups.

Preferred bicyclic alkenyleneamino groups are unsubstituted or substituted and contain 5 or 6 ring members in each ring and 1 to 3 double bonds in the isocyclic nucleus. Especially preferred radicals are benzoalkenyleneamino radicals and corresponding dihydro- and tetrahydro-benzoalkenyleneamino radicals, in which radicals the alkenyleneamino portion contains 5 or 6 ring members and which may be unsubstituted or substituted, in the aromatic portion, for example, by substituents listed above that may substitute the phenylene radical Ph, especially by one of the same or different radicals selected from lower alkyl, free, etherified and esterified hydroxy and mercapto radicals, for example, lower alkoxy and lower alkanoyloxy radicals, and halogeno radicals and/or in the aliphatic portion by one or more oxo and/or one or more thiono groups. As examples of such groups there may be mentioned 1-indolinyl, 2-iso-indolinyl, 1,2,3,4-tetrahydro-1-quinolinyl and 1,2,3,4-tetrahydro-2-isoquinolinyl radicals, as well as 4,5,6,7-tetrahydro-1-indolinyl, 4,5,6,7-tetrahydro-2-isoindolinyl, 4,7-dihydro-1-indolinyl, 4,7-dihydro-2-isoindolinyl, 1,2,3,4,5,6,7,8-octahydro-1-quinolinyl, 1,2,3,4,5,6,7,8-octahydro-2-isoquinolinyl, 1,2,3,4,5,8-hexahydro-1-quinolinyl and 1,2,3,4,5,8-hexahydro-2-isoquinolinyl radicals, which may be unsubstituted or substituted, for example, as mentioned above.

Suitable esters of acids of the formula I include, for example, lower alkyl and lower alkenyl esters, cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl and cycloalkenyl-lower alkyl esters, wherein the cycloaliphatic radical contains 3 to 7 ring members, aryl and aryl-lower alkyl esters, in which the aromatic radical is preferably a phenyl group which is unsubstituted or substituted, for example, by one or more of the same or different substituents listed above that may substitute the Ph radical free and etherified hydroxy-lower

alkyl radicals, for example, lower alkoxy-lower alkyl and cycloalkoxy-lower alkyl esters, wherein a cycloalkyl radical contains 3 to 7 ring members, and tert-amino-lower alkyl esters, wherein the tert-amino group, for example, is a di-lower alkylamino group, e.g. dimethylamino and diethylamino groups, lower alkyleneamino, e.g. pyrrolidino or piperidino, radicals and monoaza-, monooxa- and monothia-lower alkyleneamino radicals, for example, piperazino and 4-lower alkyl-piperazino radicals, e.g. 4 - methyl - piperazino and 4 - ethyl - piperazino, morpholino and thiomorpholino radicals. In ester radicals containing hetero atoms, such atoms are separated from one another and from the oxygens of the carboxyl group by at least 2, preferably 2 or 3, carbon atoms.

Suitable amides, thioamides and hydroxamic acids of acids of the formula I include, for example, unsubstituted and substituted amides and thioamides, for example mono- and di-lower alkyl-amides, aryl-amides and aryl-lower alkyl-amides, wherein the aromatic radical is preferably a phenyl group which is unsubstituted or substituted, for example, by one or more of the same or different substituents that may substitute the Ph radical and monocyclic lower alkylene, monoaza-lower alkylene, monooxa-lower alkylene and monothia-lower alkylene-amides, and also the corresponding thioamides and hydroxamic acids.

Suitable salts of compounds of formula I include for example, ammonium and metal salts, as well as acid addition salts.

The pharmacological properties such as the analgesic and antifungal and especially the anti-inflammatory properties may be demonstrated *in vitro* tests or by means of animal experiments, with mammals, such as mice, rats or guinea pigs, being preferably used as experimental animals. The *in vitro* antifungal tests can be performed according to the gradient plate method using fungi strains, for example, from *Trichophyton*, *Microsporum* or *Epidermophyton*, e.g. *Trichophyton mentagrophytes*, *Trichophyton rubrum* or *Trichophyton sinil*; *Microsporum canis* or *Microsporum gypseum*; or *Epidermophyton floccosum*. The antifungal activity can also be shown in *in vivo* tests, e.g. by the method described by Molinas, J. *Investig. Dermatol.*, Vol. 25 p. 33 (1955), according to which guinea pigs are infected on the shaven back with a homogenous agar suspension of a 10 day old culture of *Trichophyton mentagrophytes* grown on Sabouraud's agar. Treatment with 0.5—2% medicated solutions or ointments is started after 24 hours and continued once daily for 10 days. During this time, portions of hair and skin scales are taken from 5 different sites of the infected area and subcultured on Mycosel agar plates, which are incubated and examined for growth.

The analgesic effects can be demonstrated, for example, according to the mouse writhing test, described, for example, by Siegmund et al. *Proc. Soc. Exp. Biol. & Med.*, Vol. 95, p. 729 (1957), with oral doses between about 0.05 and about 0.2 g/kg/day. The antiinflammatory activity can be shown, for example, according to Winter et al, *Proc. Soc. Exptl. Biol. & Med.*, Vol. 111, p. 544 (1962). In this test, the compounds of the present invention are administered in the form of aqueous solutions or suspensions, which may contain carboxymethyl-cellulose or polyethylene glycol as solubilizers, by stomach tube to male and female mature rats, in doses ranging from about 0.0001 to about 0.075 g/kg/day, preferably from about 0.005 to about 0.05 g/kg/day, advantageously from about 0.001 to about 0.025 g/kg/day. About 1 hour later, 0.06 ml of a 1% aqueous saline suspension of carrageenin is injected into the rat's left hind paw. After 3—4 hours the volume and/or weight of the edematous left hind paw are compared with that 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 activity of the experimental compounds. According to the adjuvant arthritis test, male rats are sensitized with 0.05 ml of the above 1% carrageenin suspension, applied under ether anesthesia to all four paws. After 24 hours, 0.1 ml of a 1% suspension of *Mycobacterium butyricum* in mineral oil is injected intradermally into the tail and 7 days later the compounds of the invention are applied as shown above over a 14 day period. The rats are weighed once weekly and the secondary arthritic lesions scored three times a week as to number and severity. The results obtained are compared with those of untreated arthritic rats.

The compounds of the present invention are, therefore, useful as antifungal and analgesic agents, especially as anti-inflammatory agents, primarily in the treatment of arthritic and dermatopathological symptoms. They may also be used as intermediates in the manufacturing of other pharmacologically active compounds.

Especially preferred compounds of the present invention are those of the formula I, wherein



represents a bicyclic alkenyleneamino group with 5 or 6-membered rings and 1 to 3 double bonds, the latter advantageously in the isocyclic nucleus, especially a benzo-alkenylamino group with 5 or 6 ring mem-

bers in the alkenyleneamino portion, which groups may be substituted by 1 to 3, especially 1 or 2, oxo groups, preferably in one or both of the positions adjacent to the nitrogen atom, Ph represents a phenylene radical which is unsubstituted or substituted by 1 or 2 of the same or different substituents selected from lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkyl-mercapto, trifluoromethyl, nitro, amino, di-lower alkylamino, lower alkanoylamino, carboxyl, cyano, carbamoyl, di-lower alkylcarbamoyl, lower alkylsulphonyl, sulpho, sulphamoyl, di-lower alkylsulphamoyl and halogeno radicals, R_1 represents a hydrogen atom or a lower alkyl radical, and R_2 represents a hydrogen atom or a lower alkyl or lower alkenyl radical, or a cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl radical, wherein the cycloaliphatic radical contains from 3 to 7 ring members, as well as a lower alkyl or lower alkenyl ester, a cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl ester, wherein the cycloaliphatic radical contains from 3 to 7 ring members, a phenyl or phenyl-lower alkyl ester, wherein the phenyl radical is unsubstituted or may, for example, be substituted by one or two identical or different substituents listed that may substitute the group Ph defined in this paragraph, a hydroxyl-lower alkyl, lower alkoxy-lower alkyl, di-lower alkylamino-lower alkyl, lower alkenyleneamino-lower alkyl or monoaza-, monooxa- or monothia-lower alkenyleneamino-lower alkyl ester thereof, two hetero atoms in these esters being separated from one another and from the oxygens of the carboxyl group by at least two carbon atoms, the amide or thioamide, a mono- or di-lower alkylamide, a mono- or di-lower alkylthioamide, a lower alkenyleneamide or a lower alkenethioamide, a phenylamide, phenylthioamide, phenyl-lower alkylamide or phenyl-lower alkylthioamide, wherein a phenyl radical is unsubstituted or may, for example, be substituted by one or two identical or different substituents that may substitute the group Ph defined in this paragraph, the morpholide or thiomorpholide or the hydroxamic acid thereof, or salts, especially the pharmaceutically useful physiologically tolerable salts, of such compounds.

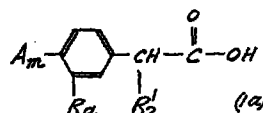
Compounds with especially useful anti-inflammatory properties are those of the formula I, wherein



denotes a bicyclic alkenyleneamino radical with 1 to 3 double bonds in the isocyclic ring and 5 or 6 ring members in each ring, especially a benzoalkenylamino radical with

5 or 6 ring members in the cycloaliphatic portion, whereby such radicals may contain an oxo group in one or two of the positions adjacent to the ring nitrogen, Ph represents a 1,3- or 1,4-phenylene, (lower alkoxy) - 1,3- or -1,4-phenylene, (mono- or di-halogeno) - 1,3- or -1,4-phenylene, (trifluoromethyl) - 1,3- or -1,4-phenylene, (nitro) - 1,3- or -1,4-phenylene, (amino) - 1,3- or -1,4-phenylene or (di-lower alkylamino) - 1,3- or -1,4-phenylene radical, R_1 represents a hydrogen atom, and R_2 represents a hydrogen atom or a lower alkyl, 3 to 7-membered cycloalkyl or 3 to 7-membered cycloalkyl-lower alkyl radical, as well as lower alkyl esters, or amides or mono- or di-lower alkylamides thereof, or salts, especially pharmaceutically useful, physiologically tolerable ammonium, alkali metal, alkaline earth metal or acid addition salts thereof.

Especially pronounced anti-inflammatory properties are shown by compounds of the formula

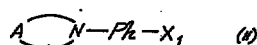


wherein A_m represents a 1-indoliny, 2-isoindoliny, 1,2,3,4-tetrahydro-1-quinoliny or 1,2,3,4-tetrahydro-2-isoquinoliny radical, which radicals may contain oxo group on one or both of the ring carbon atoms adjacent to the ring nitrogen atom, R_1 represents a hydrogen atom or an alkyl or alkoxy radical with up to 4 carbon atoms, a trifluoromethyl, nitro, amino or halogeno radical, and R_2' denotes a hydrogen atom or an alkyl radical with up to 4 carbon atoms, or a cycloalkyl or cycloalkylmethyl radical, wherein a cycloalkyl radical contains 3 or 4 ring members, or lower alkyl esters thereof with up to 4 carbon atoms in the ester group, for example methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl esters, or salts, especially pharmaceutically useful, physiologically tolerable ammonium, alkali metal, for example, sodium or potassium, or acid addition, salts thereof.

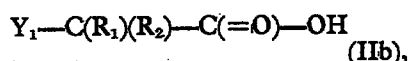
Among these compounds, there should especially be mentioned those of the formula Ia, in which A_m represents a 2-isoindoliny radical, primarily a 1-oxo-2-isoindoliny, as well as 1,3-dioxo-2-isoindoliny, 1-oxo-1,2,3,4-tetrahydro-2-isoquinoliny or 1,3-dioxo-1,2,3,4-tetrahydro-2-isoquinoliny radical, R_1 denotes a hydrogen atom or a nitro, amino or chloro, as well as fluoro or trifluoromethyl radical, and R_2' represents a hydrogen atom or a methyl, cyclopropyl or cyclopropylmethyl radical, as well

as a methyl or ethyl ester or a salt, especially the pharmaceutically useful physiologically tolerable ammonium, sodium, potassium or acid addition salts thereof; these compound, and especially the α - [3 - chloro - 4 - (1 - oxo - 2 - isoindolinyl) - phenyl] - propionic acid, show excellent anti-inflammatory properties in the above-mentioned tests at daily doses of about 0.001 to about 0.025 g/kg.

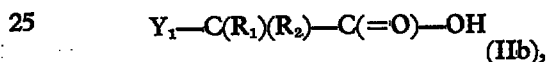
The compounds of the present invention may be manufactured according to methods which are known *per se*, for example, a) a compound of the formula



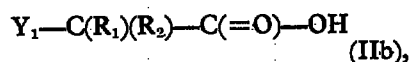
wherein X_1 represents a hydrogen atom, is reacted with a compound of the formula



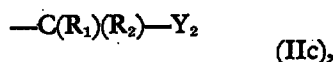
in which Y_1 stands for a free or reactive esterified hydroxy group, or a salt, ester, amide, thioamide, nitrile or hydroxyamic acid thereof, or (b) a compound of the formula II, in which X_1 represents a metal radical, is reacted with a compound of the formula



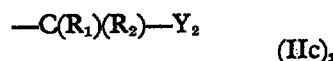
in which Y_1 stands for a reactive esterified hydroxy group, or a salt, ester, amide, thioamide, nitrile or hydroxamic acid thereof, or (c) a compound of the formula II, in which represents a reactive esterified hydroxy group, is reacted with a compound of the formula



in which Y_1 stands for a metal radical, or an ester, amide, thioamide, nitrile or hydroxamic acid thereof, or (d) a compound of the formula II, in which X_1 represents the group of the formula

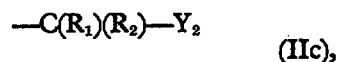


in which Y_2 stands for a metal radical, is reacted with a metal-free, reactive derivative of carbonic or formic acid, or (e) a compound of the formula II, in which X_1 represents the grouping of the formula

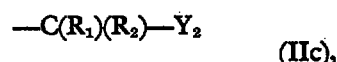


in which Y_2 stands for an unsubstituted or

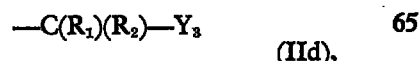
substituted ammonium group, is reacted with a reactive metal-containing derivative of carbonic or formic acid, or (f) a compound of the formula II, in which X_1 represents the group of the formula



in which Y_2 stands for a free or reactive, functionality converted hydroxy group, is reacted with a reactive metal-containing derivative of carbonic or formic acid, or (g) a compound of the formula II, in which X_1 represents the group of the formula



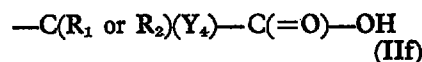
in which Y_2 stands for a free, esterified or salfied hydroxy group, or represents a 1-lower alkenyl radical, is reacted with carbon monoxide, or (h) in a compound of the formula II, in which X_1 represents the group of the formula



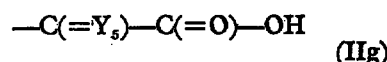
in which Y_3 stands for a methyl, hydroxymethyl, borylmethyl, hydroxyiminomethyl, formyl, 1-lower alkenyl, 1-lower alkynyl, 1,2 - dihydroxy - lower alkyl or an acyl group or a free or functionally modified carboxy-carbonyl group, Y_3 is converted into a free, esterified amidated or thioamidated carboxyl group or a cyano group or hydroxamic acid by oxidation or rearrangement, or (i) in a compound of the formula II, in which X_1 represents the group of the formula



in which Y_3 stands for a free or esterified carboxycarbonyl group, Y_3 is converted into a free or esterified carboxy group by oxidation or decarbonylation, or (j) a compound of the formula II, in which X_1 represents a group of the formula

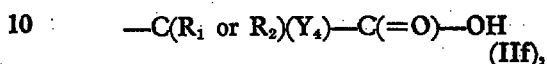


or of the formula

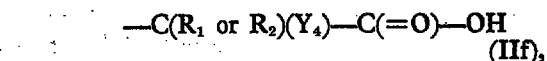


in which Y_4 represents a free or reactive esterified or etherified hydroxy or free or reactive esterified or etherified mercapto group or a disubstituted amino group, and Y_5 represents a lower alkylidene, cycloalkylidene or cycloalkyl-lower alkylidene group or an oxo group or a free or ketalized thio group,

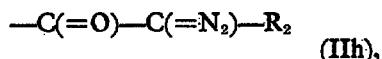
or a corresponding ester, amide, thioamide or nitrile or a corresponding quaternary ortho- or para-quinone methide of such compound is treated with catalytically activated or electrolytically generated hydrogen or with a chemical reducing agent, if desired, in the presence of a desulphurising agent, or (k) a compound of the formula II, in which X_1 represents the group of the formula



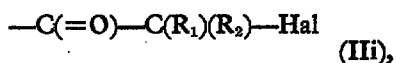
in which Y_4 represents a carboxy group, or an ester, amide thioamide, nitrile or hydroxamic acid thereof is decarboxylated by pyrolysis, or (l) a compound of the formula II, in which X_1 represents a group of the formula



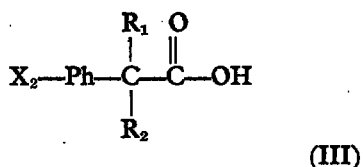
in which Y_4 represents an acyl group, or an ester amide, thioamide, nitrile or hydroxamic acid is subjected to β -keto-acid splitting by treatment with a strongly alkaline agent, or (m) a compound of the formula II, in which X_1 represents an acetyl group, is treated with sulphur in the presence of ammonia or a primary or secondary amine, or (n) a compound of the formula II, in which X_1 represents a group of the formula



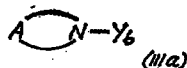
is subjected to hydrolysis, alcoholysis, ammonolysis or aminolysis, or (o) a compound of the formula II, in which X_1 represents a group of the formula



in which Hal stands for a halogen atom, is treated with a strongly alkaline agent or with a soluble silver salt, or (p) a compound of the formula



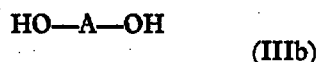
or an ester, amide, thioamide, nitrile or hydroxamic acid thereof, is reacted with a compound of the formula



one of the radicals X_2 and Y_6 representing a hydrogen atom or a metal radical and the other a free or reactive esterified hydroxy group, or (q) a compound of the formula III or an ester, an amide, a thioamide, nitrile or hydroxamic acid thereof, in which X_2 represents a primary, secondary or tertiary amino group, is reacted with an amine of the formula



or (r) a compound of the formula III, in which X_2 represents a primary amino group, or an ester, amide, thioamide, nitrile or hydroxamic acid thereof, is reacted with a compound of the formula



or with a reactive derivative thereof or with a corresponding dehydrated compound thereof, or (s) a compound of the formula III, in which X_2 represents a radical of the formula



which stands for a bicyclic alkyleneamino group having 5 or 6 ring members in each ring, which group contains as substituents, preferably in the iso cyclic ring, one or more of the same or different substituents selected from hydroxy, mercapto, amino, ammonium, hydrazino and hydrazono groups and functionally converted groups corresponding to these, or an ester, an amide, a thioamide, nitrile or hydroxamic acid thereof, is dehydrated, dehydro-sulphidated, deaminated or pyrolysed, and, if desired, a resulting compound is converted within the scope defined into another compound of this invention, and/or, if desired, a resulting free compound is converted into a salt or a resulting salt into the free compound, and/or, if desired, a resulting mixture of isomers is resolved into the individual isomers.

Suitable metal radical include, for example, alkali metal, e.g. lithium, atom, substituted zinc, cadmium or alkaline-earth metal, atoms, e.g. halogeno-magnesium groups, lower alkyl zinc and lower alkyl cadmium groups, for example, chloro-, bromo- and iodo-magnesium groups, methyl- and ethyl-zinc and methyl- and ethyl-cadmium groups.

Preferred reactive esterified hydroxyl groups are hydroxyl groups esterified by a strong mineral acid or sulphonic acid, for example a hydrohalic acid, sulphuric, lower alkane-

sulphonic or benzenesulphonic acid, for example, hydrochloric, hydrobromic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid.

- 5 In the methods a) b) and c) reactions may be carried out according to the Grignard or Friedel-Crafts synthesis, in which a new carbon-to-carbon bond is formed from various reagents. The Friedel-Crafts reaction is carried out in the presence of a Lewis acid, for example an aluminium salt, as well as a boron, antimony-V, iron-III or zinc salt, especially the chloride of hydrofluoric, sulphuric or preferably polyphosphoric acid, with the latter especially being used with compounds of the formula IIb or derivatives thereof in which Y_1 represents a hydroxyl group.

- 20 Suitable ammonium groups include tri-lower alkyl-ammonium and di-lower alkyl-aryl-lower alkyl-ammonium groups, for example, trimethylammonium and dimethylbenzylammonium groups.

- 25 Suitable reactive functionally converted hydroxyl groups include esterified, etherified and salified hydroxyl groups 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 converted into a corresponding salt group for example, into an alkaline or alkaline earth metal group, for example a sodium, potassium or calcium salt group.

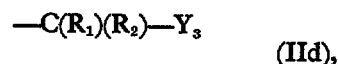
- 30 In methods d) to f) a metal, ester, ether or alcoholate compound of the formula II is reacted with a reactive derivative of carbonic or formic acid, with only one of the two reagents containing a metal radical A metal compound or Grignard compound of the formula II may be reacted with a suitable metal-free carbonic acid or formic acid derivative, preferably with carbon dioxide, as well as carbon disulphide, but also with an appropriate carbonate or halogenoformic acid ester, for example, diethylcarbonate or diethyl thiocarbonate, orthoformic acid lower alkyl esters, for example orthoformic acid ethyl ester or propyl ester, halogenoformic acid lower alkyl, phenyl or phenyl-lower alkyl esters, wherein a lower alkyl, phenyl or phenyl-lower alkyl group may be unsubstituted or substituted, for example chloroformic acid ethyl ester, tert.-butyl ester, allyl ester, 2-methoxyethyl ester, phenyl ester or benzyl ester, or cyanogen halide or carbamoyl halide, for example, cyanogen bromide or diethylcarbamoyl chloride.

- 60 A starting material of the formula II having a group of the formula IIc, wherein Y_2 denotes an ammonium group or a free or reactive, functionally converted hydroxyl group, especially an esterified, as well as an etherified hydroxyl group, is preferably reacted with a metal cyanide, for example

an alkali metal cyanide, for example, sodium or potassium cyanide. 65

In method g a starting material, wherein Y_2 in a group of the formula IIc represents a free, esterified or salified hydroxyl group, or a corresponding dehydrated compound of the formula II, wherein X_1 represents a 1-lower alkenyl radical, may also be reacted with carbon monoxide. The latter is used under neutral, basic or acid conditions, for example, in the presence of sulphuric acid, and under high pressures and/or temperatures, for example, at up to about 400 atmospheres and about 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 may also be evolved from suitable reagents, for example formic acid, in the presence of high-boiling mineral acids, for example sulphuric acid or phosphoric acid. 70 75 80 85

In method h, in a starting wherein X_1 is a group of the formula



wherein Y_3 represents a radical which can be converted into a free or esterified, amidated or thioamidated modified carboxyl group or a cyano or hydroxamic acid group, the desired conversion of Y_3 be effected by oxidation or rearrangement. A group Y_3 , which can be converted by oxidation, is a methyl hydroxy-methyl, 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 group, for example a lower alkanoyl or lower alkenoyl group, as well as a free or functionally modified, for example, esterified, carboxycarbonyl group. The reaction may be performed by standard oxidation methods, for example, by treatment with oxygen (either in the 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 oxidising agents, for example hydrogen peroxide, or a nitrogen oxide, oxidising acids or salts thereof, for example hypohalous acids, periodic acid, nitric acid or percarboxylic acids or corresponding salts, for example alkali metal salts thereof, for example, 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 sulphates, or silver, mercury, vanadium-V-, chromium-VI- or manganese-IV-oxides, in an acid or alkaline medium. Usually, the free acids of the formula I or salts thereof are obtained as products according to the above oxidation 90 95 100 105 110 115 120 125

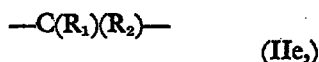
methods, whereby starting materials are used, in which a radical



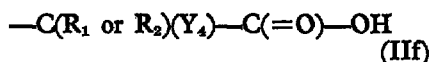
is more stable than the group Y_3 to the oxidizing reagent. If, on the other hand, for example, a starting material having a hydroxyiminomethyl group as the radical Y_3 , that is to say an oxime, is used and the Beckmann rearrangement is carried out, for example, by treatment with sulphuric acid, *p*-toluenesulphonyl chloride or phosphorus pentachloride, or is subjected to oxidation, for example, with hydrogen peroxide or one of the above percarboxylic acids, or if a compound having a formyl or acyl group Y_3 , 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 sulphuric acid, or if a compound having a formyl group Y_3 is treated with a sulphonyl-hydroxamate or nitro-hydroxamate, a cyanide, an amide or a hydroxamic acid compound respectively is obtained.

In method i) in a starting material having the above group of the formula II*d*, wherein Y_3 represents a free or esterified carboxycarbonyl group, for example a carbonyl-alkoxy-carbonyl group, may be converted into the desired compound of the formula I either by oxidation, for example, with hydrogen peroxide in an acidic 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.

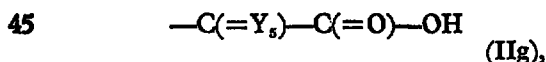
In process j) to l) in the starting material of the formula II X_1 represents a radical which is suitable for the formation of the group of the formula



that is a group of the formula



or of the formula



or an ester, amide, thioamide, nitrile or hydroxamic acid thereof, wherein the radical Y_4 may be converted to the group R_1 or R_2 , respectively, and the radical Y_5 into the group R_2 together with a hydrogen atom by reduction, decarboxylation, deacylation or desul-

phurisation. Thus, Y_4 may represent a free or reactive esterified or etherified hydroxyl or mercapto group, for example, one of the above-mentioned corresponding groups or the corresponding mercapto equivalents, for example, a hydroxyl or a mercapto group, or a chloro, bromo or iodo group, a benzyloxy or benzylmercapto group, or a disubstituted amino group, for example a di-lower alkyl-amino, for example, dimethyl-amino or diethylamino, group, and Y_5 may, for example, denote a lower alkylidene, cycloalkylidene or cycloalkyl-lower alkylidene group or an oxo or free or ketalized thio group. Starting materials with such groups or corresponding quaternary *o*- or *p*-quinone methides (which may be obtained by splitting off the elements of a compound of formula $Y_4\text{---H}$ from a starting material of the formula II, having a group of the formula II*f*, for example, on treatment with strong mineral acids or alkali metal hydroxides) may 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, for example an alkali metal hydroxide, or an alcohol, for example, with zinc, amalgamated zinc, iron or tin, preferably in the presence of an aqueous mineral acid or carboxylic acid, for example, hydrochloric acid or acetic acid, with zinc-nickel or aluminium-nickel alloys, preferably in the presence of an aqueous alkali metal hydroxide, or with an alkali metal for example sodium or potassium, or corresponding amalgams, in the presence of a lower alkanol. In the reduction of a starting material having a mercapto group or a free or ketalised thio group, desulphurising agents, for example mercury or copper oxide, as well as Raney nickel, are preferably used.

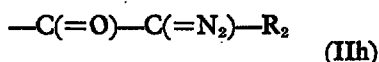
In the case where Y_4 represents a free hydroxyl group, it is also possible to use an aqueous suspension of phosphorus and iodine, hydriodic acid, tin-II-chloride or an alkali metal, for example, sodium sulphite or dithionite, as reducing agent, and in the case where Y_4 denotes an esterified hydroxyl group, for example a halogeno group, one may also use a lower alkyl, lower alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl 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_5 represents an oxo group, the Clemmensen or Wolff-Kishner reduction (including the Huang-Minlon modification) may be

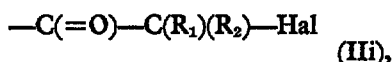
used for its removal, using a chemical reducing agent (nascent hydrogen) or hydrazine, the latter being preferably employed in the presence of a strong alkali metal hydroxide, for example a high-boiling aqueous or glycolic solution of sodium or potassium hydroxide.

If Y_4 represents a carboxyl group and the starting material represents a corresponding malonic acid derivative, then such a starting material may be decarboxylated by pyrolysis, preferably in an acid medium. If Y_4 represents another acyl group, for example a lower alkanoyl, aroyl or aryl-lower alkanoyl group, for example, an acetyl or benzoyl group, the corresponding β -keto-acid starting material may be subjected to acid splitting by the action of a strongly alkaline agent, for example an alkali metal hydroxide, for example, one of those mentioned above.

In methods m) to o) substituent X_1 , which also yields the above-mentioned grouping of the formula IIe, is an unsubstituted or substituted acetyl group, for example, a group of the formulae



or



wherein Hal denotes a halogen atom. A corresponding acetyl starting material may be converted into compounds of the present invention in accordance with the Willgerodt-Kindler reaction, for example, by treatment with sulphur in the presence of ammonia or of a primary or secondary amine, especially of morpholine, and preferably of a sulphonic acid, for example, *p*-toluenesulphonic acid. A corresponding α -diazoacetyl starting material may be converted into compounds of the present invention according to the Wolff reaction (Arnd-Eistert), for example, by hydrolysis, alcoholysis, ammonolysis or aminolysis, preferably with irradiation or heating in the presence of heavy metal catalysts, for example, copper or silver catalysts. A corresponding α -halogeno-acetyl starting material may be converted into compounds of the present invention according to the Favorskii (Wallach) rearrangement, for example, by treatment with a strongly alkaline agent, such as an alkali metal hydroxide, or a soluble silver salt, such as silver nitrate.

According to other processes p) to s), it is possible either to introduce the group of the formula



into the phenyl radical or to convert a radical present capable of being converted into the group



for example a primary, secondary or tertiary, for example, an acyclic, amino group or a radical



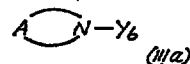
which is a bicyclic alkyleneamino group corresponding to the radical



into the desired bicyclic alkylene group



Thus, X_2 in a starting material of the formula III may, for example, represent a hydrogen atom, or a metal group or a free or reactive esterified hydroxyl group, for example one of the above-mentioned groups, preferably an alkali metal atom or halogen atom. The corresponding starting material of the formula III may be reacted with a compound of the formula

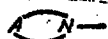


whereby one of the radicals X_2 and Y_6 represents a hydrogen atom or the metal group, for example, lithium or sodium, and the other represents a free or reactive esterified hydroxyl group, especially a fluorine or chlorine atom.

If X_2 represents a hydrogen atom and Y_6 represents a halogeno radical, the reaction may be carried out by analogy with the above-mentioned Friedel-Crafts reaction, for example, in the presence of a Lewis acid or, if Y_6 represents a hydroxyl group, in the presence of an alkaline agent, for example, potassium hydroxide. If X_2 denotes a hydroxyl or lower alkanoyloxy group, the process is preferably carried out in the presence of a dehydrating or dehydrogenating agent, for

example a mineral acid or a salt thereof, for example, hydrochloric acid, ammonium sulphite or sodium hydrogen sulphite, activated aluminium oxide, Raney nickel or palladium on charcoal.

The conversion of a primary, secondary or tertiary amino group X_2 in a starting material of the formula III into the group



- 10 may, for example, be carried out by transamination with an amine of the formula



In this reaction, the latter is used in excess, either in the absence or the presence of a catalyst, for example, one of the above-mentioned dehydrating or dehydrogenating agents, and under elevated temperature and/or increased pressure.

- 15 A starting material of the formula III, wherein X_2 represents a primary amino group, may be reacted with a glycol, glycollic acid or dicarboxylic acid compound of the formula



(IIIb)

- 25 or preferably with a reactive derivative of a hydroxyl compound of formula IIIb, for example a reactive ester, for example an ester with a hydrohalic acid, or a cyclic ether, as well as a corresponding dehydrated, unsaturated derivative of a glycol or glycollic acid compound, furthermore with a lactone of a hydroxy-acid compound of the formula IIIb or a halide, ester or anhydride of an acid of the formula IIIb. This reaction is preferably carried out in the presence of water or an acid-binding reagent, for example an alkali metal or an alkali metal alcoholate or carbonate, the addition of an unsaturated compound being preferably carried out in the presence of a catalyst, for example a copper, cobalt or molybdenum catalyst, and/or of acids or basic reagents.

A saturated group



- 45 may be converted into the desired group



by dehydration, dehydrosulphuration, splitting-off of the elements of an acid or deamination of compounds with a bicyclic alkylene-amino



having suitable substituents. The latter are hydroxy, mercapto, amino, ammonium, hydrazino or hydrazono groups or the corresponding reactive, functionally converted groups, such as, for example, a hydroxy group esterified, for example, by a mineral acid, for example a hydrohalic acid, e.g. hydrochloric or hydrobromic acid, or sulphuric acid, or an organic carboxylic or sulphonic acid, e.g. acetic, propionic, benzoic, *p*-toluenesulphonic or *p*-bromophenylsulphonic acid, as well as dithiocarbonic acid or a hydroxy or mercapto group etherified, for example, by a tert.-butyl group, or acyl derivatives of nitrogen containing groups.

Dehydration is preferably carried out in the presence of an acid, for example a concentrated inorganic acid, e.g. hydrobromic, sulphuric or phosphoric acid, an organic sulphonic acid, e.g. *p*-toluenesulphonic acid, or a suitable acid derivative, e.g. polyphosphoric acid or acetic acid anhydride, and the splitting-off of an esterified hydroxy group together with hydrogen in the form of the elements of an acid, for example, by pyrolysis or in the presence of a suitable base, for example an alkali metal hydroxide or alcoholate. The dehydrosulphuration may be carried out, for example, by using heavy metal oxides, for example mercury or lead oxides, and the deamination, for example, by thermal decomposition of ammonium salts. Acyl derivatives of hydrazones may be split pyrolytically, preferably under decreased pressure, while introducing the desired double bond.

Resulting compounds may be converted into one another in a manner which is known *per se*. Thus, for example, resulting free acids may be esterified using alcohols in the presence of esterifying reagents, for example strong acids, for example, hydrochloric, sulphuric, benzenesulphonic or *p*-toluenesulphonic acid, as well as dicyclohexylcarbodiimide, or diazo compounds, and may also be converted into acid halides by treatment with suitable halogenating reagents for example thionyl halides, for example, thionyl chloride, or phosphorus halides or oxyhalides, for example, phosphorus chloride or oxychloride.

Resulting esters may be hydrolysed to the free acids, for example, by treatment with suitable basic agents, for example aqueous alkali metal hydroxides, or may be transesterified into other esters with alcohols in the presence of acid or alkaline agents, for

example mineral acids or complex heavy metal acids, as well as alkali metal carbonates or or alcoholates. Esters may be converted into amides by treatment with ammonia or appropriate amines.

Resulting acid halides may, on treatment with alcohols, as well as ammonia or amines, and resulting metal or ammonium salts by means of alcohols or corresponding halides, for example, chlorides or bromides, or corresponding chlorosulphites, thionyl halides, for example, thionyl chloride, phosphorus pentoxide, phosphorus pentasulphide, phosphorus halides, for example, phosphorus pentachloride, or phosphorus oxyhalides, for example, phosphorus oxychloride, or other acyl halides, for example, chlorides, depending on the choice of the starting materials and the reagents, be converted into esters, halides, anhydrides, amides, thioamides and nitriles, respectively.

Resulting amides or thioamides (products of the Willgerodt-Kindler reaction) may be hydrolysed under acid or alkaline conditions, for example, by treatment with aqueous mineral acids and/or carboxylic acids, or alkali metal hydroxides, as well as alcoholysed or transaminated, furthermore desulphurised, for example, by treatment with mercury(II)-oxide and lower alkyl halides, followed by hydrolysis.

Resulting nitriles may be hydrolysed or alcoholysed, for example, by treatment with concentrated aqueous or alcoholic acids or with alkaline agents, for example alkali metal hydroxides, as well as alkaline hydrogen peroxide.

Compounds with oxo groups may be converted into corresponding compounds with thio groups, for example, by treatment with phosphorus pentasulphide. In a bicyclic radical

organic alkali metal compounds, for example, phenyl lithium or triphenylmethyl sodium, or with alkali metal, for example sodium, hydrides, amides or alcoholates, and may then be reacted with a reactive ester of an alcohol of formula R_1-OH and/or R_2-OH , for example a corresponding halide, R_1 or R_2 being thus introduced into the α -position.

Resulting compounds may be halogenated in the aromatic radical Ph, for example, using halogen, preferably in the presence of a Lewis acid, for example, an iron-III, aluminium, antimony-III or tin-IV halide, or a halogenating agent, for example, hydrochloric acid in the presence of hydrogen peroxide, or an alkali metal chlorate, for example, sodium chlorate, a nitrosyl halide, for example, nitrosyl chloride or bromide, or a halogenosuccinimide or halogenophthalimide, for example, bromosuccinimide or bromophthalimide.

Furthermore, a nitro group may be introduced into the aromatic radical Ph, for example, by treatment with nitric acid or with nitrate salts under acid conditions, for example, in the presence of sulphuric acid and trifluoroacetic acid, respectively. In a resulting nitro compound, the nitro group may be reduced to the amino group, for example, by treatment with catalytically activated hydrogen or with chemical reducing agents (nascent hydrogen). In these or other reducing procedures care has to be taken that the unsaturated alkyleneamino radicals remains intact.

Resulting compounds having a primary amino group may be reacted with reactive esters of alcohols or glycols as well as reactive functional derivatives, for example halides, e.g. chlorides, or anhydrides of acids, and thus be converted into compounds with secondary or tertiary amino or quaternary ammonium, as well as acylated amino, groups. On treatment with nitrous acid, resulting compounds having a free amino group yield diazonium salts, which may be converted according to the Sandmeyer reaction, for example, by hydrolysis at elevated temperatures, treatment with copper-II halides or cyanide, and with a lower alkanol or lower alkylmercaptan, preferably under neutral or weakly acid or alkaline conditions, into the corresponding hydroxyl, halogeno- cyano, lower alkoxy or lower alkylmercapto compounds, respectively.

In resulting phenolic products the phenolic hydroxyl and mercapto groups may be etherified, for example, using the corresponding metal, for example alkali metal phenolates and thiophenolates, by treatment with reactive esters of lower alkanols and cycloalkanols, for example lower alkyl or cycloalkyl halides, sulphates or sulphonates, as well as diazo compounds, for example lower diazoalkanes. Resulting phenol ethers may be split, for example, by treatment with strong acids or

without oxo groups, such groups may be introduced into that portion of the radical which contains the nitrogen atom attached to the phenylene radical Ph, especially into one or both of the positions adjacent to such ring nitrogen atom, by oxidation, for example, with oxygen (e.g. in the form of air) or with other mild oxidation reagents, for example those mentioned above. One thus obtains the lactam and imide compounds from the corresponding amines.

Resulting esters, salts or nitriles, in which at least one of R_1 and R_2 represents a hydrogen atom, may be metallised in the position α to the functionally modified carboxyl group, for example, by treatment with alkali metals or derivatives thereof, for example

acid salts, for example hydrobromic acid and acetic acid, as well as pyridine hydrochloride.

- Resulting unsaturated compounds may be saturated as described above, for example,
- 5 by treatment with catalytically activated hydrogen or with chemical reducing agents (nascent hydrogen) with the elimination of double bonds, for example in an R_2 and/or ester group.
- 10 In resulting compounds with removable, free or esterified hydroxyl groups in the radical



- such groups may, if desired, be split off together with hydrogen, i.e. with the introduction of a double bond, for example, as described above.
- 15

- A resulting free acid may be converted into a salt in a manner which is known *per se*, 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. Ammonium or metal salts of this type
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- 25 may be converted into the free acid by treatment with an acid, for example, hydrochloric acid, sulphuric acid or acetic acid, until the required pH-value is reached.

- 30 A resulting basic compound may be converted into an acid addition salt, for example, by reaction with an inorganic or organic acid or a corresponding anion exchange preparation and isolation of the resulting salt.
- 35 A resulting acid addition salt may 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
- 40 example pharmaceutically useful, physiologically tolerable acid addition salts, are for example, those with inorganic acids, for example hydrochloric, hydrobromic, sulphuric, phosphoric, nitric or perchloric acid, or with
- 45 organic acids, especially organic carboxylic or sulphonic acids, e.g. formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, aminosalicylic, embonic or nicotinic acid, as
- 50 well as methanesulphonic, ethanesulphonic, hydroxyethanesulphonic, ethylenesulphonic, benzenesulphonic, halogenobenzenesulphonic, toluenesulphonic, naphthalenesulphonic, sulph
- 55 phanilic or cyclohexylsulphamic acid.

- These and other salts, for example, the picrates, may also be used for the purification, as well as identification of the free
- 60 compounds; thus, free compounds may be

converted into their salts, these salts may be separated from the crude mixture, and the corresponding free compounds may then be obtained from the isolated salts.

Resulting isomer mixtures may be resolved into the individual isomers in a manner which is known *per se*, for example, by fractionated distillation or crystallisation and/or by chromatography. Racemic products may be resolved into the optical antipodes, for example, by resolution, such as fractionated crystallisation, of mixtures of diastereoisomeric 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, liberation of the free antipodes from the salts.

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

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The present invention also provides modifications of the above process, according to which a compound formed at any stage as an intermediate product is used as the starting material and the remaining stage or stages is or are carried out with this compound, or according to which the process is interrupted at any stage, or according to which starting materials are formed under the reaction conditions or used in the form of salts or reactive derivatives thereof. Thus, for example, in most of the above-mentioned oxidation reactions, in which the radical Y_3 is converted into a free or functionally modified carboxyl group, the corresponding aldehydes, in which Y_3 represents a formyl group, are formed as intermediates. Also, for example, it is possible to hydrolyse the trihalogenomethyl compounds formed as intermediate products in the haloform reaction, under the prevailing alkaline reaction conditions, to yield the corresponding salts of acids of the formula I. Quaternary o- or p-quinone methide compounds may also be formed as intermediate compounds during the reaction from the corresponding starting materials, in which Y_4 of the grouping of the formula III is a free or reactive esterified hydroxyl group, for example, under strongly acidic or alkaline conditions, or from the corresponding starting materials in which Y_5 represents an oxo or thiono group. Furthermore, it is possible to use the α -diazoketones, formed according to the Arndt-Eistert method from the acid halides by reaction with diazo compounds, in the Wolff rearrangement without isolation. In addition, various intermediate products may be formed from the corresponding start-

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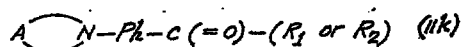
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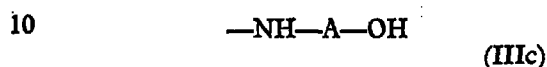
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ing materials during the synthesis of the group



5 If, for example, X_2 represents a primary amino group and a corresponding starting material is reacted with a glycol of formula IIIb or a reactive functional derivative thereof, then an intermediate product having a secondary amino group X_2 of the formula



or a reactive derivative thereof is usually obtained.

15 According to the process, those starting materials are preferably employed which lead to the formation of those compounds of the invention, which are described above as being especially preferred.

20 The starting materials are known or, if they are new, may be manufactured in a manner which is known *per se*. Thus, starting materials of the formula II may generally be obtained in analogy to processes p) to s), i.e. by the introduction or synthesis of the group



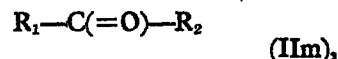
30 If X_1 , for example, represents a reactive esterified hydroxyl group, such group may be introduced by halogenation or by nitration, followed by reduction, diazotisation and the Sandmeyer reaction. The resulting starting material may subsequently be converted into a metallic compound, for example, by reaction with an alkali or alkaline earth metal, e.g. lithium or magnesium, or with a di-lower alkyl-zinc or-cadmium compound. 3 - Carboxy - 2 - lower alkenylether starting materials used in the Claisen rearrangement may, for example, be obtained according to the method described in J.Chem.Soc., Vol. 40 1963, p. 4210, for example by treatment of the corresponding alkali metal phenolates with free or functionally modified 3 - bromo - 1 - alkenecarboxylic acids.

45 Starting substances wherein Y_2 represents a metal radical may be manufactured in an analogous manner, for example, by reaction of the reactive ester of a corresponding benzyl alcohol compound with an alkali or alkaline earth metal or a di-lower alkyl-zinc or -cadmium compound. On the other hand it is possible, for example, to reduce the compounds of formula

55 which may be manufactured in a simple manner according to the Friedel-Crafts method, e.g. with lithium aluminium hydride or (R_1 — or R_2)—magnesium halide compounds, in which R_1 or R_2 represents one of the organic radicals mentioned above, or to react Grignard compounds having the radicals of the formula 60



with an oxo compound of the formula

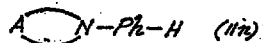


whereupon the corresponding benzyl alcohol 65 compounds are obtained. In these, the hydroxyl group may be converted into a reactive esterified hydroxyl group or into a salified hydroxyl group in a manner which is known *per se*, for example, by treatment with a phosphorus halide, thionyl halide or sulphonyl halide, or an alkali metal or alkaline earth metal, respectively. Resulting esters or salts may 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 may be obtained from the above reactive esters by reaction with tertiary amines or with secondary amines, followed by quaternisation of the resulting tertiary amines according to the usual methods, for example, by reaction with lower alkyl halides or aryl-lower alkyl halides. 80

Starting materials with a group Y_3 may be obtained from the above-mentioned compounds having a metallic group Y_2 by treatment with a methyl halide, formaldehyde, a formyl halide, a lower alkanal, a lower alkenal or a hydroxy-lower alkanal, or a lower alkanoyl halide, a lower alkenoyl halide or oxalyl halide, respectively, and, if desired, a resulting alcohol may be dehydrated, for example, by treatment with acidic reagents, for example sulphuric 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 boryl-methyl compounds, while aldehydes on treatment with hydroxylamine yield the corresponding hydroxyiminomethyl compounds, that is to say oxime compounds. Aldehyde starting materials, wherein Y_3 represents a formyl group, may also be formed from ketones of the formula IIk by reaction with dimethyl- 105

14 sulphonium methylide or dimethyloxysulphonium methylide (obtained from the corresponding trimethylsulphonium salts) and rearrangement of the resulting ethylene oxides to the corresponding aldehydes by reaction with Lewis acids, for example *p*-toluenesulphonic acid or boron trifluoride. They may also be formed according to the Darzens condensation by treatment of ketones of the formula IIk with α - halogeno - alkanecarboxylic or α - halogeno - alkenecarboxylic acid esters in the presence of suitable alkali metal alcohates, for example, potassium tert.-butoxide, hydrolysis 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 sulphuric acid.

20 The starting materials, having a free, esterified or etherified hydroxyl or mercapto group Y_4 , may be obtained according to the cyanohydrin method or analogous syntheses, for example, by reaction of a compound of the formula IIk or a thio analogue 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 wherein Y_4 represents a disubstituted amino, for example, dimethylamino group, may be formed from starting materials of the formula II, wherein X_1 represents an acetyl group, for example, by treatment with an alkali methyl cyanide and ammonium carbonate, followed by a base or an acid, and disubstitution of the free amino group, for example, with formaldehyde and formic acid. Compounds wherein Y_5 represents an oxo or thio group, may be formed according to the Friedel-Crafts reaction using suitable compounds of the formula



50 and oxalyl halides, for example, oxalyl chloride. A resulting phenylglyoxylic acid ester may then be reduced by treatment with an $(R_1\text{--} \text{ or } R_2)\text{--}$ Grignard compound and may be dehydrated, if desired. They are also obtained according to the Ando synthesis on treating a compound of the formula II, in which X_1 stands for a hydrogen atom, with a mesoxalic acid ester in the presence of tin-IV chloride; the resulting adduct may be hydrogenated with removal of the hydroxyl group and the resulting malonic acid ester compound may be metallised and then reacted

with a reactive ester of an alcohol of the formula $(R_1\text{--} \text{ or } R_2)\text{--OH}$ or saponified and decarboxylated.

Furthermore, it is possible to obtain α -diazoketone compounds, when a corresponding benzoic acid halide is treated with an $(R_1 \text{ or } R_2)$ -diazocompound. α -Halogenoketone compounds are obtained, for example, when a corresponding lower alkanophenone compound is halogenated or one of the above α -diazoketone compounds is reacted with a hydrohalic acid.

Starting materials of the formula III may be formed in analogy to the method a) to o) if starting materials are used in which in place of the group



there is used the group X_2 or by a group which is easily converted into such a radical, for example, by reduction, preferably a nitro group.

Intermediate products and starting substances obtainable according to the above processes may also be converted into one another according to the methods described for the final substances.

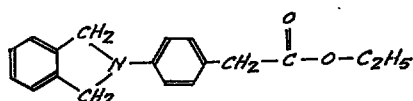
The compounds of the present invention may, for example, be used for the manufacture of pharmaceutical preparations which contain an effective amount of the active substance in admixture or conjunction with inorganic or organic, solid or liquid, pharmaceutically suitable carriers, which are suitable 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 glycin, and lubricants, for example, silica, talc, stearic acid or salts thereof, for example magnesium or calcium stearate, and/or polyethylene glycol; tablets may also contain binders, for example, magnesium aluminium 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 effervescent mixtures and/or adsorbents, dyestuffs, flavours and sweeteners. Injectable preparations are preferably isotonic aqueous solutions or suspensions, suppositories and ointments, primarily fat emulsions or suspensions. The pharmaceutical preparations may be sterilised and/or may contain auxiliary substances, for example, preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or

buffers. The present pharmaceutical preparations of the present invention may be manufactured in known manner, for example, by means of conventional mixing, granulating or dragee-making processes, and they contain from about 0.1% to about 75%, especially from about 1% to about 50%, of the active substance and may, if desired, contain further pharmacologically useful substances.

The following Examples illustrate the invention. Temperatures are given in degrees Centigrade.

Example 1

A mixture of 10 g of ethyl 4 - aminophenyl - acetate, 16.4 g of α, α' - dibromo - *o* - xylene, 17.8 g of sodium carbonate and 250 ml of dimethylformamide is boiled under reflux for 6 hours while stirring. After cooling, the mixture is diluted with water and extracted with diethyl ether; the organic extract is washed with water, dried, filtered and evaporated and the residue is recrystallised from diethyl ether to yield the ethyl α - [4 - (2 - isoindoliny) - phenyl] - acetate of the formula



m.p. 118—120°.

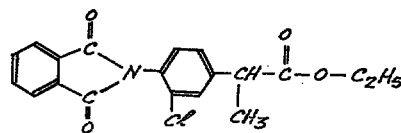
The starting material can be manufactured as follows:

A mixture of 5000 ml of anhydrous ethanol and 1000 g of 4 - aminophenyl - acetic acid is treated for 5½ hours with dry hydrogen chloride gas while stirring and boiling under reflux; the mixture is stirred and heated for an additional 4 hours and is then cooled at 10° for 16 hours. The mixture is filtered; the filter residue is washed with cold anhydrous ethanol and dissolved in 8000 ml of water. The solution is rendered basic by adding 50 ml portions of a 50% aqueous sodium hydroxide solution while stirring and is then stirred for one hour at room temperature. The resulting precipitate is filtered off and washed with water; the ethyl 4 - amino - phenyl - acetate melts at 47—49°.

Example 2

A mixture of 13.2 g of ethyl α - (4 - amino - 3 - chlorophenyl) - propionate hydrochloride, 7.4 g of phthalic acid anhydride, 10.1 g of triethylamine and 200 ml of toluene is boiled under reflux for 6 hours and evaporated under reduced pressure. The residue is taken up in water and the aqueous mixture is extracted with diethyl ether. The organic extract is dried, filtered and evaporated and the residue is recrystallised from

diethyl ether to yield the ethyl α - [3 - chloro - 4 - (1,3 - dioxo - 2 - isoindoliny) - phenyl] - propionate of the formula



m.p. 107—110°.

The starting material can be obtained as follows:

A solution of 52 g of ethyl 4 - nitrophenyl - acetate in 350 ml of a 1:1-mixture of dimethylformamide and toluene is treated in portions, while stirring and cooling, with 9.5 g of a 50% suspension of sodium hydride in mineral oil. After 1½ hours stirring at room temperature, 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 diethyl 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 left 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 the hydrogen uptake ceases. The mixture is filtered and the filtrate is evaporated to yield the ethyl α - (4 - aminophenyl) - propionate; its hydrochloride melts at 137—140°.

A mixture of 25 g of ethyl α - (4 - aminophenyl) - propionate and 100 ml of acetic acid anhydride, prepared while stirring and cooling, is left to stand for one hour at room temperature and is then evaporated under reduced pressure. The residue is recrystallised from diethyl ether; the resulting ethyl α - (4 - acetylaminophenyl) - propionate melts at 88—90°.

Chlorine gas is allowed to bubble through a solution of 25 g of ethyl α - (4 - acetylaminophenyl) - propionate in 100 ml acetic acid while stirring and cooling; the course of the chlorination is followed by means of thin layer chromatography (silica gel; 1:4-mixture of hexane and ether). When 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 bubbled through the solution for 45 minutes. The mixture is then boiled under reflux for 15 hours and evaporated. The residue is recrystallised from a mixture of ethanol and diethyl

ether to yield the ethyl α - (4 - amino - 3 - chloro - phenyl) - propionate hydrochloride, m.p. 164—168°.

The starting material can also be manufactured as follows:

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-aminophenylacetic acid boiling under reflux; stirring and boiling is continued for 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. A 50% aqueous sodium hydroxide solution is added in 50 ml portions while stirring until the mixture is basic and this mixture is stirred for one hour at room temperature. The resulting precipitate is filtered off and washed with water to yield the ethyl 4-aminophenylacetate, m.p. 47—49°.

A solution of 200 g of ethyl 4 - amino - phenylacetate in 250 ml of acetic acid anhydride is left to stand for 10 minutes and is then poured into 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°.

A solution of 170 g of ethyl 4 - acetyl-amino - phenylacetate in 25 ml of diethyl ether is added over the course of 25 minutes to a mixture consisting of 20.38 g of sodium, 2000 ml of anhydrous ammonia and a few crystals of iron-III-nitrate nonahydrate, while stirring. A mixture of 120.28 g of methyl iodide and 50 ml of diethyl ether is then added dropwise over the course of 20 minutes and the reaction mixture is stirred for one hour, then treated with 50 g of ammonium chloride and evaporated. The residue is taken up in diethyl ether and a dilute aqueous sodium hydroxide solution. The basic solution is extracted with diethyl ether and the combined organic solutions are evaporated to yield the ethyl α - (4 - acetylaminophenyl) - propionate, m.p. 84—86°. The material, which is about 90% pure, is distilled in a short path distillation apparatus and the fraction boiling at 170—183°/0.15 mm Hg is collected.

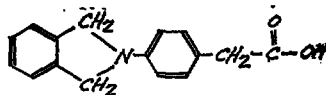
A solution of 72 g of ethyl α - (4 - acetylaminophenyl) - propionate in 200 ml of acetic acid is treated with gaseous chlorine which is allowed to bubble through the solution while stirring and maintaining a temperature of 15—20°. The course of the reaction is followed by means of thin layer chromatography using, as the mobile phase, a 4:1-mixture of diethyl ether and hexane, 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 represents the ethyl α - (4 - acetylamino - 3 - chloro - phenyl) - propionate.

A mixture of 60 g of ethyl α - (4 - acetyl-amino - 3 - chloro - phenyl) - propionate and 200 ml of ethanol is saturated with gaseous hydrogen chloride and boiled for one 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 diethyl ether. The organic extract is evaporated and the residue is chromatographed on aluminium oxide, the ethyl α - (4 - amino - 3 - chloro - phenyl) - propionate, melting at 168—170°, being eluted with a 95:5-mixture of cyclohexane and ethyl acetate. The free compound may be converted into the hydrochloride salt according to the previously described procedure.

Example 3

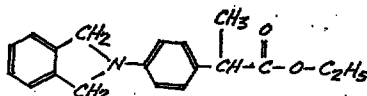
A mixture of 4.6 g of ethyl α - [4 - (2 - isoindoliny) - phenyl] - acetate and 80 ml of a 25% aqueous sodium hydroxide solution is boiled for 3 hours under reflux and then cooled and diluted with water. The mixture is acidified with hydrochloric acid; the precipitate is filtered off and recrystallised from ethyl acetate to yield the α - [4 - (2 - isoindoliny) - phenyl] - acetic acid of the formula



m.p. 237—239°.

Example 4

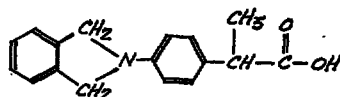
A mixture of 10 g of ethyl α - (4 - amino-phenyl) - propionate hydrochloride, 15 g of α,α' - dibromo - *o* - xylene, 16.5 g of sodium carbonate and 250 ml of dimethylformamide is boiled for 5 hours under reflux while stirring. After cooling, the mixture is filtered; the filtrate is concentrated under reduced pressure, diluted with water and extracted with diethyl ether. The organic extract is washed with water, dried, filtered and concentrated under reduced pressure. The precipitate is filtered off, recrystallised from ethanol and taken up in a minimal amount of benzene. The solution is passed through a small column of silica gel being eluted with benzene. The first eluate is evaporated and the residue is recrystallised from ethanol to yield the ethyl α - [4 - (2 - isoindoliny) - phenyl] - propionate of the formula



m.p. 111—113°.

Example 5

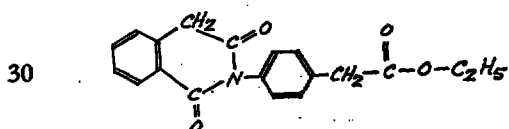
A mixture of 1.8 g of ethyl α - [4 - (2 - isoindolinyl) - phenyl] - propionate, 5 ml of a 50% aqueous sodium hydroxide solution, 25 ml of water and 100 ml of ethanol is boiled under reflux for 1½ hours and concentrated under reduced pressure. The concentrate is diluted with water and the resulting suspension is acidified to pH=3 with 6N hydrochloric acid, then extracted with ethyl acetate. The organic extract is dried, filtered and evaporated under reduced pressure. The residue is recrystallised from ethyl acetate to yield the α - [4 - (2 - isoindolinyl) - phenyl] - propionic acid of formula



m.p. 247—250°.

Example 6

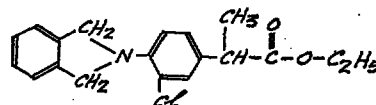
A mixture of 5 g of ethyl 4 - aminophenyl - acetate, 4.9 g of homophthalic acid anhydride, 100 ml of toluene and 0.5 ml of triethylamine is boiled under reflux for 16 hours, with the resulting water being collected in a water separator. The mixture is evaporated under reduced pressure and the residue is recrystallised from ethanol using active charcoal to yield the ethyl α - [4 - (1,3 - dioxo - 1,2,3,4 - tetrahydro - 2 - isoquinoliny) - phenyl] - acetate of the formula



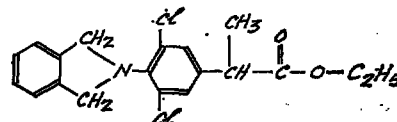
m.p. 89—91°.

Example 7

A solution of 0.5 g of ethyl α - [4 - (2 - isoindolinyl) - phenyl] - propionate in 50 ml of glacial acetic acid is mixed dropwise with 6 ml of a saturated solution of chlorine in glacial acetic acid while stirring; the mixture is then evaporated under reduced pressure, the residue is taken up in an aqueous sodium hydrogen carbonate solution and extracted with diethyl ether. The organic extract is dried, filtered and evaporated, and the residue is chromatographed on silica gel, using a 1:1-mixture of benzene and hexane as the mobile phase. The ethyl α - [3 - chloro - 4 - (2 - isoindolinyl) - phenyl] - propionate of the formula



with an Rf-value of 0.30 (starting material: Rf=0.26) is obtained as the main product, and the ethyl α - [3,5 - dichloro - 4 - (2 - isoindolinyl) - phenyl] - propionate of the formula



having an Rf=0.395 as the second product.

Example 8

Tablets, each containing 0.05 g of the active substance can be manufactured as follows:

Composition (for 10,000 tablets):
ethyl α - [4 - (2 - isoindolinyl) - phenyl] - acetate

500 g	
lactose	1706 g
corn starch	90 g
polyethylene glycol 6000	90 g
talc powder	90 g
magnesium stearate	24 g
purified water	q.s.

The pulverulent constituents are forced through a sieve of 0.6 mm openings. The ethyl α - [4 - (2 - isoindolinyl) - phenyl] - acetate, 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 the 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°, comminuted on a sieve of sieve size 1.2 mm, and processed into tablets using punches of 7.1 mm diameter, the upper being bisected.

Instead of the ethyl α - [4 - (2 - isoindolinyl) - phenyl] - acetate, other compounds of the formula I and especially the preferred compounds of the formula Ia, can be processed into tablets in an analogous manner.

Example 9

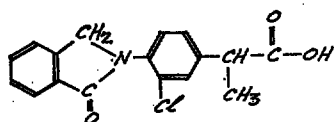
A mixture of 12 g of ethyl α - (4 - amino - 3 - chlorophenyl) - propionate, 11.6 g of α,α' - dibromo - o - xylene, 17 g of sodium carbonate and 250 ml of dimethylformamide is refluxed for 6 hours under a nitrogen atmosphere. After cooling, the reaction mixture is filtered; the filtrate is diluted with water and extracted with diethyl ether. The

organic extract is washed with water, dried, filtered and evaporated. The residue is distilled; the fraction boiling at 190—200°/0.4 mm Hg yields the ethyl α - [3 - chloro - 4 - (2 - isoindoliny)] - phenyl] - propionate, which is identical with the compound obtained according to the procedure described in Example 7.

The α - [3 - chloro - 4 - (2 - isoindoliny)] - phenyl] - propionic acid, prepared e.g. according to the procedure described in Example 3, melts at 148—150°.

Example 10

A mixture of 22.8 g of ethyl α - (4 - amino - 3 - chlorophenyl) - propionate, 19.8 g of ethyl 2 - chloromethyl - benzoate, 15 ml of triethylamine and 300 ml of ethanol is allowed to stand for 16 hours and slowly evaporated. The residue is taken up in water and extracted with diethyl ether; the organic extract is washed with 5% hydrochloric acid and water, dried, filtered and evaporated. The residue, containing the ethyl α - [3 - chloro - 4 - (1 - oxo - 2 - isoindoliny)] - phenyl] - propionate, m.p. 111—113°, is taken up in 250 ml of ethanol; 100 ml of a 10% aqueous potassium carbonate solution are added and the mixture is slowly evaporated under reduced pressure. The residue is taken up in water; the solution is filtered, the pH of the filtrate is adjusted to 4 with hydrochloric acid and the mixture is extracted with ethyl acetate. The organic extract is washed with water, dried and concentrated, to yield the α - [3 - chloro - 4 - (1 - oxo - 2 - isoindoliny)] - phenyl] - propionic acid of the formula



which melts at 178—180°.

Instead of the ethyl 2-chloromethylbenzoate, the 2 - chloromethyl - benzoic acid chloride may be used in the above procedure.

The starting material may be prepared as follows: A total of 4.8 g of a 50% suspension of sodium hydride in mineral oil is added to 100 ml of hexamethylphosphoric triamide while stirring under a nitrogen atmosphere, followed by 17.1 g of diethyl α -methylmalonate. The mixture is slowly heated to 100°, then treated dropwise with a solution of 19.2 g of 2,4 - dichloro - nitrobenzene in 20 ml of hexamethylphosphoric triamide, which is added within 30 minutes. The temperature is kept at 100° for 7 hours; after cooling, the mixture is diluted with water, concentrated under reduced pressure, the residue is taken up in water and extracted with benzene. The organic extract is washed with water, dried,

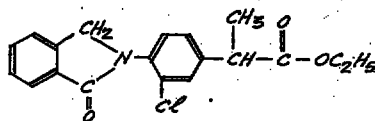
filtered and evaporated, and the residue is distilled. The fraction boiling at 147—148°/0.25 mm Hg yields the diethyl α - (3 - chloro - 4 - nitro - phenyl) - α - methyl - malonate.

Over a period of 5 minutes hydrogen chloride is bubbled through a solution of 4 g of diethyl α - (3 - chloro - 4 - nitro - phenyl) - α - methyl - malonate in 50 ml of anhydrous ethanol; 0.5 g of a 10% palladium-on-charcoal catalyst is added and the mixture is hydrogenated during 10 minutes at an initial pressure of 3 atmospheres, 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 the diethyl α - (4 - amino - 3 - chloro - phenyl) - α - methyl - malonate, showing in the infrared absorption spectrum characteristic bands at 1720 cm^{-1} , 3370 cm^{-1} 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 ethanolic hydrogen chloride solution; the mixture is refluxed for 6 hours and evaporated. The residue is recrystallized from a mixture of ethanol and diethyl ether to yield the ethyl α - (4 - amino - 3 - chloro - phenyl) - propionate hydrochloride, m.p. 164—168°, which may be converted into the free compound according to per se known methods, for example, by treatment with a basic reagent, such as sodium hydroxide, and extraction with an organic solvent, such as diethyl ether.

Example 11

Upon bubbling air through a concentrated solution of ethyl α - [3 - chloro - 4 - (2 - isoindoliny)] - phenyl] - propionate in dimethylformamide for 2 hours while maintaining a temperature of 60° and stirring, the ethyl α - [3 - chloro - 4 - (1 - oxo - 2 - isoindoliny)] - phenyl] - propionate of the formula



is obtained, which is isolated by evaporating the reaction mixture under reduced pressure and distilling the residue; the desired

product is collected as the fraction boiling at 200—210°/0.4 mm Hg.

- 5 The α - [3 - chloro - 4 - (5 - chloro - 1 - oxo - 2 - isoindolinyl) - phenyl] - propionic acid as well as its methyl and ethyl esters, or the sodium or potassium salts thereof may be obtained by selecting the appropriate starting materials and proceeding according to the previously described and
- 10 illustrated procedure.

Example 12

A cream containing 2% of the active ingredient is prepared as follows:

Composition:

- 15 α - [3 - chloro - 4 - (1 - oxo - 2 - isoindolinyl) - phenyl] - propionic acid 20 g
- White Petroleum 50 g
- Spermaceti 40 g
- 20 Stearyl Alcohol 50 g
- Cetyl Alcohol 50 g
- Stearic Acid 20 g
- Glycerol 120 g
- Sodium Lauryl Sulphate 10 g
- 25 Purified Water 610 g

The mixture of the petrolatum, the spermaceti, the stearyl alcohol, the cetyl alcohol and the stearic acid is molten and the liquid sieved into a mixing kettle heated to about 70°. The α - [3 - chloro - 4 - (1 - oxo - 2 - isoindolinyl) - phenyl] - propionic acid, mixed with the sodium lauryl sulfate, is suspended in the glycerol-water solution, which is heated to 72°, and slowly added to the mixture of the fatty substances while mixing vigorously until a homogenous cream is being formed.

Example 13

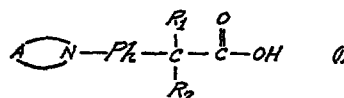
- 40 Tablets each containing 0.04 g of the active substance can be manufactured as follows:
- Composition (for 5000 tablets)

- α - [3 - chloro - 4 - (1 - oxo - 2 - isoindolinyl) - phenyl] - propionic acid 200 g
- 45 lactose 900 g
- corn starch 45 g
- polyethylene glycol 6000 45 g
- talc powder 45 g
- magnesium stearate 12 g
- 50 purified water q.s.

The tablets are prepared according to the procedure described in Example 8.

WHAT WE CLAIM IS:—

- 55 1. An α - (amino - phenyl) - aliphatic carboxylic acid compound of the Formula I



in which



represents an unsubstituted or substituted bicyclic alkenylene-amino group with 5 or 6 members in each ring and with from 1 to 3 double bonds in the ring system, Ph represents an unsubstituted or substituted phenylene radical, R₁ represents a hydrogen atom or a lower alkyl group, and R₂ represents a hydrogen atom or a lower alkyl, lower alkenyl, unsubstituted or lower alkyl-substituted cycloalkyl, unsubstituted or lower alkyl-substituted cycloalkenyl, cycloalkyl-lower alkyl or cycloalkenyl lower alkyl group.

2. An ester, amide, thioamide, nitrile or hydroxamic acid of an acid as claimed in claim 1.

3. A compound as claimed in claim 1, wherein



represents an unsubstituted or substituted bicyclic alkyleneamino group with from 1 to 3 double bonds in the isocyclic portion and 5 or 6 ring members in each ring.

4. An ester, amide, thioamide, nitrile or hydroxamic acid of an acid as claimed in claim 3.

5. A compound as claimed in claim 1, wherein



represents an unsubstituted or substituted benzoalkenyleneamino radical or a corresponding dihydro- or tetra - hydro - benzoalkenyleneamino radical in which the alkenyleneamino portion contains 5 or 6 ring members.

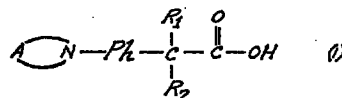
6. An ester, amide, thioamide, nitrile or hydroxamic acid of an acid as claimed in claim 5.

7. A compound as claimed in claim 1, wherein the group



product is collected as the fraction boiling at 200—210°/0.4 mm Hg.

- The α - [3 - chloro - 4 - (5 - chloro - 1 - oxo - 2 - isoindoliny) - phenyl] - propionic acid as well as its methyl and ethyl esters, or the sodium or potassium salts thereof may be obtained by selecting the appropriate starting materials and proceeding according to the previously described and illustrated procedure.



in which



Example 12

A cream containing 2% of the active ingredient is prepared as follows:

Composition:

- | | | |
|----|---|-------|
| 15 | α - [3 - chloro - 4 - (1 - oxo - 2 - isoindoliny) - phenyl] - propionic acid | 20 g |
| | White Petroleum | 50 g |
| | Spermaceti | 40 g |
| 20 | Stearyl Alcohol | 50 g |
| | Cetyl Alcohol | 50 g |
| | Stearic Acid | 20 g |
| | Glycerol | 120 g |
| | Sodium Lauryl Sulphate | 10 g |
| 25 | Purified Water | 610 g |

The mixture of the petrolatum, the spermaceti, the stearyl alcohol, the cetyl alcohol and the stearic acid is molten and the liquid sieved into a mixing kettle heated to about 70°. The α - [3 - chloro - 4 - (1 - oxo - 2 - isoindoliny) - phenyl] - propionic acid, mixed with the sodium lauryl sulfate, is suspended in the glycerol-water solution, which is heated to 72°, and slowly added to the mixture of the fatty substances while mixing vigorously until a homogenous cream is being formed.

Example 13

- 40 Tablets each containing 0.04 g of the active substance can be manufactured as follows:
Composition (for 5000 tablets)

- | | | |
|----|---|-------|
| | α - [3 - chloro - 4 - (1 - oxo - 2 - isoindoliny) - phenyl] - propionic acid | 200 g |
| 45 | lactose | 900 g |
| | corn starch | 45 g |
| | polyethylene glycol 6000 | 45 g |
| | talc powder | 45 g |
| | magnesium stearate | 12 g |
| 50 | purified water | q.s. |

The tablets are prepared according to the procedure described in Example 8.

WHAT WE CLAIM IS:—

- 55 1. An α - (amino - phenyl) - aliphatic carboxylic acid compound of the Formula I

represents an unsubstituted or substituted bicyclic alkenylene-amino group with 5 or 6 members in each ring and with from 1 to 3 double bonds in the ring system, Ph represents an unsubstituted or substituted phenylene radical, R₁ represents a hydrogen atom or a lower alkyl group, and R₂ represents a hydrogen atom or a lower alkyl, lower alkenyl, unsubstituted or lower alkyl-substituted cycloalkyl, unsubstituted or lower alkyl-substituted cycloalkenyl, cycloalkyl-lower alkyl or cycloalkenyl lower alkyl group.

2. An ester, amide, thioamide, nitrile or hydroxamic acid of an acid as claimed in claim 1.

3. A compound as claimed in claim 1, wherein



represents an unsubstituted or substituted bicyclic alkenyleneamino group with from 1 to 3 double bonds in the isocyclic portion and 5 or 6 ring members in each ring.

4. An ester, amide, thioamide, nitrile or hydroxamic acid of an acid as claimed in claim 3.

5. A compound as claimed in claim 1, wherein



represents an unsubstituted or substituted benzoalkenyleneamino radical or a corresponding dihydro- or tetra - hydro - benzoalkenyleneamino radical in which the alkenyleneamino portion contains 5 or 6 ring members.

6. An ester, amide, thioamide, nitrile or hydroxamic acid of an acid as claimed in claim 5.

7. A compound as claimed in claim 1, wherein the group



may be substituted by 1 to 3 oxo groups, the phenylene radical Ph is unsubstituted or substituted by 1 or 2 of the same or different substituents selected from lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkyl-mercapto, trifluoromethyl, nitro, amino, di-lower alkylamino, lower alkanoylamino, carbony, cyano, carbamoyl, di-lower alkylcarbamoyl, lower alkylsulphonyl, sulpho, sulphamoyl and di-lower alkylsulphamoyl groups and halogen atoms. R₁ represents a hydrogen atom or a lower alkyl group, and R₂ stands for a hydrogen atom or a lower alkyl or lower alkenyl group, or an unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkenyl, cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl group, in which the cycloaliphatic radical (R₂) contains from 3 to 7 ring members.

8. A lower alkyl or lower alkenyl ester, a cycloalkyl, a cycloalkenyl, cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl ester, in which a cycloaliphatic radical contains from 3 to 7 ring members, a phenyl or phenyl-lower alkyl ester, in which the phenyl radical is unsubstituted or substituted by one or more of the same or different groups listed in claim 7 that may substitute the group Ph, a hydroxy-lower alkyl, lower alkoxy-lower alkyl, di-lower alkyl-amino-lower alkyl, lower alkyleneamino-lower alkyl or monoaza- mono-oxa- or monothia-lower alkylene-amino-lower alkyl ester, two hetero-atoms in these ester radicals being separated from one another and the oxygens of the carboxyl group by at least 2 carbon atoms, an amide or thioamide, a mono- or di-lower alkyl-amide, a mono- or di-lower alkyl-thioamide, lower alkyleneamide or lower alkylene-thioamide, a phenylamide, phenylthioamide, phenyl-lower alkyl-amide or phenyl-lower alkyl-thioamide, a phenyl radical unsubstituted or substituted by one or more of the same or different groups listed in claim 7 that may substitute the group Ph, the morpholide or thiomorpholide, or the hydroxamic acid, of a compound claimed in claim 7.

9. A compound as claimed in claim 1, in which Ph, R₁ and R₂ have the meanings given in claim 7 in which the group



represents an unsubstituted or substituted bicyclic alkenyleneamino group with 1—3 double bonds in the isocyclic portion and with 5—6 ring members in each ring, and may be unsubstituted or substituted by 1 or 2 oxo groups.

10. A lower alkyl or lower alkenyl ester, a cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl ester, in which a cycloaliphatic radical contains 3 to

7 ring members, a phenyl or phenyl-lower alkyl ester, in which the phenyl radical is unsubstituted or substituted by one or more of the same or different substituents listed in claim 7 that may substitute the group Ph, a hydroxy-lower alkyl, lower alkoxy-lower alkyl, di-lower alkylamino-lower alkyl, lower alkyleneamino-lower alkyl or monoaza- mono-oxa- or monothia-lower alkylene-amino-lower alkyl ester, two hetero-atoms in these ester radicals being separated from one another and from the oxygen atoms of the carboxyl group by at least 2 carbon atoms, an amide or thioamide, a mono- or di-lower alkyl-amide, a mono- or di-lower alkyl-thioamide, a lower alkyleneamide or lower alkylene-thioamide, a phenylamide, phenyl-thioamide, phenyl-lower alkyl-amide or phenyl-lower alkyl-thioamide, a phenyl radical being unsubstituted or substituted by one or more of the same or different groups listed in claim 7 that may substitute the group Ph, the morpholide or thiomorpholide, or the hydroxamic acid, of a compound as claimed in claim 9.

11. A compound as claimed in claim 1, in which Ph, R₁ and R₂ have the meanings given in claim 7 and in which the group



represents an unsubstituted or substituted benzoalkenyleneamino group with 5 or 6 ring members in the alkenyleneamino portion, which group may be unsubstituted or substituted by 1 or 2 oxo groups.

12. A lower alkyl or lower alkenyl ester, a cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl ester, in which a cycloaliphatic radical contains 3 to 7 ring members, a phenyl or phenyl-lower alkyl ester, in which the phenyl radical is unsubstituted or substituted by one or more of the same or different groups listed in claim 7 that may substitute the group Ph, a hydroxy-lower alkyl, lower alkoxy-lower alkyl, di-lower alkyl-amino-lower alkyl, lower alkyleneamino-lower alkyl or monoaza- mono-oxa- or monothia-lower alkylene-amino-lower alkyl ester, 2 heteroatoms in these ester radicals being separated from one another and from the oxygen atoms of the carboxyl group by at least 2 carbon atoms, an amide or thioamide, a mono- or di-lower alkyl-amide, a mono- or di-lower alkyl-thioamide, a lower alkyleneamide or lower alkylene-thioamide, a phenylamide, phenyl-thioamide, phenyl-lower alkylamide or phenyl-lower alkyl-thioamide, a phenyl radical being unsubstituted or substituted by one or more of the same or different substituents listed in claim 7 that may substitute the group Ph, the morpholide or thiomorpholide or the hydroxamic acid of a compound as claimed in claim 11.





13. A compound as claimed in claim 1, in which the group



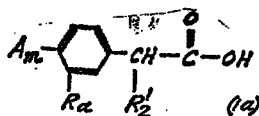
- has 1 to 3 double bonds in the isocyclic portion, Ph represents a 1,3- or 1,4-phenylene, (lower alkyl)-1,3- or 1,4-phenylene, (lower alkoxy)-1,3- or -1,4-phenylene, (mono- or di-halogeno)-1,3- or -1,4-phenylene, (trifluoromethyl)-1,3 or -1,4-phenylene, (nitro)-1,3- or -1,4-phenylene, (amino)-1,3- or -1,4-phenylene or (di-lower alkylamino)-1,3 or -1,4-phenylene radical, R_1 represents a hydrogen atom and R_2 represents a hydrogen atom or a lower alkyl, 3 to 7-membered cycloalkyl or 3 to 7-membered cycloalkyl-lower alkyl group.
14. A lower alkyl ester, amide or mono- or di-lower alkylamide of a compound as claimed in claim 13.
15. A compound as claimed in claim 1, wherein Ph, R_1 and R_2 have the meanings given in claim 13, and the group



- stands for an unsubstituted or substituted bicyclic alkenylamino group having 1 to 3 double bonds in the isocyclic portion and 5 or 6 ring members in each ring, and one or both carbon atoms adjacent to the ring nitrogen atom in the group may carry an oxo group.
16. A lower alkyl ester, amide or mono or di-lower alkylamide of a compound as claimed in claim 15.
17. A compound as claimed in claim 1, wherein Ph, R_1 and R_2 have the meanings given in claim 13, and the group



- represents an unsubstituted or substituted benzoalkenyleneamino radical with 5 or 6 ring members in the alkenyleneamino ring, and one or both carbon atoms adjacent to the ring nitrogen atom in this radical carry an oxo group.
18. A lower alkyl ester, amide or mono- or di-lower alkylamide of a compound as claimed in claim 17.
19. A compound of the formula



in which Am represents the 1-indolinyl, 2-isoinolinyl, 1,2,3,4 - tetrahydro - 1 - quinolinyl or 1,2,3,4 - tetrahydro - 2 - isoquinolinyl radical, R_a represents a hydrogen atom or an alkyl or alkoxy group with up to 4 carbon atoms, a trifluoromethyl, nitro or amino group or a halogen atom, and R_2' represents a hydrogen atom, an alkyl group with up to 4 carbon atoms, or a cycloalkyl or cycloalkylmethyl group, in which a cycloalkyl radical contains 3 or 4 ring members.

20. A methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl ester of a compound as claimed in claim 19.

21. A lower alkyl ester with up to 4 carbon atoms of a compound as claimed in claim 19.

22. A compound of the formula Ia as claimed in claim 19, wherein, in the radical Am, one or both ring carbon atoms adjacent to the ring nitrogen atom may carry an oxo group.

23. A methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl ester of a compound as claimed in claim 22.

24. A lower alkyl ester of a compound as claimed in claim 22.

25. A compound as claimed in claim 19, wherein Am represents the 2-isoinolinyl group, R_a represents a hydrogen atom or a nitro or amino group or a chlorine atom, and R_2' represents a hydrogen atom or a methyl, cyclopropyl or cyclopropylmethyl group.

26. A methyl or ethyl ester of a compound as claimed in claim 25.

27. A compound as claimed in claim 19, wherein Am represents the 2-isoinolinyl, 1 - oxo - 2 - isoinolinyl, 1,3 - dioxo - 2 - isoinolinyl or 1,3 - dioxo - 1,2,3,4 - tetrahydro - 2 - isoquinolinyl group, R_a represents a hydrogen atom, or a trifluoromethyl group or a fluorine or chlorine atom, and R_2' represents a hydrogen atom or a methyl, ethyl, n-propyl, isopropyl, cyclopropyl or cyclopropylmethyl group.

28. A methyl or ethyl ester of a compound as claimed in claim 27.

29. A compound as claimed in claim 19, in which Am represents the 2-isoinolinyl, 1 - oxo 2 - isoinolinyl, 1,3 - dioxo - 2 - isoinolinyl, 1 - oxo - 1,2,3,4 - tetrahydro - 2 - isoquinolinyl or 1,3 - dioxo - 1,2,3,4 - tetrahydro - 2 - isoquinolinyl group, R_a represents a hydrogen atom, or a nitro, amino or trifluoromethyl group or a fluorine or chlorine atom, and R_2' has the meaning given in claim 27.

30. A methyl or ethyl ester of a compound as claimed in claim 29.

31. Ethyl α - [4 - (2 - Isoindolinyl) - phenyl] - acetate.

32. Ethyl α - [3 - chloro - 4 - (1,3 - dioxo - 2 - isoinolinyl) - phenyl] - propionate.

33. α - [4 - (2 - Isoindoliny) - phenyl] - acetic acid.

34. Ethyl α - [4 - (2 - isoindoliny) - phenyl] - propionate.

35. α - [4 - (2 - Isoindoliny) - phenyl] - propionic acid.

36. Ethyl α - [4 - (1,3 - dioxo - 1,2,3,4 - tetrahydro - 2 - isoquinoliny) - phenyl] - acetate.

37. Ethyl α - [3 - chloro - 4 - (2 - isoindoliny) - phenyl] - propionate.

38. Ethyl α - [3,5 - dichloro - 4 - (2 - isoindoliny) - phenyl] - propionate.

39. Ethyl α - [3 - chloro - 4 - (1 - oxo - 2 - isoindoliny) - phenyl] - propionate.

40. α - [3 - Chloro - 4 - (1 - oxo - 2 - isoindoliny) - phenyl] - propionic acid.

41. A salt of a compound claimed in any one of claims 1, 2, 7, 8, 13, 14, 19, 20, 25, 26 and 31.

42. A physiologically tolerable salt of a compound claimed in any one of claims 1, 2, 7, 8, 13, 14, 19, 20, 25, 26, and 31.

43. A salt of a compound claimed in any one of claims 33-35, 37 and 38.

44. A physiologically tolerable salt of a compound claimed in any one of claims 33-35, 37 and 38.

45. A salt of a compound claimed in any one of claims 3, 4, 9, 10 and 21.

46. A physiologically tolerable salt of a compound claimed in any one of claims 3, 4, 9, 10 and 21.

47. A salt of a compound claimed in any one of claims 22, 23, 27, 28 and 40.

48. A physiologically tolerable salt of a compound claimed in any one of claims 15, 16, 22, 23, 27, 28 and 40.

49. A salt of a compound claimed in any one of claims 5, 6, 11, 12, 17, 18, 24, 29 and 30.

50. A physiologically tolerable salt of a compound claimed in any one of claims 5, 6, 11, 12, 17, 18, 24, 29 and 30.

51. A pharmaceutical preparation comprising a compound as claimed in any one of claims 1, 2, 7, 8, 13, 14, 19, 20, 25, 26, 31, 32 and 42 in admixture or conjunction with a pharmaceutically suitable carrier.

52. A pharmaceutical preparation comprising a compound as claimed in any one of claims 33 to 38 and 44 in admixture or conjunction with a pharmaceutically suitable carrier.

53. A pharmaceutical preparation comprising a compound as claimed in any one of claims 3, 4, 9, 10, 21 and 46 in admixture or conjunction with a pharmaceutically suitable carrier.

54. A pharmaceutical preparation comprising a compound as claimed in any one of claims 15, 16, 22, 23, 27, 28, 39, 40 and 48 in admixture or conjunction with a pharmaceutically suitable carrier.

55. A pharmaceutical preparation compris-

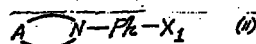
ing a compound as claimed in any one of claims 5, 6, 11, 12, 17, 18, 24, 29, 30 and 50 in admixture or conjunction with a pharmaceutically suitable carrier.

56. A compound as claimed in claim 5 or claim 6, as described in either of Examples 1 and 2.

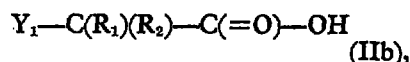
57. A compound as claimed in claim 3 or claim 4, as described in any one of Examples 3 to 7.

58. A compound as claimed in claim 1 or claim 2, described in any one of Examples 9 to 11.

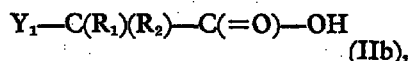
59. A process for the manufacture of a α - (amino - phenyl) - aliphatic carboxylic acid as claimed in claim 1, wherein, (a) a compound of Formula



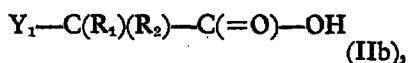
wherein X_1 represents a hydrogen atom, is reacted with a compound of the formula



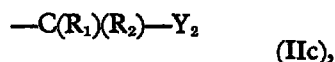
in which Y_1 stands for a free or reactive esterified hydroxy group, or a salt, ester, amide, thioamide, nitrile or hydroxamic acid thereof, or (b) a compound of the formula II, in which X_1 represents a metal radical, is reacted with a compound of the formula



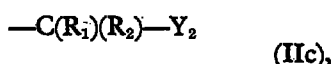
in which Y_1 stands for a reactive esterified hydroxy group, or a salt, ester, amide, thioamide, nitrile or hydroxamic acid thereof, or (c) a compound of the formula II, in which X_1 represents a reactive esterified hydroxy group, is reacted with a compound of the formula



in which Y_1 stands for a metal radical, or an ester, amide, thioamide, nitrile or hydroxamic acid thereof, or (d) a compound of the formula II, in which X_1 represents the group of the formula

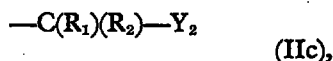


in which Y_2 stands for a metal radical, is reacted with a metal-free, reactive derivative of carbonic or formic acid, or (e) a compound of the formula II, in which X_1 represents the group of the formula

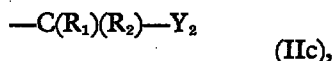




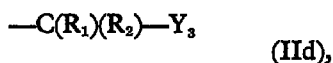
- 5 in which Y_2 stands for an unsubstituted or substituted ammonium group, is reacted with a reactive metal-containing derivative of carbonic or formic acid, or (f) a compound of the formula II, in which X_1 represents the group of the formula



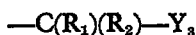
- 10 in which Y_2 stands for a free or reactive, functionality converted hydroxy group, is reacted with a reactive metal-containing derivative of carbonic or formic acid, or (g) a compound of the formula II, in which X_1 represents the group of the formula



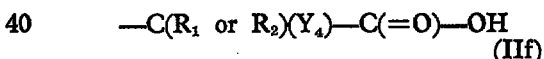
- 15 in which Y_2 stands for a free, esterified or salfied hydroxy group, or represents a 1-lower alkenyl radical, is reacted with carbon monoxide, or (h) in a compound of the formula II, in which X_1 represents the group of the formula



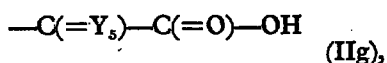
- 25 in which Y_3 stands for a methyl, hydroxymethyl, borylmethyl, hydroxyimino methyl, formyl, 1-lower alkenyl, 1-lower alkynyl, 1,2-dihydroxy-lower alkyl group, an acyl group or a free or functionally modified carboxy carbonyl group, Y_3 is converted into a free, esterified, amidated or thioamidated carboxyl group or a cyano group or hydroxamic acid by oxidation or rearrangement, or (i) in a compound of the formula II, in which X_1 represents the group of the formula



- 35 in which Y_3 stands for a free or esterified carboxycarbonyl group, Y_3 is converted into a free or esterified carboxy group by oxidation or decarbonylation, or (j) a compound of the formula II, in which X_1 represents a group of the formula

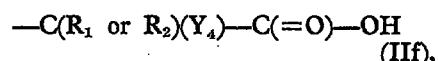


or of the formula

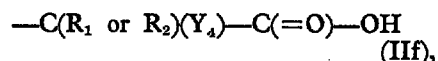


- 45 in which Y_4 represents a free or reactive esterified or etherified hydroxy or free or reactive esterified or etherified mercapto group, and Y_5 represents a lower alkylidene, cycloalkylidene or cycloalkyl-lower alkylidene group or an oxo group or a free or ketalized

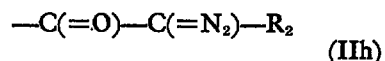
thio group, or a corresponding ester, amide, thioamide or nitrile or a corresponding quaternary ortho- or para-quinone methide of such compound is treated with catalytically activated or electrolytically generated hydrogen or with a chemical reducing agent, if desired, in the presence of a desulphurising agent, or (k) a compound of the formula II, in which X_1 represents the group of the formula



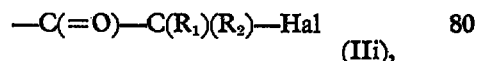
60 in which Y_4 represents a carboxy group, or an ester, amide, thioamide, nitrile or hydroxamic acid thereof is decarboxylated by pyrolysis, or (l) a compound of the formula II, in which X_1 represents a group of the formula



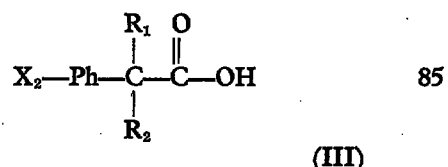
65 in which Y_4 represents an acyl group, or an ester, amide, thioamide, nitrile or hydroxamic acid is subjected to β -keto-acid splitting by treatment with a strongly alkaline agent, or (m) a compound of the formula II, in which X_1 represents an acetyl group, is treated with sulphur in the presence of ammonia or a primary or secondary amine, or (n) a compound of the formula II, in which X_1 represents a group of the formula



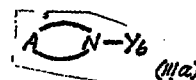
75 is subjected to hydrolysis, alcoholysis, ammonolysis or aminolysis, or (o) a compound of the formula II, in which X_1 represents a group of the formula



80 in which Hal stands for a halogen atom, is treated with a strongly alkaline agent or with a soluble silver salt, or (p) a compound of the formula



or an ester, amide, thioamide, nitrile or hydroxamic acid thereof, is reacted with a compound of the formula



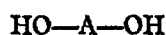


one of the radicals X_2 and Y_6 representing a hydrogen atom or a metal group and the other a free or reactive esterified hydroxy group, or (q) a compound of the formula III or an ester, an amide, a thioamide, nitrile or hydroxamic acid thereof, in which X_2 represents a primary, secondary or tertiary amino group, is reacted with an amine of the formula



10

or (r) a compound of the formula III, in which X_2 represents a primary amino group, of an ester, amide, thioamide, nitrile or hydroxamic acid thereof, is reacted with a compound of the formula



(IIIb)

or with a reactive derivative thereof or with a corresponding dehydrated compound thereof, or (s) a compound of the formula III, in which X_2 represents a radical of the formula



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which stands for a bicyclic alkyleneamino group having 5 or 6 ring members in each ring, and which group contains one or more of the same or different substituents selected from hydroxy, mercapto, amino, ammonium, hydrazino and hydrazono groups and functionally converted groups corresponding to these, or an ester, amide, thioamide, nitrile or hydroxamic acid thereof, is dehydrated, dehydrosulphidated, deaminated or pyrolysed, and, if desired, a resulting compound is converted within the scope defined into another compound of this invention, and/or, if desired, a resulting free compound is converted into a salt or a resulting salt into a free compound, and/or, if desired, a resulting mixture of isomers is resolved into the individual isomers.

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60. A process as claimed in claim 59, wherein the reaction (a) is performed in the presence of a Lewis acid.

61. A process as claimed in claim 59, wherein Y_6 in the process (h) represents a methyl, hydroxymethyl, borylmethyl, hydroxyiminomethyl, formyl, 1-lower alkenyl, 1-lower alkynyl, 1,2 - dihydroxy - lower alkyl or acyl group and is converted into a free carboxy, cyano, carbamoyl or hydroxycarbamyl group by oxidation or rearrangement.

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62. A process as claimed in claim 59,

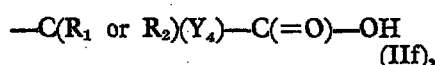
wherein a free hydroxy group Y_4 in the process (j) is reduced by treatment with phosphorus and iodine, hydriodic acid, tin-II-chloride or an alkali metal sulphite or dithionite.

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63. A process as claimed in claim 59, wherein an oxo group Y_6 in the process (j) is reduced by treatment with hydrazine.

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64. A process as claimed in claim 59, wherein X_1 in the starting material of the formula II represents a group of the formula



(IIf),

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in which Y_4 represents a disubstituted amino group, and in the corresponding starting material or an ester, amide, thioamide, nitrile or hydroxamic acid thereof the group Y_4 is split off by reduction.

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65. A process as claimed in claim 59, wherein a starting material of the formula III in process (P) in which X_2 represents a halogen atom, is reacted with a compound of the formula

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66. A process as claimed in claim 65, wherein X_2 represents a fluorine atom.

67. A process as claimed in claim 59, wherein the reaction (r) is performed with a reactive ester or a cyclic ether of a hydroxy compound of the formula IIIb.

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68. A process as claimed in claim 59, wherein the reaction (r) is performed with a halide or anhydride of an acid compound of the formula IIIb.

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69. A process as claimed in claim 59, wherein the reaction (r) is performed with an ester of an acid compound of the formula IIIb.

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70. A process as claimed in claim 59, wherein X_2 in a starting material of the formula III represents a radical



which stands for a bicyclic alkyleneamino group corresponding to the radical

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which group is substituted by one or more

- of the same or different substituents selected from hydroxy, mercapto, amino, ammonium, hydrazino and hydrazono groups and functionally converted groups corresponding to these, and the corresponding starting material or an ester, amide, thioamide, or nitrile or hydroxamic acid thereof is converted by dehydration, dehydrosulphidation, deamination or pyrolysis.
71. A process as claimed in any one of claims 59 to 63 and 65 to 68, wherein a resulting ester, amide, thioamide, nitrile or hydroxamic acid is hydrolysed to form the free acid.
72. A process as claimed in claim 64, wherein a resulting ester, amide, thioamide, nitrile or hydroxamic acid is hydrolysed to form the free acid.
73. A process as claimed in claim 70, wherein a resulting ester, amide, thioamide, nitrile or hydroxamic acid is hydrolysed to form the free acid.
74. A process as claimed in claim 69, wherein a resulting ester, amide, thioamide, nitrile or hydroxamic acid is hydrolysed to form the free acid.
75. A process as claimed in any one of claims 59 to 63, 65 to 68 and 71, wherein a free carboxy group in a resulting compound is converted into an esterified carboxy group.
76. A process as claimed in claim 64 or claim 72, wherein a free carboxy group in a resulting compound is converted into an esterified carboxy group.
77. A process as claimed in claim 70 or claim 73, wherein a free carboxy group in a resulting compound is converted into an esterified carboxy group.
78. A process as claimed in claim 69 or claim 74, wherein a free carboxy group in a resulting compound is converted into an esterified carboxy group.
79. A process as claimed in any one of claims 59 to 63, 65 to 68 and 71, wherein a resulting compound having a free carboxyl group is converted into an acid halide and the resulting acid halide is treated with an alcohol, ammonia or an amine.
80. A process as claimed in claim 64 or claim 72, wherein a resulting compound having a free carboxyl group is converted into an acid halide and the resulting acid halide is treated with an alcohol, ammonia or an amine.
81. A process as claimed in claim 70 or claim 73, wherein a resulting compound having a free carboxyl group is converted into an acid halide and the resulting acid halide is treated with an alcohol, ammonia or an amine.
82. A process as claimed in claim 69 or claim 74, wherein a resulting compound having a free carboxyl group is converted into an acid halide and the resulting acid halide is treated with an alcohol, ammonia or an amine.
83. A process as claimed in any one of claims 59 to 63, 65 to 68, 71, 75 and 79, wherein a resulting ester, salt or nitrile having a hydrogen atom in the α -position is metalised and reacted with a reactive ester of an alcohol of the formula R_1-OH and/or R_2-OH .
84. A process as claimed in any one of claims 64, 72, 76, and 80, wherein a resulting ester, salt or nitrile having a hydrogen atom in the α -position is metalised and reacted with a reactive ester of an alcohol of the formula R_1-OH and/or R_2-OH .
85. A process as claimed in any one of claims 70, 73, 77 and 81, wherein a resulting ester, salt or nitrile having a hydrogen atom in the α -position is metalised and reacted with a reactive ester of an alcohol of the formula R_1-OH and/or R_2-OH .
86. A process as claimed in any one of claims 69, 74, 78 and 82, wherein a resulting ester, salt or nitrile having a hydrogen atom in the α -position is metalised and reacted with a reactive ester of an alcohol of the formula R_1-OH and/or R_2-OH .
87. A process as claimed in claim 59, carried out substantially as described in Example 1 or Example 2.
88. A process as claimed in claim 59 carried out substantially as described in any one of Examples 3 to 7.
89. A process as claimed in claim 59 carried out substantially as described in any one of Examples 9 to 11.
90. A compound as claimed in claim 1 or claim 2 whenever prepared by a process claimed in any one of claims 59 to 63, 65 to 68, 71, 75, 79 and 83.
91. A compound as claimed in claim 1 or claim 2 whenever prepared by a process claimed in any one of claims 59 to 68, 71, 72, 75, 76, 79, 80, 83 and 84.
92. A compound as claimed in claim 1 or claim 2, whenever prepared by a process claimed in any one of claims 59 to 68, 70 to 73, 75 to 77, 79 to 81 and 83 to 85.
93. A compound as claimed in claim 1 or claim 2 whenever prepared by a process claimed in any one of claims 59 to 88.
94. A salt of a compound as claimed in claim 1, whenever prepared by a process as claimed in any one of claims 59 to 88.
95. A physiologically tolerable salt of a compound as claimed in claim 1, whenever prepared by a process as claimed in any one of claims 59 to 88.
96. A pharmaceutical preparation comprising a compound as claimed in any one of claims 56 to 59, 90 to 93 and 95, in admixture or conjunction with a pharmaceutically suitable carrier.



97. A pharmaceutical preparation comprising a compound as claimed in claim 1, in admixture or conjunction with a pharmaceutically suitable carrier, having a composition substantially as described in Examples 12 or 13.

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